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Review Article

A comprehensive review on COVID-19 with main focus on management and treatment options

Raghavendra Rao, Rama Bhat, Nitin Bhat, Sneha Seshadri
Department of Medicine, Kasturba Medical College, Manipal, Manipal Academy of Higher Education, India

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ABSTRACT

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a novel coronavirus of the same family as SARS-CoV and Middle East respiratory syndrome coronavirus, has spread globally, leading the World Health Organization to announce it as a pandemic. The disease caused by SARS-CoV-2, 2019 coronavirus disease (COVID-19), causes flu-like symptoms that may become severe in people at high risk. Infection is known to spread from human to human and through contact with contaminated surfaces. COVID-19's main symptoms include nausea, cough, fatigue, mild dyspnea, sore throat, headache and gastrointestinal problems. Real time polymerase chain reaction is used as a diagnostic device using nasal swab, oropharyngeal swab, tracheal aspiration or bronchoalveolar lavage samples. Antiviral medications, steroids, IL-6 antagonist and respiratory support devices are the primary treatments being used to treat the condition. In addition, while several interventions have been suggested, quarantine is the only method that seems to be successful in lowering the risk of infection. The COVID-19 pandemic reflects the present generation's major global public health issue, following the 1918 pandemic influenza epidemic. The pace and frequency of clinical trials conducted to evaluate possible COVID-19 therapies underscore both the need and capacity to deliver high-quality evidence even in the midst of a pandemic. Various vaccines have been developed which are in different phases and we hope to have a vaccine for the general population soon, as it could prevent the spread of the disease.

KEY WORDS: clinical trials, SARS-CoV-2, therapeutics, vaccines, viral pneumonia

INTRODUCTION

According to the World Health Organization, viral diseases tend to arise and pose a significant public health problem. Numerous viral epidemics, such as the severe acute respiratory coronavirus syndrome (SARS-CoV) and H1N1 influenza have been recorded in the last two decades[1].

The Middle East respiratory syndrome coronavirus (MERS-CoV) was also identified early in this decade. On 31st December 2019, an outbreak with several cases of unidentified lower respiratory infections was first reported in Wuhan, China's largest metropolitan area in the Hubei province. Those first cases were listed as "pneumonia of unknown etiology" since they were unable to classify the causative agent.

The new virus was at first named 2019-nCoV. Eventually, the International Committee on Virus Taxonomy experts named it the SARS-CoV-2 virus, as it is very identical to that which caused the SARS outbreak (SARS-CoVs)[2].

SARS-CoV-2 is a β-coronavirus, enveloped by non-segmented positive-sense RNA virus (subgenus sarbecovirus, subfamily Orthocoronaviridae)[3]. It was figured that SARS-CoV-2's genome sequence is 96.2% identical to a bat CoV RaTG13, while it represents SARS-CoV's identity at 79.5%. Based on the results of virus genome sequencing and evolutionary research, bats were believed to be the natural host of virus origin, and SARS-CoV-2 could be transmitted via unspecified intermediate hosts from bats to infect humans. It has become apparent that SARS-CoV-2 may use angiotensin-converting enzyme 2 for its entry into the cell[4].

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Scientists are engaged in research works day-in and day-out, and knowledge on transmission processes, clinical disease continuum, new treatments and strategies for prevention are increasingly emerging. The therapeutic approaches for coping with the infection have improved the chances of survival in moderate-severe cases and prevention is aimed at minimizing social transmission and developing an efficacious vaccine.

The present review explores the symptoms, diagnosis, associated complications, and the challenges associated with COVID-19. The management strategies and the possible therapeutic interventions that can be employed in the treatment of the disease are also discussed.

LITERATURE REVIEW

Fever, cough, malaise, mild dyspnea, sore throat and headache are typical symptoms of the disease[5]. Therefore, differentiating COVID-19 from other respiratory disorders is difficult[6]. Gastrointestinal involvement, with diarrhea, nausea and vomiting were documented in a lower percentage of cases. In about 80-90% of cases, the pattern of infection is mild or asymptomatic. It only becomes severe in about 10% of cases, with dyspnea, hypoxemia and significant radiological involvement of the lung parenchyma (>50%). In about 5% of cases, a severe condition progresses with respiratory failure, pneumonia, shock, multiorgan failure and, in the most extreme cases, death, which is almost always the case. Typical pathology pattern involves the presence of apparent dyspnea six days after the start of flu-like symptoms, hospitalization after another eight days, and tracheal intubation 10 days after hospitalization[7]. It has been recorded that COVID-19 mortality is about 3% and hence continues to be lower than SARS-CoV (10%) and MERS-CoV (35%)[8]. However, in light of COVID-19's recent and rapid progress, it is far too premature to establish the specific mortality rate of the disease. Ongoing research implies that age, ischemic heart disease, diabetes, hypertension and immunosuppression are the key risk factors for poor outcome[9].

Diagnostic approach

The diagnosis of COVID-19 at a clinical stage is centred on epidemiological evidence, clinical symptoms and certain complementary tests, namely blood analysis, nucleic acid detection, CT screening, immune-related tests (IgM or IgG levels) and enzyme-linked immunosorbent tests (ELISA)[10]. Reverse transcription-polymerase chain reaction (RT-PCR) is a diagnostic test which uses specimens of nasal swab, oropharyngeal swab, tracheal aspirate, or bronchoalveolar lavage. The predominant and favoured diagnostic method is to obtain the upper respiratory samples through nasopharyngeal and oropharyngeal swabs[11]. The gene targets for RT-PCR test are one or more of nucleocapsid, envelope, spike, RNA-dependent RNA polymerase and ORF1 genes[12]. RT-PCR positivity is highest in bronchoalveolar lavage specimens (93%), followed by sputum (72%), nasal swab (63%) and pharyngeal swab (32%)[13]. Specificity of this test has been 100% as the primer design is specific to the genome sequence of SARS-CoV-2 and false positivity may be seen due to technical errors and reagent contamination. Serological diagnosis of SARS-CoV-2 infection could be especially important in patients with mild-moderate illness who present late, *i.e.* two weeks after onset of illness[12]. IgM and IgG seroconversion occurred in almost all patients between the 3rd and 4th week of clinical illness[14,15]. There is a decline in IgM levels by week 5 and disappearance by week 7, whereas IgG persists for more than 7 weeks[16]. The combined sensitivity of PCR and IgM ELISA directed at nucleocapsid antigen was 98.6% vs. 51.9% with a single PCR test in a study done on 140 patients, highlighting the importance of combined testing for SARS-CoV-2 infection. Quantitative PCR had a higher positivity rate than IgM ELISA during the first 5.5 days of illness[17]. High-resolution computed tomography of the thorax should be considered in all patients with hypoxia to grade the severity of lung involvement.

Associated complications

Acute respiratory distress syndrome, arrhythmia, shock, acute kidney injury, acute myocardial injury, liver disease, stroke, pulmonary thromboembolism and secondary infection are reported to be the major complications[18]. The inconsistent clinical result is associated with the severity of the disease. The disease tends to progress faster in the elderly (aged 65 or older)[19,20].

The elderly male with acute respiratory distress syndrome and comorbidities had an increased risk of death[21]. Furthermore, many children were diagnosed with the infection, the youngest being 30 hours after childbirth[22]. Neonates and the elderly do need care and treatment, given their weak or impaired immune system.

Challenges

COVID-19 has raised high health concerns worldwide. Specific approaches should be introduced at the national and global levels in healthcare settings to prevent the spread of the disease. However, irrespective of stringent measures taken to curtail the spread, huge challenges persist in paving the way that leads to controlling the spread. Antiviral

medications, steroids, tocilizumab along with oxygen therapy, ventilatory management, fluid control and the use of broad-spectrum antibiotics to ameliorate secondary infections continue to remain the most viable management strategy. Huge research efforts are underway which would culminate in the development of potential vaccines that would prove to be a viable effective prevention technique in limiting the spread.

Possible strategies to control the spread

Various strategies are adopted in every sphere to control the spread of the disease. The strategies which need to be followed upon are discussed below.

Unfortunately, the health care environment may be a significant origin of viral transmission. Suspected patients with signs of respiratory infections at clinics and hospitals need to wear a face mask and stick explicitly to triage protocol. They should not be required to wait at the hospitals with other patients in the waiting zones for availing medical treatment. Instead, they should be put in a distinct, completely ventilated space, about 2 m from the other patients with adequate respiratory hygiene supplies[23]. Additionally, if a confirmed COVID-19 individual needs hospitalization, they must be put in a single space with negative air pressure – at least six switches of air in every hour. The depleted air must be filtered by high-efficiency particulate air, and health workers entering the room should use personal protective equipment such as gloves, gowns and disposable N95 masks. It is important to raise public awareness to understand and recognize unusual symptoms such as chronic cough or shortness of breath, so that they can seek medical attention to detect the virus early on. When large-scale group transmission emerges, social events should be mitigated, temporary school closures, home isolation and close monitoring of the symptomatic patient should be advocated[24].

Treatment options

Below discussed are a group of drugs with their mechanism of action that are extensively researched upon for the treatment of the stated disease. Much of the existing evidence for pharmacological interventions are derived from drugs employed during the pandemic of SARS-CoV or MERS-CoV or from in vitro studies[25]. There is lack of proof stating the fact that antibiotic prophylaxis can resist bacterial super infection. The bulk of the data available come from descriptive research and common knowledge.

The following section discusses the frontline drugs that are investigated to be used as potential therapies for the circumvention of COVID-19 in the near future (Table 1)[26-31].

Listed below are the various drugs which have undergone trials for their use in COVID-19 infection.

Hydroxychloroquine

An observational study conducted in New York City on 1376 patients revealed that administration of hydroxychloroquine was not associated with increased risk of intubation or death (composite end point)[32]. A meta-analysis which included a total of 23 studies, of which three were randomized controlled trials (all from China)[33-35], affirmed the evidence was weak and conflicting considering the benefit and harms of using chloroquine or hydroxychloroquine in treating COVID-19 patients[36]. The studies have shown that this drug is not useful in the treatment of COVID-19 infection.

Hydroxychloroquine with azithromycin

Results of an open-label, non-randomized clinical trial in France coordinated by The Méditerranée Infection University Hospital Institute has stated that there is significant reduction in viral load/disappearance in patients with COVID-19 on hydroxychloroquine and azithromycin[37]. More studies are required to know if this combination therapy would be useful in treating the disease.

Remdesivir

In a multinational double-blind, randomized, placebo-controlled trial on 1063 adult patients who were hospitalized with lower respiratory tract involvement of COVID-19 infection, intravenous remdesivir (200 mg loading dose on day 1, followed by 100 mg daily for up to nine more days) was found to be superior to placebo in shortening the time to recovery (median: 11 days vs. 15 days; rate ratio of recovery: 1.32; 95% confidence interval [CI]: 1.12 to 1.55; P <0.001). However, the Kaplan-Meier mortality by 14 days in the remdesivir and placebo group was 7.1% and 11.9% respectively without any significance[38]. In one more multinational study involving 53 patients, where remdesivir was given on compassionate-use basis to patients with severe COVID-19 infection (oxygen saturation of 94% or less on breathing ambient air/needing oxygen support), clinical improvement was seen in 68% of the patients[39]. A randomized, open-label, phase 3 trial funded by Gilead Sciences was conducted on 397 patients (multinational) with severe COVID-19 infection who underwent randomization in a 1:1 ratio and received intravenous remdesivir for either 5 or 10 days. This trial did not show any significant difference in a 5-day course / 10-day course of remdesivir in patients who did not require mechanical ventilation[40]. A more randomised, double-blind, placebo-controlled, multicentric trial was conducted in China on 237 patients with severe COVID-19 infection. Patients underwent randomization in a 2:1 ratio to receive intravenous remdesivir or same volume of placebo for 10 days. However, concomitant use of interferon,

Table 1: Potential drugs for the treatment of COVID-19

Drug	Medication class	Developer	Original indications	Rationale for use in COVID-19
Remdesivir[26]	Antiviral	Gilead Sciences	Treatment for Ebola and Marburg virus infections	Remdesivir, an intravenous drug inhibiting viral replication, has demonstrated activity against SARS-CoV-2 as shown by in vitro and in vivo results. It was initially established as a therapy for Ebola that eventually proved less successful than other interventions, but showed efficacy against other coronaviruses as evidenced in animal studies.
Hydroxychloroquine (Plaquenil) and chloroquine (Aralen) [27]	Antimalarial	Sanofi (Plaquenil and Aralen); Mylan, Teva, Novartis, Bayer, Rising Pharmaceuticals (generics)	Hydroxychloroquine (HCQ) is recommended for both the prevention of acute malaria attacks attributable to susceptible Plasmodium strains and for suppressive care as well. Chloroquine is recommended for treating uncomplicated malaria and for malaria prophylaxis where resistance to chloroquine is not observed. The drug has also shown efficacy in the treatment of rheumatoid arthritis, systemic lupus erythematosus and porphyria cutanea tarda.	In vitro and in vivo results suggests potential therapeutic efficacy of both HCQ and chloroquine against SARS-CoV-2.
Convalescent plasma[28,29]	Immunoglobulin			Research teams have hypothesized the use of convalescent plasma as passive immunotherapy in other coronaviruses such as MERS and in SARS-CoV-2 to neutralize the effects produced by virus.
Favipiravir[30]	Antiviral	Fujifilm Toyama Chemical (as Avigan) and Zhejiang Hisun Pharmaceutical	Favipiravir is approved in China and Italy to treat COVID-19.	Scientific publications in China have reported favipiravir to be clinically effective against COVID-19.
Tocilizumab[31]	Interleukin-6 (IL-6) receptor antagonist	Roche	Tocilizumab is indicated for treating moderately to seriously active rheumatoid arthritis in adults with sufficient response from one or more DMARDs, adult giant cell arteritis, active polyarticular juvenile idiopathic arthritis (JIA) in patients (2 years of age or older), systemic JIA in patients 2 years of age or older, CRS in patients 2 years of age or older and CRS induced by chimeric antigen receptor T-cell (CAR-T) treatment.	Research reports have indicated that tocilizumab can be an effective therapy for patients with extreme COVID-19 symptoms.

lopinavir-ritonavir and corticosteroids were permitted. It concluded that the time to improvement as well as the duration of invasive mechanical ventilation was not significant in both the groups[41]. Remdesivir has been found to be effective in the treatment of severe COVID-19 infection and could be considered as the therapy of choice in treating such a disease.

Favipiravir

A prospective, randomized, controlled, open-label multicentre trial was conducted in three hospitals of China involving 240 adult patients with COVID-19 infection. Patients were randomized in 1:1 ratio and received Favipiravir (1600 mg twice on the first day, followed by 600 mg twice daily for the following days) or Umifenovir (200 mg three times daily) plus standard care for seven days. Differences in clinical recovery at day 7 were observed in patients with moderate infections (71.4% favipiravir and 55.9% Arbidol, *P*=0.019). No significant differences were observed in the severe or severe and moderate (combined) arms[42]. An observational study was done in Japan on 2,158

cases where favipiravir was given on compassionate-use basis. Rates of clinical improvement at 14 days in mild, moderate and severe cases were 87.8%, 84.5% and 60.3% respectively, with rates of clinical worsening being 5.9%, 8.8% and 25.2% respectively[43]. The open-label randomized, multicenter clinical trial was conducted on 150 patients across India to evaluate the efficacy by Glenmark Pharmaceuticals. They found that 69.8% of patients in the favipiravir treatment arm of the study achieved clinical cure by day four vs. 44.9% of participants achieving the measure by the same point in the control arm[44]. Hence, this could be a potential drug to treat mild-moderate cases of COVID-19 infection.

Convalescent plasma (CP)

A pilot study was conducted in three different hospitals of Wuhan, China on 10 patients. Patients with severe COVID-19 infection were selected for the study. All patients received antiviral therapy with supportive care. A single dose of inactivated CP (200 mL) with neutralizing activity of >1:640 titres was transfused to the patients within four hours. The case fatality rate was 0% and SARS-CoV-2 RNA reduced to undetectable levels in three patients on day 2, three patients on day 3 and one patient on day 6 after CP therapy[45]. A systematic review from various sources on CP therapy in severe COVID-19 infection was done, which included five studies. The major findings were reduced mortality in critically ill patients, increase in neutralizing antibody titres and disappearance of SARS-CoV-2 RNA, and improvement in clinical symptoms[46]. Multicenter clinical study was done on 189 patients with documented hypoxia, which included 115 patients in the plasma therapy group and 74 patients in the control group. There were more discharges in plasma therapy group compared to the control group, *i.e.* 98.2% vs 78.7% respectively. The need for intubation was significantly lower in the plasma therapy group compared to the control group, *i.e.* 7% vs 20% respectively, providing strong evidence to treat COVID-19 patients with CP therapy[47].

Tocilizumab

A retrospective observational cohort study in 544 adults from Italy with severe COVID-19 pneumonia was done. One group received standard care (antivirals and supportive therapy) and the other group received tocilizumab along with standard care. Of the patients who required mechanical ventilation, the mortality rate was 20% in standard care group compared to 7% in patients who received tocilizumab (P <0.0001). There was also reduced risk of invasive mechanical ventilation in tocilizumab group (adjusted hazard ratio 0.61, 95% CI: 0.40-0.92; P=0.02)[48]. Phase II, single-arm, open-label, prospective, blinded, clinical trial with tocilizumab as the sole agent has already started in Mexico, in which 200 participants are expected to take part[49]. The randomized, double-blind COVACTA trial conducted in patients with severe COVID-19 pneumonia did not meet its primary end points, including a difference in patient mortality at week 4[50]. Hence, we cannot really comment about its efficacy in treating severe COVID-19 infection, though it is being used in some countries to treat cytokine storm.

Dexamethasone

The Randomised Evaluation of COVID-19 therapy trial is a randomized, controlled, open-label, adaptive, platform trial which compares various possible treatments with usual care in hospitalized COVID-19 patients. Preliminary results of the study for the comparison of dexamethasone 6 mg given once daily for up to ten days vs. usual care alone are out. The primary outcome of the study was 28-day mortality. Dexamethasone was given to 2104 patients who were randomly allocated and compared with 4321 patients who received usual care. The mortality within 28 days was 21.6% in patients who received dexamethasone compared to 24.6% in those who received usual care (age-adjusted rate ratio [RR]: 0.83; 95% CI: 0.74-0.92; P <0.001). Dexamethasone reduced deaths by one-fifth in patients receiving oxygen without invasive mechanical ventilation (21.5% vs. 25%, RR: 0.80 [95% CI: 0.70-0.92]; P=0.002), by one-third in patients receiving invasive mechanical ventilation (29% vs. 40.7%, RR: 0.65 [95% CI: 0.51-0.82]; P <0.001), but did not reduce mortality in patients not receiving respiratory support at randomization (17% vs. 13.2%, RR: 1.22 [95% CI: 0.93-1.61]; P=0.14). Hence, dexamethasone was useful in reducing the 28-day mortality among those receiving oxygen or invasive mechanical ventilation at randomization[51]. Prospective randomized controlled trials are going on in China regarding the safety and efficacy of glucocorticoids (methylprednisolone) for the treatment of COVID-19 pneumonia.

Anticoagulation

There is growing evidence that COVID-19 causes thrombus formation due to the damage of endothelium. A retrospective multicentre cohort study from China analysed 191 patients with COVID-19 infection. They found coagulopathy in 50% of the 54 non-surviving patients, compared to 7% of 137 surviving patients (P <0.0001)[52]. A recent study done on 184 ICU patients with COVID-19 pneumonia showed the presence of pulmonary embolism (computed tomography pulmonary angiogram proven) in 27% of the cases, necessitating the use of anticoagulants in severely ill patients. These patients also had no evidence of disseminated intravascular coagulation[53]. Therefore, it is recommended to start anticoagulation

in moderate-severe COVID-19 patients, and in patients with elevated D-dimer levels.

Vaccines

Vaccines typically demand years of research and testing prior to clinical usage; however, scientists are highly engaged to produce a safe and efficient coronavirus vaccine in the coming year. Vaccines may be the safest, most efficacious way to prevent COVID-19 infection and bring the current progressing pandemic under control[54].

As of 21st February 2021, the draft landscape summary of World Health Organization states that there are 64 vaccine candidates in the clinical evaluation stage[55]. 179 vaccine candidates are in the preclinical evaluation stage.

We briefly describe published trials of vaccine candidates who are in stage 3 and those which are approved for clinical use. The vaccines for which published data is not available but have reached phase 3 and the ones that are approved for use are mentioned in Table 2[55].

University of Oxford/AstraZeneca vaccine

It is a chimpanzee adenovirus-vectored vaccine (ChAdOx1 nCoV-19). Phase 3 trials of this vaccine candidate are at an advanced stage. Results of phase 1/2 trials involving 1077 adults are published[56]. The adverse effects were mild and were reduced with prophylactic paracetamol. Humoral response peaked by day 28. Cellular T-cell response is induced by day 14. Interim data from phase 3 trial in the UK, Brazil and South Africa have shown an overall efficacy of 70%, with vaccine efficacy at 62.1% in a group of participants receiving two standard doses and 90% in a group receiving one half dose followed by a standard dose[57] . Presently it is approved for use in any country.

CanSino Biological Inc. /Beijing Institute of Biotechnology vaccine

In phase 2, it was found that a single dose schedule of vaccine is enough for healthy adults. However, older people have significantly lower immune response. Additional doses may be needed for them. Phase 3 trials are being conducted[58].

Gamaleya Research Institute vaccine (Sputnik V)

It is a vaccine with two different adenoviral vectors (recombinant Ad26 [rAd26] and recombinant Ad5 [rAd5]), both carrying the gene for SARS-CoV-2 spike glycoprotein (rAd26-S and rAd5-S). Small phase 1 and 2 human trials with 38 volunteers have

Table 2: Potential vaccines to prevent COVID-19 infection

Developer / manufacturer	Vaccine platform	Type of candidate vaccine	Number of doses	Timing of doses	Route of administration	Stage of trial
University of Oxford / AstraZeneca	Non-replicating viral vector	ChAdOx1-S	2	0, 28 days	Intramuscular	Approved
CanSino Biological Inc./ Beijing Institute of Biotechnology	Non-replicating viral vector	Adenovirus type 5 vector	1		Intramuscular	Approved
Gamaleya Research Institute	Non-replicating viral vector	Adeno-based (rAd26-S+rAd5-S)	2	0, 21 days	Intramuscular	Approved
Janssen Pharmaceutical Companies	Non-replicating viral vector	Ad26COVS1	1-2	day 0 or day 0, 56days	Intramuscular	Phase 3
Sinovac	Inactivated	Inactivated	2	0, 14 days	Intramuscular	Approved
Wuhan Institute of Biological Products / Sinopharm	Inactivated	Inactivated	2	0, 14 days or 0, 21 days	Intramuscular	Approved
Beijing Institute of Biological Products / Sinopharm	Inactivated	Inactivated	2	0, 14 days or 0, 21 days	Intramuscular	Approved
Moderna / NIAID	RNA	LNP-encapsulated mRNA	2	0, 28 days	Intramuscular	Approved
BioNTech / Fosun Pharma / Pfizer	RNA	3 LNP-mRNAs	2	0, 28 days	Intramuscular	Approved
Novavax	Protein subunit	Full length recombinant SARS CoV-2 glycoprotein nanoparticle vaccine adjuvanted with Matrix M	2	0, 21 days	Intramuscular	Phase 3

Table 3: Treatment protocol of Kasturba Medical College, Manipal

Mild cases	Moderate cases	Severe / critical cases
Only supportive therapy	**Anticoagulation / anti-inflammatory** • Inj. Enoxaparin 0.6mg SC once daily • Inj. Dexamethasone 6mg IV once daily x 5-7 days **Antiviral therapy** • Inj. Remdesivir 200mg IV on day 1 followed by 100mg IV daily for 4 days **Convalescent plasma therapy** • 4-13 ml/kg given slowly over not less than 2 hours	**Anticoagulation / anti-inflammatory** • Inj. Enoxaparin 0.6mg SC twice daily • Inj. Dexamethasone 6mg IV twice daily x 5-7 days **Antiviral therapy** • Inj. Remdesivir 200mg IV on day 1 followed by 100mg IV daily for 4 days **Anti-IL therapy** • Inj. Tocilizumab 8mg/kg given slowly in 100 ml NS over 1 hour • Inj. Itolizumab 1.6mg/kg dose as IV infusion **Oxygenation** • Oxygen by face mask or non-rebreathing mask at 8-10L/min based on PaO_2/FiO_2 ratio • High flow nasal oxygen (HFNC) / non-invasive ventilation • If patient deteriorates, intubation should be considered. **Prone ventilation and advanced ventilatory strategies** **Antibiotics** • Inj. Ceftriaxone 2gm IV once daily and escalated according to local antibiogram if needed in procalcitonin positive individuals

been conducted. Vaccine has been proved safe and efficacious in these small trials[59]. Phase 3 trials were conducted in Russia involving 21,977 participants. Vaccine efficacy was reported to be 91.6% and it is approved for use[60].

Wuhan Institute of Biological Products/Sinopharm vaccine

It is an inactivated whole virus vaccine. Two placebo controlled randomized phases 1 (96 participants) and 2 (224 participants) were conducted. The vaccine demonstrated good immunogenicity by detecting neutralizing antibody response by day 14. Adverse effects were mild. Phase 3 trials were conducted[61]. The vaccine is approved for use.

Janssen Pharmaceutical Companies vaccine

It uses a non-replicating adenovirus 26 based vector vaccine expressing the stabilized pre-fusion spike (S) protein of SARS-CoV-2. A multi-center phase 1/2 randomized, double-blinded, placebo-controlled clinical study was conducted. Early data in preprint showed robust immune response after only one dose. Phase 3 trials involving 43,738 participants are ongoing[62]. In topline phase 3 data from 43,783 participants, J&J has announced their vaccine has shown overall efficacy of 66% with 72% protection against moderate or severe disease in the United States, 66% in Latin America and 57% in South Africa[63]. Final results are awaited.

Moderna/NIAID vaccine

It uses mRNA-1273 which encodes the stabilized pre-fusion SARS-CoV-2 spike protein. A phase 1, dose-escalation, open-label trial including 45 healthy adults was conducted. Two doses were given at 0 and 28 days. There were mild to moderate but no major trial limiting adverse effects. Immune response was induced in all[64]. Phase 3 trial involving 30,000 volunteers was conducted in USA demonstrating 94% efficacy, and the vaccine is approved for use[65].

BioNTech/Fosun Pharma/Pfizer vaccine

It uses BNT162b1 mRNA vaccine that encodes the trimerized receptor-binding domain of the spike glycoprotein of SARS-CoV-2. A placebo-controlled, observer-blinded dose-escalation study (45 participants) was carried out. Adverse effects were mild to moderate. Humoral antibodies were induced after 14 days. Phase 3 trials were conducted involving 43,448 people[66]. It was found to be 95% effective and the vaccine is approved for use[67].

Novavax vaccine

It is a protein subunit vaccine using trimeric full-length SARS-CoV-2 spike glycoproteins and Matrix-M1 adjuvant. A randomized, placebo-controlled, phase 1-2 trial with 131 healthy adults was performed. Adverse effects were mild. It elicited immune responses that exceeded levels in COVID-19 convalescent serum[68]. The company has announced phase 3 data from UK trial showing vaccine efficacy to be 89.3%, and in phase 2b clinical trial going on in South Africa, it was found to be 60% effective. Final results of the trials are still awaited[69].

An ideal vaccine must be safe and should have high efficacy. It should also be able to be readily mass produced inexpensively, be easily transportable with minimal cold chain requirements. Table 3 depicts the treatment protocol of our hospital.

CONCLUSION

The emerging pandemic of COVID-19 is obviously a global public health concern. Under such a complicated scenario, aggressive multifaceted action against COVID-19 should be enforced to trigger the disease's deceleration process. To reduce the accelerated spread, it is important to encourage social isolation, avoid crowds, and wear masks and gloves, along with frequent washing of hands with soap and water. Since asymptomatic patients may transmit the disease, there is a necessity to investigate studies about its transmission. Treating the patients with antiviral medication early in the course of disease could be the key to success and may also reduce mortality. Preventative vaccination is the need of the day that will help prevent potential COV-related complications.

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Original Article

Postoperative pancreatic fistula: Low preoperative ejection fraction may be another contributing factor

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ABSTRACT

Objective: We investigated if ejection fraction (EF) was a predisposing factor for postoperative pancreatic fistula (POPF) as a perfusion indicator, or not.
Design: This was a retrospective single center study.
Setting: Türkiye Yüksek İhtisas Training and Research Hospital, Clinic of Gastroenterologic Surgery, Ankara, Turkey
Subjects: A total of 77 patients who underwent pancreaticoduodenectomy
Intervention: EF values were divided into three groups with demographic similarity as 40-49, 50-59, and 60 and above. The relationship between EF and POPF was investigated.
Main outcome measures: Preoperative EF, albumin, bilirubin, hemoglobin, C-reactive protein, white blood cells, neutrophil, lymphocyte, aspartate aminotransferase, alanine transaminase, gamma glutamyl transferase, carcinoembryonic antigen, CA19-9 values; intraoperative data such as operation type, ductus diameter in pancreas after resection, the presence of porta resection; postoperative pathology results, fistula grades, and 1st and 3rd day drain and blood amylases were retrospectively recorded.
Results: EF value was found to be between 40-49 in 10 (13%) patients, between 50-59 in 37 (48%) patients, and 60 or above in 30 (39%) patients. EF values of cases with leakage were found to be statistically significantly lower than the cases without leakage (P <0,05). In case of leakage, optimal cut-off value was calculated as ≤52.
Conclusion: EF values of cases with leakage in pancreas fistulas were found to be statistically significantly lower than the cases without leakage (P <0.05). Cut-off value was found as 52 (area under curve, with 93% interval of confidence). EF value below 52 in patients who underwent pancreaticoduodenectomy statistically increases pancreatic fistulas.

KEY WORDS: ejection fraction, pancreaticoduodenectomy, postoperative pancreatic fistula

INTRODUCTION

Pancreaticoduodenectomy (PD) is a standard treatment method for many bening and malign diseases in pancreas head and in the periampullary region. PD associated mortality has decreased below 5% in recent years. Despite such a decrease in mortality, morbidity remains close to 50%[1-2].

Pancreaticojejunostomy is the achilles heel of this procedure. Any problem at this point causes postoperative pancreatic fistula (POPF), which increases hospital stay, cost, morbidity and mortality[3]. Many factors such as age, gender, pancreatic duct diameter, operation time, anastomosis techniques, structure of the remaining pancreas, presence of pancreatic stent, hepatitis, intraoperative blood loss and perfusion disorders were searched as predisposing factors in pancreatic fistula, developing by the deterioration of achilles heel[4-6]. However, there is no particular test that can preoperatively measure the perfusion capacity of the tissue. In our study, we sought to answer if ejection fraction (EF), representing the ratio of the

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blood pumped from ventricle to the amount of blood remaining in the ventricle at the end of diastole, could be used as a preoperative indicator for anastomotic leakage or not.

SUBJECTS AND METHODS

Patients

A total of 390 PD cases operated between 2014-2018 in Türkiye Yüksek Ihtisas Training and Research Hospital Gastroenterology Surgery Clinic were analysed in an electronic environment. Seventy-seven patients who underwent preoperative echocardiography and had their EF values recorded were included in the study.

Data collection

Preoperative EF, albumin, bilirubin, hemoglobin, C-reactive protein, white blood cells, neutrophil, lymphocyte, aspartate aminotransferase, alanine transaminase, gamma glutamyl transferase, carcinoembryonic antigen, CA19-9 values; intraoperative operation types, ductus diameter in the remaining pancreas, presence of major vein resection; postoperative pathology results, fistula grades, and 1st and 3rd day drain and blood amylases were retrospectively recorded. EF values were divided into three groups with demographic similarity as 40-49, 50-59, and 60 and above.

Peroperative management

Decision to operate for preoperative patients were made by a council of physicians composed of gastroenterologists, gastroenterology surgeons, medical oncologists, radiation oncologists, radiologists and pathologists. The patients with distant metastases were directed to medical oncology. Prophylactic antibiotherapy was administered to all intraoperative patients (1 gr, cefazolin sodium, generic drug, Turkey). All patients who underwent PD were implanted with internal stents, and generally duct-to-mucosa technique was performed in pancreaticojejunostomy anastomosis (PJ), with 12 mm synthetic monofilament absorbable 5-0 (Maxon, Covidien, USA). If end-to-end anastomis is not suitable after port resection in patients with portal invasion, either iliac arterY-graft or falciform patch from cadaver was used in our clinic where liver transplantation is also accomplished. Falciform patch was preferably used in lateral port resection operations, while in resections greater than 4 cm, first choice was artery graft from cadaver. Vein graft was preferred when there was no artery graft available. Ductal diameter and pancreatic consistency were noted. Routine drainage was placed in all patients. Drain amylase content was checked on postoperative 1st and 3rd days, and in case it was three-fold higher than blood amylase, then it was evaluated as significant for fistula. In patients who had fistula, Sandostatin was used, but it was not used routinely. Drains were removed when drainage decreased below <50 ml in 24 hours. In case where percutaneous drain was required, it was placed by interventional radiology. Discharged patients were called to control at 1st week, 1st month, 3rd month, 6th month and 12th month, and every 6 months in the 2nd and the following years.

Statistical analysis

Statistical analysis of the data was performed by IBM SPSS Statistics version 24 package software. Pearson Chi-Square, Fisher's Exact test and Chi-square trend analysis were used for comparing categorical variables between groups, while Mann-Whitney U statistical analyses were used for comparing continuous variables between groups. Cut-off value of EF results was calculated by receiver operating characteristic analysis, in case of leakage. P <0.05 was considered as statistically significant.

This research did not receive any specific grant from funding agencies in the public or commercial domain. The study was performed in compliance with the Declaration of Helsinki. We confirm that all patient identifiers have been removed or disguised so that the patients described are not identifiable and cannot be identified through the details of the script.

RESULTS

As for gender, 45 of the patients were male and 32 were female. Median age was 77 years. Leakage was observed in 36 (46%) patients, out of which 23% were grade A, 18% were grade B and 5% were grade C. Major vascular revision was performed in six (7.8%) patients, porta repair in three patients, superior mesenteric vein resection in two patients, and graft repair between hepatic artery and aorta by artery graft in one patient. We preferred Wirsung jejunostomy (WJ) in 63 patients (81.8%), PJ in 11 patients (14.3%) and dunking in three (3.9%) patients.

Most preferred choice was WJ anastomosis, and most frequently observed case in pathology results was adenocarcinoma. EF value was between 40-49 in 10 (13%) patients, between 50-59 in 37 (48%) patients and 60 and above in 30 (39%) patients. EF values of the cases with leakage were found to be statistically significantly lower than that of the cases without leakage (P <0.05). Also, 1st and 3rd day drain and serum amylase values of the cases with leakage were statistically significantly higher than those of the cases without leakage (P <0.05). Ductal diameters of the

Table 1: General features of fistula/non fistula cases

General features	Non fistula cases	Fistula cases	Z	*P*
	Median (min-max)	Median (min-max)		
EF	65 (40-70)	50 (40-62)	-6.716	<0.001
Drain amylase 1 (U/L)	151 (13-54000)	1521.5 (13-63000)	-3.696	<0.001
Blood amylase 1(U/L)	62 (13-933)	291.5 (12-3246)	-3.870	<0.001
Drain amylase1 / blood amylase1 rate	1.88 (0.18-819.49)	5.5 (0.17-238.64)	-1.634	0.102
Drain amylase 3 (U/L)	34.5 (1.77-20000)	486 (4-6729)	-4.832	<0.001
Blood amylase 3 (U/L)	22 (6-300)	49 (6-227)	-3.326	0.001
Drain amylase 3 / blood amylase 3 rate	1.33 (0.15-194.17)	5.95 (0.35-129.4)	-3.993	<0.001
Ductal diameter (mm)	6 (1-12)	2.5 (2-4)	-5.979	<0.001
Bilirubin levels (mg/Dl)	2.26 (0.25-33.53)	1.49 (0.3-19)	-0.664	0.507
Albumin (g/L)	3.7 (2.69-4.74)	3.55 (2.2-5)	-0.391	0.696
CRP (mg/L)	9 (0.4-130)	7.08 (0.6-258)	-0.153	0.878
WBC (x10^3/uL)	7 (4-17.2)	7.8 (4.32-13.3)	-1.205	0.228
Neutrophil (%)(x10^3/uL)	65 (31.8-90)	63.55 (20.4-79)	-0.730	0.465
Lymphocyte (x10^3/uL)	25 (13-50.1)	25.7 (11-73)	-0.944	0.345
Haemoglobin (g/Dl)	12.6 (8.4-16)	12.55 (7.8-15.5)	-1.047	0.295
ASA 1-2	30	10	16.948	<0.001
ASA 3-4	10	26		
Pancreatic consistency	30	8		
Hard	8	7	44.811	<0.001
Middle	10	21		
Soft	2 (0-16.69)	2.13 (0-104)	-0.155	0.877
CEA (ng/Ml)	64.35 (0-2016)	33.3 (0-2044)	-0.436	0.663
Ca-19-9 (ng/Ml)				

Mann Whitney U analysis
EF: ejection fraction; CRP: C-reactive protein; WBC: white blood cells; ASA: American Society of Anesthesiologists; CEA: carcinoembryonic antigen

cases with leakage were significantly smaller than those of the cases without leakage (*P* <0.05). American Society of Anesthesiologists (ASA) scores of the cases with leakage were found to be significantly higher than those of the cases without leakage (*P* <0.05). Pancreatic consistency of the cases with leakage were significantly softer than the cases without leakage (Table 1). In the subgroup analysis, and when the distribution of pathology results and EF were analysed with respect to leakage types, statistically significant difference was not found between groups (*P* >0.05, Table 2).

Statistically significant difference was not determined between groups in grade B and grade C cases with regard to EF groups (*P* >0.05, Table 3).

Optimal cut off value in the presence of leakage was found as ≤52. Accordingly, area under curve (AUC) value was calculated as 93.3% and this value was found to be statistically significant (*P* <0.001, Figure 1).

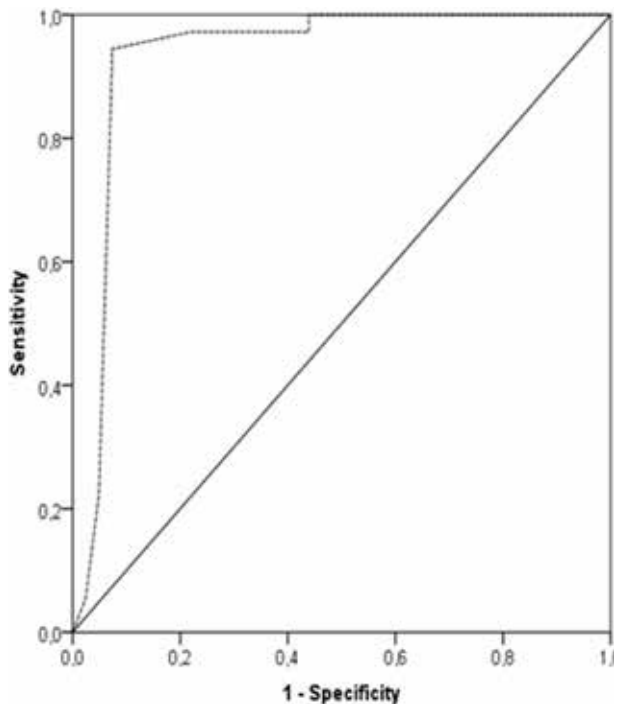

Figure 1: Results of ROC analysis, executed to determine the cut-off value of ejection fraction values in the presence of leakage/ graph

DISCUSSION

Disruption of PJ anastomosis, known as the achilles heel of whipple operation, causes POPF. The factors leading to POPF were found in our study as

Table 2: Distribution of pathology results, ejection fraction, presence of comorbid diseases and major vein resection rates with respect to leakage type

General features	Fistula grade (ABC)						X^2	*P*
	Grade A		Grade B		Grade C			
	n	%	n	%	n	%		
Pathology							10.891	0.966
Adenoca	12	66.7	9	64.3	4	100		
Pancreatitis	1	5.6	-	-	-	-		
IPMN	1	5.6	2	14.3	-	-		
Tubulovillous Adenoma	1	5.6	-	-	-	-		
NET	-	-	1	7.1	-	-		
Serous cyst adenoma	2	11.1	1	7.1	-	-		
Gastrointestinal stromal tumor	-	-	1	7.1	-	-		
Groove pancreatitis	1	5.6	-	-	-	-		
Adeno Ca							1.658	0.531
Others	6	33.3	5	35.7	-	-		
Adeno Ca	12	66.7	9	64.3	4	100		
Serous cyst adenoma							0.544	1.000
Others	16	88.9	13	92.9	4	100		
Serous cyst adenoma	2	11.1	1	7.1	-	-		
IPMN							1.080	0.696
Others	17	94.4	12	85.7	4	100		
IPMN	1	5.6	2	14.3	-	-		
NET							2.104	0.500
Others	18	100	13	92.9	4	100		
NET	-	-	1	7.1	-	-		
EF							2.051	0.152
40-49	2	11.1	4	28.6	2	50		
50-59	16	88.9	9	64.3	2	50		
60 and over	-	-	1	7.1	-	-		

Fisher's Exact test; Chi-square test for trend analysis.
IPMN: intraductal papillary mucinous neoplasia; NET: neuroendocrine tumor; EF: ejection fraction

ASA score, pancreatic consistency, ductal diameter, as well as EF, which is particular to our study.

PD is the primary treatment method for tumors at the head of the pancreas, at distal of biliary tract and at duodenal ampulla[7,8]. As indicated in the studies in the literature, the rate of pancreatic fistula that develops after PD varies between 11.4% and 64.3%[9]. POPF is a risk factor for delayed gastric emptying, sepsis and post operative bleeding[10-12].

The International Study Group for Postoperative Pancreatic Fistula was established in 2005 under the leadership of Claudio Bassi[13] from the Surgical Gastroenterology Department at Verona University.

Table 3: The relationship beween EF groups and Grade B and Grade C fistulas

EF	Grade B		Grade C		X2	*P*
	n	%	n	%		
40-49	4	28.6	2	50.0	1.157	0.681
50-59	9	64.3	2	50.0		
60-70	1	7.1	-	-		

Fisher's Exact test, EF: ejection fraction

They defined POPF biochemically as amylase value in drains determined as three times higher than blood amylase in any measurement from postoperative 3rd day on. Also, they indicated that abdominal pain, distension, delay in gastric emptying, fever (>38 ºC), C-reactive protein increase and leucocyte increase (>10.000 cells/mm^3) can be observed clinically.

Pancreatic fistula is divided into three groups as grade A, grade B and grade C. Grade A fistula represents the most frequently observed fistula group, also known as "transient fistula'', which doesn't reveal any finding clinically. It is only defined biochemically as a fistula. It doesn't increase hospital stay or therapy costs. Fistula is classified as grade B when pancreatic fluid is observed in abdominal tomography and this particularly requires drainage. Abdominal pain and fever may accompany. Antibiotics and sandostatin may be needed. It increases hospital stay and the cost. Grade C fistula indicates that sepsis and organ dysfunction may accompany. Re-operation may be needed. The risk of mortality is high.

After 11 years, Bassi *et al* again updated the grading in 2016. The term biochemical leak was used

instead of Grade A, and the gray area between grade B and Grade C was clarified[14].

van Berge Henegouwen *et al*[5] related the small size of pancreatic duct and ampullary carcinoma with POPF. In our study, ampullary carcinoma was not found as a risk factor (*P*=0.96), while a ductal diameter of small size was found to be a significant risk factor (*P* <0.01).

It was highlighted in many studies that the hardness of the remaining pancreatic tissue was advantageous for the fistula. As a result, the harder the tissue, the easier it was to suture without laser[3]. In our study too, the hardness of the pancreatic tissue was found to be a significant risk factor in the development of pancreatic fistula (*P* <0.01).

Velu *et al* found that postoperative 0th day serum amylase value >130 IU/L was a risk factor for POPF[15]. In our study, 1st and 3rd day drain amylase and serum amylase values were found to be significant for POPF. With regard to the ratio of drain amylase over serum amylase, however, only 3rd day was found to be significant (*P* <0.01, Table 1).

Dengl *et al* however, showed that fibrosis <25%, pancreatic channel <3mm and body mass index >25 were prognostic factors[16]. Kawai *et al* found male gender as a risk factor in a retrospective study investigating 1239 patients[17]. The other risk factors such as Carkopenia and visceral obesity and post operative 1st day drain amylase were found to be independent risk factors for POPF[18,19].

No effect of octreotide use could be shown to decrease POPF in the randomized controlled studies[20]. We also used octreotide in POPF patients, however, we didn't observe any statistically significant remission.

Cohort studies showed that excessively delivered intravenous fluids increased POPF risk[21]. In patients with fluid limitation by means of hypertonic saline, hospital stay and mortality decreased too, along with POPF[22]. We used saline in our cases and did not perform any fluid limitation.

Anastomosis techniques: Pancreatogastrostomy (PG) was thought to decrease POPF, since there was no enterokinase to activate trypsin at gastric epithelium and pancreatic enzymes could not be activated in stomach acid. A multicenter prospective randomized study comparing PG and PJ was conducted with 440 patients and no statistically significant difference was observed (20-22%, *P*=0.617)[23]. PJ techniques were compared within themselves as duct-to-mucosa versus invagination. No significant difference regarding POPF was determined between these two techniques in two randomized controlled studies[24,25]. It was shown in the subgroup analysis in one of the studies that invagination was more advantageous in soft pancreas (10-42%, *P*=0.010)[24]. We also used invagination technique of PG in our study with smaller size ductal diameter, but used WJ in cases with ductal diameter greater than 5 mm. However, we couldn't find any signficant difference regarding POPF.

In their study with 522 high risk patients, Ecker *et al* observed that POPF risk decreased with external stent and increased with internal stent (external 15.2%, internal 43.8%, no stent 33.8%, *P* <0.01)[26]. We routinely used internal stent in our patients.

In the 2016 PANDRA study, 395 patients were included and they were divided into two groups as the ones who had an intraoperative drain inserted and those who did not. In the group without drain, POPF speed (5.9% vs 11.9%, *P*=0.030) and fistula related complications (13% vs 26.4%, *P*=0.0008) were found to be less[27]. However, in multivariable analyses, it was noticed that the majority of the patients without drain had neoadjuvant therapy and used somatostatin analogs. Hence, drain was not assessed as an independent risk factor in POPF development. We used drains routinely in all our patients.

Another important factor providing integrity of anastomosis is the perfusion of the tissues. Tissues with poor perfusion develop ischemia by time, and thus disrupt anastomosis. In our study, we hypothesized that EF, which represents the ratio of the blood pumped out from the left ventricle to the amount of blood remaining in the ventricle at the end of diastole, could be used as an indicator for preoperative perfusion. In this sense, our study is a first in the literature (any similar publication was not seen in PUBMED search).

EF is the rate of pumping of the left ventricle wall. As of today, reliable measurements can be accomplished by three-dimensional echocardiography[28]. It is the numerical value of the pumping power of the heart. Therefore, it can be an indicator for blood perfusion of pancreas and jejunum.

We determined that EF is an effective risk factor in determining the risk of leakage, like the other factors such as ductal diameter, pancreatic consistency and ASA score (Table 1, *P* <0.001). We found the optimal cut-off value as ≤52 in case of leakage. Accordingly, we calculated AUC value as 93.3% and this AUC value was assessed to be statistically significant (*P* <0.001, Table 4). When EF was divided into three groups as 40-49, 50-59 and 60 and above, and then compared with grade A, B and C fistulas, we couldn't find any significant relationship (Table 2, *P*=0.152).

CONCLUSION

In conclusion, EF is a predisposing factor in POPF (P <0.05). Cut-off value was found as 52 (AUC, with confidence interval of 93%). EF value below 52 statistically increases pancreatic fistula in patients who underwent pancreaticoduodenectomy. In such an operation having high mortality and morbidity, preoperative EF measurement should be taken into account.

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Conflict of interest: None

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Original Article

Conventional magnetic resonance and diffusion weighted imaging features in presurgical meningioma grading

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ABSTRACT

Objective: To discuss the role of magnetic resonance and diffusion weighted imaging features in grading meningiomas
Design: Retrospective study
Setting: Selcuk University Medical Faculty, Konya, Turkey
Subjects: Pre-surgical magnetic resonance and diffusion weighted imaging examinations of 98 pathologically proven meningioma patients who were operated at our institution
Interventions: Tumor volume and location, peritumoral edema, existence of a draining vein, central necrosis and apparent diffusion coefficient (ADC) values were analyzed.
Main outcome measures: Differences between grade 1 and grade 2-3 meningiomas were evaluated.
Results: Sixty-four female and 34 male patients aged between 18 and 75 years (mean age: 54±11.7 years) were included in the study. The histopathological analysis of lesions revealed 58 benign, 40 atypical and two malignant. There was no significant difference between tumor location, peritumoral edema, existence of draining vein, central necrosis, ADC values and meningioma grade. Tumor volume was significantly different between the two groups (P=0.014).
Conclusions: Conventional magnetic resonance and diffusion weighted imaging are not reliable diagnostic tools in grading meningiomas.

KEY WORDS: diffusion weighted imaging, grade, magnetic resonance, meningioma

INTRODUCTION

Meningiomas are common intracranial tumors and constitute 13-26% of all intracranial tumors[1]. Radiological diagnosis of meningiomas is not difficult in most cases[2]. They show characteristic findings on conventional magnetic resonance imaging (MRI); thus, their differentiation from intra-axial tumors is easy. Typical MRI features encountered in meningiomas are homogeneous contrast enhancement, dural tail sign and extra-axial localization. Although radiological diagnosis of meningiomas is easy with conventional MRI, distinction based on histological types is usually not possible in routine clinical practice[3].

Benign meningiomas are classified as grade 1 according to World Health Organization and constitute 88-94% of all meningiomas. Atypical (grade 2) and malignant (grade 3) meningiomas are rare[4]. Benign meningiomas have been further classified by World Health Organization according to their histopathological characteristics as meningothelial, fibrous (fibroblastic), transitional (mixed), psammomatous, angiomatous, microcystic, secretory, lymphoplasmacyte-rich and metaplastic subtypes[5].

Atypical and malignant meningiomas are rare, however mortality and recurrence rates are higher than benign meningiomas. Thus, presurgical diagnosis of meningioma grade is important for treatment plan and predicting prognosis[6]. Patients that have a lesion with radiological features of a meningioma are observed or treated surgically. Surgical excision is recommended particularly for patients with neurological symptoms, large tumors and/or peritumoral edema in adjacent brain parenchyma[4].

The purpose of our study is to discover the relationship between meningioma grade and findings

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on pre-surgical conventional MRI and diffusion weighted imaging (DWI).

SUBJECTS AND METHODS

Patients

The institutional review board approved this retrospective study with waived informed consent. Pre-surgical MRI scans of all adult patients (age ≥18 years) with newly diagnosed, pathologically confirmed intracranial meningiomas from January 2013 to January 2019 were reviewed retrospectively. A database search of the pathology department revealed 153 patients with a diagnosis of meningioma. Patients who have a contrast enhanced cranial MRI with sufficient image quality in a period of a month before surgery were included. Meningiomas were grouped as grade 1 (benign) and grade 2-3 (atypical and malignant). A total of 98 patients with contrast enhanced MRI scan were included in the study. Patient gender, age and tumor pathologies were obtained from electronic database records.

MRI examination

Conventional cranial MRI and DWI of patients were obtained by using 3T (Skyra, Siemens Healthcare, Erlangen, Germany) and 1.5 T (Aera, Siemens Healthcare, Erlangen, Germany) MRI scanners. Eight-channel head array receiving coil was used in all patients. Routine cranial MRI protocol for meningioma in our institute include axial T1 and T2 weighted, fluid attenuated inversion recovery (FLAIR), axial, sagittal T1 weighted images, axial DWI and contrast enhanced T1 weighted axial and coronal images after administration of 0.1 mmol/kg gadolinium-based contrast agents.

Image analysis

All MRI examinations were evaluated by a neuroradiologist with an experience of 6 years and a radiology resident in the 3rd year of education together with consensus agreement. They were blinded to histopathological diagnoses. Three dimensions of tumor were measured on contrast enhanced T1 weighted axial and coronal images and volume of tumor was calculated by multiplying the three dimensions and dividing it by two. Peritumoral edema was evaluated on T2 weighted axial images and graded as 0 with no edema, grade 1 with mild edema, grade 2 with moderate edema, and grade 3 with severe edema. Lesion location was grouped as convexity, skull base, falx cerebri and posterior fossa. After the evaluation of conventional sequences, apparent diffusion coefficient (ADC) measurements were performed on the solid parts of the meningiomas. Regions of interest of 0.1-0.5 cm^2 were drawn manually.

Table 1: Age, gender, tumor location, existence of draining vein, peritumoral edema and central necrosis in benign and atypical/ malignant meningioma groups

Characteristics	Benign	Atypical/ malignant	Combined	*P*-value
Gender (n=98)				0.359
Female	40 (69%)	24 (60%)	64 (65%)	
Male	18 (31%)	16 (40%)	34 (35%)	
Age	55±10	53±13	54±11.7	0.292
Tumor location				0.36
Convexity	27	23	50	
Skull base	7	4	11	
Falx	17	6	23	
Posterior fossa	7	7	14	
Existence of draining vein				0.67
Yes	11	9	20	
No	47	31	78	
Edema				0.057
0	20	7	27	
1	19	9	28	
2	13	15	28	
3	6	9	15	
Central necrosis				0.34
Yes	4	5	9	
No	54	35	89	

During region of interest measurements on the solid portion of tumors, cystic portions were avoided.

Statistical analysis

Statistical analyses were made by SPSS 21.0 version for Windows (SPSS, Chicago, IL, USA). The Chi-square test was used to calculate the overall statistical differences for categorical variables among the benign

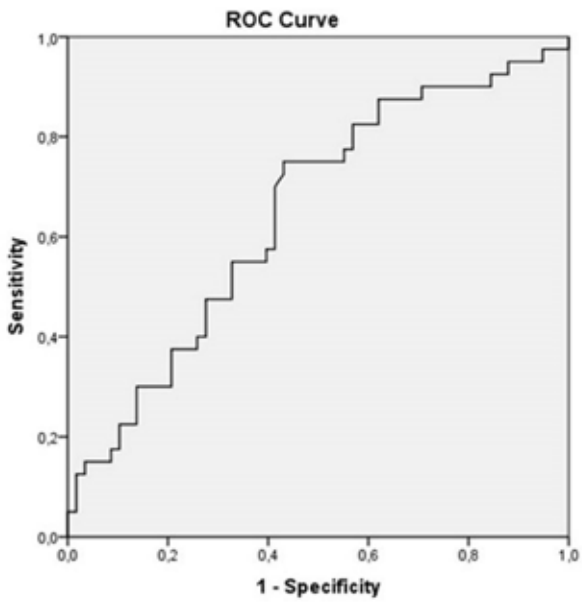

Fig 1: Receiver operating curve for tumor volume. Area under the curve is 0.647.

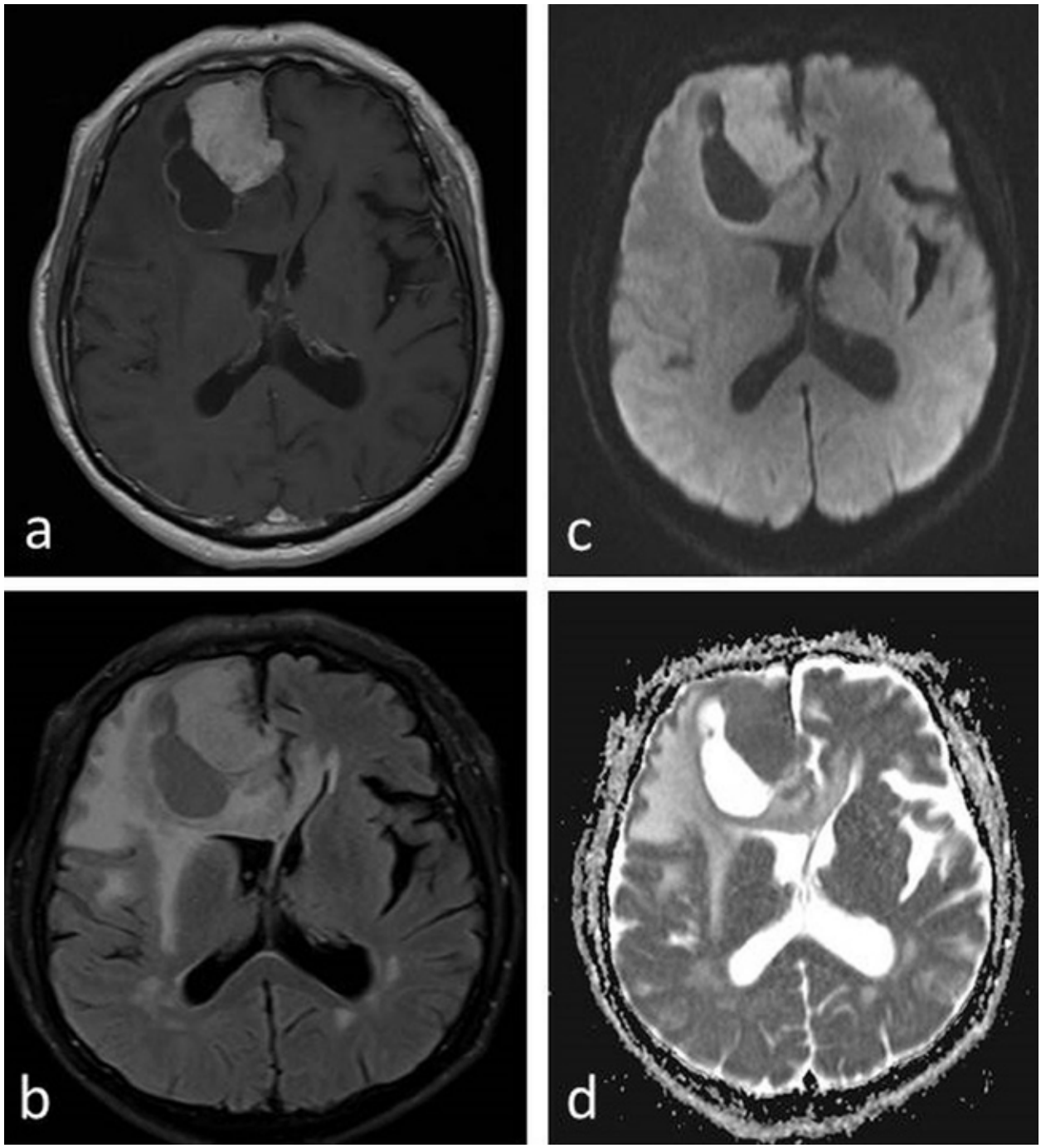

Fig 2: 70-year-old male, contrast enhanced T1 weighted (a), FLAIR (b), diffusion weighted (c) images and ADC map (d) reveal an extra-axial tumor in right frontal lobe and severe edema. Histologic diagnosis is grade 1 meningioma.

and atypical/malignant groups. T-test was conducted for calculating the differences in mean ADC values and ages at diagnosis between each group. Mann-Whitney U test was performed to evaluate the tumor volume between groups. Spearman correlation analysis was conducted to assess the correlation between tumor grade and tumor volume, peritumoral edema. Threshold for the statistical analyses were assessed as P <0.05.

RESULTS

A total of 98 patients (64 female, 34 male) were included in this retrospective study. Mean age was 54±11.7 years (range: 18-75 years). On histological

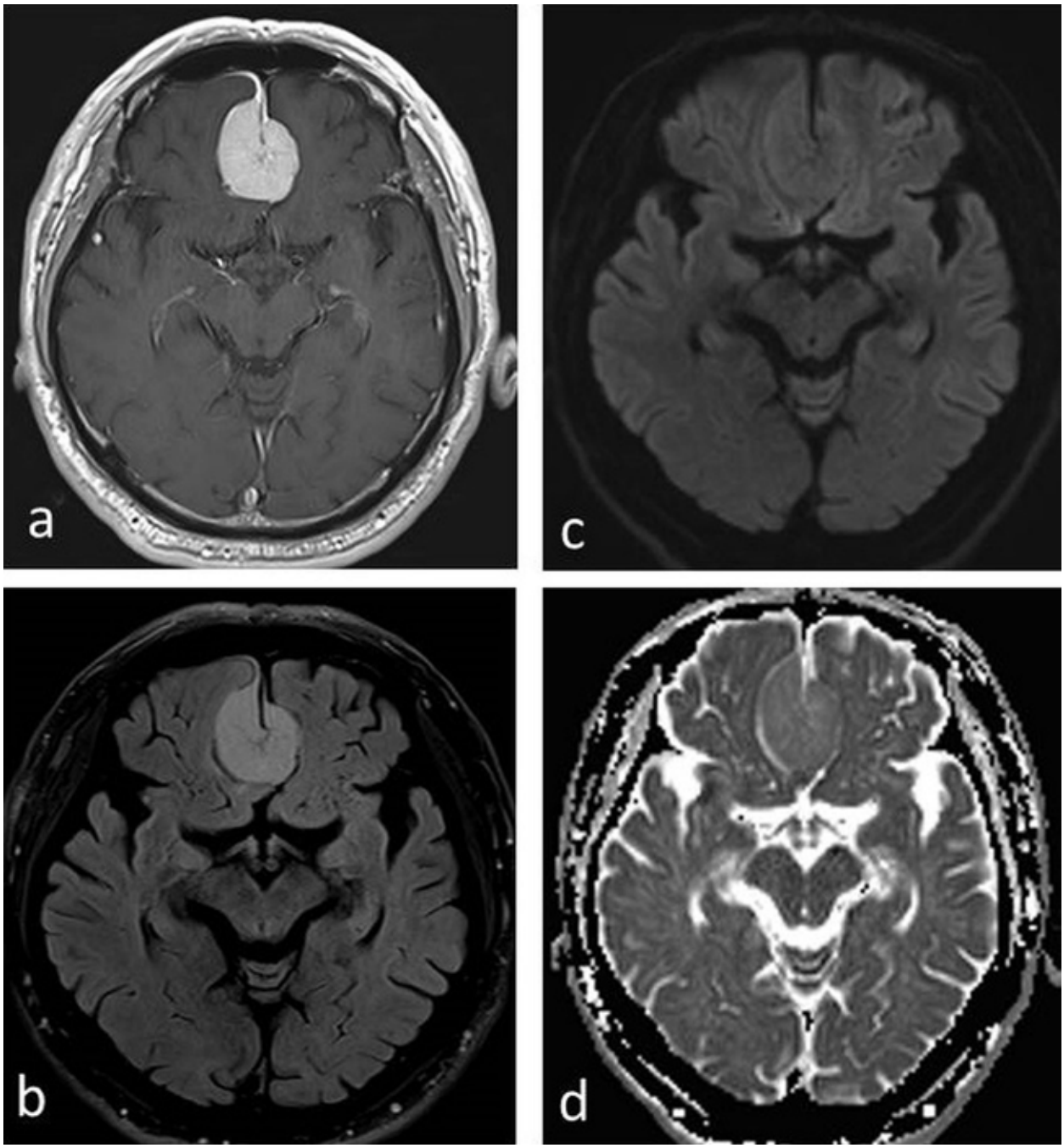

Fig 3: 65-year-old male, contrast enhanced T1 weighted (a), FLAIR (b), diffusion weighted (c) images and ADC map (d) reveal an extra-axial tumor in anterior inter-hemispheric falx and minimal edema. Histologic diagnosis is grade 1 meningioma.

grading, 58 patients had grade 1, 38 patients had grade 2 and two patients had grade 3 meningioma. Gender and age at diagnosis, tumor locations, existence of draining vein, central necrosis and peritumoral edema were demonstrated in Table 1. In conventional MRI features, tumor location, existence of a draining vein, peritumoral edema and presence of central necrosis were not different between the two groups. Tumor volume of atypical/malignant meningioma group was significantly larger than benign tumors (Table 2), however ROC analysis could not reveal a cut off level with high sensitivity and specificity (Figure 1). There was a significant positive correlation between tumor grade and volume (P=0.013, Spearman rho: 0.25). In the comparison of ADC values between benign and atypical/malignant meningiomas, there was also no significant difference. Mean ADC values of benign and atypical/malignant meningiomas are listed in Table 2.

Table 2: Volume and ADC values of benign and atypical/malignant meningioma groups

Variables	Benign	Atypical/ Malignant	P-value
Tumor volume (mm3)	22.5±23.9	39.1±42.8	0.014
ADC value	775±118	782±137	0.78

ADC: apparent diffusion coefficient

Figures 2, 3 and 4 demonstrate images of meningioma patients included in the study.

DISCUSSION

In our study, larger tumor volume was the only MRI feature associated with higher tumoral grade in meningiomas. Age, gender, presence or severity of

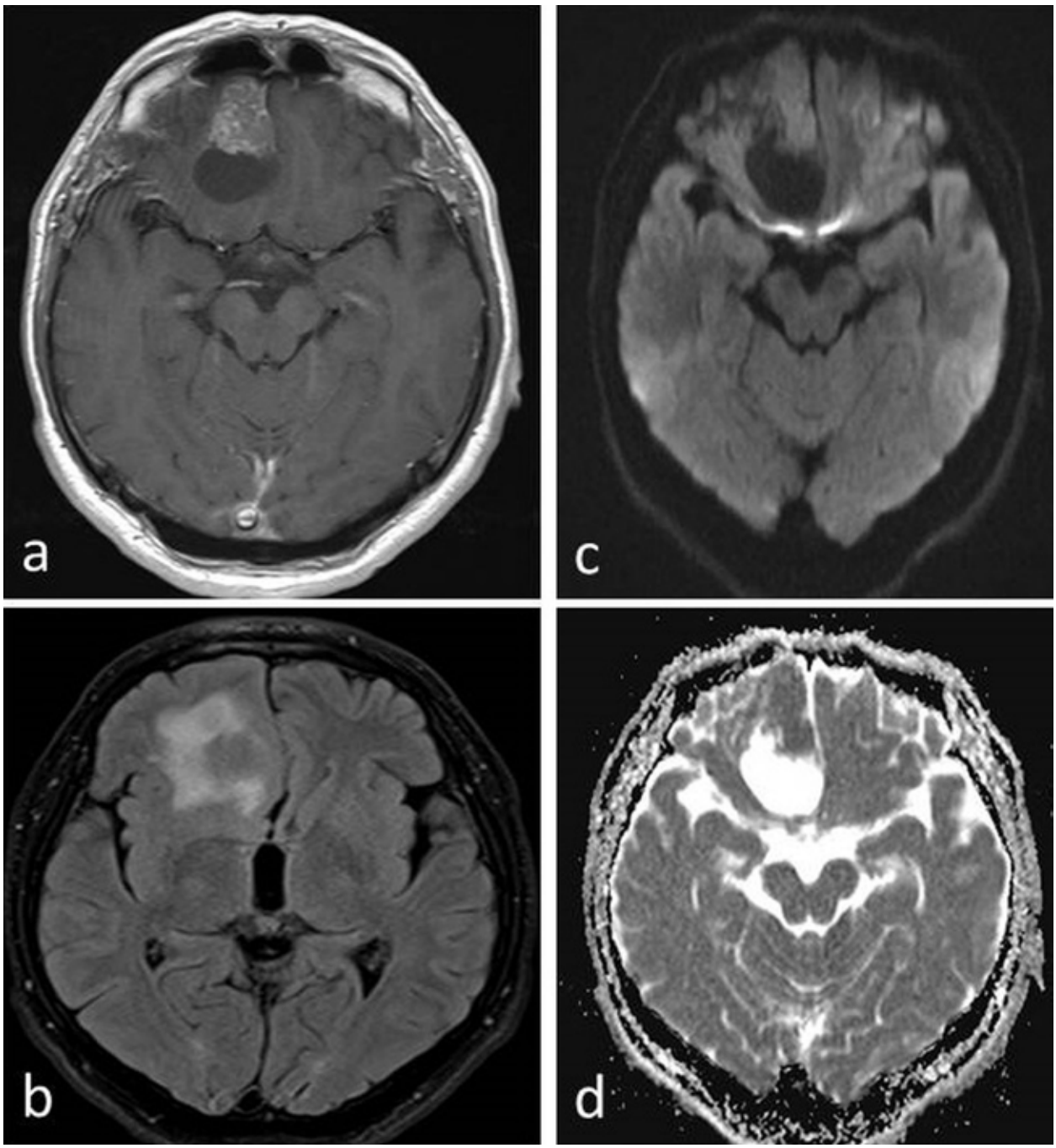

Fig 4: 49-year-old male, contrast enhanced T1 weighted (a), FLAIR (b), diffusion weighted (c) images and ADC map (d) reveal an extra-axial tumor in anterior inter-hemispheric falx and severe edema. Histologic diagnosis is grade 2 meningioma.

peritumoral edema, presence of tumoral necrosis, draining vein and tumor location were not predictive factors for grading meningiomas.

Previous studies reported mixed results concerning the relationship between age-gender and meningioma grade. Some authors noted male gender as a risk factor for atypical meningioma. Kane *et al* reported a two-fold risk in male gender[7]. However, Hale *et al* found no difference between males and females[4]. There are conflicting reports about the relationship between age and meningioma grade. Several authors declared that age is an independent predictive factor for high grade meningioma and age correlates with higher meningioma grade[8-10]. Lin *et al* reported in that, age >75 years is a factor in prediction of atypical/malignant meningioma grade[11]. However, there was no significant difference between age-gender and meningioma grade in our series.

Some authors noted that tumor location is a risk factor for higher grade in meningiomas. Some studies have reported that meningiomas with skull base locations were associated with benign grade in meningiomas[7,11,12]. In a recent study conducted by Hale *et al*, meningiomas located along the falx cerebri and convexity were more atypical than others[4]. However, we did not encounter any difference among tumor locations between benign and atypical/ malignant meningiomas.

Peritumoral edema is an MRI feature frequently seen in meningiomas, and the causes of peritumoral edema have not yet been clearly defined. Clinical symptoms become apparent in meningiomas with peritumoral edema. The presence and severity of peritumoral edema has been suggested to be associated with its location, histological type, vascularity, vascular endothelial growth factors, prostaglandin and sex hormone level[3]. Presence and severity of peritumoral edema and the relationship with meningioma grade is investigated detailed in the literature. Few studies noted that larger peritumoral edema is associated with higher grade in meningiomas. Lee *et al* reported higher peritumoral edema in atypical/malignant meningiomas(P=0.004)[13]. However, several studies concerning peritumoral edema and its relation with tumoral grade in meningiomas showed no significant correlation between histologic type and peritumoral edema[5,11,14]. In the present study, there was no statistically significant difference between benign and atypical/malignant meningiomas related to brain edema.

DWI is a commonly applied advanced imaging technique in intra-axial brain tumors, particularly in gliomas. Apparent diffusion coefficient values of primary brain tumors have been found to correlate with tumor grade[5]. However, several studies in the literature investigated the ADC values and possible correlation with meningioma grade[5,15-20]. Results of these studies were controversial. To obtain an absolute ADC value in discriminating benign from atypical/ malignant meningiomas is not probable. Different b values and different MRI scanners induce differences in ADC values. There are also differences in measuring ADC values. In the literature, some authors reported a statistically significant difference between benign and atypical/malignant meningiomas[3,21]. Conflicting with these studies, several studies reported no difference in ADC values between different histological meningioma types[5,22], consistent with the results of our study.

The retrospective study design is the major limitation of our study. Second limitation is that the interpretation of MRI images was performed by two radiologists with consensus and interobserver variability was not analyzed. Third, volume of peritumoral edema is not quantified and the severity of edema was qualitatively pointed. Fourth, the volumes of tumors were not calculated using software.

CONCLUSION

In this study, tumor volume was the only conventional MRI feature that is significantly different between low and high grade meningiomas. However, it was not possible to obtain a cut off value in discrimination meningioma grade with high sensitivity and specificity. We conclude that conventional MRI features and ADC values are not reliable tools in discriminating benign and atypical/malignant meningiomas.

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Conflict of interest: None. The authors alone are responsible for the content and writing of the paper.

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Original Article

Distribution pattern of brain tumour types and location in patients who underwent MRI scans: A survey of 1240 patients in a Tertiary Malaysian University Hospital

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ABSTRACT

Objective: This study aimed to present the distribution pattern of brain cancer types, sizes, locations and demography of patients who underwent magnetic resonance imaging (MRI) brain examination.
Design: Retrospective study
Setting: MRI Unit, Pusat Perubatan Universiti Kebangsaan Malaysia (PPUKM)
Subjects: Data of 1240 brain tumour patients from January 2012 to December 2017 scanned with MRI were retrieved from the Integrated Radiology Information System and analysed.
Interventions: None
Main outcome Measure: Demographic data of the brain tumour patients that underwent MRI brain scan in PPUKM were recorded including the types, sizes and locations of the tumour.
Result: Results revealed that 693 (55.9%) of the patients with brain tumours who underwent brain MRI examinations were female. The patients consisted of Malays (55.1%, 683), Chinese (35.8%, 444) Indians (7.5%, 93) and others (1.6%, 20). The most common brain tumour diagnosed in paediatric patients was medulloblastoma (28.10%, 34). The most common brain tumours overall were sellar/parasellar tumors (33.5%, 416), meningioma (27.2%, 337), glioma (18.4%, 228) and nerve sheath tumour (11.5%, 142). Result also shows that brain tumours increased with age (>50 years) (48%, n= 571). Gliomas (34.68%, 77) and meningiomas (45.78%, 141) tend to develop in the frontal lobe of the brain, while for nerve sheath tumour (98.59%, 140) and medulloblastoma (100%, 47), the most common site was occipital lobe. Data also revealed a little difference in result between right (468, 37.7%) and left-brain hemisphere (434, 35%) that were affected due to the brain tumour.
Conclusion: The examination of brain tumour distribution pattern is important to plan for health services and research. From the presented data, we are confident that we can accrue enough patients for functional MRI studies of the frontal lobe tumours.

KEY WORDS: brain neoplasm, imaging, magnetic resonance

INTRODUCTION

Brain tumours contribute significantly to morbidity and often have a poor prognosis. Indeed, 260,000 people are newly diagnosed with primary brain tumours each year worldwide[1]. Based on the National Cancer Registry report from year 2003 to 2005, the crude incidence of brain and other nervous system tumours alone in Peninsular Malaysia was 2.7 for male and 2.2 for female per 100,000 population in a year, respectively. Brain tumours in Malaysia are considered as an uncommon cancer compared to other types of cancers. According to Dzali *et al*[2], they represent 1.95% of all malignancies. According to Bohn *et al*[3], Japan and Asian countries, especially those with low and middle income, have a lower incidence of brain tumours as compared to developed countries, which could be due to under-diagnosis[4]. However, a study shows the trend of the cancer in South East Asian

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countries is expected to increase to 1.1 million cases in 2025 and 1.4 million in 2035, with a corresponding increase of radiotherapy need in cancer treatment as a nonsurgical modality for cancer treatment[5,6].

Brain tumours are classified according to their presumed cellular origin[7]. According to the National Cancer Institute, the grading system of tumours depends on each type of tumour. Generally, tumours are graded as 1, 2, 3 or 4, depending on the amount of abnormality. In Grade 1 tumours, the tumour cells and the organization of the tumour tissues look nearly like normal tissues. These tumours tend to grow and rarely spread into nearby tissues[8]. In contrast, the cells and tissues of Grade 3 and Grade 4 tumours look less like normal tissues and tend to grow rapidly, spreading faster than tumours with a lower grade[9].

Tumours can be considered an age-related disease, with most brain cancer incidence increasing with age and rising more rapidly in the beginning of midlife[9]. Tumours like meningioma are more prone to be diagnosed in adulthood with age ranging from 50 to 75 years old[10]. However, tumours like medulloblastoma are more easily diagnosed in pediatric patients. Medulloblastoma is relatively rare, accounting for less than 2% of all primary brain tumours and 18% of all pediatric brain tumours[11]. The peak age when children tend to develop diagnosable medulloblastoma is around 5 to 10 years old[12]. Meningioma is considered as a benign tumour by the World Health Organization histopathologic criteria (WHO grade I)[13]. Gliomas are the most common primary intracranial tumour, representing 81% of malignant brain tumours[14,15]. Although relatively rare, they cause significant mortality and morbidity, and it makes up 16% of all primary brain tumours[16].

The role of magnetic resonance imaging (MRI) in detecting brain tumours is established worldwide. Routine MRI brain scan was applied for follow up brain tumour cases[17]. The advancements in technology such as diffusion-weighted imaging (DWI), MR spectroscopy and perfusion has made MRI a tool for diagnosis in terms of differential diagnosis and follow-up of the patient[18]. One study by Raisi-Nafchi M *et al*[18] shows the role of DWI in detecting supratentorial brain tumour as pre-operative planning. This study shows the usefulness of DWI sequence in its ability to differentiate between high and low grade glioma through the apparent diffusion coefficient value[18]. Other than this, functional MRI (fMRI) can also be used as a neuroimaigng tool in terms of pre-operative planning by detecting brain activation to preserve the eloquent cortex before resection is done by using blood-oxygenated level dependant that detects blood flow changes in the brain[19].

In the present study, we aim to report the distribution of brain tumours from the MRI database in Pusat Perubatan Universiti Kebangsaan Malaysia (PPUKM) between 2012 and 2017. The tabulated data will help us evaluate the distribution pattern of brain tumours based on patient demography and the types as well as locations of the tumours. This will set a baseline for future studies aiming to study patients with brain tumours for fMRI.

MATERIALS AND METHODS

This study was carried out at the Department of Radiology, PPUKM. It is one of the primary referral centers for hospitals in Klang Valley. A total of 1240 brain tumour data from patients scanned using either 1.5T Siemens Avanto or 3.0T Siemens Magnetom Verio were acquired from January 2012 to December 2017. The Integrated Radiology Information System is a modern and flexible data collection system for the usage of the diagnostic imaging service. It allows technologists and radiologists to have two-way communication, by providing information on the patient identification, date of the patient examination, types of radiology procedures that have been performed and by allowing retrieval of previous report and previous diagnostic images such as MRI images through the Picture Archiving and Communication System system and Digital Imaging and Communications in Medicine system.

In the present study, the Integrated Radiology Information system was used to extract tumour parameters including the types, location, size, affected brain lobes and hemispheres. Demographic data of the patients including age, gender and race were retrieved using Caring Hospital Enterprise system, which stores the information that are retrievable using patient identification. This system allows the user to know the details of post operation procedure report of the patient from the neurosurgery team and future clinic appointments of the patient.

This study was supported by the Research University Grant Universiti Kebangsaan Malaysia GGPM-2017-016. The approval from ethics community has been obtained. The reference is UKM PPI/111/8/JEP-2018-040.

Data analysis

Demographic data including types of brain tumour, race, sex, age group, brain lobe and brain hemisphere that were affected due the brain tumour who underwent MRI brain scans were all analyzed in this study. The data tabulated were analyzed and transformed into table or graph using Microsoft excel to study the distribution pattern types of brain tumour according to the race, gender, brain lobe, brain hemisphere and age group.

Table 1: Total number of brain tumour cases from 2012 to 2017 scanned with 1.5 T and 3.0 T MRI machines

Year	1.5 Tesla	3 Tesla
2012	98	-
2013	116	181
2014	-	218
2015	-	256
2016	165	-
2017	-	206
Total	379	861

RESULT

In the six-year duration, from January 2012 to December 2017, a total of 1240 brain tumour patients were referred to the Radiology Department, PPUKM and underwent MRI brain imaging. The tabulation of number of cases per year is shown in Table 1.

From this total of 1240 patients, 547 (44.1%) patients were male and 693 (55.9%) were female (Table 2). Among the races, Malay (683, 55.1%) showed the highest number of patients that underwent MRI brain examination, followed by Chinese (444, 35.8%), Indian (93, 7.5%) and others (20, 1.6%). Data tabulated also showed that among the age groups studied, the highest age group that underwent MRI brain examination is in the age range of 50-59 years old (236, 19%), followed by 60-69 years old (228, 18.4%), 40-49 years old (212, 17.1%), 30-39 years old (185, 14.9%), 20-29 years old (151, 12.2%), 10-19 years old (121, 9.8%) and 70 and above (107, 8.6%).

Data in Table 3 shows the distribution of tumours according to the types of tumour, brain lobe and brain hemisphere. From the total number of cases studied, sellar / parasellar tumours (416, 33.5%) were the most common followed by meningioma (337, 27.2%), glioma (228, 18.4%), nerve sheath tumour (142, 11.5%), others (70, 5.6%), and medulloblastoma (47, 3.8%).

Data tabulated in Table 4 and 5 shows the distribution types of brain tumour versus race, gender and age groups. Based on the data, for all types of tumour, most patients were Malay with higher percentage of females being present compared to the males, and were in the age range of 50-59 years old compared to other age groups. Data recorded also showed that brain tumours were more likely with increasing age. Most of the patients who underwent MRI brain scan for brain tumour were above the age

Table 2: Demographic data

Demographic data	Count	Percentage
Total	**1240**	**100**
Gender		
Male	547	44.1
Female	693	55.9
Race		
Malay	683	55.1
Chinese	444	35.8
Indian	93	7.5
Others	20	1.6
Age group		
10-19	121	9.8
20-29	151	12.2
30-39	185	14.9
40-49	212	17.1
50-59	236	19.0
60-69	228	18.4
70 and above	107	8.6

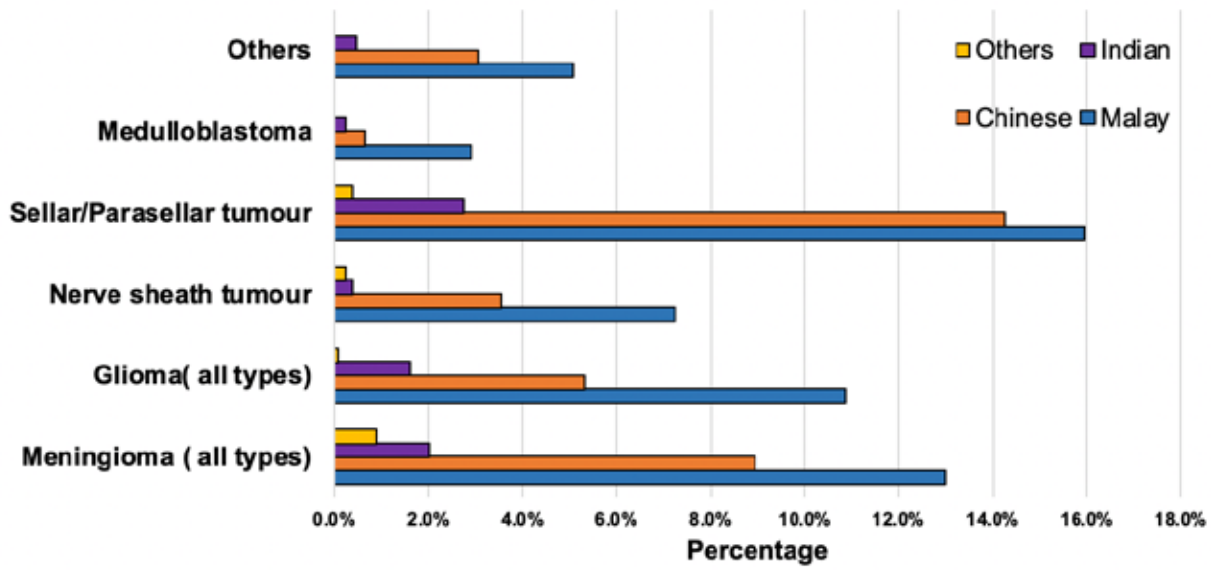

Figure 1 : Distribution types of tumour vs race

Table 3: Distribution types of tumour, brain lobe and brain hemisphere

Types of tumour	Count	Percentage
Parasagittal meningioma	215	17.3
Intraventricular meningioma	2	0.2
Foramen magnum meningioma	4	0.3
Olfactory groove meningioma	8	0.6
Posterior fossa meningioma	12	1.0
Sphenoid wing meningioma	27	2.2
Suprasellar meningioma	28	2.3
Tentorial meningioma	19	1.5
Cerebral pontine meningioma	22	1.8
Ependymoma glioma	22	1.8
Oligodendroglioma	19	1.5
Pilocytic astrocytoma	33	2.7
Diffuse astrocytoma	63	5.1
Anaplastic astrocytoma	56	4.5
Glioblastoma	35	2.8
Acoustic neuroma	142	11.5
Medulloblastoma	47	3.8
Pituitary macroadenoma	303	24.4
Pituitary microadenoma	56	4.5
Craniopharyngioma	38	3.1
Suprasellar germinoma	19	1.5
Others	70	5.6

of 50 years (46.04%, 577), except for medulloblastoma that was more likely to develop among children.

Figure 1 shows the distribution of tumour types and race of patients who underwent MRI brain scans. Sellar/parasellar tumour (414, 33.39%) were the most common type of brain tumour among all races, followed by meningioma (308, 24.84%), glioma (222, 17.9%), nerve sheath tumour (142, 11.45%), medulloblastoma (47, 3.79%) and others (107, 8.63%).

Figure 2 shows the distribution of tumour types vs brain lobe. Data showed that the most common site for meningioma (141, 11.37%) and glioma (77, 6.21%) were frontal lobe brain, whilst sellar / parasellar (413, 33.31%) was the most common tumour for temporal lobe brain. Data also revealed that for nerve sheath tumour (140, 11.29%) and medulloblastoma (47, 3.79%), the most common site is occipital lobe. This data also showed same trends for parietal lobe brain, with meningioma (77, 6.21%) and glioma (36, 2.90%) being the most common types of tumour in this lobe.

Figure 3 shows the distribution of tumour type vs brain hemisphere that was affected due to the tumour during MRI brain scan examination in PPUKM. Among 1240 cases, data showed that there is only slight difference between right and left hemispheres of brain. Data revealed that for meningioma, both right and left brain hemisphere had an equal result (144, 11.61%), meanwhile for glioma it only showed slight difference; right brain hemisphere was 96 (7.74%) and left brain hemisphere was 99 (7.98%). Data revealed that the tumour that was mostly commonly not defined was sellar/parasellar tumour (177, 14.27%), with pituitary macroadenoma and microdenoma being the most common tumour that could not be defined in sellar region.

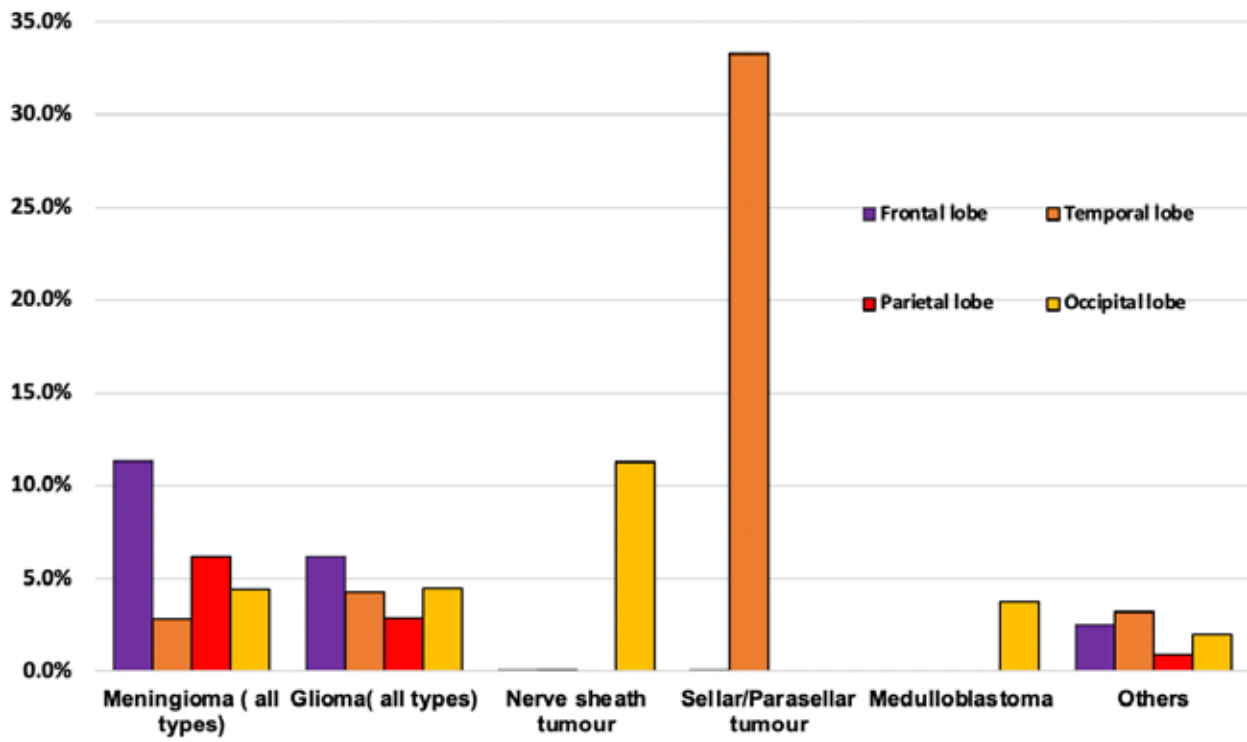

Figure 2: Distribution types of tumour vs brain lobe

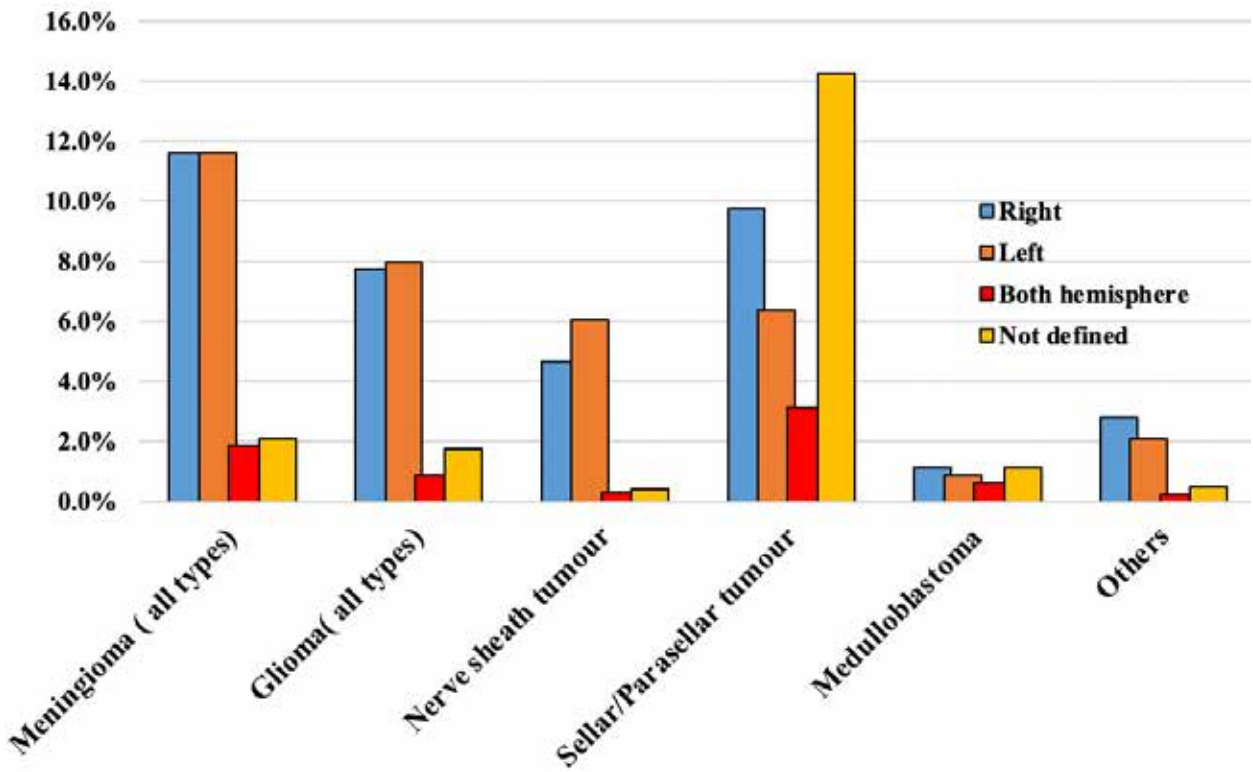

Figure 3: Distribution types of tumour vs brain hemisphere

DISCUSSION

In the present study, data shows the distribution of brain tumours from the MRI database in PPUKM between 2012 and 2017. The tabulated data helps us to evaluate the distribution pattern of brain tumours based on patient demography and types and locations of the tumours. This will set a baseline for future studies aiming to study patients with brain tumours for fMRI.

The present results showed that more female patients underwent MRI brain examination in PPUKM from January 2012 to December 2017, and thus the result also revealed that more females were diagnosed with brain cancer. This present data is in agreement with previous studies that reported females displayed slightly higher number of brain tumour cases than males[20,2]. Furthermore, Department of Statistics, Malaysia also reported that the risk of males getting cancer was 1 in 10 and it is 1 in 9 for females.

Results also revealed that Malays were the most frequent group of patients that underwent MRI brain scan examination in PPUKM as compared to other races. This finding was similar to the previous study by Goh *et al*[20] comparing four races and gender, Iban, Malay, Chinese, Bidayuh; female Malays showed the highest prevalence among all. The reasons for Malays being the most frequent for undergoing MRI brain examination is due to the supported record from Department of Statistic, Malaysia in 2010 that stated the total number of Malay residents in Kuala Lumpur

Table 4: Distribution types of tumour vs race and gender

Types of tumour	Race n(%)				Sex n(%)	
	Malay	Chinese	Indian	Others	Male	Female
Meningioma (all types)	161 (12.98)	111(8.95)	25 (2.02)	11(0.89)	114 (9.19)	223(17.98)
Glioma (all types)	135 (10.89)	66 (5.32)	20 (1.61)	1 (0.08)	109 (8.79)	119(9.60)
Nerve sheath tumor	90 (7.26)	44 (3.55)	5 (0.40)	3 (0.24)	67 (5.40)	75(6.05)
Medulloblastoma	36 (2.90)	8 (0.65)	3 (0.24)	0 (0.00)	24 (1.94)	23(1.85)
Sellar/parasellar Tumors	198 (15.97)	177 (14.27)	3 (2.74)	5 (0.40)	189 (15.24)	227(18.31)
Others	63 (5.08)	38 (3.06)	6 (0.48)	0 (0.00)	44 (3.55)	26(2.10)
Total	683 (55.08)	444 (35.8)	93 (7.49)	20 (1.61)	547 (44.11)	693(55.89)

Table 5: Distribution types of tumor vs age group

Types of tumour	Age n(%)						
	10-19	20-29	30-39	40-49	50-59	60-69	70 and above
Meningioma (all types)	8 (0.65)	14 (1.13)	30(2.42)	55(4.44)	89(7.18)	75 (6.05)	37(2.98)
Glioma (all types)	40 (3.23)	43 (3.47)	45(3.63)	42(3.39)	20(1.61)	24 (1.94)	8(0.65)
Nerve sheath tumor	3 (0.24)	10 (0.81)	26(2.10)	31(2.50)	37(2.98)	23 (1.85)	12(0.97)
Medulloblastoma	34 (2.74)	5 (0.40)	2(0.16)	4(0.32)	0(0.00)	1(0.08)	1(0.08)
Sellar/parasellar Tumors	19 (1.53)	63 (5.08)	70(5.65)	67(5.40)	75(6.05)	82 (6.61)	38(3.06)
Others	17(1.37)	16 (1.29)	12(0.97)	13(1.05)	15(1.21)	23 (1.85)	11(0.89)
Total	121(9.76)	151(12.18)	185(14.93)	212(17.10)	236(19.03)	234 (18.38)	107(8.63)

were higher than other races. The data recorded shows that in the Federal Territory of Kuala Lumpur, the number of Malays was the highest (679,236, 44.75%), followed by Chinese (655,413, 43.18%), Indian (156,16, 10.30%), other Bumiputera (17,494, 1.15%) and others (9,539, 0.63%).

Tumours can be considered as an age-related disease. Our result shows the same trends as the study by McKinney *et al*[21] that stated that the incidence of brain tumours rises with age from approximately 30-years-old onwards. Our result shows that brain tumours occurred in the ages greater than 30 years (78%, 968), with the age group of 50-59 years being the most frequent group for developing brain tumour. This data was also supported by the previous studies which revealed that age is one of the factors for developing brain tumour[2,22].

The present result showed that the sellar/parasellar tumour was the most common tumour developed by the patient that underwent MRI brain scan in PPUKM within the past six years. This is likely due to the nature of this tumour being asymptomatic[23]. Patients usually come for treatment when the signs and symptoms arise due to the tumour. Al-Dahmani *et al*[24] and Ezzat *et al*[25] all reported that through post-mortem findings, pituitary tumours were found in 10-27% of the population. Meningioma was encountered in 27.2% and it is the second most common brain tumour that was detected in the patient that underwent MRI brain scan in PPUKM. Our findings showed slightly lower percentage as compared to past studies by Dzali *et al* 2017[2], Goh *et al*[20] and Yusoff *et al*[26]; their results showed that meningioma was encountered in about 30% of the population. According to Barnholtz-Sloan *et al*[27], meningioma constitutes about 13-25% of primary intracranial neoplasms reported.

Our results indicated that most tumours were located on the temporal lobe in the brain, similar to findings reported by previous study from Johnson *et al*[28] and Philips *et al*[29] in Jamaica and UK respectively, that specified glioma as the majority of the tumours (66.7%) occurred in the left cerebral hemisphere, with the most common lobe being the temporal lobe. Based on the results, there were also unspecified brain tumour locations. The assumption is due to high brain tissue tumour infiltration. Another study by Kim *et al*[30] in New Zealand found that there was a high number of unspecified brain tumours. In a previous study by Zada *et al*[31], they stated that in the US, an increasing incidence of brain tumours was found in the frontal, parietal and occipital lobes of the brain.

Our tabulated data of six years in PPUKM also showed that there is little difference between the frequency of right and left brain hemisphere being invaded by brain tumours. A previous study by Liu *et al*[32] stated that tumour location and laterality has been shown to correlate with several specific symptoms. This study revealed that in the frontal lobe of brain, the most affected side was the left brain hemisphere. The patients with a tumour located in frontal area and in right hemisphere had poorer quality of life than those with a posterior tumour[33]. Tumour in left hemisphere may have greater problems with communication even before treatment begins[33].

Brain tumour incidence was not determined in this study due to the limited geographical location and catchment of this institution which prevents us from making a generalized conclusion. However, the information provided is helpful in presuming the brain tumour distribution in PPUKM. This study also only provides information regarding patients who underwent MRI brain examination and focusing on patients with brain tumour only. The tabulated data is able to help us in the future study in terms of data collection regarding fMRI in brain tumour patients which supplement neuroimaging studies on normal subjects[34,35].

CONCLUSION

The examination of brain tumour distribution pattern is important to plan for health services and research. Tabulating the distribution information is useful in prioritizing research questions when sufficient patients are available. With a significant number of patients with frontal lobe tumours, we are confident that we can accrue enough patients for

fMRI studies of the frontal lobe tumours alongside neuroimaging studies involving normal subjects and patients without intracranial growths. This can be a reference for others interested in the study of brain tumours in the Asian population.

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Conflict of interest: None

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Original Article

Impact of anesthesia type on transfusion-related parameters and postoperative outcome in patients undergoing elective partial hip arthroplasty

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ABSTRACT

Objective: To evaluate the impact of anesthesia on transfusion-related parameters and postoperative recovery outcome in patients undergoing elective partial hip arthroplasty
Design: Retrospective study
Setting: Orthopedics and Traumatology Clinic, Antalya Training and Research Hospital
Subjects: A total of 256 patients undergoing elective partial hip arthroplasty were included in this retrospective study.
Intervention: Non-interventional
Main outcome measures: Type and duration of anesthesia, American Society of Anesthesiologists (ASA) physical status, transfusion-related parameters, vasopressor or perioperative erythrocyte transfusion, blood loss, hemoglobin levels, postoperative transfer unit, length of hospital stay (LOS, days) and 30-day survivorship status were analyzed with respect to anesthesia type separately for patients in ASA I-II and ASA III-IV categories.
Results: For patients in ASA III-IV category, general anesthesia was associated with older patient age (P<0.001) and higher amount of perioperative erythrocyte transfusion (P<0.05) than spinal anesthesia. For patients in ASA III-IV category, general anesthesia, as compared with spinal and combined spinal-epidural anesthesia, was associated with higher intraoperative blood loss (P<0.001 and P<0.01, respectively), higher likelihood of perioperative erythrocyte transfusion (P<0.001 and P<0.01, respectively) and higher likelihood of postoperative ICU stay (P<0.001 and P<0.01, respectively). No significant impact of anesthesia type was noted on LOS and 30-day mortality, regardless of ASA class.
Conclusion: In conclusion, our findings revealed no significant impact of anesthesia type on LOS or 30-day mortality in partial hip arthroplasty patients, whereas lesser transfusion need and lesser likelihood of postoperative ICU utilization with use of neuraxial vs. general anesthesia in ASA III-IV class patients was seen.

KEY WORDS: ASA classification, general anesthesia, hip replacement, mortality, neuraxial anesthesia

INTRODUCTION

The anesthesia practice for orthopedic surgery continues to be in progress with consideration of choice of anesthesia amongst the important factors for delivering cost-effective and excellent health care[1]. Thus, in parallel with a growing increase in the number of arthroplasties performed in orthopedics practice, optimizing the anesthesia type has become one of the important aspects of hip arthroplasty surgery due to its potential to enable higher patient satisfaction and reduction in morbidity and mortality rates[2].

Improved recovery and complication outcomes have been reported in the total hip or knee arthroplasty patients with use of modern neuraxial spinal anesthesia versus general anesthesia in terms of lower rates of blood loss, transfusion need, intensive care unit (ICU) utilization and cardiopulmonary and infectious complications along with shorter length of hospital stay (LOS) and improved 30-day morbidity and mortality[3-8]. Hence, neuraxial spinal anesthesia has become one of the key metrics for a hospital to become a center of excellence in joint arthroplasty[9,10].

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However, there are also studies that reported no significant difference between general anesthesia and spinal neuraxial anesthesia in terms of postoperative outcomes in total hip arthroplasty or hip fracture repair patients[2,11,12]. Besides, use of regional anesthesia for total joint arthroplasty is considered to remain under-utilized with continuation of general anesthesia to be the main choice, particularly in centers performing a high volume of elective joint arthroplasties[1,3,10,13].

Indeed, compared to several studies on other risk factors (*i.e.* older age, male gender, bilateral joint surgery, diabetes, kidney disease, metastatic cancer, and cardiopulmonary or cerebrovascular comorbidities), type of anesthesia has been less extensively studied in relation to risk for morbidity and mortality after total joint arthroplasty[1,10].

Alongside the inconsistent findings of published studies on potential benefits of general vs. neuraxial anesthesia on the postoperative outcome in hip arthroplasty surgery[2-8], scarcity of available data on outcomes of contemporary general anesthesia practices has also been emphasized[10-14].

This study was therefore designed to evaluate the impact of anesthesia type on transfusion-related parameters and postoperative recovery outcome (ICU utility, LOS, 30-day mortality) among elective partial hip arthroplasty patients in relation to American Society of Anesthesiologists (ASA) physical status classification.

MATERIALS AND METHODS

Study population

A total of 256 patients (mean±SD age: 61.6±16.2 years, 56.3% females) who underwent elective partial hip arthroplasty in a tertiary care center between 2010 and 2017 were included in this retrospective study. Patients were divided into three groups based on type of primary anesthesia including spinal anesthesia (n=182), combined spinal and epidural anesthesia (n=34) and general anesthesia (n=40).

The study was conducted in full accordance with local Good Clinical Practice guideline, current legislations and the ethical principles stated in the Declaration of Helsinki, while the permission was obtained from the Ethics Committee of Antalya Training and Research Hospital for the use of patient data for publication purposes (Date of Approval/ Protocol No: 2019/016).

Assessments

Data on patient demographics (age, gender), type and duration of anesthesia, ASA physical status classification, intraoperative time (min), transfusion-related parameters (need for crystalloids and colloid fluids (mL) or vasopressor agent and blood loss (mL), perioperative erythrocyte transfusion need, preoperative and postoperative levels for hemoglobin (mg dL^{-1}) and creatinine (mg dL^{-1})), postoperative transfer unit (ward, intensive care unit-ICU), LOS (day) and postoperative 30-day survivorship status were recorded in each patient and analyzed with respect to the three anesthesia groups separately for patients in ASA I-II and ASA III-IV categories. Blood transfusion was not performed unless there was worsening in hemodynamic parameters (Hb <7 gdL^{-1}), while intravenous colloid replacement was based on 1:1 blood/colloid ratio. Since there were three different types of anesthesia, duration of anesthesia and operation time were evaluated equally.

Anesthesia

In the operating room, monitoring with electrocardiography, peripheral oxygen saturation, non-invasive blood pressure monitorization and invasive blood pressure monitorization in patients with high cardiovascular risk were performed.

In spinal anesthesia group, after recording basal parameters and preloading with 15 mL kg^{-1} crystalloid solution, 3-3.5 ml of 0.5% hyperbaric bupivacaine (intrathecal, L4-L5 intervertebral space) was administered in the sitting position. Patients with sensory blockade (T10 level) were evaluated.

In combined spinal and epidural anesthesia group, after recording basal parameters and preloading with 15 mL kg^{-1} crystalloid solution, 3 ml of 0.5% hyperbaric bupivacaine (intrathecal, L4-L5 intervertebral space) was administered in the sitting position and epidural catheter was placed.

Postoperatively, pain management was based on intravenous (in spinal and general anesthesia groups) or epidural (in combined spinal epidural aneshtesia group) patient-controlled anesthesia via tramadol administration. Patients with sensory blockade (T10 level) were evaluated.

In the general anesthesia group, after 2% intravenous lidocaine (1mg kg^{-1}) administration to reduce pain due to propofol, general anesthesia was induced via propofol (3mg kg^{-1}), fentanyl (1μg kg^{-1}) and rocuronium (0.6 mg kg^{-1}). For maintenance of anesthesia 50% air-oxygen, remifentanil (0.5μg $kg^{-1}min^{-1}$) infusion and desflurane inhalation (1 MAC) was performed, while end-tidal CO_2 was monitored with capnography when the bispectral index was in the range of 40-60. The procedures were performed by the same operation team in all patients.

Statistical analysis

Statistical analysis was made using IBM SPSS Statistics for Windows, version 25.0 (IBM Corp., Armonk, NY). Pearson chi-square test (Monte Carlo)

and Fisher Freeman Halton (Monte Carlo) with post hoc Benjamini-Hochberg correction were used to analyze categorical variables, while one way ANOVA (Robust Statistic: Brown-Forsythe) with post hoc Tukey HSD, Kruskal Wallis test (Monte Carlo) with post Hoc Dunn's test, Mann Whitney U test (Monte Carlo) and General Linear Model Repeated ANOVA (Wilks' Lambda) were used for analysis of numerical variables. Wilcoxon Signed Ranks test (Monte Carlo) was used for two repeated measurements. Propensity-matched analysis was used to determine the perioperative risk factors that might affect the study and to regroup the pairings. The pairing was done in pairs with the least number of reference groups. When analyzed according to the new groups obtained from the Propensity score, the first analysis results of our study did not change according to the results of the first analysis and the first analysis results are shown to reduce the number of samples. Data were expressed as "mean±standard deviation" median (minimum-maximum) and percent (%) where appropriate. *P* <0.05 was considered statistically significant.

Power analysis results

Similarly, since the reference study was not available in the literature, our study was planned as post power. Power and sample size were calculated with G * Power 3.1.9.2. All patients in the hospital database who met the inclusion criteria were included in the study. ASA (III + IV) and the number of groups (n1=11, n2=23, n3=35) with a total N=69 obtained with the available data obtained from the results of the analysis of the effect size values intraoperative bleeding (ml) for 0.862 and perioperative erythrocyte transfusion. The post power value calculated for the need (unit) for 0.482 was calculated as 99.99 and 94.82%, respectively, and according to this result, the number of samples was found to be sufficient.

RESULTS

Mean patient age was 61.6 years (range: 25 to 98 years) and females composed 56.3% of the study population. Spinal, general and combined spinal-epidural anesthesia was applied in 71.1%, 15.6% and 13.3% of patients, respectively. Most patients (73%) were in ASA I-II category. Intraoperative need for colloid or vasopressor agent (ephedrine) and perioperative need for erythrocyte transfusion was noted in 33.6%, 24.6 and 32% of patients, respectively. Postoperatively, majority of patients were transferred to a general ward (87.1%) and median LOS was 12 days. Postoperative 1-month survival rate was 94.1% (Table 1).

For patients in ASA I-II category, spinal anesthesia was associated with significantly shorter intraoperative time as compared with general and combined spinal-epidural anesthesia (median (min-max) 100 (60-200) vs. 140 (90-210) and 130 (80-200) min, *P* <0.001 for each), lesser amount of intraoperative crystalloids as compared with combined spinal-epidural anesthesia (1873 (1000-4000) vs. 2214 (1000-3500) mL, *P* <0.05, Table 2).

No significant difference was noted between anesthesia types in patients with ASA I-II category in terms of other study parameters including patient demographics, intraoperative blood loss, colloid or vasopressor need, perioperative erythrocyte transfusion need, creatinine levels, postoperative transfer unit, LOS and postoperative 1-month survival

Table 1: Patient demographics, transfusion-related and postoperative outcome (n=256)

Patient demographic characteristics	Values
Age, year	
Mean±SD	61.6±16.2
Median (min-max)	62 (25-98)
Gender, n(%)	
Female	144 (56.3)
Male	112 (43.8)
Type of anesthesia, n(%)	
Spinal	182 (71.1)
General	40 (15.6)
Combined spinal-epidural	34 (13.3)
ASA category, n(%)	
I-II	187 (73.0)
III-IV	69 (27.0)
Duration of anesthesia (min), median (min-max)	110 (60-270)
Intraoperative time (min), median (min-max)	110 (60-270)
Intraoperative blood loss (ml), median(min-max)	300 (150-950)
Intraoperative crystalloid need (mL), median(min-max)	2000 (1000- 4000)
Intraoperative colloid need	
mL, median(min-max)	500 (500-1500)
Yes, n(%)	86 (33.6)
Perioperative erythrocyte transfusion need	
Units, median (min-max)	2 (1-5)
Yes, n(%)	82 (32.0)
Intraoperative vasopressor need	
mg, median(min-max)	15 (5- 100)
Yes, n(%)	63 (24.6)
Hemoglobin (mg/dL), mean±SD	
Preoperative	12.19±1.51
Postoperative	9.44±1.19
Change (postop-preop)	-2.75±1.06
Creatinine (mg/dL), mean±SD	
Preoperative	1.00±0.55
Postoperative	1.00±0.66
Change (postop-preop)	0.01±0.38
Postoperative transfer unit, n(%)	
Ward	223 (87.1)
ICU	33 (12.9)
Length of hospital stay (day), median (min-max)	12 (3-27)
30-day survivorship status, n(%)	
Survivor	241 (94.1)
Non-survivor	15 (5.9)

SD: standard deviation; ASA: American Society of Anesthesiologists; ICU: intensive care unit

Table 2: Study parameters with respect to anesthesia type in patients with ASA I-II and ASA III-IV categories

Patient demographics, clinical and operative characteristics	Patients in ASA I-II Category				Patients in ASA III-IV Category			
	Spinal (n=147)	General (n=17)	Combined S-E (n=23)	*P*-value	Spinal (n=35)	General (n=23)	Combined S-E (n=11)	*P*-value
Gender, n(%)								
Female	85 (57.8)	7 (41.2)	13 (56.5)	0.4501	17 (48.6)	15 (65.2)	7 (63.6)	0.4301
Male	62 (42.2)	10 (58.8)	10 (43.5)		18 (51.4)	8 (34.8)	4 (36.4)	
Age (year), mean±SD	57.94±14.21	54.24±12.56	53.09±12.51	0.1622	67.80±16.88	81.43±8.90**	77.91±15.14	0.0022
Intraoperative time (min), median (min-max)	100 (60-200)	140 (90-210)***	130 (80-200)***	<0.0013	100 (60-270)	120 (90-140)	120 (80-180)	0.1053
Intraoperative blood loss (ml), median(min-max)	300 (150-950)	350 (150-600)	300 (150-800)	0.8713	300 (200-800)qq	500 (150-600)	300 (200-800)q	<0.0013
Intraoperative crystalloid need (mL), median(min-max)	1873 (1000-4000)	2128 (1000-3500)	2214 (1000-3500)*	0.0073	2000 (1000-3000)	2000 (1000-3000)	2000 (1000-3000)	0.9143
Intraoperative colloid need								
mL, median(min-max)	500 (500-1500)	500 (500-1000)	500 (500-1000)	0.9403	500 (500-1000)	500 (500-1000)	500 (500-1000)	0.7553
No, n(%)	106 (72.1)	11 (64.7)	18 (78.3)	0.6441	22 (62.9)	7 (30.4)	6 (54.5)	0.0515
Yes, n(%)	41 (27.9)	6 (35.3)	5 (21.7)		13 (37.1)	16 (69.6)	5 (45.5)	
Perioperative erythrocyte transfusion need								
Units, median (min-max)	2 (1-5)	-	2 (1-3)	0.5414	2 (1-3)	3 (1-4)*	2 (2-4)	0.0373
No, n(%)	108 (73.5)	14 (82.4)	18 (78.3)	0.7555	24 (68.6)	4 (17.4)	6 (54.5)	0.0031
Yes, n(%)	39 (26.5)	3 (17.6)	5 (21.7)		11 (31.4)qq	19 (82.6)	5 (45.5)q	
Intraoperative vasopressor need, n(%)								
No	116 (78.9)	14 (82.4)	19 (82.6)	0.8541	24 (68.6)	12 (52.2)	8 (72.7)	0.3715
Yes	31 (21.1)	3 (17.6)	4 (17.4)		11 (31.4)	11 (47.8)	3 (27.3)	
Hemoglobin (mg/dL), mean±SD								
Preoperative	12.34±1.54	12.34±1.49	12.57±1.34	0.7772	12.10±1.46	11.20±1.41*	11.58±1.18	0.0462
Postoperative	9.60±1.17	9.42±1.29	9.50±0.94	0.7802	9.41±1.25	8.56±1.13*	9.16±1.10	0.0282
Change (postop-preop)	-2.74±0.97	-2.92±1.08	-3.06±1.07	0.3592	-2.69±1.29	-2.64±1.37	-2.42±0.61	0.7742
P-value (change)[6]	<0.001	<0.001	<0.001		<0.001	<0.001	<0.001	
Creatinine (mg/dL), mean±SD				0.7253				0.3253
Preoperative	0.89 (0.51-4.29)	0.9 (0.78-2.3)	0.86 (0.71-2.4)	0.1623	0.95 (0.62-2.94)	0.98 (0.78-7)	0.92 (0.61-1.21)	0.3743
Postoperative	0.86 (0.61-2.46)	0.89 (0.73-1.76)	0.91 (0.68-4.79)	0.3083	0.91 (0.76-2.87)	0.89 (0.81-7.75)	0.86 (0.57-0.96)	0.9263
Change (postop-preop)	0 (-1.83-0.44)	-0.07 (-0.54-0.14)	0.04 (-0.42-2.39)		-0.04 (-0.43-0.64)	-0.09 (-1.11-3.97)	-0.04 (-0.4-0.15)	
P-value (change)[7]	0.646	0.153	0.567		0.318	0.811	0.267	
Postoperative transfer unit, n(%)				0.1045				<0.0015
Ward	144 (98.0)	15 (88.2)	23 (100.0)		29 (82.9)	5 (21.7)	7 (63.6)	
ICU	3 (2.0)	2 (11.8)	0 (0.0)		6 (17.1)qq	18 (78.3)	4 (36.4)q	
Length of hospital stay (day), median (min-max)	12 (3-27)	12 (4-23)	13 (6-23)	0.2943	11 (5-18)	9 (4-16)	11.5 (5-20)	0.0833
30-day survivorship status, n(%)				0.9995				0.4665
Survivor	144 (98.0)	17 (100.0)	23 (100.0)		30 (85.7)	17 (73.9)	10 (90.9)	
Non-survivor	3 (2.0)	0 (0.0)	0 (0.0)		5 (14.3)	6 (26.1)	1 (9.1)	

S-E: spinal-epidural; SD: standard deviation; min: minimum, max: maximum. [1]Pearson Chi-Square Test(Monte Carlo), [2]One Way ANOVA (Robust Statistic: Brown-Forsythe) with post Hoc Tukey HSD, [3]Kruskal Wallis Test (Monte Carlo) with post Hoc Dunn's test, [4]Mann Whitney U Test (Monte Carlo), [5]Fisher Freeman Halton (Monte Carlo) with post Hoc Benjamini-Hochberg correction, [6]General Linear Model Repeated ANOVA (Wilks' Lambda), [7]Wilcoxon Signed Ranks Test (Monte Carlo)

* $P<0.05$, ** $P<0.01$ and *** $P<0.001$; compared to spinal anesthesia group; [q]$P<0.01$ and [qq]$P<0.001$; compared to general anesthesia group

rate. Hemoglobin levels significantly decreased postoperatively in each anesthesia group (P <0.001 for each) with no significant difference between groups in terms of preoperative and postoperative levels (Table 2).

For patients in ASA III-IV category, general anesthesia was associated with older patient age (mean±SD 81.43±8.90 vs. 67.80±16.88 years, P <0.001) and higher amount of perioperative erythrocyte transfusion (median(min-max) 3 (1-4) vs. 2 (1-3) units, P <0.05) than spinal anesthesia. For patients in ASA III-IV category, general anesthesia as compared with spinal and combined spinal-epidural anesthesia was associated with higher amount of intraoperative blood loss (median (min-max) 500 (150-600) vs. 300 (200-800) and 300 (200-800) mL, P <0.001 and P <0.01, respectively), higher likelihood of perioperative erythrocyte transfusion (82.6% vs. 31.4% and 45.5%, P <0.001 and P <0.01, respectively) and higher likelihood of postoperative ICU stay (78.3% vs. 17.1% and 36.4%, P <0.001 and P <0.01, respectively) (Table 2).

Hemoglobin levels were significantly decreased postoperatively in each anesthesia group (P <0.001 for each), while both preoperative and postoperative levels were significantly lower in patients who received general anesthesia than those who received spinal anesthesia (P <0.05 for each, Table 2).

No significant difference was noted between anesthesia types in patients with ASA III-IV category in terms of other study parameters including gender, intraoperative time, colloid, crystalloid, vasopressor need, creatinine levels, LOS and postoperative 1-month survival rate (Table 2).

DISCUSSION

Our findings in a retrospective cohort of patients undergoing elective partial hip arthroplasty surgery have revealed that older patients in the ASA III-IV class who are given general anesthesia need higher amount of perioperative erythrocyte transfusion and have lower hemoglobin levels than those given spinal anesthesia, whereas higher amount of intraoperative blood loss and higher likelihood of perioperative erythrocyte transfusion and postoperative ICU utilization is seen when compared with both spinal and combined spinal-epidural anesthesia. Anesthesia type had no significant impact on transfusion-related parameters in ASA I-II class patients, while it also had no significant impact on LOS or 30-day mortality in partial hip arthroplasty patients regardless of their ASA physical status.

Past studies in total hip arthroplasty patients revealed that neuraxial anesthesia as compared to general anesthesia was associated with a significant reduction in blood loss[7], lesser risk of deep surgical site infection[4,15] and shorter LOS[4,6,7,16], alongside reduction in the rates of cardiopulmonary complications[3,5,6,8], ICU utilization[6] and 30-day mortality[4,5,7].

Although our findings support the less favorable outcome of general anesthesia as compared with neuraxial anesthesia in partial hip arthroplasty patients, this was valid only for ASA III-IV class patients and particularly for transfusion-related parameters[17] (low hemoglobin levels, higher intraoperative blood loss, increased erythrocyte transfusion need) along with ICU utilization. Notably, regardless of the ASA class, no significant impact of anesthesia type was noted on LOS or 30-day mortality in our cohort of partial hip arthroplasty patients.

Similarly, in a past study among bilateral total hip arthroplasty patients, authors reported higher rate of perioperative transfusion in the general anesthesia group as compared with the neuraxial anesthesia group, whereas no significant difference was noted between anesthesia groups in terms of postoperative outcomes including LOS, 30-day postoperative pulmonary complications, sepsis and surgical site infection[2]. Two large database studies among bilateral hip or knee arthroplasty patients also reported that apart from a decrease in transfusion need, neuraxial anesthesia had no superiority over general anesthesia in terms of complication rates, LOS and postoperative ICU utilization[2,11]. In a large scale observational study of elderly patients with hip fracture, use of regional anesthesia was also reported not to be associated with better outcome than general anesthesia in surgical repair in terms of morbidity and mortality[2].

In the present cohort, general anesthesia is associated with older patients, increased intraoperative blood loss, perioperative erythrocyte transfusion need and higher likelihood of postoperative ICU utilization as compared with spinal neuraxial anesthesia in ASA III-IV patients but not in ASA I-II class patients. This seems notable given that older patients with poorer ASA classification are considered to have a higher incidence of perioperative complications[1,18]. Neuraxial anesthesia has also been reported to be a favorable anesthesia in the presence of multiple comorbidities, particularly for elderly patients with significant cardiopulmonary comorbidities[6,16].

Importantly, identification of hemodynamic disadvantages of general anesthesia only in ASA III-IV class patients in our cohort seems to emphasize consideration of ASA physical status classification in anesthesia-based risk stratification of patients undergoing hip arthroplasty for better allocation of resources and improved patient care and experiences.

However, it should also be noted that in a study with total arthroplasty (54.9% ASA I-II, 44.9% ASA III-IV) and total knee arthroplasty (50.6% ASA I-II,

49.7% ASA III-IV) patients, implementation of a modern rapid-recovery general anesthesia protocol was reported to be associated with excellent outcomes with early mobilization and limited complications or adverse events[10]. In addition, while the anesthesia type was addressed among unilateral partial arthroplasty patients in the current study, unilateral arthroplasties as compared with bilateral arthroplasties are known to be associated with lower rates of complications and erythrocyte transfusion, with higher postoperative hemoglobin levels and higher improvement in postoperative pain scores[19,20].

Nonetheless, association of spinal and combined spinal-epidural anesthesia with improved transfusion-related parameters (lesser blood loss and transfusion need) in our ASA III-IV class patients is important, given the correlated immunological interplay between blood transfusion and infection with higher rate of infection in patients who required more blood transfusion reported in several studies[21-23]. In fact, use of epidural anesthesia alone was reported to be associated not only with reduction of intra- and postoperative blood loss[24,25], but also with faster postoperative red blood cell recovery in patients undergoing total hip arthroplasty when compared to use of general anesthesia with or without epidural anesthesia[25]. Improved hemodynamics with neuraxial anesthesia in hip arthroplasty patients seems also important in terms of its additional putative advantages reported for homeostasis, cardiopulmonary, metabolic and immune functions as well as for better postoperative outcome in patients after major orthopedic surgery[24-27].

Certain limitations of this study should be considered. Firstly, due to retrospective single center design of the present study, establishing the temporality between cause and effect as well as generalizing our findings to overall arthroplasty surgical population does not seem possible. Second, lack of data on co-morbid conditions, postoperative cardiopulmonary complications and surgical site infection rates is another limitation, which otherwise would extend the knowledge achieved in the current study. Nevertheless, despite these limitations, providing data on transfusion-related and postoperative recovery outcome under different types of anesthesia in unilateral partial hip arthroplasty patients in relation to different ASA subgroups, our findings represent a valuable contribution to the literature.

CONCLUSION

Our findings revealed no significant impact of anesthesia type on LOS or 30-day mortality in partial hip arthroplasty patients, whereas improved transfusion-related and lesser likelihood of postoperative ICU utilization with use of neuraxial vs. general anesthesia in ASA III-IV class patients. This emphasizes the variable impact of anesthesia type on transfusion-related parameters in partial hip arthroplasty patients depending on the ASA class, implicating the need to consider ASA physical status in risk stratification and consequent resource allocation in this type of surgery. Larger scale prospective randomized controlled trials are needed to address the impact of anesthesia type on outcomes in relation to patient demographics, clinical status, reason and type of specific surgery in hip arthroplasty patients to identify the optimal anesthesia procedure with potential benefits on perioperative morbidity and mortality in this surgical population.

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Original Article

Can we trust change of potassium levels measured by blood gases analyzer in patients who presented to emergency department with hyperkalemia?

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ABSTRACT

Objective: To determine whether the amount of change in potassium levels (ΔK^+) pre- and post-treatment differ in hyperkalemia patients depending on whether the measurements were made using blood gas analyzer (BGA) or laboratory auto analyzer (LAA)
Design: Prospective-observational study
Setting: Emergency department of a training and research hospital
Subjects: This study was conducted with hyperkalemia patients between May and December 2016.
Intervention: In this study, several potassium lowering treatments (insulin, salbutamol, *etc*.) were performed; standardized-controlled intervention was not performed.
Main outcome measure: During the study period, ΔK^+ in venous blood gas and routine laboratory results before and after hyperkalemia treatment in patients with hyperkalemia was observed. Correlations and agreements between ΔK^+ of BGA and LAA were evaluated using Spearman Correlation test and Bland-Altman test respectively.
Results: Ninety-nine patients' laboratory results were evaluated for statistical analysis. On evaluation of the correlation between ΔK^+ levels measured by BGA and LAA, we found moderate correlation (P<0.001, r=0.67). However, when agreements between ΔK^+ levels measured by BGA and LAA were assessed, the mean difference was -0.22±0.7mmol/L and agreement limits were calculated as -1.63-1.19mmol/L.
Conclusion: Though most physicians prefer to use BGA test results to manage hyperkalemia patients in the early stages, the present study found that BGA results are not a reliable basis for decision-making when managing hyperkalemia patients, particularly regarding whether post-treatment K^+ levels have decreased sufficiently.

KEY WORDS: blood gas analysis; hyperkalemia; potassium; venous blood gases

INTRODUCTION

Hyperkalemia can be a life-threatening situation and is a common reason for admission to emergency departments (EDs), especially for patients who have acute or chronic kidney diseases or who are using multiple drugs, including angiotensin-converting-enzyme inhibitors and potassium-sparing diuretics[1-3].

Since hyperkalemia is a potentially life-threatening situation, its diagnosis should be made quickly and reliably. However, in daily practice, potassium (K^+) values are measured using a laboratory auto-analyzer (LAA), which is a time-consuming method. Therefore, many physicians increasingly prefer to use a blood gas analyzer (BGA) in routine clinical practice for several reasons[4,5]. The most important concern when using a BGA is whether its results are reliable. Several studies have addressed whether BGAs are reliable by comparing their results, including those regarding K^+, for venous blood gas (VBG) and biochemistry to those measured using LAA, but the results of these studies have been very contradictory[6-9]. Therefore, many physicians have approached K^+ results obtained using BGA with caution, instead preferring to wait for biochemistry results, which can cause delay in beginning hyperkalemia treatment and may contribute to ED overcrowding.

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For these reasons, the present study aimed to determine whether the amount of change in potassium levels (ΔK^+) pre- and post-treatment differ in hyperkalemia patients depending on whether the measurements were made using BGA or LAA. In contrast to previous studies, the present study hypothesized that if there is a correlation between the ΔK^+ amounts measured using BGA and LAA after hyperkalemia treatments, then K^+ levels can be predicted quickly by evaluating only the BGA results, without waiting for the LAA results. Thus, the study's results may contribute to more prompt treatment of hyperkalemia and shorter waiting time in EDs.

SUBJECTS AND METHODS

Ethics committee approval

The study was approved by the local ethics committee at Kecioren Training and Research Hospital**.** This prospective-observational study was conducted using patients admitted to the ED of a training and research hospital and diagnosed with hyperkalemia between May and December 2016.

Study population

The study included all consenting patients with hyperkalemia (>5.5 mmol/L) who were admitted during the study period and who had both VBG and routine laboratory results taken at admission. The study excluded patients younger than 18 or older than 80, those who had received any anti-potassium treatment before venous blood sampling, those whose blood sampling failed in the first three attempts, and those who were diagnosed with cardiopulmonary arrest at admission or during the study period.

Study protocol

This study aimed to observe changes in pre- and post-treatment potassium levels in the VBG and routine laboratory results of hyperkalemia patients. At no time during the study period did the researchers intervene in the hyperkalemia treatment. All decisions on which treatment options to use were made by the physicians responsible for the patients.

When patients were diagnosed with hyperkalemia, their potassium levels as measured using BGA and LAA were recorded on a study form. Then, all patients were treated using anti-potassium treatments, including sodium bicarbonate, insulin-glucose tamponade fluid, diuretics and hemodialysis, according to the decision of the patients' physicians. Finally, 30 min after these anti-potassium treatments, venous blood sampling was used to again measure patients' potassium levels using BGA and LAA. Similarly, these second potassium levels were recorded on the study form.

Potassium measurements

To measure VBG, venous blood samples were obtained using heparinized syringes (PICO70 Arterial Blood Sampler; Radiometer Medical ApS; Brønshøj, Denmark) at bedside in the ED and analyzed at bedside using a BGA (GASTAT-1800 series pH/Blood Gas Analyzer; Techno Medica; St. Ingbert, Germany). During the study period, the BGA was calibrated four times daily. The venous blood samples were also sent to the hospital's core laboratory for analysis using LAA biochemistry tests that relied on an ion-selective electrode-diluted (indirect ISE) method (The ARCHITECT c8000 Clinical Chemistry Analyzer; IL, USA). The material used in this Clinical Chemistry Analyzer was a 2P32 ICT sample diluent (ICTD5) kit. During the study period, the core laboratory determined the calibration time for the biochemistry analyzer at 24-hour intervals, according to the manufacturers' instructions. Two types of controls (normal and abnormal) were to be run every eight hours and following the calibration. The imprecision of the ICT assays for serum samples was as follows: sodium 1.5% and potassium 2.7%. All blood samples were transferred from the ED to the core laboratory within 30 minutes using a pneumatic system.

Statistical analyses

Statistical analyses were performed using SPSS version 16.0 (Chicago, IL, USA). The Shapiro-Wilk test was used to assess the normal distribution of all parameters. Non-parametric data were expressed as median values and inter-quartile range (IQR) (25-

Table 1: Demographic and clinical characteristics of patients

Type of characteristics	Value
Age (years) median (IQR25%-75%)	72 (62-80)
Sex, n (%)	
Male	56 (56)
Female	43 (44)
Comorbidities, n (%)	
Ischemic heart disease	13 (13)
Diabetes mellitus	26 (26)
Hypertension	36 (36)
Chronic obstructive pulmonary disease	5 (5)
Congestive heart failure	18 (18)
Chronic kidney disease	31 (31)
Vital signs	
Mean arterial pressure mmHg	90 (73-103)
Respiratory rate rate/min	18 (16-20)
Heart rate beat/min	94 (81-108)
SO_2 %	92 (90-95)
Hyperkalaemia treatment, n (%)	
Insulin and dextrose infusion	93 (94)
NaHCO3 infusion	6 (6)
Inhaler salbutamol	80 (81)
Haemodialysis	25 (25)
Calcium treatment	25 (25)

Table 2: Venous blood gases and routine laboratory results of patients

Time of analysis	Blood parameters	Venous blood gas	Routine laboratory results
Pretreatment values	Sodium (mmol/L)	132 (127-137)	135 (129-137)
	Potassium (mmol/L)	6.1 (5.7-6.6)	6.6 (6.1-7.0)
	Creatine (g/dL)	–	2.3 (1.5-7.4)
	pH	7.30 (7.23-7.35)	–
After-treatment Values	Sodium (mmol/L)	133 (128-137)	134 (130-138)
	Potassium (mmol/L)	4.9 (4.4-5.5)	5.3 (4.5-5.7)
	Creatine (g/dL)	–	1.9 (1.2-5.3)
	pH	7.31 (7.24-7.36)	–

75%). The correlations between ΔK^+ as measured using the BGA and LAA methods were evaluated using the Spearman Correlation test, and an R-value higher than 0.80 was considered a strong correlation. Agreements between the ΔK^+ measurements obtained using the two methods were assessed using the Bland-Altman test, with 95% CI limits of agreement. Finally, to estimate the ΔK^+ level as measured using LAA after anti-potassium treatment, linear regression analysis was performed using the formula y = a + bx, where x = [ΔK^+ in BGA] and y = [ΔK^+ in LAA]. A *P*-value of <0.05 was considered statistically significant.

RESULTS

During the study period, 121 patients who had been diagnosed with hyperkalemia, whether they had any symptoms or not, had their blood sampled. The study excluded 22 patients who lacked both VBG and routine laboratory results (pre- or post-treatment). Therefore, the laboratory results of 99 patients were evaluated using statistical analysis. The median age of all patients was 72 (IQR 25-75%: 62-80), and 56 patients (56%) were female. Table 1 contains the demographic and clinical characteristics of all patients. The median value of pre-treatment potassium was 6.1 (5.7-6.6) using BGA measurements and 6.5 (6.1-7.1) using LAA measurements. The median values of post-treatment potassium were 4.9 (4.3-5.4) using BGA measurements and 5.3 (4.5-5.7) using LAA measurements. Table 2 shows the results of BGA and LAA measurements for all patients.

The present study's most important finding is that when pre- and post-treatment ΔK^+ was measured using both BGA and routine LAA, the median ΔK^+ value was 1.09 (0.5-1.9) using BGA and 1.35 (0.8-2.1) using LAA. When the correlation between ΔK^+ as measured using BGA and LAA was evaluated, it was found to be moderate (*P* <0.001, r=0.67; Figure 1). However, when agreements were assessed between ΔK^+ levels as measured using BGA and LAA, the mean difference was found to be (mean ± SD) -0.22±0.7 mmol/L, and the agreement limits were calculated as being -1.63 to 1.19 mmol/L. The Bland-Altman analyses found poor agreement for ΔK^+ for clinical use (Figure 2). Finally,

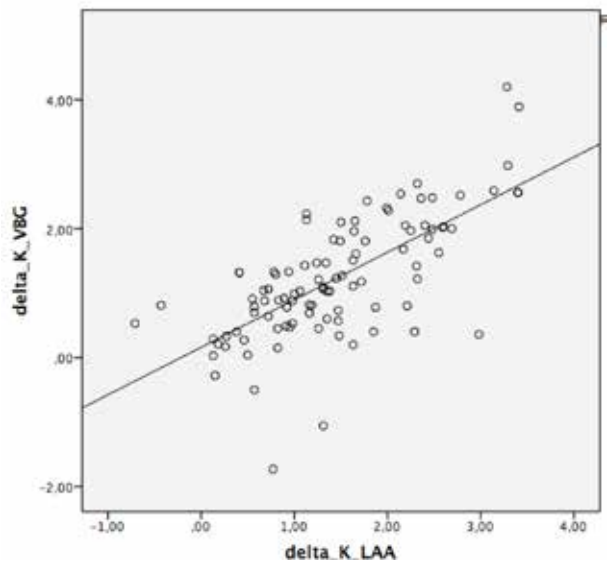

Figure 1: Scatter plots for the correlation between ΔK^+ levels measured by blood gas analyzer and laboratory auto-analyzer

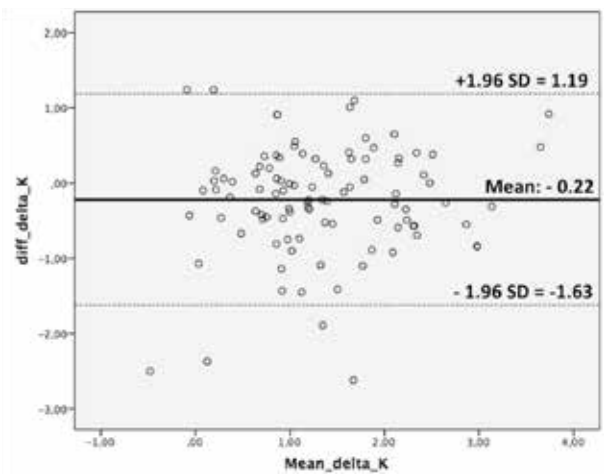

Figure 2: Agreements limits of ΔK^+ levels measured by BGA and LAA according to Bland-Altman analysis. Flat lines showed the mean differences of ΔK^+ levels in blood gas analyzer and laboratory auto-analyzer; dotted lines showed agreements limits with 95% CI.

regression analysis to estimate ΔK^+_{LAA} after anti-potassium treatment found that $\Delta K^+_{LAA} = 0.659 \times (0.644 \times \Delta K^+_{VBG})$ (P <0.001).

DISCUSSION

An evaluation of previous studies found no strong correlations or agreements between the results of BGA and LAA measurements of K^+. Therefore, we hypothesized that there might be a strong correlation or good agreement between pre- and post-treatment amounts of K^+ change as measured using BGA and LAA. However, the present study's main findings indicate that K^+ results measured using the BGA method are not reliable for use in deciding whether K^+ levels have decreased sufficiently in hyperkalemia patients. The results found that although there is a moderate correlation between the results of the BGA and LAA methods of measuring ΔK^+, there is not an acceptable agreement between the two methods. In addition, although the study performed regression analyses to estimate ΔK^+_{LAA} by considering ΔK^+_{VBG}, this formula was not found to be reliable for use in daily ED practice because of the lack of a strong correlation between BGA and LAA measurements of ΔK^+.

Quick, reliable measurement of K^+ is crucial in hyperkalemia patients, especially when making decisions regarding hemodialysis and to prevent life-threatening ventricular dysrhythmia. Therefore, most physicians rely on BGA in daily clinical practice, especially to manage hyperkalemia patients[7]. Despite this general use of BGA, several studies in the literature that have addressed its reliability have reached conflicting results.

For example, Budak *et al* used LAA and BGA to evaluate the agreement between Na^+ and K^+ measurements of 1105 test samples, finding wide-ranging agreement limits (mean diff: 0.25, LoA: -0.5 to 1.1) for K^+. The researchers concluded that K^+ results obtained using BGA and LAA cannot be used interchangeably in clinical practice[8]. Acikgoz *et al* analyzed the blood sample results of 118 patients, finding that although there was a strong correlation between the results of a biochemistry analyzer and BGA, the agreement was poor; the mean difference between the two methods was 0.62±0.43 mEq/dL, and the agreement limits ranged from 0.19-1.05 mEq/dL[9]. Similarly, studies conducted Zhang *et al* and Uysal *et al* found wide ranges of agreement limits for K^+ measurements (mean diff: 0.43, LoA:-0.29 to 1.16 and mean diff:-0.46, LoA: -1.34 to 0.42, respectively)[10-11]. In contrast to the results of these studies, others have reported good agreement between these two methods of measuring K^+. For example, Kozacı *et al* analyzed the blood sample results of 100 patients and found that the mean difference in K^+ values as measured using routine biochemistry and BGA was 0.5 and that the agreement limits ranged from 0.36-0.62[12]. Similarly, Mirzazadeh *et al* reported that the mean difference for K^+ measurements between the two methods was -0.08 mmol/L and that the 95% CI of the agreement limits raged from -0.63 to 0.46 mmol/L[13].

Due to the conflicting results in the literature, the present study did not plan to evaluate the agreement of K^+ measurements made using the two methods. Instead, the study evaluated the agreement between the BGA and LAA methods regarding the amount of change in K^+ between pre- and post-treatment measurements. We believed that if there is strong correlation and agreement between the ΔK^+ amounts measured using BGA and LAA, then after hyperkalemia treatment, K^+ levels can be predicted quickly by evaluating only the BGA results, without waiting for the LAA results, leading to more prompt treatment of hyperkalemia and shorter wait times in EDs. However, it is our opinion that the results of the present study do not support this hypothesis because of the relatively poor agreement limits.

Limitations

The present study has some limitations. First, its sample size was relatively small; however, we believe that this is permissible because the probability of a type-2 error is low. Second, although BGA devices are calibrated daily in routine practice, in the present study, standardization of the daily calibration may not have been sufficient. However, we believe that the results obtained because of this limitation may better compare to those in real clinical practice. Finally, the study analyzed only venous blood samples, not arterial samples.

CONCLUSION

Although most physicians prefer to use BGA test results to manage hyperkalemia patients in the early stages, the present study found that BGA results are not a reliable basis for decision-making when managing hyperkalemia patients, particularly regarding whether post-treatment K^+ levels have decreased sufficiently.

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Author contributions: Osman Lutfi Demirci conceived, designed and performed the experiments, analyzed and interpreted the data, and wrote the paper; Seref Kerem Corbacioglu conceived, designed and performed the experiments, analyzed and interpreted the data, contributed reagents, materials, analysis tools or data and wrote the paper; Seda Dagar conceived, designed and performed the experiments, analyzed and interpreted the data; Yunsur Cevik

contributed reagents, materials, analysis tools or data, and analyzed and interpreted the data.
Conflict of interest: None
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Original Article

A comparison of intraoperative epidural analgesia and intraoperative periarticular injection on pain control in total knee arthroplasty

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ABSTRACT

Objectives: Multi-modal analgesia is achieved by the combined use of analgesic agents acting on different parts of the pain pathway. This study aims to compare the effects of epidural analgesia and periarticular injection on postoperative pain for 48 hours following total knee arthroplasty (TKA) and on the early functional outcomes.
Design: Single-center, prospective, randomized-controlled, and double-blind study
Setting: Health Sciences University, Bursa Yuksek Ihtisas Training and Research Hospital, Bursa, Turkey
Subjects: Patients who underwent unilateral TKA were included the study.
Intervention(s): The patients were divided into two groups: epidural morphine (Group E) and periarticular injection including 100 mL cocktail solutions (bupivacaine, adrenaline, dexmedetomidine, magnesium sulphate, methylprednisolone, morphine and normal saline) (Group P).
Main outcome measure(s): Our primary outcomes were visual analogue scale (VAS) pain scores, dynamic visual analogue scale (DVAS) pain scores, and consumption of analgesics. Secondary outcomes were maximum range of motion (ROM) and side effects.
Results: A total of 24 and 27 patients were analyzed in Group P and Group E, respectively. Group P had significantly lower VAS and DVAS scores within the first 48 hours, lower amount of consumed analgesics at 24 and 48 hours, higher ROM values on days 2 and 3, and more severe nausea, vomiting and itching at 12 and 24 hours.
Conclusion: Our study results show that periarticular injection with multi-modal drugs in TKA is superior to epidural analgesia with lower VAS-DVAS scores, less analgesic consumption, fewer side effects and improved ROM.

KEY WORDS: dexmedetomidine, epidural analgesia, magnesium sulfate, morphine, periarticular injection

INTRODUCTION

Total knee arthroplasty (TKA) is one of the frequent major orthopedic surgeries[1]. Postoperative pain is a major concern for patients and can directly affect functional recovery[2,3]. In the postoperative period, good pain control increases patient satisfaction, facilitates rehabilitation, and shortens the length of hospital stay[3]. Early mobilization also decreases the risks of complications, such as deep venous thrombosis, pulmonary embolism, pneumonia and urinary retention. Early rehabilitation can also be possible with early recovered maximum range of

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motion (ROM) postoperatively[4]. Analgesia following TKA is usually multi-modal and involves the use of intravenous opioids, peripheral nerve block, epidural analgesia, joint or synovial opioid or local anesthetics injection and use of oral analgesics[1,3,5]. Although there is no consensus yet on what the gold standard for postoperative pain is[6], there has been a tendency toward multi-modal approaches with regional anesthesia to minimize opioid consumption and to avoid side effects associated with opioids[7]. Post-TKA liposomal bupivacaine has also been in use in recent years[8]. Several prospective studies have demonstrated that liposomal bupivacaine neither improves the quality of postoperative pain, nor improves the quality of recovery in these patients[8,9].

In the present study, we aimed to compare the effect of epidural morphine analgesia and periarticular injection on postoperative pain, analgesic consumption and early period ROM following TKA.

SUBJECTS AND METHODS

Patients

A written informed consent was obtained from each patient. The study protocol was approved by the Local Ethics Committee and Australian New Zealand Clinical Trials Registry (Ref: ACTRN12616000226404). The study was conducted in accordance with the principles of the Declaration of Helsinki. This single-center, prospective, randomized-controlled, and double-blind study included a total of 60 patients who were older than 18 years old and underwent unilateral TKA with a knee prosthesis due to primary varus knee osteoarthritis. Exclusion criteria were as follows: being allergic to the drugs used, previous knee surgery or bilateral total knee prosthesis, severe liver and kidney failure, stroke, coronary heart disease, cognitive impairment, being uncooperative or under chronic opioid treatment, a body mass index of >40 and regional anesthesia contraindication. Patients in whom an epidural catheter was unable to be placed, who developed epidural catheter migration, in whom general anesthesia was switched, who had cardiopulmonary arrest, and whose postoperative epidural catheter dislocated were also excluded (Figure 1). All patients were randomly divided into two groups using a sealed envelope system. Patients and the anesthesiologist who evaluate postoperative pain were blinded to the study.

Anesthesia management

For premedication, 0.01-0.02 mg/kg IV midazolam (Zolamid®, Defarma, Ankara, Turkey) was administered. An 18G Touhy needle (Epifix Standart®, Egemen, Izmir, Turkey) was placed into the L_{3-4} or L_{4-5} interval spaces at the middle in the sitting position to reach the epidural space with loss of resistance method. The catheter was then advanced through a 27G Quinke spinal needle into the subarachnoid space and bupivacaine 3 mL 0.5% spinal heavy (Spinal Heavy Bustesin®, Vem, Ankara, Turkey) was administered intrathecally. The epidural catheter was advanced 4-5 cm further. Following spinal anesthesia, sensory block level was determined by pinprick test, and motor block level was determined by the Bromage score (Grade 0: no motor block; Grade 1: inability to raise extended leg, able to move knees and feet; Grade 2: inability to raise extended leg and move knee, able to move feet; Grade 3: complete block of motor limb). The surgical procedure was initiated, when the sensory block reached T_{10} level and Bromage score was 2.

Surgery management

All operations were performed by a single surgeon. All operations were conducted under pneumatic tourniquet. The tourniquet pressure was set to a level that it would be 150 mmHg higher than the systolic blood pressure of the patient. An anterior incision approach was used in all patients. To reach the joint, medial parapatellar arthrotomy was performed. Then, in accordance with the technique which was described by Sahin *et al*[10], a cemented posterior-stabilized and fixed-insert total knee prosthesis (GENESIS II, Smith & Nephew Inc. Memphis, USA) was applied in all patients. A drain was placed in all patients postoperatively.

Procedure of periarticular analgesia (Group P, n=30)

A cocktail of 100 mL containing 20 mL of 0.5% bupivacaine (Bustesin®, Vem, Ankara, Turkey), 0.6 mL of 1 mg/mL of adrenaline (Adrenalin®, Oesel, Istanbul, Turkey), 1 mL of 100 μg/mL dexmedetomidine (Precedex®, Meditera, Izmir, Turkey), 4 mL of 8.4% magnesium sulphate (Magnezyum Sulfat®, Biofarma, Istanbul, Turkey), 4 mL of 10 mg/mL methylprednisolone (Prednol-L®, Mustafa Nevzat, Istanbul, Turkey), 0.5 mL of 10 mg/mL morphine (Morphine HCl®, Galen, Istanbul, Turkey), and 69.9 mL normal saline solution were prepared into two of 50 mL injectors. In the administration of injections, the areas with increased neurosensory and mechanoreceptors were selected, as described by Dye *et al*[11] based on the technique described by Guild *et al*[12], 60 mL of the solution was administered to the medial retinaculum, medial collateral ligament, medial meniscocapsular component, at the attachment site of posterior cruciate ligament to tibia, at the attachment site of the anterior cruciate ligament to femur, lateral retinaculum, lateral collateral ligament and lateral meniscocapsular junction, following the tibial and femoral incisions. The injection was applied to each spot at one time not to exceed 2-3 mL and to avoid

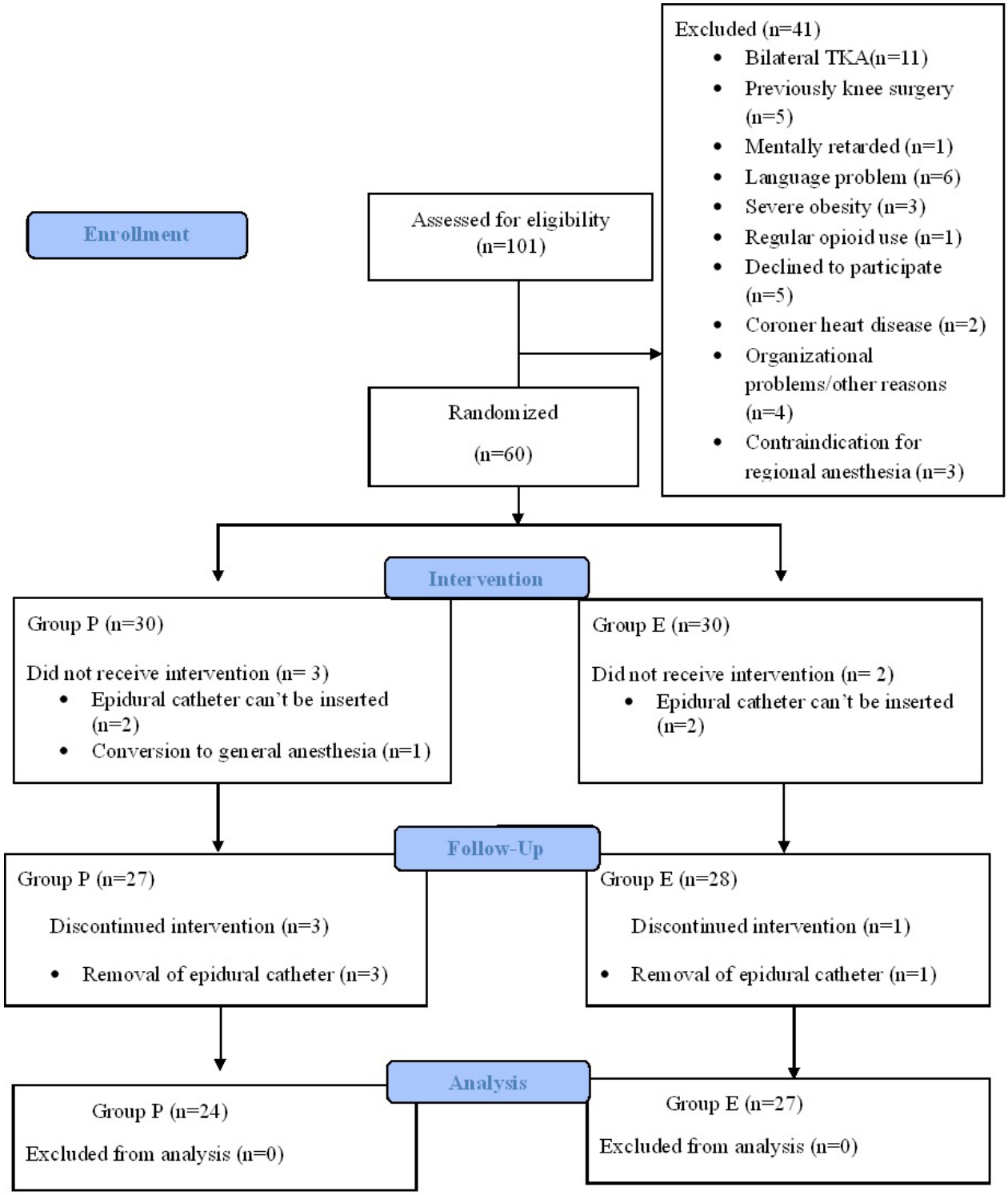
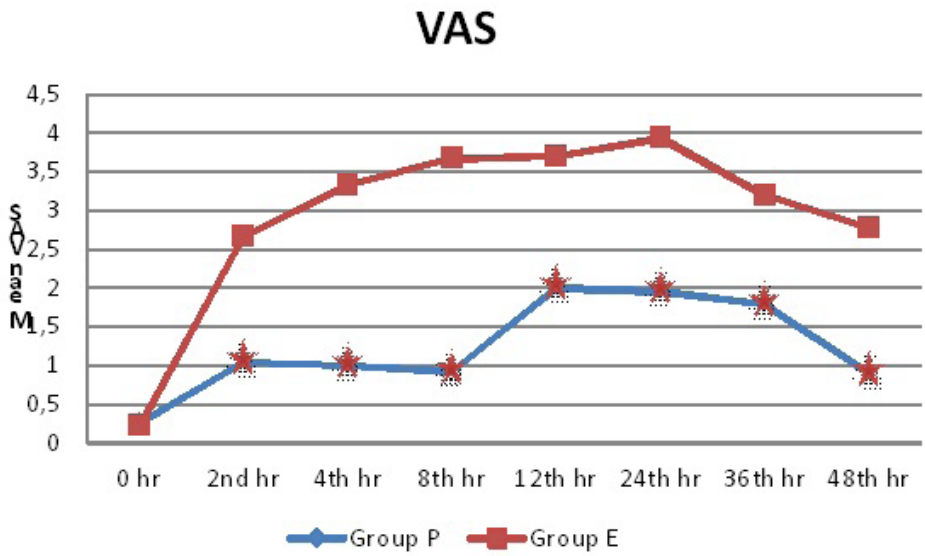


Fig 1: Trial flow diagram

overflowing of the active ingredient from the soft tissue. Following placement of the tibial and femoral components, the remaining 40 mL of the cocktail was administered to the suprapatellar pouch, quadriceps tendon, patellar tendon and patellar fat pad.

Epidural analgesia management (Group E, n=30)

A total of 10 mL solution containing 3 mg morphine (3 mL) and normal saline was administered from the epidural catheter to all patients, before the incision was closed.



*p<0.05

Fig 2: Mean values of visual analogue scale (VAS) according to groups

Postoperative analgesia management

A patient-controlled epidural analgesia (PCEA) (CADD-Legacy® PCA, Smiths Medical, St Paul, USA) device was connected for 48 hours. A total of 160 mL of epidural solution containing 40 mL of 0.5% bupivacaine + 10 mL of 500 μg of fentanyl + 110 mL of 0.9% NaCl was prepared. Without basal infusion, the bolus dose was set at 10 mL, the lock duration was set at 20 minutes, and the hourly limit was set at 30 mL. A special program for postoperative rehabilitation was not performed, and all patients were instructed to do knee ROM exercises as much as they could tolerate pain. In the first postoperative day, all patients were mobilized with full load and with the assistance of a walker.

Primary outcomes

To evaluate the postoperative pain level, the visual analogue scale (VAS) (where 0=no pain, 10=worst imaginable pain) was used at rest, while the dynamic VAS (DVAS) was used to evaluate pain during exercise. Postoperative pain was assessed at 2, 4, 8, 12, 24, 36, and 48 hours by another anesthesiologist. Tramadol HCl (Tramosel®, Haver, Istanbul, Turkey) 50 mg IV was administered as a rescue analgesic in patients with a VAS score of >3 whose pain did not relieve, despite bolus dosing. Total analgesic consumption and rescue analgesic doses were also added for 48 hours.

Secondary outcomes

Patient characteristics were recorded. Of the patients, total ROM between the active maximal flexion and maximal extension was evaluated on postoperative 1, 2 and 3 days, and complications which developed within 48 hours were also noted. Requirement for rescue analgesia and side effects, including nausea, vomiting and itching during 48h follow-up were also evaluated.

Statistical analyses

The power calculation for the present study is based on an effect size of 0.75 with an alpha (α) value of 0.05. The required sample size to obtain a power of 0.8 under these assumptions was 23 for each group. Statistical analysis was performed using SPSS version 21.0 software (Statistical Package for the Social Sciences, Armonk, NY, USA). The Shapiro-Wilk test was used to analyze normal distribution of the data. T-test was used to compare two groups with normally distributed data, while the Mann-Whitney U test was used to compare more than two groups with abnormally distributed data. The Wilcoxon sign-rank test was used to compare the dependent samples. In the analysis of repeated measures, percentage changes from baseline were calculated and compared using these values. The Pearson's chi-square, Fisher's exact chi-square, and Fisher-Freeman-Halton tests were used to analyze categorical data. A *P*-value of 0.05 was statistically significant.

RESULTS

Of the 60 patients included in the study, 51 were evaluated (Figure 1). There was no significant difference in demographic characteristics between the two groups (Table 1).

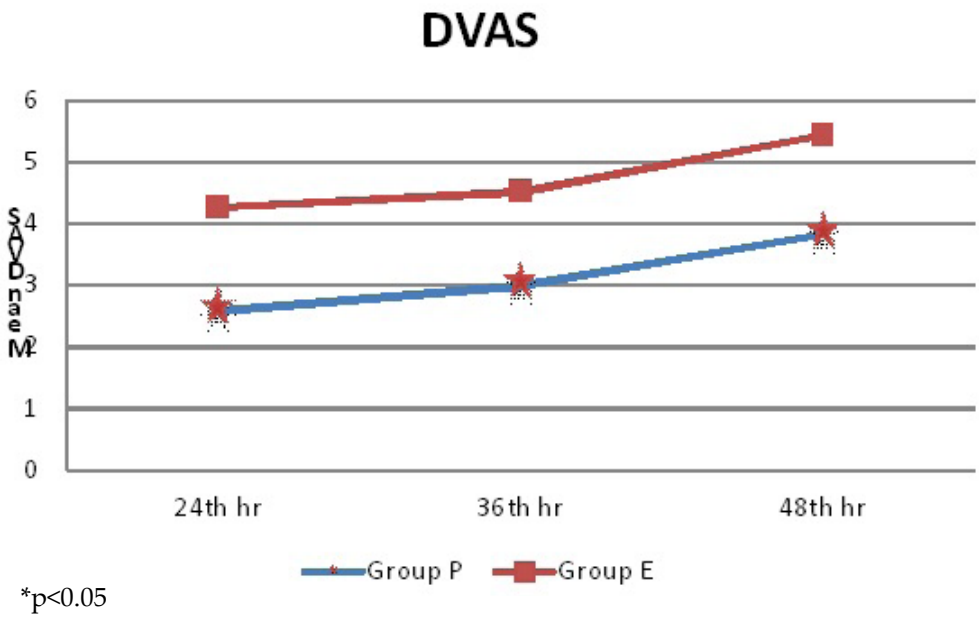


Fig 3: Mean values of dynamic visual analogue scale (DVAS) according to groups

The VAS scores in Group P were significantly lower than the baseline during the first 48 hours (P <0.05; Figure 2). The DVAS scores at 24, 36, and 48 hours were also significantly lower in Group P (P <0.05; Figure 3). The amount of analgesics consumed with the PCEA device was significantly lower in Group P during 48 hours (P <0.05; Table 2). The need for rescue analgesics were not significantly between the two groups (P >0.05; Table 2).

There was no significant difference in the ROM values on first day (P >0.05), however, the ROM values were significantly higher on days 2 and 3 in Group P (P <0.05; Table 3).

The rate of nausea, vomiting and itching at 12 and 24 hours was significantly higher in Group E (P <0.05; Table 4).

Table 1: Patient characteristics

Patient characteristics	Group P (n=24)	Group E (n=27)	*P*
Age (year)*	65.92±7.30	66.56±7.88	0.766
Sex (female) **	19 (79.2)	20 (74.1)	0.669
Height (cm)*	163.17±5.88	162.19±7.23	0.601
Weight (kg)*	77.71±13.22	74.15±10.37	0.287
ASA			0.707
I	3 (12.5)	5 (18.5)	
II	21 (87.5)	21 (77.8)	
III	0	1 (3.7)	

*mean ± standard deviation; **n(%)
ASA: American Society of Anesthesiology

Table 2: Range of motion according to groups

Range of motion	Group P (n=24)	Group E (n=27)	*P*
1st day*	96.04±13.18	100.56±13.61	0.236
2nd day*	103.33±13.40	100.93±10.83	0.001
3rd day*	107.08±9.43	104.07±10.09	0.002

*mean ± standard deviation

Group P significantly predicted overall mean VAS scores (P <0.001) while the age, sex and body mass index were not significant (Table 5).

DISCUSSION

In this prospective, randomized trial, we evaluated the efficacy of epidural analgesia and single administration of a multi-modal periarticular injection for pain control following TKA. In the periarticular injection group, the VAS and DVAS scores were significantly lower within the first 48 hours, the amount of epidural analgesics consumed at 24 and 48 hours were significantly lower, the ROM values on days 2 and 3 were significantly higher, and nausea, vomiting and itching at 12 and 24 hours were significantly lower.

Currently, several pain control modalities are in use for the management of TKA; however, opioids and patient-controlled analgesia morphine are the main compounds in primary postoperative relief thanks to their efficacy in relieving moderate-to-severe pain[13]. However, their sole use has been falling out of favor

Table 3: Analgesic usage profile of the groups

Analgesic usage profile	Group P (n=24)	Group E (n=27)	*P*
Amount of consumed analgesics (ml)*			
0-24 hours	147.91±26.20	171.85±32.82	0.006
24-48 hours	133.75±33.98	160.74±33.38	0.003
Requirement of rescue analgesics**	2 (8.3)	7 (25.9)	0.100

*mean±standard deviation; **n(%)

due to their potential side effects and intolerance, particularly in the elderly population with multiple comorbidities[14]. Epidural analgesia including opioids and local anesthetic agents were suggested as the gold standard for postoperative pain control by Bromage *et al*[15]. In a meta-analysis comparing epidural analgesia and paranteral opioids, it was shown that epidural analgesia provided better pain control for all surgical types[16]. However, lumbar epidural analgesia has been also associated with poor postoperative mobility and complications, such as epidural hematomas and perioperative hypotension[13,17]. In today's practice, periarticular injection is frequently used for pain management at the surgical site of TKA to avoid potential complications of other nerve blocks[13].

Table 4: Side effects

Side effects	Group P (n=24)	Group E (n=27)	*P*
Nausea*			
12th hour	4 (16.7)	21(77.8)	<0.001
24th hour	2(8.3)	15(55.6)	<0.001
48th hour	0(0)	2(7.4)	0.492
Vomiting*			
12th hour	2(8.3)	18(66.7)	<0.001
24th hour	1(4.2)	10(37)	0.004
48th hour	0(0)	0(0)	
Itching*			
12th hour	1(4.2)	21(77.8)	<0.001
24th hour	1(4.2)	18(66.7)	<0.001
48th hour	0(0)	4(14.8)	0.113

*n(%)

In the literature, agents used in periarticular injections vary, and the amounts of cocktail ranges between 20 and 150 mL[18-24]. In our study, we used 100 mL of cocktail. To maximize the benefit from the combination effect of the drugs, we used bupivacaine, adrenaline, dexmedetomidine, magnesium sulphate, methylprednisolone and morphine combination. To the best of our knowledge, there are few studies on the periarticular use of dexmedetomidine and magnesium[22,23]. We, therefore, believe that our study contributes to the literature data, as this is the first study which combined dexmedetomidine and magnesium sulphate in the periarticular use.

Table 5: Multivariable regression analysis results for overall average VAS pain scores

VAS pain scores	Coefficients	*P*
Age	0.044	0.711
Male versus female	0.026	0.818
Body mass index	-0.100	0.378
Group P versus Group E	0.709	<0.001

VAS: visual analogue scale

Tsukada *et al*[25] compared periarticular injection with epidural anesthesia. They administered ropivacaine (200 mg) and morphine infusion (8 mg) in the epidural analgesia group and 60 mL of cocktail (ropivacaine, morphine, epinephrine, methylprednisolone, ketoprofen and saline) in the periarticular injection group. In the aforementioned study, significant difference was observed between the VAS scores, and no significant difference was observed between the DVAS scores and the use of rescue analgesics during the first three days[25]. Our results are different from these results. In the study comparing epidural analgesia (ropivacaine infusion) with intraarticular analgesia (intraarticular infusion after incision site infiltration) by Andersen *et al*[24], the VAS and DVAS scores and morphine consumption were found to be significantly higher in the epidural group during 72 hours. Our results are consistent with these results. However, contrary to our study, the aforementioned authors performed intraarticular infusion and evaluated morphine consumption. In the regression analysis of another study, postoperative pain scores after TKA were found to be higher in females and younger patients[26]. In our study, these two variables were not found to be significantly correlated, while only Group P variables were significant. In a study comparing epidural analgesia (bupivacaine + fentanyl) and intraarticular infusion (bupivacaine + ketorolac), there was no significant difference in the VAS scores during 48-hour follow-up[27]. In addition, Niemelainen *et al*[20] compared the periarticular injections containing 100 mL multi-drug medications and those containing 100 mL of saline. The multi-drug injected group required significantly less morphine for 48 hours. In our study, 48-hour analgesic consumption was found to be significantly lower in the periarticular group. In a meta-analysis carried out by Teng *et al*[28], periarticular injection with multi-modal drugs significantly improved pain relief and straight leg raise in the early postoperative period.

On the other hand, the majority of previous studies in the literature were not designed as blinded studies[24,25,27]. One of the strengths of our study is,

therefore, that it was carried out as a double-blind study. Since the PCEA was applied to all patients, the investigator who evaluated postoperative pain remained blind to the study.

In a study comparing epidural morphine and periarticular injection, nausea was significantly lower on postoperative 24 hours in the periarticular group, although no significant difference in complications on other days was observed[25]. In our study, nausea, vomiting and itching were significantly higher at 12 and 24 hours in the epidural analgesia group, unlike the aforementioned study. Andersen *et al*[24] compared intraarticular and epidural analgesia, and did not report any toxic symptoms associated with local anesthesia. There is also a meta-analysis reporting complications such as nausea and vomiting due to epidural analgesia[16]. In another study comparing epidural analgesia and intraarticular infusion, hypotension, paresthesia and abdominal distension were observed more often in the epidural group[27]. Tsukada *et al*[25] reported the rate of transient peroneal nerve palsy was higher in the periarticular injection group. In our periarticular group, there was no transient peroneal nerve palsy.

Furthermore, a study comparing epidural morphine and periarticular injection showed that flexion motion significantly improved in the periarticular injection group, although there was no significant difference in the extension angle[25]. Milani *et al*[18] compared the patients who were administered periarticular injection with ropivacaine and those with no periarticular injection, and found no significant difference in the ROM values between the two groups. In a study comparing epidural analgesia and intraarticular injection, the patients with intraarticular infusion were able to stand up earlier[27]. In addition, in a study comparing periarticular injections with levobupivacaine and the control group in which periarticular injection with saline was used, there was significant difference in the ROM values at 6 hours, but not at 24 and 48 hours[20]. In our study, the ROM values on 48 and 72 hours were significantly higher in the periarticular injection group.

Limitations

Nonetheless, this study has some limitations. First, plasma concentrations of bupivacaine could not be measured. Secondly, the results of this study are only limited to patients undergoing regional anesthesia and are unable to be generalized for general anesthesia procedures. Third, it is inadequate to provide information on the long-term effects of analgesia methods used. The effects of acute pain relief following TKA on chronic pain and functional outcomes at one year can be the subject of another study.

CONCLUSION

Our study results show that as postoperative multi-modal analgesia in TKA, periarticular injection provides less complication and improved pain control with improved ROM than epidural analgesia. Therefore, we suggest that the multi-modal drug periarticular injection is an effective and safe method for postoperative analgesia in TKA.

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Conflict of interest: None

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Original Article

Hybrid surgical resection for ruptured intracranial arteriovenous malformation in the acute stage: A report from a single center

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ABSTRACT

Objective: To investigate the advantages of intracranial arteriovenous malformation (AVM) treatment in a hybrid operating room (OR)
Design: Retrospective analyses of prospectively recorded data
Setting: Department of Neurosurgery, The First Hospital of Jilin University, Jilin Province, China
Subject: We continuously collected the data of 15 AVM patients treated with surgical resection assisted by intraoperative digital subtraction angiography (DSA).
Intervention: The AVM treatments were divided into two categories: in Type I, intraoperative DSA was mainly used to embolize difficult-to-expose feeding arteries and part of the AVM to reduce intraoperative bleeding. In Type II, intraoperative DSA was mainly used to simplify determination of the AVM position and check for residuals after surgical removal.
Main outcome measure: The Hunt-Hess (HH) scale was used to determine the preoperative patient status. The prognosis was evaluated with the Glasgow Outcome Scale (GOS).
Results: The distribution of patients according to the HH scale was as follows: grade I in one case, grade II in 11 cases and grade III in three cases. In seven patients with Type I AVM, the AVM was completely removed after embolization. In eight patients with Type II AVM, DSA confirmed complete removal of the AVM. Ten patients had a GOS score of 5 points, and five patients had a score of 4 points.
Conclusions: DSA is the most promising method to surgically remove an AVM in a hybrid OR. AVMs can reasonably be classified as Type I and Type II for further treatment.

KEY WORDS: arteriovenous malformation, embolization, hybrid operating room, resection

INTRODUCTION

Intracranial arteriovenous malformation (AVM) is a type of neurosurgical disease that is difficult to treat, especially when the AVM ruptures[1]. Endovascular embolization is an option for treatment of a ruptured AVM, but the AVM may subsequently show hemodynamic changes and redistribution of blood flow, creating the possibility of AVM hemorrhage[2]. Therefore, resection is the most radical method for ruptured AVM treatment. However, for large AVMs, direct surgical removal is very risky, while for small AVMs, which are sometimes diffuse or difficult to localize, the procedure is prone to residuals[3]. Hence, if the treatment of an intracranial AVM is carried out in a hybrid operating room (OR) with digital subtraction angiography (DSA), the disadvantages of surgical resection of the intracranial AVM can be minimized[4,5]. To date, there have been few studies investigating hybrid operation for ruptured AVMs in hybrid ORs; therefore, this study retrospectively summarized 15 patients treated in a single center, classified the treatments according to the different roles of DSA, and reported the quality of the results.

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SUBJECTS AND METHODS

Approval was obtained from the ethics committee of the First Hospital of Jilin University.

General information

This study included 15 intracranial AVM patients who were treated at the Neurosurgery Department of the First Hospital of Jilin University since January 2016, all of whom were treated in a hybrid OR using DSA. Among them, nine patients were males and six were females; the ages of the subjects ranged from 4 to 54 years (27.8 years on average). Computed tomography (CT) examination after onset showed that the 15 patients included nine patients with onset of intracerebral hematoma, two patients with intracerebral hematoma rupture into the ventricle, three patients with ventricular hemorrhage, and one patient without hemorrhage but with headache. The patients were classified on the Hunt-Hess scale as follows: grade I in one case, grade II in 11 cases, and grade III in three cases.

Imaging examination

CT angiography and Xper-CT DSA (Philips Healthcare, Netherlands) were used to observe the AVM site and the relationship between the AVM and hematomas. DSA examination was also used to observe the anterior and posterior circulation, identify the arteries supplying the AVM and the presence/absence of aneurysms, and verify the drainage vein.

Among the 15 patients, the AVM site was located in the frontal lobe in four cases, the fronto-parietal lobes in two cases, the temporal lobe in three cases, the temporo-parietal lobes in one case, the parietal lobe in two cases, the parieto-occipital lobes in two cases, and the occipital lobe in one case. Additionally, among the 15 patients, four exhibited aneurysms on the feeding arteries. The Spetzler-Martin (SM) grades for the 15 AVMs were as follows: 1 point in seven cases, 2 points in five cases and 3 points in three cases.

Treatment classification

During resection of the AVM in the hybrid OR, after assessing the AVM angioarchitecture, a decision was made regarding whether intraoperative embolization of the AVM was necessary. When AVMs with SM grades of 2-3 have large feeding arteries, control of the feeding arteries to prevent intraoperative bleeding may be difficult, and intraoperative embolization may be necessary. However, for SM grade 1-2 AVMs that are small, diffuse and deep, their feeding arteries should be easy to control, but DSA is necessary to determine the position of the AVM. Therefore, AVM hybrid surgical resection can be divided into two categories: in Type I, intraoperative DSA is mainly used to embolize difficult-to-expose feeding arteries and part of the AVM to reduce the intraoperative bleeding. In Type II, intraoperative DSA is mainly used to simplify determining the position of the AVM and checking for residuals after surgical removal.

Postoperative treatment and follow-up

Patients were given symptomatic treatments after surgery. The patients were followed up at approximately half a year after surgery and evaluated using the Glasgow Outcome Scale.

RESULTS

Classification results and treatments

The Type I group included seven cases, with an SM grade of 2 points in four cases and 3 points in three cases. The Type II group included eight cases, with an SM grade of 2 points in one case and 1 point in seven cases. In the Type I group, one patient exhibited cortical and perforating feeders to the AVM, and six patients had only cortical feeders. In the Type II group, four patients had cortical and perforating feeders to the AVM, and four patients had cortical feeders.

After admission, when preoperative preparation was sufficient, treatment was arranged. The interval between onset and treatment ranged from 8 to 72 hours (19.9 hours on average). Among seven patients with Type I AVM, two patients achieved 30% embolization with Onyx gel (Medtronic Neurovascular, Minneapolis, MN), two patients had 40% embolization, one patient had 60% embolization, and two patients had 80% embolization. DSA examination showed that all AVMs were completely removed after embolization. Eight patients with Type II AVM underwent multiple DSA examinations during resection, which confirmed complete removal of the AVM.

AVM treatments combined with aneurysm of a feeding artery

Among the 15 patients, four had combined aneurysms: in two cases, the aneurysms were close to the AVM and were embolized with Onyx gel during AVM embolization; in one case, the aneurysm was located at the beginning part of feeding artery and was clipped while the AVM was being resected; and in one case, the aneurysm was located at the anterior communicating artery and was small, regular in shape and far from the AVM; therefore, regular follow-up was performed.

Follow-up results

The follow-up duration was 6-12 months (average: 9.1 months). Regarding the Glasgow Outcome Scale, ten patients had a score of 5 points, and five patients had a score of 4 points. The treatments and follow-

Table 1: Summary of clinical data

Types	No.	Age/ Gender	Onset	HH grade	AVM site	SM grade	Arterial feeders	Accompanying aneurysm	Interval between onset and treatment	AVM embolization	Treatment of aneurysm	Follow-up	GOS
Type I	1	48/M	IH	II	L frontal lobe	3	Multiple cortical branches of the ACA and MCA	--	24 hours	30% embolization with Onyx gel	--	12	5
	2	50/M	IH	II	L occipital lobe	2	Three cortical branches of the PCA	--	12 hours	80% embolization with Onyx gel	--	12	5
	3	29/F	IVH	II	L fronto-parietal lobe	3	Multiple cortical and perforating branches of the ACA and MCA	An aneurysm on the feeding artery	16 hours	40% embolization with Onyx gel	Embolization with Onyx gel	8	4
	4	54/M	IH	II	L temporal lobe	2	Three cortical branches of the MCA	--	38 hours	40% embolization with Onyx gel	--	6	5
	5	54/M	IH	II	R temporal lobe	2	Multiple cortical branches of the MCA	--	8 hours	30% embolization with Onyx gel	--	6	5
	6	15/M	IH	III	R temporo-parietal lobe	3	Multiple cortical branches of the MCA	A small AcomA aneurysm	15 hours	60% embolization with Onyx	Follow-up	9	4
	7	16/F	IH	III	L frontal lobe	2	Multiple cortical branches of the ACA	An aneurysm on the feeding artery	9 hours	80% embolization with Onyx gel	Embolization with Onyx gel	8	4
Type II	1	54/M	Headache	I	R frontal lobe	2	Three cortical branches of the ACA	An aneurysm on the feeding artery	72 hours	No	Clipping	12	5
	2	18/M	IH and IVH	II	R fronto-parietal lobe	1	Two cortical and perforating branches of the MCA	No	12 hours	No	--	12	4
	3	9/F	IH	II	R parieto-occipital lobe	1	Two cortical branches of the MCA and PCA	No	18 hours	No	--	6	5
	4	9/M	IH and IVH	II	L parieto-occipital lobe	1	Three cortical and perforating branches of the MCA and PCA	No	26 hours	No	--	9	5
	5	7/F	IH	II	R temporal lobe	1	Two cortical branches of the MCA	No	15 hours	No	--	10	5
	6	40/F	IVH	III	L parietal lobe	1	Multiple cortical and perforating branches of the MCA	No	17 hours	No	--	8	4
	7	4/M	IH	II	R frontal lobe	1	Four cortical branches of the ACA	No	8 hours	No	--	7	5
	8	10/F	IVH	II	R parietal lobe	1	Two cortical and perforating branches of the MCA	No	9 hours	No	--	12	5

ACA: anterior cerebral artery; AcomA: anterior communicating artery; AVM: arteriovenous malformation; F: female; GOS: Glasgow Outcome Scale; HH grade: Hunt-Hess grade; IH: intracerebral hemorrhage; IVH: intraventricular hemorrhage; L: left; M: male; MCA: middle cerebral artery; PCA: posterior cerebral artery; R: right; SM grade: Spetzler-Martin grade

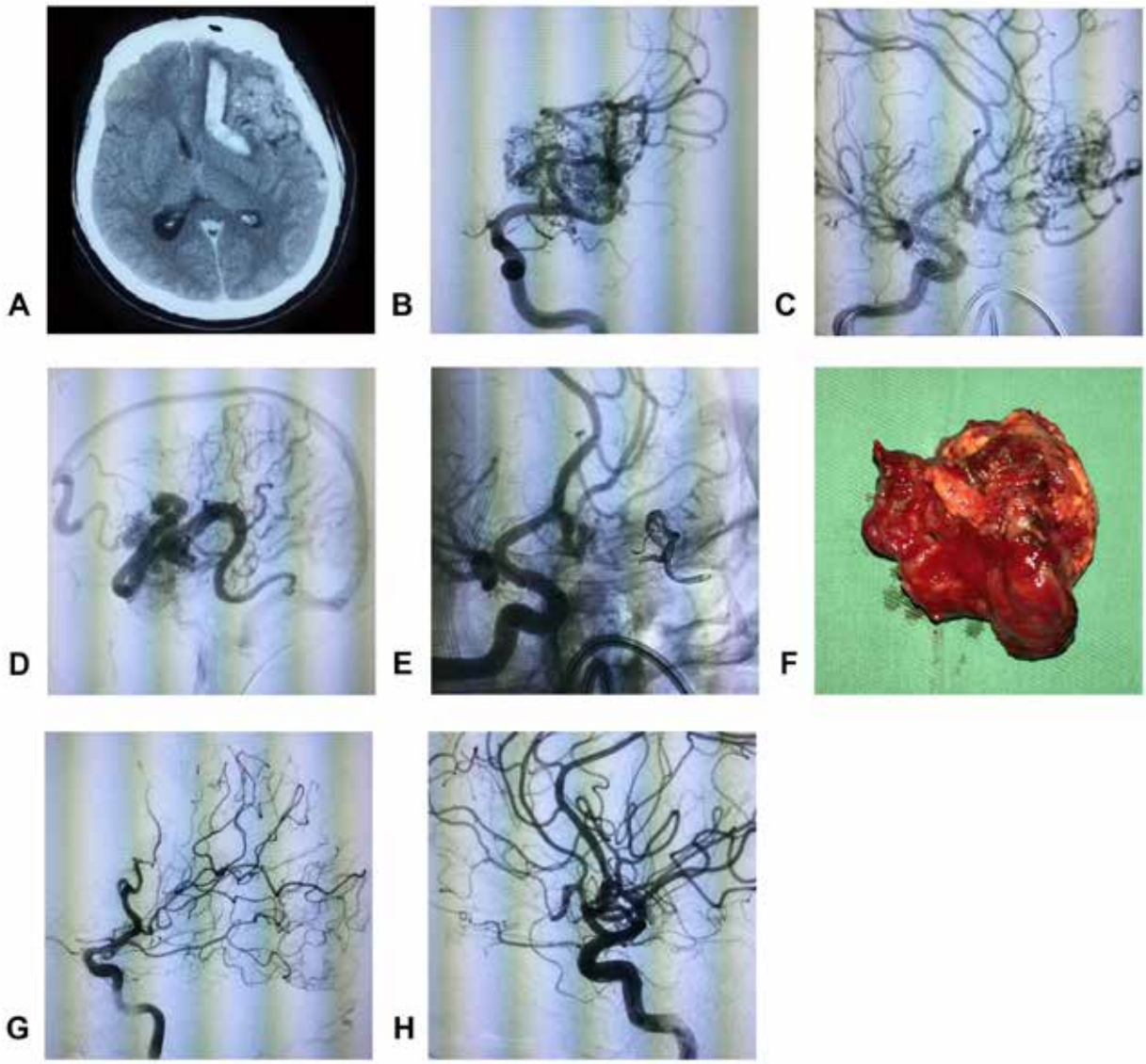

Fig. 1: Image of Case 1 (Type I) **A**: A head CT image of the left frontal lobe revealed abnormal density, uniform and slightly high density in the lateral side, a band-shaped pattern of hemorrhage on the medial side, and a deformed anterior angle of the lateral ventricle due to compression; **B-D**: Head DSA showed an AVM of the left frontal lobe with a blood supply from the middle cerebral artery and anterior cerebral artery; the drainage vein ran forward into the sagittal sinus and backward to the transverse sinus through the intravenous drainage of the Sylvian fissure; **E**: Onyx gel was used to embolize a part of the AVM that received its blood supply from the anterior cerebral artery, and the embolism accounted for approximately 30% of the AVM; **F**: Gross specimen after surgical removal of the AVM; **G-H**: Postoperative DSA showed total resection of the AVM, with no residual.

up results are shown in Table 1, and typical cases are shown in Figures 1-4.

DISCUSSION

Intracranial AVM is one of the most difficult cerebrovascular diseases to treat. Due to their rich blood flow, large AVMs with multiple blood supply arteries are prone to bleeding during surgical resection. Additionally, in the case of small and diffuse AVMs, accurate positioning and complete removal during the operation can also be difficult[6-8]. Endovascular embolization is a safe procedure, but complete embolization of the AVM is difficult[9,10]. Therefore, a combination of the two methods should be used to improve treatment for AVMs[11]. Currently, there are few studies on hybrid surgery for intracranial AVM[12]. Therefore, this paper summarized the experiences of 15 patients with intracranial AVM treated with hybrid surgical resection in our center. The treatments were classified into two types according to the role of intraoperative DSA in effective hybrid surgical resection, and good curative effects were achieved.

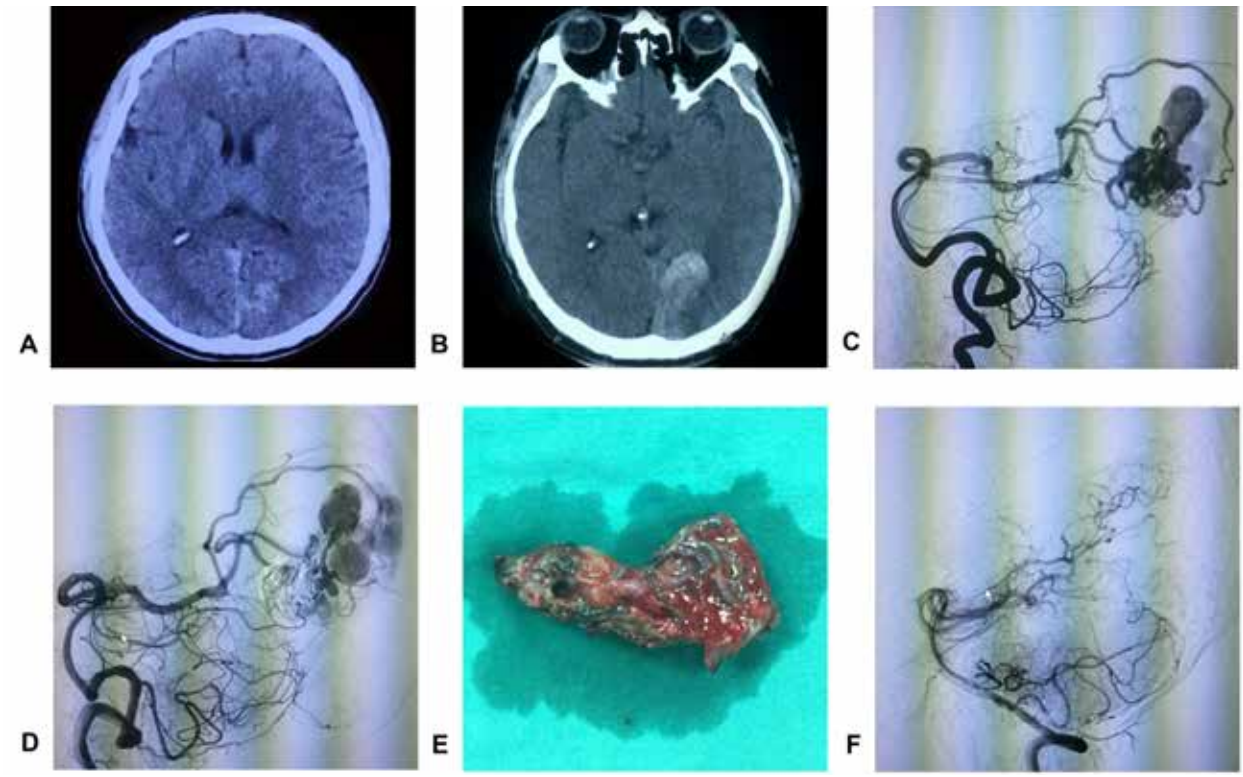

Fig 2: Image of Case 2 (Type I) **A**: A CT image at 6 months before onset showed a slightly high hybrid density shadow in the left occipital lobe, without rupture of the AVM; **B**: CT at onset showed a ruptured and hemorrhaging AVM in the occipital lobe; **C**: DSA showed that the AVM was supplied by multiple branches of the left cerebral posterior artery and drained to the transverse sinus; venous expansion was observed in the drainage vein; **D**: Onyx gel was used to embolize the AVM nidus, and the embolism accounted for approximately 80% of the AVM; **E**: Specimen after surgical removal of the AVM; **F**: Postoperative DSA showed total resection of the AVM, with no residual.

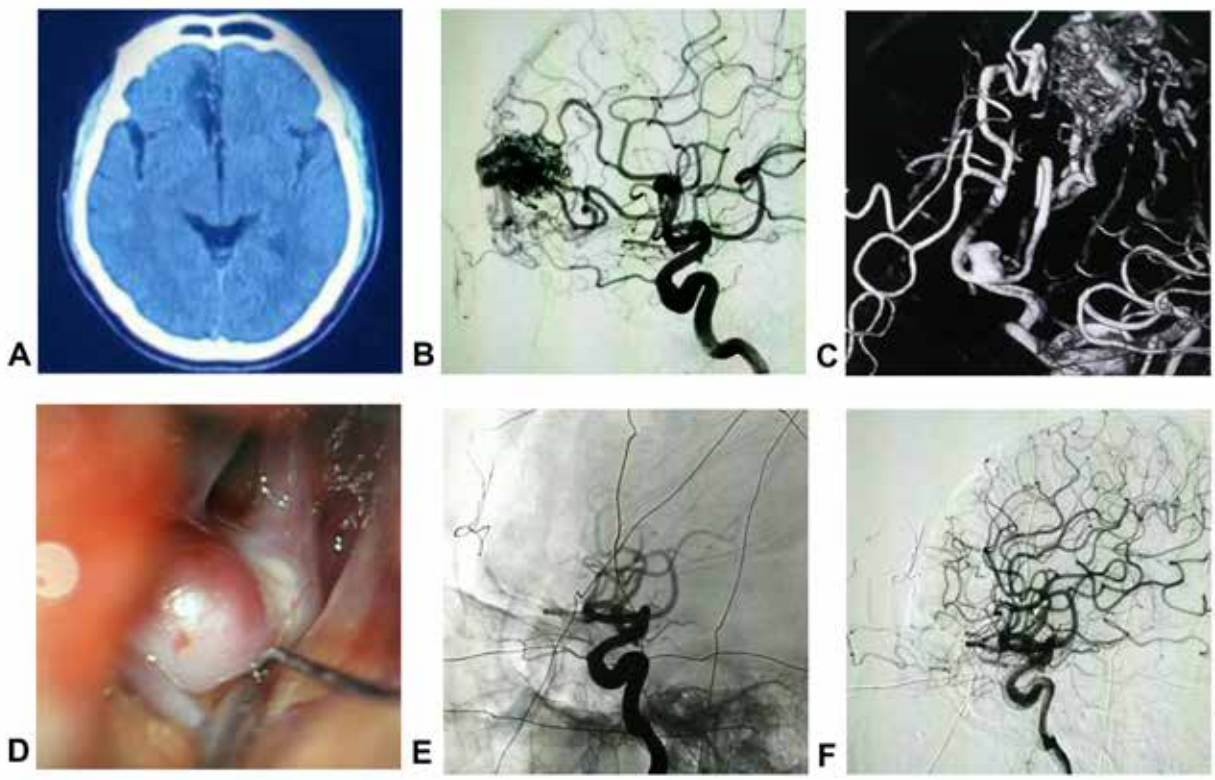

Fig 3: Image of Case 1 (Type II) **A**: Head CT showed low density in the right medial frontal lobe and what was considered a softened focus due to past hemorrhage; **B-C**: DSA and 3D reconstruction showed a frontal lobe AVM, which was mainly supplied by a branch of the anterior cerebral artery, and a berry aneurysm was observed at the beginning of the blood supply artery; **D**: A longitudinal fissure approach was adopted, and the aneurysm was located the beginning of the blood supply artery during the operation and then clipped; **E-F**: Postoperative DSA showed total resection of the AVM, and the artery was completely clipped.

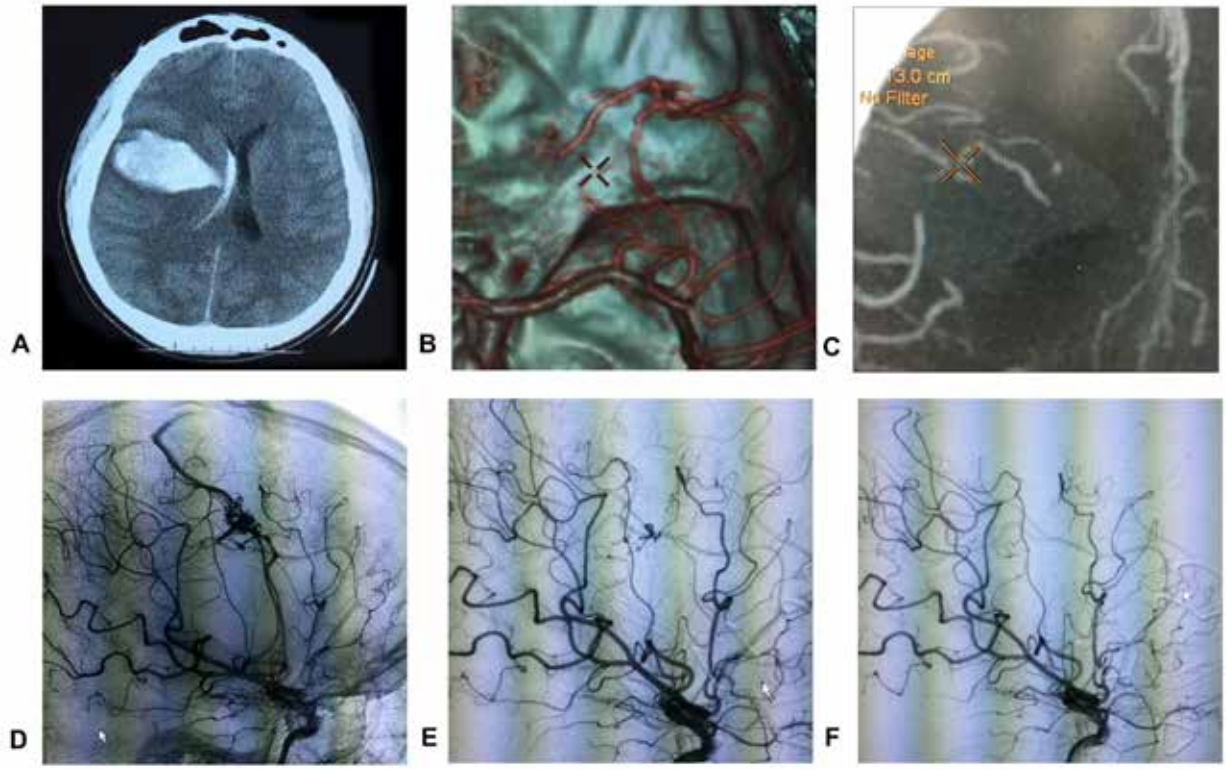

Fig 4: Image of Case 2 (Type II) **A**: Head CT showed right frontal-parietal hemorrhage into the lateral ventricle; **B-C**: CTA and maximum intensity projection (MIP) showed an AVM located above the intracerebral hematoma and supplied by the cerebral middle artery; **D**: Preoperative DSA showed that the AVM was supplied by the middle cerebral artery and that the drainage vein ascended into the sagittal sinus; **E**: A residual AVM was observed during resection; **F**: DSA after resection showed total resection of the AVM.

DSA can play different roles in hybrid surgery. Although early DSA can provide only intraoperative imaging for AVMs due to the limitations of the equipment and neurosurgical intervention technology, the technique could nonetheless be very convenient for surgical resection of AVMs[13]. Munshi *et al* reported a study of intraoperative DSA on 25 patients with intracranial AVMs in 1999. In that study, DSA after AVM resection showed residual AVMs in two cases, suggesting the important value of applying intraoperative DSA during AVM resection[14]. Endovascular embolization has rapidly developed in recent years, and many effective microcatheters for AVM embolization, such as the Marathon catheter (Medtronic Neurovascular, Minneapolis, MN)[15], Sonic catheter (Balt, Montmorency, France)[16], and Headway Duo catheter (MicroVention, Tustin, California)[17], have emerged. Another important development has been Onyx gel, which has resulted in a revolutionary change in AVM embolization[18]. All of these developments have made AVM embolization more convenient. Therefore, the above methods have been adopted to embolize the difficult-to-expose feeding arteries and part of the AVM during its removal, thereby reliably reducing the difficulty of AVM removal.

Classification of the therapeutic strategy according to the role of intraoperative DSA is a reasonable method. Since Type I AVMs often have a high SM grade (in our study, all cases were greater than grade 2), they often have a large volume and complex arterial feeders. Preoperative targeted embolization for these arterial feeders and part of the AVM was crucial. However, a high embolization degree was not pursued, and the therapeutic strategy was to reduce the blood flow of the AVM to decrease the surgical difficulty. For Type II AVMs, embolization of feeding arteries was unnecessary because most Type II AVMs in this study were SM grade 1 and 2. These AVMs mostly had a small volume, with fine and diffuse blood supply arteries; therefore, they could be directly surgically resected after accurate positioning. The role of intraoperative DSA in these cases mainly included locating the AVM, helping to find the AVM intraoperatively, and determining the presence of residuals.

In addition to the convenience that intraoperative DSA treatment can provide for AVM treatment, modern DSA equipment with a CT function, such as Dyna-CT (Siemens, Erlangen, Germany) or Xper-CT, can integrate intraoperative CT scans and images of the AVM into 3D images[19,20]. This can facilitate

preoperative and intraoperative AVM location and the detection of intracranial hemorrhage.

Intracranial AVM is often associated with aneurysms; some aneurysms are flow-related aneurysms of the feeding arteries, while others are sporadic aneurysms lacking any association with the AVM[21]. When the aneurysm is near the AVM, it can be embolized at the same time as the AVM. However, if the aneurysm is distant from the AVM, it can be followed up by observation. A previous study found that an aneurysm on a feeding artery may disappear after AVM resection[22]. Among the 15 patients, four AVMs were combined with four unruptured aneurysms of the feeding artery without subarachnoid hemorrhage. Two aneurysms close to the AVM and were embolized together with the part of the AVM; one aneurysm was located at the beginning part of the feeding artery and was clipped during resection of the AVM, and one regular and small aneurysm located in the anterior communicating artery away from the AVM was not treated. Therefore, aneurysms accompanied by AVM can be treated differently depending on the location of the aneurysm[23].

CONCLUSION

Currently, there are many treatment methods for intracranial AVM, among which surgical resection and embolization are the most popular. However, it is sometimes difficult to work with only one method. The most promising single method is to surgically remove the AVM in a hybrid operating room with the assistance of DSA. In our study, AVMs were classified as Type I and Type II for further treatment, which led to favorable results.

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Kailing Li and Yunbao Guo contributed equally to this manuscript, and they are co-first authors.

Author contribution: Jinlu Yu and Kan Xu designed the study, Kailing Li collected the images, and Yunbao Guo and Baofeng Xu collected the data.

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Original Article

Metabolic syndrome in different clinical forms of primary hyperparathyroidism

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ABSTRACT

Objective: This study aimed to investigate the prevalence of metabolic syndrome (MetS) and other cardiometabolic disorders in various clinical forms of primary hyperparathyroidism (PHPT) such as symptomatic, asymptomatic, low-risk asymptomatic and high-risk asymptomatic primary hyperparathyroidism.
Design: Percentage of MetS was determined.
Setting: PHPT stratified into two groups: symptomatic (n=80) and asymptomatic PHPT (n=71)
Subjects: One hundred and fifty-one PHPT patients who underwent parathyroidectomy and 93 age, gender and BMI-matched controls
Intervention: Furthermore, asymptomatic PHPT were divided into two subgroups according to long-term end-organ damage risk: high risk-asymptomatic (n=45) and low risk-asymptomatic PHPT (n=26).
Main outcome measures: Anthropometric measurements and serum glucose, insulin and lipid profile were compared.
Results: MetS was more prevalent in PHPT compared to controls (52.31% vs. 18.5%, OR=3.8, 95% CI: 2.57-8.01, *P*=0.002). Diabetes (15.2% vs 0%, *P*=0.001), hypertension (56% vs 14.8%, *P*=0.001), dyslipidemia (24.8% vs 5.8%, *P*=0.002) and insulin resistance (49.6% vs 27.5%, *P*=0.013) were more prevalent in PHPT than controls. MetS (48.8%, 56.3%, 53.8%, 57.8%), diabetes (12.5%, 18.3%, 19.2% and 17.8%), hypertension (55%, 57.1%, 73.1% and 47.7%), dyslipidemia (11.3%, 12.7%, 23.1% and 6.7%) and insulin resistance (47.1%, 52.5%, 57.1% and 50%) prevalence did not differ between symptomatic, asymptomatic (whole), low risk- and high risk-asymptomatic (respectively, *P*>0.05).
Conclusion: MetS was more prevalent in PHPT, independent of the degree of the disease (symptomatic, low risk-asymptomatic or high risk-asymptomatic). Cardiovascular and metabolic disorders were increased in various forms of PHPT, even in low risk-asymptomatic.

KEY WORDS: cardiometabolic disorders, hyperparathyroidism, metabolic syndrome

INTRODUCTION

Previously, osteitis fibrosis cystica, nephrolithiasis, rheumatic and gastrointestinal complaints, neuropsychological symptoms and cardiovascular disease would be defined as the most obvious manifestations of primary hyperparathyroidism (PHPT)[1,2]. Clinical profile of PHPT ranges from an asymptomatic form that is characterized by mild hypercalcemia without organ damage to a symptomatic form that is characterized by renal stones and/or overt bone disease and/or hypercalcemic crises[1]. Today, hypercalcemia is usually found incidentally during routine biochemical screening. Overt bone disease and nephrolithiasis are seen and fracture risk is increased at the nonvertebral and vertebral sites[3]. Furthermore, rheumatic and gastrointestinal diseases such as pancreatitis are not seen in sporadic cases of PHPT. Today, asymptomatic PHPT accounts for more than 80% of all PHPT cases in developed countries[1-3]. High-risk asymptomatic PHPT cases as well as symptomatic PHPT cases are usually referred to surgery and rest of the asymptomatic cases are considered to be at low risk for end-organ damage and followed-up conservatively without necessarily resorting to surgery[3].

PHPT cases usually exhibit traditional manifestations, including bone disease and renal stones;

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however, this disease has also been associated with non-traditional manifestations, including cardiovascular and metabolic abnormalities that can lead to increased mortality and morbidity[1,2,4]. Several cross-sectional clinical and epidemiological studies observe that moderate and severe forms of PHPT were associated with metabolic syndrome (MetS) and other disorders, including hypertension, dyslipidemia, glucose intolerance, obesity and insulin resistance. These studies concluded that each of the above mentioned disorders was a cause of increased cardiovascular mortality and morbidity in PHPT[1,3]. Recent studies reported cardiometabolic improvements following parathyroidectomy, which is the sole curative therapy for symptomatic PHPT[1,4]. However, such data are usually limited to symptomatic PHPT, and it remains unclear whether or not asymptomatic PHPT, which is a very widespread condition, is also accompanied by cardiovascular involvement which may be hidden manifestation. Studies investigating the effect of parathyroidectomy on cardiometabolic disorders in mild PHPT came to conflicting results[4]. In this respect, the literature lacks studies investigating the prevalence of MetS and its components, including dyslipidemia, hypertension and obesity in asymptomatic PHPT patients who are at low risk for end-organ damage. Therefore, we aimed to investigate the prevalence of MetS and other cardiometabolic disorders in various clinical forms of PHPT (symptomatic, asymptomatic, low-risk asymptomatic and high-risk asymptomatic).

SUBJECTS AND METHODS

This retrospective study was approved by Diskapi Yildirim Beyazit Teaching and Research Hospital Ethics Board (No: 03.11.2014-17/34) and informed consent was obtained from the patients.

The diagnosis of PHPT was based on elevated serum calcium levels with inappropriate high serum parathyroid hormone levels. Most of the asymptomatic PHPT patients presented with osteoporosis and symptoms unrelated to hyperparathyroidism. The patients were incidentally diagnosed in population-based screening programs. Most asymptomatic PHPT patients were referred from the osteoporosis outpatient clinic. We evaluated symptoms related with hypercalcemia (repeated nephrolithiasis, gastritis, polyuria, muscle weakness, osteoporosis or psychiatric disorders) and bone fractures. Hypercalcemic crisis was defined as serum calcium ≥14 mg/dL. Patients with hypercalcemic crisis were not included. All patients collected 24-hour urine to exclude familial hypocalcuric hypercalcemia. We classified patients as 'asymptomatic' when no symptoms normally associated with elevated calcium or parathyroid hormone, no symptomatic kidney stones, no impairment of kidney function [estimated glomerular filtration rate <60 mL/min], and no trauma fragile fracture, no osteoporosis (bone mineral densitometry (BMD) <-2.5 at any site) where present. BMD was performed through dual-energy X-ray absorptiometry using Hologic QDR-4500 device (HologicInc, Waltham, USA) to evaluate osteopenia or osteoporosis. Patients were performed for localization studies such as neck ultrasonography and Tc99-sesamibi scintigraphy. After surgery, histopathology report was reviewed. Patients with incomplete clinical, pathology or biochemical evaluation were eliminated. Demographic characteristics, previous diseases such as hypertension, diabetes mellitus, dyslipidemia and obesity were recorded. Each subject signed an informed consent form in accordance with the Declaration of Helsinki, and this study was approved by the local ethics committee of our hospital.

Among the subjects referred to tertiary hospital, Endocrinology and Metabolism Clinics, from 2010 to 2014, 151 patients underwent surgery for PHPT and 93 age, gender and body mass index (BMI)-matched controls were recruited to perform this case-control study. Patients were stratified into two groups, *i.e.*, symptomatic PHPT (n=80, 52.98%) and asymptomatic PHPT (n=71, 47.01%) according to bone and/or stone disease and/or hypercalcemic crisis. Furthermore, asymptomatic PHPT patients were divided in two subgroups according to risk of long-term end-organ damage, based on guidelines on Asymptomatic PHPT stated in the Fourth International Workshop (3): (a) patients with at least one of following parameters was defined as high risk-asymptomatic PHPT (n=45, 29.8%), *i.e.*, serum calcium >1.0 mg/dl above upper limit of normal range; BMD T-score ≤ 2.5 at total hip, lumbar spine, femoral neck or distal 1/3 radius or fracture; 24-h urine for calcium >400 mg/dl; creatinine clearance <60 ml/min, nephrolithiasis and age <50 years; (b) patients with hypercalcemia ≤1.0 mg/dl above upper limit of normal range; BMD T score >-2.5 at the three sites; 24-hour urine for calcium ≤400 mg/dl and creatinine clearance ≥60 ml/min and age ≥50 years was defined as low risk-asymptomatic PHPT (n=26, 17.21%).

Anthropometric measurements were performed in patients with PHPT before surgery. BMI was calculated as weight divided by height to the square. Hypertension was confirmed by repeated blood pressure measurements of systolic blood pressure >140 mmHg and diastolic blood pressure >90 mmHg. Patients with BMI ≥25 kg/m^2 were considered as overweight/obese according to World Health Organization criteria. Calcium, phosphorus, 25-hydroxyvitamin D3 (25OH vitamin D), intact parathyroid hormone (iPTH), creatinine, total cholesterol, triglycerides, low-density-lipoprotein cholesterol, high-density-lipoprotein cholesterol, glucose and insulin levels were measured

Table 1: Baseline characteristics of controls, patients with symptomatic, low risk-asymptomatic and high risk-asymptomatic

Variables	Controls (n=93)	Symptomatic PHPT (n=80)	Low risk-asymptomatic PHPT (n=26)	High risk-asymptomatic PHPT (n=45)	*P*-value for four groups	*P*-value for three PHPT groups	*P*-value for two asymptomatic PHPT groups
SBP (mmHg)	122.04±8.25	139.62±16.89	137.20±12.26	138.56±16.20	0.015	0.063	0.789
DBP (mmHg)	72.75±4.76	84.68±8.38	82.84±5.73	84.3±7.85	0.020	0.078	0.654
iPTH (pg/ml)	60.08±35.32	279.55±286.06	172.54±89.65	254.29±261.62	<0.001	0.045	0.038
Calcium (mg/dl)	8.86±1.52	11.88±0.77	10.42±0.52	10.79±0.63	<0.001	0.041	0.042
Phosphorus (mg/dl)	3.34±0.61	2.56±0.48	2.85±0.39	2.57±0.46	0.005	0.056	0.058
Glucose (mg/dl)	86.89±6.73	94.03±17.05	98.00±18.99	95.64±16.18	0.025	0.075	0.563
Total cholesterol (mg/dl)	193.85±22.07	197.14±34.42	216.17±41.32	200.61±30.73	0.038	0.081	0.785
LDL-C (mg/dl)	112.38±15.98	118.79±26.66	129.00±32.76	121.29±26.42	0.058	0.064	0.652
HDL-C (mg/dl)	55.67±13.25	48.51±12.73	52.62±15.15	50.22±10.47	0.065	0.057	0.458
TG (mg/dl)	131.15±50.67	149.55±72.79	172.77±83.35	145.51±65.78	0.029	0.043	0.034
Insulin (μIU/ml)	9.08±3.24	12.67±7.39	15.44±10.61	11.99±4.44	0.017	0.044	0.041
HOMA-IR	2.00±0.87	2.91±1.97	3.51±2.57	2.78±1.20	0.039	0.032	0.035
Femur neck BMD-Tscore	-	-1.94±1.2	-1.20±1.01	-1.61±1.32	-	0.062	0.089
Lumbal spine BMD-T score	-	-2.8±1.15	-1.32±0.99	-1.73±1.33	-	0.029	0.076

Data are presented as mean±SD
SBP: systolic blood pressure; DBP: diastolic blood pressure; iPTH: intact parathyroid hormone; HDL-C: high-density-lipoprotein cholesterol; LDL-C: low-density-lipoprotein cholesterol; TG: triglycerides; HOMA-IR: homeostasis model assessment-insulin resistance index; BMD: bone mineral densitometry

after an overnight fasting. iPTH was measured using a radioimmunoassay method (DiaSorinInc, Stillwater, USA). Insulin resistance was calculated by the homeostasis model assessment (HOMA-IR)[5]: [fasting plasma insulin (μIU/ml) X fasting serum glucose (mg/dl)] / 405. Metabolic syndrome was defined according to Adult Treatment Panel III criteria, and its diagnosis required three or more of the following: (1) waist circumference ≥94 cm for men and ≥80 cm for women; (2) triglyceride ≥150 mg/dl; (3) high-density-lipoprotein cholesterol <40 mg/dl for men and <50 mg/dl for women; (4) fasting glucose levels ≥100 mg/dl; and (5) systolic blood pressure ≥130 mmHg and diastolic blood pressure ≥85 mmHg[6].

Statistical analyses

Statistical analysis was performed using SPSS 18.0 (SPSS, Inc) software. Variables are presented as mean±standard deviation or median (with interquartile range), percentages (%), 95% confidence intervals (CI) and odds ratios (OR). Normality was tested using the Kolmogorov-Smirnov and Shapiro-Wilk *W* test. The categorical variables were analyzed with the Chi-square test or Fisher's exact test, where appropriate. Comparison of continuous variables between the three and four groups was compared with analysis of variance with Bonferroni adjustment or Kruskal Wallis test when appropriate. Unpaired Student's t test or Mann-Whitney U test was used for continuous variables which were not normally distributed and Student's *t* test was used for normally distributed continuous variables between two groups. The associations between calcium metabolism parameters and cardiometabolic disorders were tested by Pearson and Spearman's correlation coefficients. Multivariate logistic regression analyses were used to assess the relationship between PHPT and metabolic syndrome after adjusting age, sex and BMI. Statistical significance was defined as a $P < 0.05$.

RESULTS

Of the patients with PHPT, 47% were asymptomatic. There were no differences for female (84.8% vs 76.4%), mean age (53.95±11.17 vs 54.68±6.78 years) and BMI (29.62±4.34 vs 30.76±4.56 kg/m^2) between PHPT and controls ($P > 0.05$). Female gender was prevalent only in asymptomatic (whole) than in symptomatic, low risk-asymptomatic and high risk-asymptomatic group (91.5%, 78.8%, 88.5% and 93.3%, respectively, $P=0.019$). Age was higher only in low risk-asymptomatic than in symptomatic, asymptomatic (whole) and high risk-asymptomatic group (58.01±7.00, 52.94±12.24, 55.97±9.92 and 51.64±10.67 years, $P=0.028$). BMI was similar among symptomatic, asymptomatic (whole), low risk-asymptomatic and high risk-asymptomatic group (30.83±5.75, 31.16±5.28, 31.21±4.63 and 31.15±5.68 kg/m^2; $P>0.05$, respectively). Glucose, insulin HOMA-IR and lipids did not differ between various forms of PHPT ($P>0.05$). Baseline characteristics of various PHPT groups are shown in Table 1.

MetS was more prevalent in PHPT than in controls (52.31% vs 18.5%, $P=0.001$). MetS prevalence did not differ between symptomatic, asymptomatic (whole), low risk- and high risk-asymptomatic (48.8, 56.3, 53.8 and 57.8, $P>0.05$). Diabetes (15.2% vs 0%, $P=0.001$), hypertension (56% vs 14.8%, $P=0.001$), dyslipidemia

(24.8% vs 5.8%, *P*=0.002) and insulin resistance (49.6% vs 27.5%, *P*=0.013) were more prevalent in PHPT than in controls. Diabetes (12.5%, 18.3%, 19.2% and 17.8%), hypertension (55%, 57.1%, 73.1% and 47.7%), dyslipidemia (11.3%, 12.7%, 23.1% and 6.7%) and insulin resistance (47.1%, 52.5%, 57.1% and 50%) did not differ between symptomatic, asymptomatic (whole), low risk- and high risk-asymptomatic (respectively, *P*>0.05). Systolic and diastolic blood pressure was positively correlated with serum iPTH and calcium levels (Table 2). PHPT was independently associated with MetS, after adjusting age, sex and BMI (OR=3.745, 95% CI 2.679-8.132, p=0.003).

Table 2: Univarite analysis of serum iPTH and calcium with cardiometabolic parameters in PHPT patients and controls

Variables	iPTH		Calcium	
	R	*P*	R	*P*
SBP (mmHg)	0.497	<0.001	0.514	<0.001
DBP (mmHg)	0.307	<0.001	0.331	<0.001

Data are presented as Spearman's *r* coefficient and *P*-value.
SBP: systolic blood pressure; DBP: diastolic blood pressure; iPTH: intact parathyroid hormone

DISCUSSION

MetS was more prevalent in PHPT patients compared to controls, independent of the degree of the diasese (symptomatic, low risk-asymptomatic or high risk-asymptomatic). Cardiovascular and metabolic disorders were increased in various forms of PHPT compared to controls, even in low risk-asymptomatic.

In developed countries, asymptomatic PHPT accounts for approximately 70-80% of all PHPT cases[4]. In developing countries, on the other hand, PHPT cases usually present with traditional symptoms[7,8]. As is the case with patients in developing countries[7-9], a majority of the patients in the present study were symptomatic (almost 53%). Present study showed that PHPT was associated with an increase in MetS prevalence, independent of age, sex and BMI (OR=3.745, *P*=0.003), far higher than in the general population of Turkey[10]. MetS prevalence in patients with PHPT was reported to be 32.3% in Spain[11] and 60% in Mexico, where general population already has a higher prevalence of MetS (36%)[12]. Tassone *et al* reported that the prevalence of MetS prevalence in patients with PHPT (22.1%) was similar to Italian population, but it was higher in asymptomatic (30.2%) compared to symptomatic PHPT (16.5%)[13]. Luboshitzky *et al* observed that the prevalence of MetS was lower in mild PHPT (34.3%) than in severe PHPT (37.5%)[4].

Clinical and epidemiological studies observed that moderate and severe forms of PHPT were associated with increased MetS and other cardiometabolic disorders, including hypertension, dyslipidemia, glucose intolerance, obesity and insulin resistance. Each of these disorders that were observed in PHPT have contributed to increase in cardiovascular mortality and morbidity[1,2,4]. In our study, cardiovascular and metabolic disorders such as hypertension, diabetes, insulin resistance and dyslipidemia increased in patients with PHPT, independent of symptomatic or low risk- or high risk-asymptomatic compared to controls. This results are compatible with previous studies[4,11,13-15]. Procopio *et al* reported an increase in cardiovascular risk scores in symptomatic and low-risk asymptomatic PHPT. Since MetS was more prevalent in low-risk asymptomatic PHPT (47.6%) compared to symptomatic (8.7%) and high risk-asymptomatic PHPT (8.3%), cardiovascular mortality and morbidity risk was suggested to increase in both low risk-asymptomatic and symptomatic PHPT[15]. Both mild PHPT and symptomatic/severe PHPT were observed to increase all-cause morbidity and cardiovascular-mortality risk[2].

Increased calcium and iPTH values in patients with PHPT might contribute to worse metabolic disorders and cardiovascular involvement. Hypertension and insulin resistance might be associated with cardiometabolic alterations[15-17]. Not only hypercalcemic PHPT, but also asymptomatic normocalcemic PHPT was observed to increase cardiovascular risk[16]. This study suggested that increase in blood pressure related to serum calcium and iPTH values might contribute to cardiometabolic disorders, even in asymptomatic phase of the diasease.

Cardiometabolic disorders have improved after parathyroidectomy, especially in symptomatic PHPT. Conflicting results about cardiovascular mortality and morbidity have been reported in mild PHPT[14,18]. Parathyroidectomy improved blood pressures even in asymptomatic PHPT[14]. Reduced cardiovascular morbidity has been suggested in asymptomatic or mild PHPT following surgical intervention[16]. Swedish population reported that cardiometabolic disorders improved after 5-year-follow-up in normocalcemic PHPT after parathyroidectomy, compared to observation[18]. Scandinavian population reported no improvement in cardiovascular risk after parathyroidectomy in mild PHPT, compared to observation[19]. Vascular structure abnormality occurs within PHPT for long years due to the permenant damage on cardiovascular system that is associated with iPTH. Parathyroidectomy might be suggested as a therapy in early phase of the disease[15]. Metabolic disorders have also been observed in normocalcemic PHPT[18]. Renal failure, renal stone, bone fracture, hypertension and diabetes have been associated with

increase in non-fatal cardiovascular disorders in mild PHPT[15,20].

Small sample size was a limitation of this case-control study.

CONCLUSION

Our study showed that MetS was more prevalent in PHPT patients, independent of the degree of the disease, compared to control. Cardiovascular and metabolic disorders were increased in various forms of PHPT, even in low risk-asymptomatic, compared to control. All PHPT patients are advised to examine for potential cardiovascular and metabolic disorders and think of parathyroidectomy even in low risk-asymptomatic PHPT patients.

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Original Article

Patient outcomes under new oral anticoagulants therapy in daily practice

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ABSTRACT

Objective: Atrial fibrillation is the most common cardiac arrhythmia causing thromboembolism. Non-vitamin K oral anticoagulants (NOACs) have been demonstrated to be at least as effective and safe as warfarin. We aimed to assess the safety and efficacy of NOACs through real world experience.
Design: Retrospective observational study
Setting: Sakarya Education Hospital, Turkey
Subjects: A total of 726 patients under NOACs therapy were included.
Intervention: Demographic, clinical characteristics, bleeding and/or embolic events were analyzed.
Main outcome measures: Patients were analyzed for the primary effectiveness outcome of ischemic stroke (IS)/ systemic embolism and for the principal safety outcome of any bleeding events.
Results: The mean age was 72.7±10 years and 62.5% were female. Embolic events were seen in 58 (8%) patients. Dabigatran, apixaban, rivaroxaban, edoxaban as well as low doses of these drugs had equal effectivity. Although CHA2DS2-VASc (*P*<0.001) and HASBLED (*P*=0.002) scores as well as malignancy (*P*=0.012) were statically significant in recurrent cerebrovascular events, only previous IS or transient ischemic attack (HR:7.246; 95%CI: 1.201-43.478; r=0.267; *P*<0.001) were predictive. Major bleeding was noted in 18 (2.5%) patients with low glomerular filtration rate (*P*=0.009), high CHA2DS2-VASc (*P*=0.002) and high HASBLED score (*P*=0.01). Age was the main determinant of bleeding (HR:1.090; 95%CI: 1.025-1.158; r=0.139; *P*=0.006), and bleeding was increasing significantly over 75 years (HR:5.025; 95%CI: 1.457-17.241; r=0.144; *P*=0.003).
Conclusion: High CHA2DS2-VASc and HASBLED scores, and low CrCl were risk for thromboembolic and hemorrhagic complications. Advanced age was main determinant of safety in NOACs use. NOACs prescription and dose adjustment should be made according to the patient's clinical characteristics.

KEY WORDS: atrial fibrillation, bleeding, embolic complication

INTRODUCTION

Atrial fibrillation (AF) is the most common cardiac arrhythmia causing systemic thromboembolic events and cardiac mortality[1,2]. Oral anticoagulants are the main therapy for cardioembolic prevention in AF and the treatment of venous thromboembolism (VTE). Non-vitamin K oral anticoagulants (NOACs), rivaroxaban, apixaban, dabigatran and edoxaban have been shown to be at least as effective and safe as warfarin in preventing thromboembolic events without increasing risk of life threatening haemorrhages, particularly intracranial (ICH)[3-9]. NOACs were approved for prevention of stroke in non-valvular AF and VTE[10,11] and have become widely available drugs for clinical use. The real-world data with NOACs is valuable to clarify their safety and efficacy in particular patient subgroups, including the elderly, and those with chronic heart failure (CHF), chronic renal failure (CRF), malignancy and with multiple comorbidities requiring polypharmacy. In our study, the primary efficacy endpoint was a composite of stroke and systemic embolic events, while primary safety outcome was either major bleeding or clinically relevant non-major bleeding.

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SUBJECTS AND METHODS

This study was designed as a unicenter retrospective observational study. A total of 726 patients who were taking NOACs due to nonvalvular AF or secondary prevention from thromboembolic events were recruited between 2015 to 2018 from the patient pool of Cardiology Clinic of Sakarya University. Elderly patient was defined as ≥75 years old. Obesity was defined according to body mass index (BMI); underweight was BMI less than 18.5 kg/m^2, and obesity was BMI greater than 30 kg/m^2. The CrCl values <50 mL/min was evaluated as moderate to severe renal impairment. Patients were evaluated at baseline for demographic, laboratory and clinical characteristics and their medications. Most of our patients were taking warfarin previously. All patients were evaluated for their CHA2DS2-VASc (CHF, hypertension, age ≥75 or 65-74 years, diabetes, history of stroke or thromboembolism, vascular disease and sex)[12] and HASBLED (hypertension, renal or liver failure, stroke history, bleeding history, labile INR, age >65 years, drugs predisposing to bleeding, alcohol use)[13] score to assess risk of stroke, thromboembolism and bleeding.

Primary end-point events including thromboembolic [ischemic stroke (IS), transient ischemic attack (TIA), acute coronary syndrome (ACS), VTE], bleeding [intracranial, gastrointestinal (GI), lung or urinary] and all cause death were collected from clinical records retrospectively. Major bleeding was defined according to the International Society on Thrombosis and Haemostasis criteria[14].

Ethics approval was granted by the Sakarya Universty Education and Research Hospital Ethics Committee (application number 71522473/050.01.04/10).

Statistical analysis

Data were analyzed by Statistical Package for Social Sciences version 21.0 for Windows (IBM, Armonk, New York, USA). Distributions of continuous variables were assessed by the Kolmogorov-Smirnov test. Continuous variables were presented as mean±standard deviation or median and interquartile ranges according to mode of distribution. Categorical variables are presented as counts and percentages. Mean differences between groups were compared by Student's t-test, whereas the Mann-Whitney U test was applied for comparisons of the not normally distributed data. Multiple group comparisons were tested by ANOVA and categorical variables were analyzed by chi-square or Fisher's exact test, where applicable. The risk of an event was reported as incident per month, which was calculated by dividing the total number of patients with events by the total number of patient-month of follow-up. Independent predictor(s) of each clinical outcome (*i.e.*, bleeding, other embolic events, mortality) was assessed by using the multiple logistic regression with backward LR method. Any variable with a *P*-value <0.25 in a univariate model was accepted as a candidate for the multiple model along with all variables of known clinical importance. Odds ratios and 95% confidence intervals for each independent variable were also calculated. Statistical significance was accepted as $P<0.05$.

RESULTS

The characteristics of the study population were summarized in Table 1. This study included 726 AF patients under NOACs therapy aged 28 to 94 years (mean age: 72.7±10) and 62.5% of the population were female. Most patients had nonvalvular AF including permanent AF (86.3%) and paroxysmal AF (9.8%), and received NOACs therapy because of IS (38.6%), pulmonary embolism (3%), deep vein thrombosis (2.9%). The history of hypertension, CHF, diabetes mellitus (DM), CRF, coronary artery disease and dyslipidemia were 76%, 45.5%, 28.9%, 22.8%, 22.5% and 19.1% respectively. Nine percent of patients were smokers and 4.5% had malignancy. The mean time in therapeutic range (TTR) was between 24-40%, and there was no significant difference among NOACs groups.

Rivaroxaban, apixaban, dabigatran and edoxaban were prescribed to 45.1%, 27%, 21.4% and 6.5% of patients, respectively. The percentage of patients receiving edoxaban was low, because its registration in marketing took place at a later date. Standard doses of NOACs were used in 396 (54.5%) patients, especially for secondary prophylaxis (59.7%). The most commonly prescribed reduced-dose NOACs was dabigatran (51%), followed by rivaroxaban (49.7%), edoxaban (44.7%) and apixaban (34.2%). Absence of indications for dose reduction was identified in 145 (43.9%) patients. Otherwise, 72 patients (9.9%) were taking inappropriate high-dose medication.

There was no significant difference among the groups regarding the gender, hypertension, DM, CHF, coronary artery disease, dyslipidemia and malignancy. As expected, CrCl and BMI were lower in patients treated with reduced dose NOACs than recommended dose NOACs, while age, the CHA2DS2-VASc and the HASBLED scores were higher (Table 1).

The prevention of stroke or systemic embolism didn't reveal any statistical difference among high-dose dabigatran, apixaban, rivaroxaban, edoxaban as well as low-doses of these drugs (Tables 2, 3). Embolic events including IS or TIA, VTE or ACS were seen in 58 (8%) of the patients. Twelve of these patients who had embolic events had irregular drug intake. Different treatment regimens were applied after the

Table 1: Demographics and clinical characteristics of the study population

Characteristics/ comorbidities	DA 150mg (n=76)	DA 110mg (n=79)	RI 20mg (n=165)	RI 15mg (n=163)	AP 5mg (n=129)	AP 2.5mg (n=67)	ED 60mg (n=26)	ED 30mg (n=21)	*P*
Lenght of followup (patientmonth)	1352	1475	3509	2948	2251	812	181	128	
Age, years	68.3±11.3	76.3±9.5	67.5±10	76.4±8.8	71.1±7.8	78.8±8	72.3±6.8	77.6±7.3	0.000
Gender									0.630
Male, n(%)	29(38.2)	34(43)	66(40)	61(37.4)	40(31)	22(32.8)	12(46.2)	8(38.1)	
Female, n(%)	47(61.8)	45(57)	99(60)	102(62.6)	89(69)	45(67.2)	14(53.8)	13(61.9)	
BMI (kg/m^2)	33.1±14.1	30.5±7.3	31±6.8	29.1±6	31.1±5.8	28±5	32.3±7.9	28.3±4.7	0.001
LVEF	53±10.1	54±10	51±13.5	52.8±11.2	54.4±10.2	51.1±12.5	56.1±7.1	54.8±6.4	0.101
Medical history, n(%)									
Hypertension	59(77.6)	59(74.7)	113(68.5)	128(78.5)	108(83.7)	53(79.1)	20(76.9)	16(76.2)	0.163
DM	23(30.3)	17(21.5)	52(31.5)	45(27.6)	44(34.1)	18(26.9)	5(19.2)	6(28.6)	0.558
CrCl, mL/min	75.7±17.8	63±20.2	79.3±20.2	64±20.1	72.3±20.5	55.7±22.4	73.4±17.2	64.8±17.7	0.000
>50	68(89.5)	52(65.8)	146(88.5)	116(71.2)	106(82.2)	33(49.3)	23(88.5)	16(76.2)	
30-50	8(10.5)	27(34.2)	17(10.3)	40(24.5)	17(13.2)	29(43.3)	3(11.5)	5(23.8)	
<30			2(1.2)	7(4.3)	6(4.7)	5(7.5)			
CAD	15(19.7)	19(24.1)	39(23.6)	37(22.7)	26(20.2)	20(29.9)	3(11.5)	4(19)	0.663
CHF	28(36.8)	35(44.3)	67(40.6)	73(44.8)	58(45)	37(55.2)	17(65.4)	15(71.4)	0.019
PAD		1(1.3)	2(1.2)		1(0.8)	2(3)			0.265
COAH	7(9.2)	10(12.7)	20(12.1)	30(18.4)	19(14.7)	11(16.4)	6(23.1)	1(4.8)	0.040
Malignancy	4(5.3)	5(6.3)	3(1.8)	7(4.3)	9(7)	4(6)	1(3.8)	8(38.1)	0.464
Smoking	7(9.2)	13(16.5)	21(12.7)	15(9.2)	4(3.1)		2(7.7)	3(14.3)	0.003
AF type, n(%)									0.322
Permanent AF	60(78.9)	74(93.7)	131(79.4)	143(87.7)	111(86)	61(91)	25(96.2)	19(90.5)	
Paroxysmal AF	14(18.4)	3(3.8)	20(12.1)	16(9,8)	13(10.1)	5(7.5)	1(3.8)	1(4.8)	
SR	2(2.6)	2(2.5)	14(8.5)	4(2.5)	5(3.9)	1(1.5)		1(4.8)	
IS	29(38.2)	24(30.4)	62(37.6)	49(30.1)	41(31.8)	20(29.9)	3(11.5)	4(19)	0.224
TIA	5(6.6)	5(6,3)	10(6.1)	6(3.7)	10(7.8)	6(9)	6(23.1)		
Deep vein thrombosis	3(3.9)	1(1.3)	7(4.2)	3(1.8)	6(4.7)		1(3.8)		0.443
Pulmonary embolism		1(1.3)	11(6.7)	5(3.1)	2(1.6)	2(3)		1(1.8)	0.081
Baseline risk analysis									
CHA2DS2-VASc score	3.8±1.7	4.1±1.6	3.9±1.7	4.4±1.5	4.2±1.6	4.8±1.6	3.9±1.4	3.9±1	0.003
HASBLED score	2.2±1.1	2.7±0.9	2.2±1	2.8±1	2.5±1.1	3.1±0.9	2.6±1.1	2.7±0.8	0.000
TTR	34.7±22.3	40.1±20.4	42.5±23.2	37.4±21	40.9±21.4	37±22.2	27.6±26.8	30±20.4	0.419
Co-medications									
Aspirin	3(3.9)	3(3.8)	12(7.3)	8(4.9)	6(4.7)	4(6)			0.499
Klopidogrel	2(2.6)	4(5.1)	4(2.4)	10(6.1)	2(2.3)	3(5.4)			0.631
Aspirin+ klopidogrel		2(2.5)			3(2.4)	2(3)	1(3.8)		0.124
non-DHP CCB	8(10.5)	10(12.7)	27(16.4)	30(18.4)	19(14.7)	10(14.9)	4(15.4)		0.865
Beta-blocker	47(61.8)	61(77.2)	112(67.9)	111(68.1)	90(69.8)	39(58.2)	19(73.1)	7(33.3)	0.316
Digoxin	10(13.2)	26(32.9)	25(15.2)	34(20.9)	21(16.3)	13(19.4)	5(19.2)	13(61.9)	0.029
Propafenone	1(1.3)		2(1.2)	1(0.6)	2(1.6)		1(3.8)	2(9.5)	0.691
Amiodarone	3(3.9)		3(1.8)	3(1.8)					0.218
NSAID	3(3.9)	8(10.1)	9(5.5)	14(8.6)	5(3.9)	1(1.5)	1(3.8)		0.168
Antidepressant	9(11.8)	6(7.6)	7(4.2)	9(5.5)	4(3.1)		1(3.8)		0.040
ACEI or ARB	51(67.1)	48(60.8)	104(63)	111(68.1)	92(71.3)	41(61.2)	18(69.2)	15(71.4)	0.700
Doksazosin	4(5.3)	2(2.5)	5(3)	5(3.1)	8(6.2)	4(6)	2(7.7)		0.535
Statin	19(25)	13(16.5)	30(18.2)	22(13.5)	31(24)	15(22.4)	5(19.2)	4(19)	0.622
DHP CCB	10(13.2)	8(1.1)	18(10.8)	15(9.2)	19(14.7)	5(7.5)	6(23.1)	5(23.8)	0.765
Spironolacton	14(18.4)	17(21.5)	30(18.2)	28(17.2)	12(9.3)	11(16.4)	5(19.2)	6(28.6)	0.246
Furosemide	28(36.8)	35(44.3)	63(38.2)	76(46.6)	58(45)	34(50.7)	14(53.8)	15(71.4)	0.086

ACEI: angiotensin-converting enzyme inhibitors; ARB: angiotensin receptor blocker; AP: apixaban; AF: atrial fibrillation; BMI: body mass index; CAD: coronary artery disease; CHF: chronic heart failure; CrCl: creatinine clearance; DA: dabigatran; DM: diabetes mellitus; DVT: deep venous thrombosis; ED: edoxaban; GFR-glomerular filtration; IS: ischemic stroke; LVEF: left ventricular ejection fraction; NSAID: non-steroidal anti-inflammatory drugs; non-DHP CCB: non-dihydropyridine calcium channel blocker; PAD: peripheral artery disease; PE: pulmonary embolism; RI: rivaroxaban; TIA: transient ischemic attack; TTR: time in therapeutic range

embolic events: NOAC treatment was stopped and warfarin treatment was initiated, NOAC doses were increased, another NOAC treatment was initiated or antiagregan including acetylsalicylic acid (ASA) or clopidogrel was added to NOAC treatment. Dabigatran 150mg appears to be the preferred choice after embolic event for the majority of patients. Although CHA2DS2-VASc (P<0.001; r=0.224) and HASBLED (P=0.002; r=0.112) scores, and malignancy (P=0.012; r=0.090) were statically significant in

Table 2: Events encountered during treatment with NOACs

Outcomes	DA 150mg	DA 110mg	RI 20mg	RI 15mg	AP 5mg	AP 2.5mg	ED 60mg	ED 30mg
Stroke*, n(%)	2 (2.6)	5 (6.5)	16 (9.2)	9(5.4)	8(6.4)	2(3)	1(3.8)	
Major bleeding n(%)		4 (5.2)	3(1.8)	5(3)	1(0.8)	4(6)		1(4.8)
GIS		3 (3.9)	1(0.6)	4(2.4)	1(0.8)	4(6)		1(4.8)
IC		1(1.3)	2(1.2)	1(0.6)				
Minor bleeding n(%)	3 (3.9)	6 (7.8)	9(5.6)	6(3.6)	6(4.8)	3(4.5)	1(3.8)	
Ecchymosis	2 (2.6)		5(3)	2(1.2)	2(1.6)			
Vaginal	1(1.3)	1(1.3)		1(0.6)			1(3.8)	
GIS		3 (3.9)	1(0.6)	2(2.4)	2(1.6)	2(3)		
Hematuria		1(1.3)	3(1.8)	1(0.6)		1(1.5)		
Epistaxis		1(1.3)	2(1.2)	2(1.2)	1(0.8)			
Conjunctival			2(1.2)					
Hemoptysi						1(1.5)		
ACS		1(1.3)	1(0.6)	5(3)	3(2.4)	1(1.5)		
VTE			2(1.2)				1(3.8)	
PE			2(1.2)					
DVT							1(3.8)	
Death	2 (2.6)	8 (10.4)	7(4.2)	12(7.2)	5(4)	6(9)		1(4.8)
Cardiac	1(1.3)	3 (3.9)	2(1.2)	4(2.4)	2(1.6)	4(6)		
Other	1(1.3)	5 (6.5)	5 (3)	8(4.8)	3(2.4)	2(3)		1(4.8)

n: number of patients; *irregular drug intake not counted
DA: dabigatran; RI: rivaroxaban; AP: apixaban; ED: edoxaban; GIS: gastrointestinal; IC: intracranial; ACS: acute coronary syndrome; VTE: venous thromboembolism; PE: pulmonary embolism; DVT: deep venous thrombosis

recurrent cerebrovascular events, only previous IS or TIA (HR: 7.246; 95% CI: 1.201-43.478; r=0.267; *P*<0.001) were predictive (Table 4).

Major bleeding was noted in 18 (2.5%) patients, especially over 75 years of age (83% of them). Three of four patients with ICH used rivaroxaban, one of them used dabigatran. Twenty-five patients had GI haemorrhage and 14 of them were life-threatening (Table 2). The GI bleeding carried high mortality and led to death in eight (32%) patients. Although, risk of bleeding was increased in patients with low glomerular filtration rate (*P*=0.009; r=-0.097), high CHA2DS2-VASc (*P*=0.002; r=0.115) and high HASBLED score (*P*=0.01; r=0.095), age was the sole determinant of bleeding (HR: 1.090; 95% CI: 1.025-1.158; *P*=0.006; r=0.139) in multivariate analysis. Bleeding was increasingly significant with age (HR: 5.025; 95% CI: 1.457-17.241; *P*=0.003; r=0.144; Table 5). Interestingly, unlike previous studies, major bleeding except ICH were considered, apixaban 2.5 mg showed significant high rates compared with rivaroxaban 20mg (*P*=0.009), and apixaban 5mg (*P*=0.006) (Table 6). Other non-life-threatening bleeding were seen in 37 (5.1%) patients and observed in all NOACs groups similarly (Table 2).

Our study included 145 (20%) patients with mild to moderate renal insufficiency (CrCl: 30-49 mL/min) and 20 (2.8%) patients with CrCl <30 mL/min (Table 1). Although there was no statistically significant relationship between CrCl and embolic events (*P*=0.325; r=0.034), rates of major bleeding (*P*=0.009;

Table 3: The one-to-one comparison of NOACs efficacy outcomes for thromboembolic events and corresponding *P* values per patient-month follow up using chi-square test.

Number of events/ Patient month follow up	DA 150mg 2/1352	DA 110mg 5/1475	RI 20mg 16/3509	RI 15mg 9/2948	AP 5mg 8/2251	AP 2.5mg 2/812
DA 150mg 2/1352		0.379	0.186	0.578	0.763	0.831
DA 110mg 5/1475	0.379		0.709	0.636	0.484	0.353
RI 20mg 16/3509	0.186	0.709		0.282	0.203	0.213
RI 15mg 9/2948	0.578	0.636	0.282		0.765	0.505
AP 5mg 8/2251	0.763	0.484	0.203	0.765		0.640
AP 2.5mg 2/812	0.831	0.353	0.213	0.505	0.640	

DA: dabigatran; RI: rivaroxaban; AP: apixaban

Table 4: Predictors of embolic events

Risk factors	Odds ratio*	95% CI	R	*P*
CHA2DS2-VASc			0.224	0.000
HAS-BLED			0.112	0.002
Malignancy			0.093	0.012
IS	7.246	1.201-43.478	0.267	0.000
Age			0.036	0.335
CrCl			0.037	0.325
Gender			0.015	0.681
CHF			0.025	0.496
Rivaroxaban			0.072	0.053
Dabidatran			0.036	0.337
Apixaban			-0.062	0.096
Edoxaban			-0.022	0.547
Low BMI			0.017	0.687
Obesity			-0.108	0.004

*Odds ratio for multivariate analaysis
IS: ischemic stroke; CrCl: creatinine clearance; CHF: chronic heart failure; BMI: body mass index

Table 5: Predictors of bleeding

Risk factors	Odds ratio*	95% CI	R	*P*
Age	1.090	1.025-1.158	0.139	0.006
≥75age	5.025	1.457-17.241	0.144	0.003
CHA2DS2-VASc			0.115	0.002
HAS-BLED			0.095	0.010
CrCl			-0.097	0.009
Gender			0.009	0.818
IS			0.027	0.471
HF			0.031	0.405
Xarento			-0.005	0.898
Dabidatran			0.034	0.366
Apixaban			-0.010	0.796
Edoxaban			-0.013	0.736
ASA+Clopidogrel			0.018	0.632
Clopidogrel			0.011	0.760
Aspirin			0.039	0.293
History of bleeding			0.027	0.473
Low BMI			0.017	0.647
Obesity			-0.089	0.017

*Odds ratio for multivariate analaysis
CrCl: creatinine clearance; IS: ischemic stroke; HF: heart failure; ASA: acetylsalicylic acid; BMI: body mass index

r=-0.097) and all-cause mortality (*P*=0.003; r=-0.110) increased as renal function decreased. Even if the renal function is normal initially, it worsened (as defined by a reduction in CrCl >20 mL/min on treatment) in 17 (2.3%) patients, especially over 75 years (*P*=0.026; r=0.083), due to bleeding, infection or low cardiac output during follow up. Basal CrCl values (*P*<0.001; r=-0.154) were predictive of worsening renal function, which was predictive of all-cause mortality (HR: 2.808; 95% CI: 1.090-7.246; r=199; *P*<0.001).

Our study included 320 (27%) older patients and 64.1% of them were taking educed dose NOACs. Elderly patients had higher CHA2DS2-VASc (4.84±1.4 and 3.63±1.5; *P*<0.001) and HASBLED (2.94±0.9 and 2.25±1.1; *P*<0.001) score, while BMI (28.3±5.2 and 32.1±8.6; *P*<0.001) and CrCl (60.7±19.8 and 76.7±20.2; *P*<0.001) values were lower. Although thromboembolic events were similar (9.4% and 7.4%; *P*=0.335), bleeding complications were higher in the elderly than younger patients (4.7% and 0.7%; *P*<0.001). Moreover, age was the main determinant of mortality (HR: 1.060; 95%CI: 1.019-1.104; r=0.156; *P*<0.001; Table 7).

The prevalence of CHF was 45.6% in our study population with AF. Almost half of the patients with heart failure (43.9%) had moderately advanced valve dysfunction including mitral or tricuspid insufficiency (42.4%), aortic stenosis (1.5%); only one-fourth of patients (23.1%) had left ventricular systolic dysfunction. The major bleeding and IS rates were similar in both heart failure and non-heart failure patients, and systolic dysfunction was an independent risk factor for mortality (HR: 1.026; 95%CI: 1.004-1.049; r=-0.145; *P*<0.001).

ACS was observed in 11 patients under NOACs treatment but there was no stent thrombosis or

Table 6: The one-to-one comparison of NOACs safety outcomes and corresponding *P* values for major bleeding per patient-month follow up using chi-square test

Number of events/ Patient month follow up	DA 150mg 2/1352	DA 110mg 5/1475	RI 20mg 16/3509	RI 15mg 9/2948	AP 5mg 8/2251	AP 2.5mg 2/812
DA150mg 0/1352		0.185	0.900	0.435	0.715	0.133
DA110mg 4/1475	0.185		0.087	0.415	0.052	0.450
RI 20mg 3/3509	0.900	0.087		0.338	0.563	0.009
RI 15mg 5/2948	0.435	0.415	0.338		0.187	0.095
AP 5mg 1/2251	0.715	0.052	0.563	0.187		0.006
AP 2.5mg 4/812	0.133	0.450	0.009	0.095	0.006	

DA: dabigatran; RI: rivaroxaban; AP: apixaban

Table 7: Predictors of mortality

Risk factors	Odds ratio*	95% CI	R	*P*
CHA2DS2-VASc			0.137	0.000
HAS-BLED			0.115	0.002
Malignancy	2.610	1.084-6.329	0.109	0.003
EF	1.026	1.004-1.049	-0.145	0.000
CHF			0.111	0.003
Age	2.695	1.310-5.524	0.156	0.000
ACS			0.109	0.002
WRF	2.808	1.090-7.246	0.199	0.000
CKD			0.110	0.003
Gender			-0.008	0.681
Rivaroxaban			0.000	0.992
Dabidatran			0.030	0.419
Apixaban			-0.004	0.916
Edoxaban			-0.019	0.602
Obesity			-0.083	0.026
Low BMI	2.409	1.219-4.784	0.133	0.000
Major bleeding	3.344	1.658-6.756	0.360	0.000
Reduced doses	1.969	1.025-3.783	0.100	0.007

*Odds ratio for multivariate analysis
EF: ejection fraction; CHF: chronic heart failure; ACS: acute coronary syndrome; WRF: worsening renal failure; CKD: chronic kidney

reinfarction among them (Table 2). Additional antiplatelet treatment was detected in 9.5% of the patients, with 5% of them receiving ASA. Only 1.1% of these patient's prescription involved triple therapy including ASA, clopidogrel and NOAC. Although combination therapy of antiaggregants and anticoagulants increases bleeding risk, in this study, the use of ASA or clopidogrel appeared safe for bleeding in the setting of dual or triple therapy (Table 5).

Most of our AF patients had different comorbidity with polypharmacy (Table 1). One of the biggest problems the clinician faces during anticoagulant therapy is drug-drug interaction. It is therefore important to ensure safe NOAC use with other drugs. Our study demonstrated that NOACs can be safely used with many antihypertensive, diuretic, statin, beta-blockers, non-dihydropyridine calcium channel blockers, digoxin and antiarrhythmics used in heart rate and rhythm controls. All these drugs were seen to be safe, particularly with regard to bleeding in all NOACs groups.

The cancer prevalence was 5% and all of them were clinically stable, and didn't receive active chemotherapy. While major bleeding rates were similar in both cancer and non-cancer patients (*P*=0.293), thromboembolic risk slightly increased in cancer patients (*P*=0.012; r=0.093). However, cancer was not an independent risk factor for stroke. Malignancy was found as an independent risk factor for mortality (HR: 2.610; 95%CI: 1.084-6.329; r=0.109; *P*=0.003).

Body weight has an effect on the pharmacokinetics of drugs. In our study, 297 adults (40.9%) were obese and 85 adults (11.6%) had low body weight. There was inverse relationship between obesity and embolic events (*P*=0.004; r=-0.108). There was no correlation between bleeding and low weight (*P*=0.647; r=0.017), but bleeding was less in obese patients (*P*=0.017; r=-0.089). Low weight was a main determinant of mortality (HR: 2.406; 95%CI: 1.219-4.784; r=0.133; *P*<0.001).

Mortality rate was 5.6% (41 patients) and the most important cause was heart failure (12 patients), followed by hemorrhage including GI (8 patients) and ICH (3 patients), infection (6 patients), renal failure (5 patients), malignancy (3 patients), ACS (2 patients) and IS (2 patients). As expected, mortality was particularly high in the reduced-dose NOACs therapy groups with advanced age, high CHA2DS2-VASc and HASBLED score, low CrCl and low BMI (Table 7).

DISCUSSION

The purpose of this study was to assess the safety and efficacy of NOACs in patients who were not well represented in the randomized controlled trials (RCTs). The mean age, gender distribution and frequency of hypertension, CHF, renal failure and DM were similar as previous RCTs. The anticoagulation control with low TTR during warfarin treatment before NOAC use was suboptimal compared with RCTs (TTR was 62%, 64% and 55% respectively in ARISTOTLE, RE-LY and ROCKET AF)[5-8]. Also, the mean values for the CHA2DS2-VASc and the HASBLED score were higher in our study than RCTs.

Rivaroxaban and apixaban were both more preferred than dabigatran and edoxaban. The frequencies of standard and reduced doses prescribed were similar for dabigatran, rivaroxaban, edoxaban; while apixaban was prescribed more frequently in the standard-dose regimen. Almost half of the patients were using lower doses of NOACs, which is definitely much more than RCTs[5-9]. Consistent with previous observational studies, reduced doses of NOACs, especially apixaban, were prescribed more frequently to older patients with high risk of thromboembolic and bleeding events[15,16]. Also, reduced dose NOACs use was preferred in primary prophylaxis.

NOACs trials have shown that compared to warfarin, NOACs are associated with decrease in mortality, stroke or systemic embolisation, and reduction in ICH[3-9], but the incidence of GI bleeding was higher with both doses of dabigatran[17], high-dose edoxaban[6,18] and rivaroxaban[19]. Apixaban had advantage regarding major bleedings in patients with renal dysfunction and absolute benefits of apixaban were greater in the older population[4-8,20,21]. In our study, the risk of bleeding and mortality were significantly high in patients treated with reduced

doses of NOACs, especially among patients over 75 years. GI bleeding was one of the most frequently encountered bleeds during NOACs therapy. Unlike some studies[4-9,20], low dose apixaban particularly showed higher ratio for GI bleedings, compared with rivaroxaban 20mg and apixaban 5mg. However, ICH was most common in the rivaroxaban group.

The incidence of thromboembolic events was higher than other NOACs study[5-8,16]. Although CHA2DS2-VASc and HASBLED scores, and malignancy were statistically significant in recurrent cerebrovascular events, only previous IS was predictive of recurrent cerebrovascular events despite anticoagulation in our study. One-fifth of patients with stroke under NOACs treatment didn't receive regular medication. Irregular uptake or drug withdrawal were most frequently detected in groups receiving rivoraxaban and then dabigatran. After the IS, different treatment regimens were applied in study population. As stated in guidelines, there is no evidence from RCTs to prefer one NOACs over the other or to switch from one NOACs to another in patients with a history of IS under NOACs therapy[11]. The treatment protocol to be applied after the embolic event under treatment of NOACs isn't clear for the clinicians.

Advanced age should not be a criteria for giving up anticoagulation therapy, because the clinical benefit of NOAC is shown in old patients[22]. NOACs were associated with similar efficacy to vitamin K antagonists and incidence of major bleeding events was lower with NOACs in older patients[23-25]. The prevention of stroke or systemic embolism didn't reveal any statistical difference depending on age in our study. The risk of major bleeding was similar with RCTs that estimated at 2-4%[5-8,22,26] and the risk of bleeding was increased in the elderly with a high risk profile including high CHA2DS2-VASc and HASBLED score and low glomerular filtration rate.

Although all used NOACs undergo some renal excretion, NOACs provide protection from systemic embolization and stroke, and they are safe without excessive bleeding in patients with moderate renal dysfunction[8,27-29]. In indirect comparisons of randomized controlled trials and meta-analysis, it has been suggested that apixaban and edoxaban may be safer than dabigatran and rivaroxaban in terms of major bleeding in the presence of moderate CRF[5-8,30,31]. In our study, the prevalence of patients with renal dysfunction was similar or slightly higher than RCTs[5-8].There was no significant relationship between the renal functions and thromboembolic events, but basal CrCl values were predictive of bleeding complication and all-cause mortality. Therefore, renal function should be determined before starting treatment and more frequent monitoring should be considered in the presence of baseline renal dysfunction, particularly in the elderly population.

NOACs are at least as effective as warfarin for thromboprohpylaxis and may reduce bleeding rates compared to warfarin in nonvalvular AF with CHF[5-8,32]. The majority of our patients were suffering from CHF with multiple drug use and high mortality. NOACs use in heart failure patients was found to be effective and safe.

Studies suggest that the use of anticoagulation therapy with P2Y12 inhibitor monotherapy in AF patients who undergo coronary revascularization is safe[33-34]. Addition of aspirin or clopidogrel to NOACs was not associated with more bleeding complications. Otherwise, combination treatment rate was low and there was no use of newer P2Y12 inhibitor such as ticagrelor or prasugrel as a part of dual therapy in our population. It supports that the combination of antiplatelet with NOACs therapy can be used safely in high risk thrombotic events like ACS or prior stent thrombosis[11].

Co-medications are important because of unfavourable drug-drug interactions. Although NOACs present with fewer interactions with other drugs than vitamin K antagonists, the importance of drug interaction with NOACs is still largely unknown for many drugs[10,35]. Many antihypertensives, diuretics, drugs used for rhythm and rate control, statins and NSAID appeared safe for bleeding in our study.

Cancer has been associated with higher rates of thromboembolism and bleeding, and NOACs are prescribed increasingly[36,37]. In our study, cancer patients with AF under NOACs therapy had similar risk of thromboembolic or bleeding events as non-cancer patients, similar to other studies[36,37].

The body mass affects both occurrence of AF and plasma levels of anticoagulants[38] and can affect the pharmacokinetics of drugs. There was inverse relationship between obesity and IS in the study of Boriani *et al*[39]. An increased BMI is associated with a lower risk of embolic events, bleeding and better survival while low weight was a main determinant of mortality.

The all-cause mortality rate was higher than RCT[5-8]. There was high mortality rate in patients under reduced NOACs therapy with high CHA2DS2-VASc and HASBLED score. Age, major bleeding, renal failure, low ejection fraction, low BMI and malignancy were predictive of all-cause mortality.

Study limitations

Our study has a number of limitations. First, the number of patients was less and results cannot be generalized to all patients, but it gives us valuable information in routine clinical use. Second, patients

admitted to the cardiology clinic were included in the study. However, as some hemorrhagic and ischemic events were obtained indirectly from hospital records, the data may not be complete. Another limitation is that it is a retrospective study with its own inherent limitations.

CONCLUSION

The rates of stroke or systemic embolism and mortality were higher than other NOACs study because we encountered more high risk patients than RCTs in clinical practice. The use of low dose NOACs was definitely much more than RCTs. However, there was no difference among high-doses of dabigatran, apixaban, rivaroxaban, edoxaban as well as low-doses of these drugs in terms of stroke or systemic embolism. Low adherence rates severely diminish the benefit of treatment. Patients should be educated about the importance of adherence to their treatment. Major bleeding rates were similar to other RCTs. Advanced age was a main determinant of bleeding complications. GI haemorrhage was one of the most frequently encountered bleeding events. The population in the low-dose apixaban group had the highest risk of bleeding and thromboembolic events, and the frequency of GI bleeding was the highest in this group. ICH was most common in the rivaroxaban group. Although this wasn't a RCT, the conclusions demonstrated once again the importance of an accurate assessment of thromboembolic and haemorrhagic risk, and appropriate NOACs prescription and dose adjustment according to the patient characteristics including age, renal function, weight and other comorbidity requiring medical therapy.

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Original Article

Successful treatment of patients with acute myeloid leukemia and Myelodysplastic Syndrome by decitabine

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ABSTRACT

Objectives: The goal of this study was to identify the safety and efficacy of decitabine.
Design: Retrospective study
Setting: Department of Hematology, Ege University Faculty of Medicine
Subjects: Data of patients with myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) who were treated with decitabine were evaluated retrospectively.
Intervention(s): Decitabine was administered 20 mg/m^2 by intravenous infusion daily for five consecutive days every four weeks. The primary end point was overall response rate (ORR). Survival, overall improvement rate (OIR), hematologic improvement (HI) and drug toxicity were analyzed.
Main outcome measure(s): Overall survival (OS), progression-free survival (PFS), ORR and hematologic adverse event for both AML and MDS, OIR including HI for MDS.
Results: Twenty-five MDS and thirteen AML patients were enrolled. In MDS group, median OS and PFS were 21 months and 14 months, respectively. The ORR was 48% and OIR was 60%, which included 12% HI. Seventy-two of the patients experienced stable disease or better. For AML, ORR was 46.2%, and median OS and PFS data were not reached as 76% (n=10) of patients are still alive, and 38% (n=5) of patients are still receiving treatment. At one year, OS and PFS were 61.4% and 77.8%, respectively.
Conclusion: Decitabine is effective and safe with acceptable toxicity in intermediate and high-risk MDS patients and elderly patients with AML.

KEY WORDS: administration and dosage, adverse effects, survival analysis

INTRODUCTION

Myelodysplastic syndrome (MDS) is a collection of neoplastic disorders of hematopoietic stem cells characterized by inefficient hematopoiesis, peripheral blood cytopenia, morphologic dysplasia and susceptibility to acute myeloid leukemia (AML). AML is characterized by the accumulation of immature myeloid 'blasts' in the bone marrow and peripheral blood[1]. MDS and AML lie along a disease continuum, with a distinction between the two largely made based upon the blast percentage. In the current World Health Organization classification system, blast forms account for at least 20% of the total nucleated cells in AML[2]. Gene mutations that affect DNA methylation have been identified in patients with AML. These mutations may result in the expression of genes that are normally silenced or in the silencing of genes that are normally expressed. DNA methylation patterns may also have prognostic significance[3]. Also, abnormal cytosine methylation patterns are widespread in MDS and hypermethylation-associated silencing of expression of tumor suppressor genes is thought to contribute to MDS pathobiology[4,5]. Decitabine (5-aza-2′-deoxycytidine) is commonly used as a single agent to treat patients with MDS and elderly patients with AML[6]. The drug is a hypomethylating agent that irreversibly inhibits DNA methyltransferase I, leading to genome-wide global DNA hypomethylation. Decitabine induces leukemic differentiation and re-expression of tumor-associated genes that had been epigenetically silenced[7]. At high doses, cells die from apoptosis triggered by DNA synthesis arrest,

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and at low doses, cells survive but change their gene expression profile to favour differentiation, reduced proliferation and increased apoptosis. In addition, maximum effects of DNA hypomethylation have been observed at low doses and with fewer side-effects[8,9]. Decitabine demonstrated promising results in patients with high-risk myelodysplastic syndrome[10,11]. Two prospective trials in elderly AML patients had been conducted, which showed improved clinical outcomes and acceptable safety profiles compared to conventional treatments[12,13].

SUBJECTS AND METHODS

The study was performed in the Department of Hematology at Ege University Hospital. Following the approval of the study protocol by the local Ethics Committee, data of patients with MDS and AML who were treated with decitabine between January 2011 and December 2016 were retrospectively analyzed.

Patients

Eligible patients who were older than 18 years old and diagnosed with MDS or AML according to the 2008 World Health Organization classification were enrolled. Patients with MDS were required to have an International Prognostic Scoring System (IPSS) score of ≥0.5.

Study design

The study was single centered and retrospective. Decitabine was administered as a 20 mg/m^2 intravenous infusion daily for five consecutive days (D1-5) every four weeks.

All results, except adverse events, for AML and MDS were assessed separately. IPSS and Revised International Prognostic Scoring System (IPSS-R) were used to calculate the risk assessment of MDS. For MDS, age, gender, IPSS and IPSS-R, RAEB 1 or 2 and Eastern Cooperative Oncology Group (ECOG) performance status, cytogenetic classification and number of decitabine treatment cycles were observed. For AML, age, gender, nature (secondary or de novo), blast ratio at the time of diagnosis, ECOG performance status, cycle number were noted. Treatment response was assessed by monthly complete blood counts (CBCs) in all patients and bone marrow examination after four cycles in patients, except those who underwent allogeneic hematopoietic stem cell transplantation (AHSCT). The timing of bone marrow aspiration biopsy for AHSCT candidates was planned based on improvement in CBCs. The decrease in neutrophil, erythrocyte or platelet was not included in the cytopenia grading system in patients with cytopenia at the beginning of decitabine treatment and was assessed as worsening cytopenia.

Study end points and response assessment

The primary end-point was the overall response rate (ORR). Secondary end points were hematological improvement (HI) (calculated only for MDS), overall survival (OS) and progression free survival (PFS). In MDS, ORR was assessed by International Working Group 2006 response criteria. According to this criteria, a complete response (CR) is defined as normalization of peripheral blood counts (hemoglobin >11 g/dL without transfusion or erythropoietin use, neutrophils ≥1.0 x 10^9/L in the absence of growth factor use, and platelets ≥100 x 10^9/L without transfusion or growth factors) and bone marrow blasts less than 5% for at least four weeks; marrow complete response (mCR) is defined by ≥50% myeloblast reduction from more than 5% myeloblasts to ≤5%, but without recovery of peripheral counts to a level meeting criteria for CR. Criteria for partial response (PR) are the same as for CR, except for a decrease of ≥50% in the percentage of blasts over pretreatment (but still ≥5%), or improvement to a less advanced MDS FAB classification than pretreatment. In AML, a CR was defined by ≥50% myeloblast reduction from more than 5% myeloblasts to ≤5%, and a PR is defined by the decrease of ≥50% in the percentage of blasts over pretreatment (but still ≥5%). OS was calculated from the date of the first dose of study drug to the date of death from any cause. PFS was defined as the interval from the date that a CR or PR was documented to the date that the patient experienced recurrence/progression of the disease.

Table 1: Patient characteristics for MDS at baseline

Patient characteristic	n(%)
Median age [years]	67 [23-82]
Gender (Female/Male)	11/14 (44/56)
MDS RAEB-1	11 (44)
MDS RAEB-2	14 (56)
IPSS intermediate 1	8 (32)
IPSS intermediate 2 or high	12 (48)
IPSS unknown (N/A)	5 (20)
R-IPSS intermediate	5 (20)
R-IPSS high or very high	14 (56)
Cytogenetic classification of risk	
Intermediate	16 (64)
Poor	4 (16)
Unknown	5 (20)
ECOG performance status (0-2)	25 (100)
ECOG 0	6 (24)
ECOG 1	16 (64)
ECOG 2	3 (12)
Median cycle	4 cycles [1-32]

MDS: Myelodysplastic syndrome; ECOG: Eastern Cooperative Oncology Group performance status; N/A: not assessed; IPSS: International Prognostic Scoring System; R-IPSS: Revised International Prognostic Scoring System; RAEB: refractory anemia with excess blasts; n: number of patients

Table.2: Treatment response to decitabine in MDS patients

Response assessment	n(%)
Complete response (CR)	3 (12)
Marrow complete response (mCR*)	8 (32)
mCR with HI	5
mCR without	3
Partial response (PR)	1 (4)
Hematologic improvement (HI) only	3 (12)
Stable disease (SD)	3 (12)
Progressive disease	3 (12)
Not assessable	4 (16)
Overall complete response rate, CR+mCR	11 (44)
Overall response rate, CR+mCR+PR	12 (48)
Overall improvement rate, CR+mCR+PR+HI	15 (60)
Rate of stable disease or better, CR +mCR + PR + HI + SD	18 (72)

*mCR: A total of 4 patients were not assessable for a response assessment because post-therapy bone marrow and/or CBC values were not available

Statistical analysis

OS, PFS and overall improvement rate (OIR) were calculated using Kaplan-Meier product-limit estimates, along with 95% confidence interval (CI). Survival data of patients who underwent AHSCT were not included into the survival data of patients with MDS and AML.

Table 3: HIs were detected at the end of median two cycles

HI	n(%)
HI-Neu	2 (8)
HI-E	8 (32)
HI-PLT	4 (16)
Total	11 (44)

HI: hematologic improvement, Neu: neutrophil, E: erythroid, PLT: platelets

RESULTS

Results for MDS

The median age was 67 years (23-82 years), female to male ratio was 44% to 56%, and patients with MDS RAEB-1 and RAEB-2 were 44% and 56%, respectively. Patients with IPSS intermediate-1 were 32%, and patients with IPSS intermediate-2 or high were 48% and all patients had ECOG performance score less than 3. IPSS and IPSS-R scores of 20% of patients couldn't be calculated because their cytogenetics were not reached (Table 1).

Treatment response

Twelve of the 25 patients experienced CR (12%), mCR (32%) or PR (4%); ORR, which included CR+PR+mCR, was found to be 44%. OIR was found to be 60%, which included ORR plus HI. 72% of patients experienced stable disease or better (Table 2).

HI was detected at the end of median 2 cycles. Best results were observed in hemoglobin levels as 32%, followed by platelets with 16% improvement. HIs were observed in 44% of all MDS patients (Table 3). Median OS was 38 months in patients with MDS who achieved HI, whereas it was 11 months in patients who couldn't achieve HI. This finding was not statistically significant (P=0.288, P >0.05).

When we assessed according to IPSS score, response rates of IPSS with intermediate 1 and IPSS with 2 or higher were observed to be quite similar to each other (ORR: 50% vs. 41.6%, OIR: 62.5% vs. 58.3% respectively; Table 4).

Table 4: Response results according to IPSS scores

Response assessment	Intermediate 1 (n=8)	Intermediate-2 or high (n=12)
CR+mCR n (%)	4 (50)	4 (33.3)
Partial response, n(%)	-	1 (8.3)
Stable disease, n(%)	1 (12.5)	2 (16.6)
Hematologic improvement (total), n(%)	4 (50)	6 (50)
Hematologic improvement (only), n (%)	1 (12.5)	2 (16.6)
Overall improvement rate, n(%)	5 (62.5)	7 (58.3)
Progressive disease, n(%)	1 (12.5)	2 (16.6)
N/A %	12.5	8.3
Overall response rate (%)	50	41.6

CR: complete response; mCR: Marrow CR; N/A: Not assessed; IPSS: International Prognostic Scoring System, n: number of patients

OS in 1, 2 and 5 years were 62%, 47% and 17% respectively. PFS at 1, 2 and 5 years were 54%, 45% and 30% respectively (Table 5). Median OS was 21 months (95% CI: 0-46.153) and median PFS was 14 months (95% CI: 0-37.308), as shown in Figure 1. The OS and PFS outcomes of patients who achieved response (CR+mCR+PR) were observed to be statistically significantly better than the others (P<0.013 and P<0.005, respectively), as shown in Figs 2a and 2b. The OS and PFS of patients who couldn't achieve response were 11 and 8 months, respectively.

Results for AML

The median age was seventy-five years (range: 18-81 years) and the female to male ratio was 7 to 6. Three patients had secondary, and 10 patients had de novo AML. The median blast was 70% (range 25-95%) at the time of diagnosis, and they received a median two

Table 5: One, two and five-year overall survival and progression free survival

Survival	1 year	2 year	5 year
Overall survival	62.9%±12.2	47.1%±13.3	17.7%±14.4
Progression free survival	54.9%±13.9	45.8%±13	30.5%±15.4

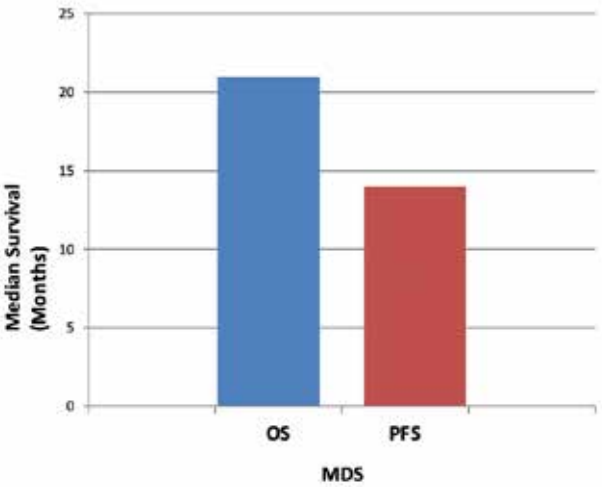

Fig 1: Median OS and PFS were 21 and 14 months respectively.

cycles of treatment (range 1-10). All patients had an ECOG performance score of less than 3. The patient's characteristics are summarized in Table 6.

Treatment response

Eight patients were evaluated by bone marrow examination to determine treatment response. The treatment response could not be evaluated in five patients until completion of the fourth cycle of treatment, three patients died, and two patients discontinued decitabine treatment because of an inadequate hematologic response of peripheral blood and poor performance status. In this trial, CR and PR were observed in four and two patients, respectively. As a result, six of thirteen AML patients experienced CR (n=4) or PR (n=2), and ORR was found as 46%. Two patients couldn't achieve a response. All six patients who achieved response had de novo AML. Median OS and PFS rates were not reached due to 76% of the patients (n=10) were alive, and 38% of the patients' treatment continued (n=5). One-year PFS and OS were observed 77.8±13.9% and 61.4±19.7%, respectively.

Hematologic adverse events

Hematologic toxicity was observed in half of the patients and grade 3-4 hematological toxicity was observed in 39% of patients (Table 7). We also observed 33% with febrile neutropenia, 36% with grade 3 - 4 neutropenia and 13% with grade 3 - 4 thrombocytopenia. The drug mostly caused neutropenia. Neutropenic fever was observed in one-third of patients.

Seven of 25 MDS and one of 13 AML patients underwent AHSCT. Six of seven MDS and one AML patient achieved CR before transplantation. They received a median 3 cycles of decitabine, and responses were detected by the end of a median 3 cycles.

Table 6: Patient characteristics for AML

Patient characteristic at baseline	Values
Median age (years)	75 (18-81)
Gender: Female/Male	7/6
Secondary, n	3
De novo, n	10
Median cycle	2 cycles (1-10)
ECOG 0-2, n	13
ECOG 0, n	3
ECOG 1, n	4
ECOG 2, n	6
Initial median blast ratio	70% (25-95)

n: number of patients

Comparison of the current study with previous reports in MDS

We compared our results with three previously reported data using a 5-day regimen (20 mg/m^2/d or 15 mg/m^2/day, Table 8)[14-16].

DISCUSSION

In the current study, we retrospectively analyzed 25 elderly patients with MDS. The effectiveness of decitabine in MDS has been reported from several clinical trials. To evaluate the efficacy of decitabine in MDS, we compared our results to the data of the previous trials. In these trials, ORR (CR+mCR+PR) were reported between 32-58%[10,14-18]. ORR in our study was better than the results of the two trials mentioned in Table 8 (48% vs. 32%, 36.7% respectively). This could be attributed mainly to the patient characteristics with the absence of patients with chronic myelomonocytic leukemia in our patient group. ORR result in decitabine of reduced dosage in Chinese patients' trial was better than our ORR result (58.2% vs. 48%); this may be due to younger median age in that trial (60 vs. 67 y; Table 8). The OS and PFS outcomes of patients who achieved overall response were observed statistically significantly better than the others (Fig 2).

Table 7: Hematologic toxicity

Grade	Neutropenia n (%)	Thrombocytopenia n (%)	Anemia n (%)
Grade 1	-	3 (7.9)	-
Grade 2	1 (2.6)	-	-
Grade 3	7 (18.4)	2 (5.3)	-
Grade 4	7 (18.4)	3 (7.9)	-
Grade 3-4	14 (36.8)	5 (13.2)	-
Worsening of cytopenias	10 (26.3)	10 (26.3)	23 (60.5)

Hematologic toxicity was observed in 50% of patients (n=19). Grade 3-4 hematological toxicity was observed in 39% of patients (n=15); n: number of patients

Our study showed similar CR rates as reported by ADOPT and DIVA trials (12% vs. 17% and 12.9% respectively). Low CR ratios can be associated with suppression of normal hematopoiesis in MDS. So, it is natural that a substantial proportion of patients showed mCR without CBC recovery after successful treatment with decitabine.

OIR result in our study, which included 32% of MDS patients with IPSS Int-1 risk was better than results of ADOPT and DIVA trials, which had over 50% of MDS patients with IPSS Int-1 risk (OIR: 60% vs 51% and 55.4%). Similarly, OIR (67.1%) of retrospective trial in Chinese patients which had 67.1% of MDS patients with IPSS Int-2 was better than the results of ADOPT and DIVA trials. We can say that decitabine is more effective in patients with Int 2 or high (Table 8). However, when we assessed according to IPSS score in our study, OIR of IPSS with Int- 1, Int-2 or higher were observed quite similar to each other (OIR: 62.5% vs 58.3%, respectively).

In our study, the achievement of HI was associated with prolonged OS (Median OS: 38 months in whom HI was achieved vs. 11 months in whom HI wasn't achieved). A previous study reported that HI was a significant predictor of OS[16]. Although our finding was not statistically significant (P=0.288, P >0.05), decitabine treatment might prolong survival in patients achieving HI.

Although it is not a head-to-head comparison, the median OS in our study was slightly better than the results of three trials mentioned in Table 8 (21 months vs 19.4, 18 and 17.7 months, respectively). This could be attributed mainly to the patient characteristics, with the absence of patients with chronic myelomonocytic leukemia in our patient group and prolonged treatment up to 32 cycles or higher mCR rate in our study (32% vs. 15%, 27.8% and 22.8%). The clinical importance of mCR is uncertain[14], but it may be of value in prolonged survival. Another importance of mCR will be bridging to marrow transplantation where decitabine may induce rapid myeloblast reduction before initiation of transplant conditioning regimens, with less risk than

Table 8: Comparison previous trials and the current study

Variable parameters	Current study	ADOPT	Decitabine of reduced dosage in Chinese patients	DIVA study
No. of patients	25	99	79	101
Study design	Retrospective	Prospective	Retrospective	Prospective
Median age, years	67 (23-82)	72 (34-87)	60 (28-82)	65 (23-80)
Eligibility	WHO (IPSS ≥0.5)	FAB MDS (IPSS ≥0.5)	FAB MDS (IPSS ≥0.5)	WHO (IPSS≥0.5)+ CMML
IPSS intermediate 1	32%	54%	32.9%	52%
IPSS intermediate 2 or high	48%	46%	67.1%	48%
Unknown	20%	-	-	-
Cytogenetic classification of risk				
Good	0 %	49%	50.6%	64.3%
Intermediate	64%	15%	24.1%	14.8%
Poor	16%	26%	25.3%	18.8%
Unknown	20%	6%	-	-
Decitabine regimen	20 mg/M2/dx5 d	20 mg/M2/dx5 d	15 mg/M2/dx5 d	20 mg/M2/dx5 d
Courses, median (range)	4 (1–32)	5 (1–17)	4 (1-11)	5 (1–18)
Treatment response				
Complete response (CR)	12%	17%	29.1%	12.9%
Marrow CR (mCR)	32%	15%	27.8%	22.8%
Partial response (PR)	4%	0%	1.3%	1%
Hematologic improvement (HI)	12%	18%	8.9%	18.8%
Stable disease (SD)	12%	24%	6.3%	10.9%
Progressive disease (PD)	12%	10%	26.6%	7%
Overall complete response rate (CR+mCR)	44%	32%	56.9%	35.7%
Overall response rate (CR+mCR+PR)	48%	32%	58.2%	36.7%
Overall improvement rate (CR+mCR+PR+HI)	60%	51%	67.1%	55.4%
Rate of stable disease or better (CR +mCR + PR + HI + SD)	72%	75%	73.4%	66.3%
Overall survival				
Median	21 months	19.4 months	18 months	17.7 months
1-year probability	62.9%	66%	63.3%	78.6%

IWG: International Working Group; WHO MDS: Myelodysplastic syndrome defined by the World Health Organization classification, IPSS: International Prognostic Scoring System, CMML: Chronic myelomonocytic leukemia, FAB MDS: MDS defined by French-American-British classification

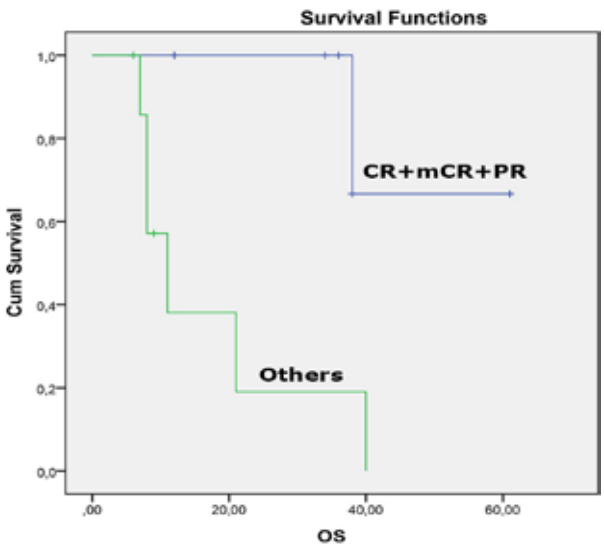

Fig 2a: OS in CR+mCR+PR

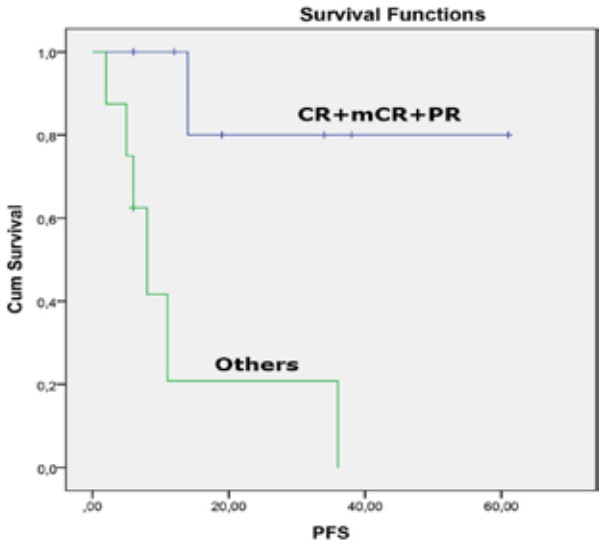

Fig 2b: PFS in CR+mCR+PR

with more intensive approaches. In our study, six of the seven patients with MDS who underwent AHSCT achieved mCR before transplantation.

AML is the most common acute leukemia in adults and accounts for approximately 80% of adult leukemia cases[19]. In adults, the median age at diagnosis is around 65 years. However, the treatment options for the elderly AML patients have been limited and they usually show poor clinical outcomes owing to their unfavorable cytogenetics, poor performance, comorbidity or prior hematologic neoplasms[20]. As a result, a substantial portion of the patients is not suitable for intensive treatment. Our results in AML were limited. In the present study, we retrospectively analyzed 13 elderly patients with AML. Decitabine was well tolerated and patients with AML received a median of 2 cycles of treatment. A subsequent phase III trial named DACO-016 was carried out in 485 patients with AML of intermediate or poor-risk cytogenetics older than 65 years and they were randomized to receive either decitabine or physician's choice. With the median age of the patients being 73 years and median four cycles, the response rate was also higher in decitabine arm, as it was associated with a significantly higher rate (17.8% vs. 7.8%, respectively, P=0.001)[13]. In our study, approximately half of patients with AML (ORR 46%) experienced CR or PR with decitabine. In a retrospective multicentre study, 80 Korean patients with AML were enrolled with the median age of patients being 73 years, and 35 of them underwent bone marrow examination after median 3 cycles reported that 10 of 35 patients (28.5%) achieved response and 1-year survival rate was 38.3%[21]. Higher ORR could be associated with a limited number of patients, a lack of cytogenetic status before decitabine treatment, and also single- center study. In another retrospective single-center study, twenty-four patients with newly diagnosed AML were enrolled. They reported that 12 of 17 patients achieved a response[22]. Similarly, in our study, six of eight patients who underwent bone marrow examination for response assessment achieved a response. Median OS was not reached due to ten of thirteen patients were alive.

Besides, in our study, patients didn't use antibacterial prophylaxis during treatment, and neutropenic fever was observed in one-third of them. So, antibacterial prophylaxis to prevent infectious complications can be a reasonable approach due to decitabine mostly caused neutropenia, and HI was observed at least in neutrophils as we reported in our study.

The current study has several limitations. Data were collected in a retrospective manner and from a single center. In MDS, the IPSS score couldn't be calculated in 20% of patients due to unknown karyotype tests before the treatment. Cytogenetic response to decitabine treatment in patients with MDS couldn't be assessed due to a lack of the genetic tests in bone marrow examination of response assessment.

In AML, we couldn't reach the cytogenetic and molecular tests. Hence, we don't know risk assessment before the treatment but in the real-world situation, there is no known effective treatment in patients with AML who cannot tolerate intensive chemotherapy with poor performance status.

CONCLUSION

Decitabine was well tolerated in both groups. The response to decitabine treatment was found to be associated with a survival benefit in MDS patients. While the treatment options for elder AML patients

have been limited, our real-world data suggest that decitabine could be an effective treatment of choice. As a result, decitabine is effective and safe with acceptable toxicity in intermediate or high-risk MDS patients and elderly patients with AML.

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Conflict of interest: None

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Original Article

Hypovitaminosis-D in chronic Hepatitis C patients: Prevalence, relation to TGF-B1 and effect of viral eradication

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ABSTRACT

Objective: We planned to explore the impact of hepatitis C virus (HCV) eradication, utilizing a sofosbuvir-construct regimen with respect to level of vitamin D, grade of fibrosis and transforming growth factor-beta 1 (TGF-B1) serum level.
Design: Prospective study
Setting: Minia University Hospital, Egypt
Subjects: One hundred and twenty patients with chronic hepatitis C (CHC) were enlisted during this research. Patients were treated by sofosbuvir and ledipasvir for 12 weeks. We classified CHC patients into 2 groups according to serum vitamin D level. Group 1 had serum vitamin D >20ng/ml, and group 2 had serum vitamin D 12-20ng/ml.
Intervention: FibroScan
Main outcome measure: Serum level of vitamin D, TGF-B1 and grade of fibrosis were estimated before and after HCV treatment.
Results: Vitamin D was deficient (15.50±2.42 ng/ml) in 30% of CHC patients. The remaining 70% of CHC patients showed insufficient vitamin D level more than healthy controls (28.88±8.55 vs. 50.8±14.18 ng/ml). The grade of fibrosis and serum TGF-B1 was higher in CHC patients with vitamin D deficiency than CHC patients with vitamin D insufficiency (mean±SD were 10.8±850.22 vs. 8.756±450 pg/ml respectively). After HCV eradication, we found a significant rise in vitamin D serum level while TGF-B1 serum level became significantly lower, with no change in the grades of fibrosis.
Conclusion: Clearing of HCV infection helps to normalize the level of vitamin D and to lower the level of TGF-B1, but with no change in the grade of fibrosis.

KEY WORDS: HCV treatment, TGF-B1, vitamin D

INTRODUCTION

Direct acting antiviral drugs will change the shape of the future of liver diseases, particularly in countries wherever hepatitis C infection (HCV) is the fundamental driver of liver pathology[1]. The Egyptian Demographic Health Survey's evaluation of HCV prevalence in persons between 15 and 59 years of age was 14.7%. Similarly, Egypt has the most elevated predominance of HCV in the world. Given the high prevalence of HCV among more established ages, Egypt obviously has the most noteworthy weight of cutting-edge liver disease from HCV all around[2]. The liver assumes a vital part in the metabolism of vitamin D that is hydroxylated in the liver into 25-hydroxyvitamin D. After that, it is transported to the kidney to experience a second hydroxylation, to form 1, 25(OH) D[3]. 25-hydroxy vitamin D can likewise change over in other cells, such as macrophages and dendritic cells, rather than the kidney cells. Liver cells, beside parathyroid organs and kidneys, express a calcium-detecting receptor that assumes a basic part in managing fundamental calcium homeostasis[4]. Vitamin D derivatives may be involved in cell proliferation, differentiation and immunomodulation[5]. Vitamin D additionally hinders

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inflammatory T cell reactions, decreasing the creation of IFNc and IL-17 for IL-4 and IL-10[6]. Liver diseases prevent the assembly of the active metabolites of vitamin D; thereby leading to abnormal Ca and bone metabolism[7]. Patients with chronic hepatitis C (CHC) have decreased 25(OH) D levels. Due to vitamin D's anti-inflammatory effects, its deficiency exacerbates chronic inflammation in HCV-positive patients. Vitamin D deficiency in chronic liver disease patients will result in advancement of hepatic fibrosis[8]. Vitamin D receptors work out hepatocytes and hepatic stellate cells restraining stellate cell proliferation[9,10]. Vitamin D receptor (VDR) ligands inhibit haematopoietic stem cell (HSC) activation and abrogate liver fibrosis. Activation of VDR signaling antagonizes a wide range of TGFβ/SMAD-dependent transcriptional responses on pro-fibrotic genes in HSCs[10]. In our study, we aimed to evaluate the prevalence of vitamin D deficiency or insufficiency among CHC patients and its relation to the level of fibrosis, and to investigate the effect of HCV eradication using a sofosbuvir-based regimen on the level of vitamin D, grade of fibrosis and TGFB1 serum level.

SUBJECTS AND METHODS

Our study is a prospective open-label randomized study that was undertaken at Tropical Medicine and Internal Medicine Departments of Minia University Hospital, Minia, Egypt, from January 2017 to December 2017. All patients signed informed written consent forms to participate in the study. The study protocol was approved by the Institutional Research Board of the Faculty of Medicine, Minia University, Egypt. The study was conducted in accordance with the ethical guidelines of 1975 Helsinki Declaration. Inclusion criteria included males and females >18 years of age, with CHC infection, who were treated naïve, genotype 4. Patient exclusion criteria included liver cirrhosis, chronic renal insufficiency (creatinine levels >1.5 mg/dL), advanced age, malabsorption syndrome, neck surgery or external radiation to the neck, alcoholism and malignancies. At the end of December 2017, the database included 127 patients with HCV. Seven patients were excluded from analysis due to incomplete follow-up data. Thirty healthy subjects of matched age and gender were included in the study as a control group (Group 3). Demographic data (*e.g.* age, gender and residence) were recorded. All participants were subjected to physical examination and laboratory investigations including complete blood count done by automated cell counter, Sysmex KX-21N (TAO Medical Incorporation, Japan), and liver-function tests and kidney-function tests done by auto-analyzer Konelab i60 (Thermo-electro, Clinical chemistry automation systems, Finland). International normalized ratio was measured using STAGO COMPACT CT Coagulation Analyzer (Diamond Diagnostics, USA), and HBsAg, HCV Abs and HIV Abs by fully automated ChemiLuminescence technology (Cobas E 411-Roche-Roche Diagnostics GmbH Germany). In addition, polymerase chain reaction (PCR) for HCV RNA and serum 25-OH vitamin D3 were done to all participants. Serum TGFB1 and FibroScan were done for CHC patients. Interpretation of results was deficiency ≤20 ng/ml, insufficiency >20 ng/ml and sufficiency ≥30ng/ml. We classified CHC patients into two groups according to serum vitamin D level. Interpretation of results was deficiency ≤20 ng/ml, insufficiency: > 20 ng/ml and sufficiency: ≥ 30ng/ml. Group 1 had serum vitamin D > 20 ng/ml, and group 2 had serum vitamin D of 12-20 ng/ml. None of the CHC patients had serum vitamin D <12 ng/ml. FibroScan grades of liver fibrosis were (F0-F1, F2, F3) and its cut-off values were 7.1 kPa for F ≥2, 9.5 kPa for F ≥3 and 12.5 kPa for F=4. Vitamin D levels were assayed by EIA method (DIA source ImmunoAssays Louvain-la Neuve, Belgium). Serum TGF-B1 level was measured using immunosorbent assay (EIA) kit supplied by abcam.com (ab100647). Imaging by abdominal ultrasound and plain X-ray of lumbosacral spine was done. CHC patients received direct acting antiviral (DAAs) sofosbuvir 400 mg plus ledipasvir 90 mg for 12 weeks as treatment for HCV. We checked the effect of HCV treatment by quantitative (q) real time (RT)-PCR in the fourth week and at the end of treatment. Plasma HCV RNA was analyzed by using the DNA technology (Moscow, Russia). HCV RNA-positive samples were genotyped using an HCV real-time genotype kit (AmpliSens® HCV-genotype-FRT PCR kit). The kit was able to detect HCV genotypes 1a, 1b, 2, 3 and 4 following the manufacturer's instructions. Serum 25-OH vitamin D3, TGFB1 and FibroScan were detected in CHC patients at the end of treatment. The study was conducted in accordance with the guidelines of 1975 Declaration of Helsinki, and the study protocol was approved by the Ethical Research Board of the faculty of Medicine, Minia University. Adherence to treatment was assessed on each visit based on tablet count.

Statistical analysis

Statistical analysis was done using IBM SPSS Statistics Program (Version 21). Quantitative data were described by the mean as a measure of central tendency and standard deviation as a measure of dispersion, while categorical variables were summarized by frequency and percent. Student's t-test was used to detect significant differences in the mean quantitative variables between two groups of patients, and a chi-square test was used to study significant association between two categorical variables. ANOVA was used

Table 1: Demographic and laboratory data of the studied groups before HCV treatment

Variable	Group 1 n=84	Group 2 n=36	Group 3 n=30	*P*-value
Age, Mean ± SD	44.9±10.09	43±10.4	42.9±11	0.522
Sex				0.995
Male	24(66.6%)	51(60.7%)	18(60%)	
Female	16(33.4%)	33(39.3%)	12(40%)	
ALT, Mean ± SD (U/ml)	37.6±24.23	47.8±28.2	22.3±13.8	0.0004
AST, Mean ± SD (U/ml)	34.8±14.97	42.4±22	24.8±10.8	0.0001
T. Bilirubin, Mean ± SD (mg/dl)	0.78±0.25	0.9±0.2	0.6±0.30	0.9684
Albumin, Mean ± SD (gm/dl)	4.3±0.41	4.4±0.5	4.5±0.2	0.0575
INR, Mean ± SD	1±0.1	0.9±0.3	1.1±0	0.000
Hb, Mean ± SD (gm/dl)	13.13±1.11	12.65±1.3	13.2±1.4	0.101
TLC (x103 cells/cmm3), Mean ± SD	6.68±1.45	6.5±1.2	7.8±1.6	0.1013
Platelets (x103cells/cmm3), Mean ± SD	270.4±84.55	260±90.45	300.4±90.65	0.1013

HCV: hepatitis C virus; ALT: alanine transaminase; AST: aspartate transaminase; INR: international normalized ratio; Hb: hemoglobin; TLC: total leucocyte count

to detect the differences between more than two groups. *P*-value was assumed to be significant if less than the threshold of 0.05 and confidence intervals were at 95% level.

RESULTS

Our study indicated that there was no statistically significant difference in age between the three groups (mean ±SD were 44.9±10.09, 43±10.4 and 42.9±11 years). Most participants of group 1, group 2 and group 3 were males (66.6%, 60.7% and 60%) respectively. All of our patients were genotype 4. Both group 1 and group 2 had a more significant increase of alanine transaminase (ALT) than the control group, while group1 had a significantly lower level than group 2 (mean±SD were 37.6±24.23, 47.8±28.2 and 22.3±13.8 U/ml)) with *P*=0.000. Also, aspartate transaminase (AST) showed a significant difference between groups (34.8±14.97, 42.4±22 and 24.8±10.8 U/ml) in groups 1, 2 and 3 respectively with *P*-value 0.000. International normalized ratio showed a significant difference between groups (0.9±0.3, 1±0.1 and 1.1±0) in groups 1, 2 and 3 respectively, with *P*=0.000. There were no significant differences in total bilirubin level, albumin level, HB, platelet or total leukocytic count between the three groups (Table 1).

Table 2 shows that the mean serum vitamin D level in the control (group 3) was 50.8±14.18 ng/ml. Eighty-four (70%) of CHC patients (group 1) had mean serum vitamin D level 28.88±8.55 ng/ml, significantly lower than the control group. Vitamin D was insufficient (15.50±2.42 ng/ml) in 30% of CHC patients (group 2).

Table 2: Comparison of vitamin D level in the three groups before treatment

Group	Number of cases	Mean ±SD ng/ml	*P*-value
Group 1	84(70%)	28.88±8.55	0.000
Group 2	36(30%)	15.50±2.42	
Group 3 (control)	30(100%)	50.8±14.18	

Table 3: Effect of vitamin D on bone mineral density

Spine X-ray	Group1	Group 2	Group 3
Spine X-ray BD			
Normal	84(100%)	36(100%)	30(100%)
Decrease bone density	0(0%)	0(0%)	0(0%)
Spine X-ray K			
Normal	70(100%)	30(100%)	30(100%)
Kyphosis	0(0%)	0(0%)	0(0%)

BD; bone density; K; kyphosis

Table 4: Grades of fibrosis and serum TGF-B1 in CHC patients before treatment

Grade of fibrosis	Group1 n=84	Group2 n=36	*P*-value
F(0-1) (N)	51(60.70%)	1(2.8%)	< 0.000
F 2 (N)	25(29.80%)	20(55.6%)	
F 3 (N)	8(9.50%)	15(41.6%)	
Serum TGF-B1, Mean ±SD (pg/ml)	8.756±450.40	10.800±850.22	0.000

TGF-B1: Transforming growth factor beta-1; N: number of patients; F: grade of fibrosis

Although vitamin D levels were significantly lower in groups 1 and 2 than group 3, and group 2 showed vitamin D insufficiency, bone density did not decrease in groups 1 or 2, and there was no kyphosis (Table 3).

Table 4 shows the grades of fibrosis and serum TGFB1 in CHC patients before treatment. Group 1 had 51 patients (60.70%) with grade F0-F1, 25 patients

Table 5: Demographic characteristic and laboratory findings of CHC patients before and after treatment

Variable	Group 1 n=84			Group 2 n=36		
	Before treatment	After treatment	*P*-value	Before treatment	After treatment	*P*-value
ALT, Mean ± SD (U/ml)	37.6±24.23	30.7±9.31	0.212	45.8±28.2	32.9±8.2	0.013
AST, Mean ± SD (U/ml)	34.8±14.97	29.8±6.42	0.327	42.4±22	28.10±4.5	0.000
T. Bilirubin, Mean ± SD (mg/dl)	0.78±0.25	0.78±0.19	0.891	0.9±0.2	0.85±0.2	0.293
Albumin, Mean ± SD (gm/dl)	4.3±0.41	4.38±0.42	0.491	4.4±0.5	4.5±0.4	0.138
INR, Mean ± SD	1±0	1±0	1	0.9±0.2	1±0.4	0.184
Hb, Mean ± SD (gm/dl)	13.13±1.11	10.32±1.01	<0.001	12.10±0.3	10.10±1.2	0.000
TLC ($x10^3$ cells/cmm^3), Mean ±SD	6.68±1.45	5.23±1.17	<0.001	6.5±1.2	5.5±1.3	0.001
Platelets ($x10^3$ cells/cmm^3), mean±SD	270.4±84.55	248.6±68.43	0.063	260±90.45	250.57±85.03	0.650

CHC: chronic hepatitis C; ALT: alanine transaminase; AST: aspartate transaminase; INR: international normalized ratio; Hb: hemoglobin; TLC: total leukocyte count

(29.80%) with grade F2 and eight patients (9.50%) with grade F3, while group 1 had one patient (2.80%) with grade F0-F1, 20 patients (55.6%) with grade F2 and 15 (41.60%) patients with grade F3. There was a significant difference in the grade of fibrosis between groups 1 and 2 with *P*=0.000. The serum level of TGFB1 was significantly higher in group 2 than group 1 (means ±SD were 10.800±850.22 and 8.756±450 pg/ml respectively) with *P*=0.000.

Table 5 shows that, after treatment with sofosbuvir 400 mg plus ledipasvir 90 mg for 12 weeks, AST and ALT showed significant decrease in groups 1 and 2 with *P*=0.013 and *P*=0.000. Also, Hb and total leukocytic count showed significant decrease in groups 1 and 2 after treatment with *P*=0.000 and *P*=0.001. No significant differences were detected in total bilirubin, albumin and platelets in groups 1 and 2 after treatment.

There was a rise in serum vitamin D level in group 1 after treatment, which was statistically significant (means±SD were 32.99±7.43 vs. 28.88±8.55 ng/ml with *P*=0.001). In group 2, however, the level was 25.66±4.88 ng/ml after treatment vs. 15.50±2.42 ng/ml before treatment with significant differences (*P*=0.000). We found a significant decrease in TGFB1 after treatment of group 1 (means±SD were 8756±450.40 pg/ml before treatment vs. 8600±500.11 pg/ml after treatment) with *P*=0.0351. Also, there was a significant decrease in TGFB1 after treatment of group 2 (means±SD were 10.800±850.22 pg/ml before treatment vs. 7.450±750 pg/ml after treatment) with *P*=0.000. We did not detect any significant changes in the grades of fibrosis before or after treatment in both groups 1 and 2 (*P*-values 0.958 and 0.888 respectively; Table 6).

DISCUSSION

HCV is viewed as one of the main reasons for liver damage around the world, ranging from liver injury and cirrhosis to hepatocellular carcinoma[11]. A decline in vitamin D 25 is an impression of decreased liver capacity or malnutrition. Another issue is that, in liver illness**,** bile creation is hampered, prompting a reduction in fat absorption and resulting in unusual take-up of vitamin D[12]. It is conceivable that HCV decreases 25(OH) D levels by changing lipid metabolism. HCV decreases creation of 7-dehydrocholesterol, the antecedent of endogenously-delivered vitamin D[13]. Under vitamin D deficiency, the transcriptional activity of VDR was decreased, leading to the down regulation of insulin-induced gene-2 expression and, thus, its inhibitory role on sterol regulatory element-binding protein 2 activation; 3-hydroxy-3-methylglutaryl-coenzyme A reductase expression was accordingly increased. So in hypovitamnosis D**,** there is an associated increase in serum cholesterol level[14]. VDR acts as an

Table 6: Vitamin D level, TGF-B1 serum level and grades of fibrosis after HCV treatment

Variable	Group 1 n=84			Group 2 n=36		
	Before treatment	After treatment	*P*-value	Before treatment	After treatment	*P*-value
Vitamin D, Mean ±SD (ng/ml)	28.88±8.55	32.99±7.43	0.001	15.50±2.42	25.66±4.88	0.000
TGF-B1, Mean ±SD (pg/ml)	8,756±450.40	8600±500.11	0.0351	10,800±850.22	7,950±750	0.000
F(0-1)	51(60.71%)	51(60.71%)	0.958	1(2.8%)	1(2.8%)	0.888
F 2	25(29.79%)	26(30.95%)		20(55.6)	22(61.1)	
(F 3	8(9.50%)	7(8.34%)		15(41.6%)	13(36.1%)	

endocrine checkpoint to modulate the wound healing response in liver, and VDR ligands can be a potential therapy for liver fibrosis. Liver fibrosis can be ameliorated by administration of the synthetic VDR agonist calcipotriol, which reduces both collagen deposition and fibrotic gene expression[10]. Up to this point, restorative destruction of chronic HCV infection needs the employment of injectable IFN that are related to a major range of facet effects and suboptimal effectiveness. Nowadays, mixes of DAA have modified the scene of hepatitis C treatment. While these spoke to a noteworthy achievement due to the high viability and ideal security profile, there is as yet a need to gather additional data about the impact of these DAA on patients after viral cure[15]. This study was undertaken at the Tropical Medicine and Internal Medicine Departments of Minia University Hospital, Minia, Egypt, in the period from January 2017 to December 2017. We intended to evaluate the prevalence of vitamin D deficiency or insufficiency among CHC genotype 4 patients and its relation to the level of fibrosis and TGFB1 serum level and to explore the impact of HCV eradication, utilizing a sofosbuvir-construct regimen with respect to the level of vitamin D, grade of fibrosis and TGFB1 serum level. One hundred and twenty CHC patients were enrolled within the study along with 30 healthy controls. Our study patients were treated with sofosbuvir at 400 mg daily and ledipasvir at 60 mg daily for 12 weeks. Our results indicated that, before HCV treatment, there were significantly lower levels of vitamin D level in chronic hepatitis patients than in the controls. We reported, in this study, that vitamin D deficiency was in 30% of CHC genotype 4 patients, while the remaining 70% CHC patients showed vitamin D insufficiency. These outcomes are in harmony with Petta *et al*, who detailed that mean serum 25(OH) D levels in CHC patients were significantly lower than age and sex-coordinated controls (25.1±9.9 ng/ml vs. 43.1±10.2 ng/ml; P <0.0001)[16]. Our study has indicated that group 2 had a statistically significant increase in liver enzymes than group 1 for ALT and AST. Our results are also in agreement with Bahreynian *et al*, who detected that higher rates of vitamin D deficiency were documented among individuals with increased levels of liver enzymes[17]. Our results also agree with Liangpunsakul *et al*, who reported that, in adult participants with elevation in serum, ALT levels had lower 25(OH)D levels than those with normal ALT levels (24.7±10.4 ng/mL vs 26.8±10.9 ng/mL, P <0.01)[18]. Also, our results agree with Barchetta *et al*, who reported different studies showing that hypovitamosis D is associated with the presence of NAFLD and steatohepatitis plus elevated transaminases level, because vitamin D inhibits the hepatic expression of pro-fibrotic mediators, such as platelet-derived growth factor and transforming growth factor β (TGF-β), and suppresses the expression of collagen, α-smooth muscle actin and tissue inhibitors of metalloproteinase-1[19]. The seriousness of vitamin D inadequacy relates to the seriousness of liver disease[20]. Vitamin D has anti-inflammatory effect so its deficiency allows the proinflammatory cytokines and chemokines advance HCV liver disease[21]. In addition, after HCV treatment, we found a significant rise of mean vitamin D in group 2 and group 1. All of the included CHC patients are cleared from HCV as documented by PCR at the end of treatment and 12 weeks afterwards. Thus, clearing of HCV infection helped to normalize the level of vitamin D. The principal question is to know the mechanism that could clarify vitamin D insufficiency in HCV patients who do not have liver cirrhosis. The active HCV infection that affects the regulatory mechanisms of vitamin D synthesis maybe decreases 25(OH) D levels by changing lipid metabolism. In the setting of DAA-based antiviral, HCV-RNA will not be detected for a number of days or weeks after the start of treatment. This is continually joined by a diminishment inflammation signals (*i.e.* normalization of transaminases) followed by normalization of vitamin D level.

TGFβ is a multifunctional cytokine with profound effects on cell division, differentiation, migration, adhesion, organization and death. Following liver injury, TGFβ1, derived from paracrine and autocrine sources, binds to type I and type II serine/threonine receptor kinases on the cell surface of HSCs. Subsequently, its downstream effectors SMAD2 and SMAD3 are phosphorylated and released into the cytosol where they form a complex with SMAD4. This SMAD complex can then translocate into the nucleus, recognize SMAD-binding elements on the genome and directly regulate target genes[22-24]. Activation of VDR signaling antagonizes a wide range of TGFβ/SMAD-dependent transcriptional responses on pro-fibrotic genes in HSCs[10]. We detected the serum level of TGFB-1 in our CHC patients before HCV treatment and we found that it significantly increased in patients with vitamin D deficiency more than in patients with insufficiency, and there were decreased levels in both groups after treatment. These results agree with Kotsiri *et al*, who reported that TGF-β1 serum levels decrease significantly at the end of therpay and remain decreased six months after the end of therapy, mostly in CHC patients who achieve sustained virologic response after pegylated interferon-α and ribavirin combination treatment[25]. Also our results agree with Chalupa *et al*, who reported that TGF-b serum levels of CHC decrease during IFN-a-based

therapy[26]. In our study, the grades of fibrosis before HCV treatment were significantly higher in the CHC patients with vitamin D deficiency than CHC patients with vitamin D insufficiency where most of group 2 patients had F2 and F3, while most of group1 patients where F0-1. Our results agree with Lange *et al*, who reported that advanced fibrosis stage F2-F4 *vs* F0-F1 is associated with low 25(OH)D[27]. Also, our results agree with Guzman-Fulgencio *et al*, who reported that low 25(OH)D deficiency is associated with advanced fibrosis (F3/4 *vs* F0-2)[28] but disagree with Esmat *et al*, who found that no correlation was found between vitamin D levels and the stage of liver fibrosis[29]. After treatment of CHC patients**,** there was no significant change in the grades of fibrosis neither in group 1 nor in group 2. Indeed, we were in need for repetition of FibroScan to our patients for a longer period of time after the sustained virologic response to confirm whether the grades of fibrosis improved after HCV treatment or not.

In conclusion, vitamin D deficiency presents in 30% of CHC patients, while the remaining 70% of patients have vitamin D insufficiency. These percentages are associated with the high level of TGF-B1 and increased grades of fibrosis. Clearing of HCV infection helped to normalize the level of vitamin D in CHC patients and decrease the serum level of TGFB-1, but with no improvement in the grades of fibrosis.

CONCLUSION

Vitamin D deficiency presents in 30% of CHC patients while 70% of CHC patients have vitamin D insufficiency. Clearing of HCV infection helps to normalize the level of vitamin D and to lower the level of TGFB1, but with no change in the grade of fibrosis.

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Original Article

The comparison of arthroscopy and mini open surgery results in femoroacetabular impingement surgical treatment

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ABSTRACT

Objective: Femoroacetabular impingement syndrome (FAIS) is a progressive condition leading to coxarthrosis in young adults, especially if left untreated. In this study, we aim to compare the early clinical results and patient satisfaction in FAIS patients who are treated with mini open surgery and arthroscopic method.
Design: Retrospective study
Setting: Department of Orthopaedics and Traumatology, Istanbul University Cerrahpasa Faculty of Medicine
Subjects: Twenty-one patients were treated with mini open surgery and 23 patients were treated with arthroscopic method. Total of 44 patients were treated between August 2009 and October 2015.
Intervention: Mini open surgery and arthroscopic method for FAIS patients
Main outcome measures: Preoperative and postoperative range of motion degrees, hip outcome score (HOS), WOMAC, visual analog scale (VAS), modified Harris Hip Score (mHHS), nonarthritic hip score (NAHS) and perioperative and postoperative complications were evaluated.
Results: We determined a statistically significant increase in mHHS, WOMAC, HOS, NAHS and a significant decrease in alfa angle, CE angle, VAS pain score in both mini open surgery and arthroscopy groups. The score results other than VAS significantly improved in favor of mini open surgery patients (P<0.05). Even though VAS score was also improved in mini open surgery group, it was not statistically significant (P<0.521).
Conclusion: Early term evaluation of FAIS treatment results of patients with both methods are found to be satisfactory. However, the determination of superiority of these techniques is not possible because of limited research available. We approve that the decision making between these techniques should be based on preoperative evaluation and surgeons' experience.

KEY WORDS: arthroscopy, femoroacetabular impingement syndrome, mini-open surgery, osteoarthritis

INTRODUCTION

Femoroacetabular impingement syndrome (FAIS) is a progressive condition leading to coxarthrosis in young adults, especially if left untreated. FAIS is usually diagnosed more frequently because of the awareness of femoroacetabular impingement syndrome in the etiology of hip pain in young athletes over the last decade. FAIS causes early osteoarthritis due to labrum and cartilage damage if left untreated. For many years, childhood diseases such as slipped capital femoral epiphysis, developmental dysplasia of the hip and Perthes disease were seen among the causes of secondary osteoarthritis of the hip. These conditions that resulted in deterioration in the normal biomechanics are the cause of the reduced contact area in the hip joint surface.

In 1975, Harris described the "pistol grip" deformity seen at the head and neck of the femur in early-onset

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osteoarthritis. The pathogenesis of femoroacetabular impingement syndrome is not clear, but the most accepted etiologic factors are anomalies resulting from the proximal femur, acetabular-induced disorders and untreated childhood diseases. Coxa profunda osteonecrosis of the femur, malalignment of the femoral neck fractures, femoral and periacetabular osteotomies, and acetabular retroversion are some known causes[1-4]. During the movement of the hip joint acetabular cartilage, labrum injury and progressive joint degeneration are thought to be caused by repetitive, abnormal and eccentric contact between the acetabulum margin and the femur head or neck[5]. The incidence has been reported as 10-15%[6]. Femoroacetabular impingement syndrome can be prevented from progressing to osteoarthritis when it is diagnosed and treated early. Activity modification and anti-inflammatory drug medication should be planned in the early period group of FAIS patients with acute hip pain. However, when conservative treatment does not work, there are several options for surgery. Arthroscopic repair of labral and chondral lesions and open osteoplasty for abnormal structures are surgical options for FAIS.

In this study, we aim to compare the early clinical results and patient satisfaction of femoroacetabular impingement syndrome patients who are treated with the mini-open surgical and arthroscopic method.

SUBJECTS AND METHODS

This study was approved by local ethics committee (Verified Project No: 83045809/604.01/02-169648) and conducted in accordance with the principles of the Declaration of Helsinki. Between August 2009 and October 2015, patients with femoroacetabular impingement that were surgically treated were retrospectively reviewed. In this period, 44 hips of 42 patients were treated surgically. Twenty-one hips of 21 patients underwent mini-open surgery and 23 hips of 23 patients underwent arthroscopic surgical treatment. Arthroscopy was performed on the same hips of one patient and mini-open surgery was performed after one year. One of the patients was examined with different methods for six years with different methods. Twelve (57.1%) male and nine (42.9%) females of 21 patients underwent open surgery. The average age of the patients is 41.1 years and the age range is 30-58 years. Eleven (52.4%) of the hips were on the right and 10 (47.6%) were on the left. The mean body mass index (BMI) on the operation date of the patients treated with the mini open method was 27.1 kg/m^2. The mean follow-up period of patients who underwent mini-open surgical treatment was 30.35 (9-67.2) months. Eleven of the 23 patients (47.8%) were male and 12 (52.2%) were female. The average age of the patients was 33.52 years. There were 10 (43.5%) right hips and 13 (56.5%) left hips in arthroscopic group. The average BMI of the arthroscopically treated patients was 25.54 kg/m^2. The mean follow-up period of patients who underwent arthroscopic treatment was 61.14 (29-74.7) months (Table 1). Twelve patients had the pincer type, seven had cam type and four had mixed type impingement of the 23 hips that underwent arthroscopic surgery (Table 2). Five patients were classified as cam type and 16 as mixed type impingement of 21 hips treated with open surgery. Preoperative and postoperative range of motion degrees, hip outcome score (HOS), Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), visual analog scale (VAS), modified Harris hip score (mHHS), nonarthritic hip score (NAHS) scores, and perioperative and postoperative complications were evaluated. The mean preoperative alfa angle was 73.71±10.77 degrees, and center-edge (CE) angle was 38.95±7.75 degrees in the mini-open surgery group. The mean preoperative alfa angle was 61.39±11.15 degree, and CE angle was 40.17±9.14 degree in arthroscopy group.

Table 1: Descriptive data according to surgical methods

Descriptive data of patients	Surgical method		*P*
	Arthroscopy (n=23) Avg±SD	Mini open (n=21) Avg±SD	
Age (year)	33.52±11.41	41.10±8.18	[a]0.016*
Body mass index (kg/m^2)	25.54±4.74	27.10±4.04	[a]0.251
Pain duration (years; median)	3.35±3.41 (3)	3.52±4.91 (2)	[b]0.800
Number of hospitalization days (median)	3.74±2.40 (3)	4.57±2.80 (3)	[b]0.128
Follow-up (month; median)	61.15±11.79 (66.2)	30.35±21.52 (23.4)	[b]0.001**

[a]Student t Test; [b]Mann Whitney U Test; [c]Pearson's Chi-square test
*P<0.05; **P<0.01

Statistical analysis

Number Cruncher Statistical System 2007 (Kaysville, Utah, USA) program was used for statistical analysis. Student t-test was used for two group comparisons of normal distribution parameters in comparison of descriptive statistical methods (mean, standard deviation, median, frequency, rate, minimum, maximum) as well as quantitative data. Mann Whitney U test was used for two groups of non-normal distribution parameters. Pearson's Chi-square test was used for comparison of qualitative data. Paired Sample t test was used for intra-group comparisons of normal distribution parameters. Wilcoxon Signed Ranks test was used for intra-group comparison of non-normal distribution parameters. Statistical significance was evaluated at P <0.01 and P <0.05 levels.

Table 2: Descriptive data according to gender and FAIS type

Descriptive data of patients	Number of patients (%)	Number of patients (%)	*P*
Gender			[c]0.537
Female	12 (52.2)	9 (42.9)	
Male	11 (47.8)	12 (57.1)	
Side			[c]0.555
Right	10 (43.5)	11 (52.4)	
Left	13 (56.5)	10 (47.6)	
Type			[c]0.001**
Cam	7 (30.4)	5 (23.8)	
Pincer	12 (52.2)	0 (0)	
Mixed	4 (17.4)	16 (76.2)	

[a]Student t Test; [b]Mann Whitney U Test; [c]Pearson's Chi-square test
*P<0.05; **P<0.01

RESULTS

Six of the 42 treated patients had no labrum rupture. A partial labrum resection was made by deciding that the present labrum rupture is not repairable in 15 of 23 arthroscopically treated hips. In 6 arthroscopically treated hips, it was decided that the labrum rupture was repairable and it was fixated with 1-3 anchors. Femoral osteoplasty was performed with high-speed burrs in all 11 hips that have cam or mixed type impingement treated arthroscopically. A partial labrum resection was made by deciding that the present labrum rupture is not repairable in five of 21 hips treated with open method. Femoral osteoplasty was performed with a high-speed burr in all 21 mixed or cam type hips treated with open method. Acetabular osteoplasty was performed to 12 hips that have mixed type impingement. Labrums' were treated with 1 or 2 suture anchors. Femoral osteoplasty was performed on 21 of 32 patients with cam-type or mixed type impingement. Acetabular osteoplasty was performed with an open method in 12 of the 32 patients with pincer type or mixed type impingement. Two patients in this group treated with the arthroscopic method. Partial excision of the labrum was performed in five patients, while anchor assisted labrum repair was performed in 12 patients treated with open method. Partial labrum excision was performed in 15 patients treated arthroscopically while labrum repair was performed in six patients.

There was a statistically significant difference between the mean age of the cases according to the surgical methods (P=0.016; P <0.05). The age of arthroscopic surgery group patients is significantly lower than open surgery group. Gender distributions and BMI measurements did not show statistically significant differences according to surgical methods (P >0.05). In terms of surgical methods, the duration of pain, the number of days in which they were involved and the operation sides did not show statistically significant differences (P >0.05). Although the mini-open method was significantly superior (P <0.05) in terms of changes in all scores except for VAS and averages of the range of motion, it was found that the improvement in VAS averages was better but statistically no arthroscopic superiority was found (P <0.521).

In patients' preoperative and postoperative comparison who were evaluated postoperative 1st week, 3rd week, 3rd month and 6th month, we determined a significant increase of 15.48±7.33 points (P <0.05) in mHHS, 10.08±5.80 points in WOMAC, 7.84±4.73 points in HOS, 13.04±7.96 points NAHS and a significant decrease of 18.38±10.32 points (P <0.05) in alfa angle, 3.95±5.08 points in CE angle, and 4.00±1.34 points in VAS pain score in mini-open surgery group. In arthroscopy group, we determined a significant increase of 7.48±7.24 points (P <0.05) in mHHS, 7.27±7.72 points in WOMAC, 4.28±5.55 points in HOS, 5.27±6.64 points in NAHS and a significant decrease of 4.22±6.51 points (P <0.05) in alfa angle, 1.17±1.95 points in CE angle, and 3.74±1.36 points in VAS pain score. The score results other than VAS were significantly improved in favor of mini-open surgery patients (P <0.05). Even though VAS score was also improved in mini-open surgery group, it was not statistically significant (P <0.521). Clinical and radiological results of patients' preoperative and postoperative comparisons were summarised in Table 3.

Table 3: Clinical and radiological results of patients' preoperative and postoperative comparisons

Clinical and radiological results	Surgical method			
	Arthroscopy (n=23)		Mini open (n=21)	
	ΔAvg±SD	*P*-value	ΔAvg±SD	*P*-value
mHHS	7.48±7.24	[b] p<0.05*	15.48±7.33	[b] p<0.05*
WOMAC	7.27±7.72	[b] p<0.05*	10.08±5.80	[b] p<0.05*
HOS	4.28±5.55	[b] p<0.05*	7.84±4.73	[b] p<0.05*
NAHS	5.27±6.64	[b] p<0.05*	13.04±7.96	[b] p<0.05*
Alfa angle	-4.22±6.51	[b] p<0.05*	-18.38±10.32	[b] p<0.05*
CE angle	-1.17±1.95	[b] p<0.05*	-3.95±5.08	[b] p<0.05*
VAS	-3.74±1.36	[b] p<0.05*	-4.00±1.34	[b] p<0.521

[a]Student t Test; [b]Mann Whitney U Test; [c]Pearson's Chi-square test
*P<0.05; **P<0.01
mHHS: modified Harris hip score; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index; HOS: hip outcome score; NAHS: nonarthritic hip score; CE: center-edge; VAS: visual analog scale

DISCUSSION

The number of studies comparing the results of mini-open surgery and arthroscopic surgery is quite limited. Arthroscopic surgery is less traumatic to soft tissues, has faster recovery and easy return to

sports activity[7-13]. Arthroscopic surgery has gained popularity today. The long duration of surgery, need to perform a capsulotomy during the procedure and difficulty of repair after capsulotomy, longer learning time curve, more technical requirements, and the need to be closer to the femoral neurovascular structures by anterolateral and the anterior portals are the disadvantages[14]. Due to these advantages and disadvantages in treatment methods, it is necessary for surgeons to evaluate patients in many different methods in the postoperative period. Thus, the preoperative optimal surgical approach will be determined.

A study of Clohisy *et al* which combined arthroscopy and open method revealed a 25-point improvement in the hip score and a 21° improvement in alpha angle, and only two patients had coxarthrosis[15]. In our study, the rates of patients treated with mini-open method were 18.3° improvement in alpha angle and 15.4 points increase in Harris score. In a study by Palmer *et al*, 60% of the patients who applied routine FAIS surgery prevented the development of osteoarthritis, and this rate is 12% for surgeons who apply mainly to conservative treatment. The same surgeons stated that they applied 78% surgery in the first treatment of the patient who came with pain preventing daily activity[16]. At this point, the surgeon must make a decision and answer the question of whether to reduce the recurrent microtraumas in the femoral head-neck junction formed during daily activities with activity modification or correct this pathology with the help of surgical intervention.

Both arthroscopic treatment and mini-open method give less damage than safe dislocation, but there is no statistically significant difference between long term clinical results. As the cause of developing coxarthrosis, the degree of cartilage damage in the preoperative period is more important than the type of surgical treatment modality[17]. Therefore, preoperative surgical timing is very important in order not to delay. The pain duration was 3.35 years in the arthroscopy group and 3.52 years in the mini-open surgery group in our study. It is statistically significant that there is no difference between the treated group of patients in the preoperative period. However, it should be kept in mind that arthritic changes begin before pain develops. For this reason, there should be no conclusive evidence regarding the superiority of the methods for preventing the development of postoperative arthrosis.

In our series, a patient who underwent arthroscopy did not pass the complaints in the early and middle period postoperatively. Total hip arthroplasty was performed at the postoperative 6th year. We believe that this situation has developed as a result of the cartilage injury that had already begun preoperatively. The fact that patients with Tönnis stage 2, 3 osteoarthritides had a high rate in the patient population who underwent safe dislocation surgery is another factor that increases the failure rates. In addition, femoral neck fracture, osteonecrosis or deep infection was not observed in our study. The most common complications in arthroscopy-assisted mini-open surgery include damage to the lateral femoral cutaneous nerve, inadequate osteoplasty, and postoperative early load-induced femoral neck fracture[18]. In the study of Matsuda *et al*, there was only one fracture of the femoral neck and two deep infections in the follow-up of patients who underwent mini-open surgery for the hip joint. None of the patients had avascular necrosis[19]. In Harris *et al*'s study, 6134 patients were screened and 1.4% had neuropraxia. 40% of this neuropraxia are pudendal nerve palsy and 99% of these are transient[20]. Sensory loss and erectile dysfunction are the most common findings in the genital area. In addition, due to the natural course of the lateral femoral cutaneous nerve over the interval between the tensor fascia lata and Sartorius, the ratio of pudendal or femoral neuropraxia due to nerve damage in the postoperative period is 45% in some publications[21,22]. In the series of Horisberger *et al*, this rate was reported as 9% sciatic, pudendal and lateral femoral cutaneous nerve neuropraxia[23]. Although the perineal region support was used in our patient who was treated arthroscopically in our study, pudendal nerve arteries developed in the postoperative period. The patient experienced perineal region loss of sensation, incontinence and impotence. During the follow-up period, these findings gradually decreased in two weeks. Loss of anterior skin sensation in the thigh developed at a patient operated with a mini-open method. In the postoperative second-year follow-up, it was found that neuropraxia of the lateral cutaneous nerve was decreased.

Matsuda *et al* reported that patients who underwent osteoplasty for more than 30% of the femoral neck diameter were at risk for the collum femoris fracture after open surgery[19]. However, contrary to this situation, FAIS clinically persists after the inadequate osteoplasty procedure due to the surgeon's overprotective attitude. Mini-open method is an alternative method to prevent inadequate treatment. In the series of patients for whom only arthroscopic labral and chondral debridement was performed and acetabular reconstruction or femoroplasty was not performed with hip pain and mechanical symptoms, a significant proportion (85%) of the patients stated that hip pain decreased or passed within two years[24,25]. The group with the best response to treatment was found to have low-grade cartilage lesions[26-28]. Labral tears and chondral lesions may be associated with trauma and exercise in both young and elderly patients[29]. As

a result, it can be concluded that not all labral lesions are due to femoroacetabular compression. Whether degeneration is caused by hip dysplasia or labral degeneration caused by impingement is extremely important in the decision-making process[7,30]. mHHS scores were reported as 89.7% in the repair group and 67% in the debridement group in Larson *et al*'s study[31]. Only if painful, labrum debridement provides palliative treatment with arthroscopic treatment, but there will be no causative intervention. In our study, we found no labrum pain and complaints in 12 patients who underwent mini-open method and labrum separation for acetabular osteoplasty followed by suture anchor fixation. Patients who underwent arthroscopically treated 15 labrum excision and six labral repairs had no statistically significant results in postoperative follow-up. A larger and homogeneous series of patients were required. We believe that labrum excision and repair can be compared in a healthier manner in patient groups that are not suitable for arthroscopic treatment, patients with non-painful Perthes, femoral head epiphyseal shift and acetabular overbearing.

CONCLUSION

Early term evaluation of femoroacetabular impingement treatment results of patients with mini-open surgery and arthroscopy methods are found to be satisfactory. Due to the long and difficult learning curve, it is noteworthy that the surgeons performing the first arthroscopy as well as experienced surgeons in the major centers have low complication rates. So mini open surgery may be chosen by young orthopedic surgeons for the first surgery method, especially in early terms of their practices of femoroacetabular impingement treatment. However, the determination of superiority of these techniques is not possible because of limited research available. We approve that the decision making between these techniques should be based on preoperative evaluation and surgeons' experience.

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Case Report

Co-occurrence of multiple thrombophilic factors with a popliteal artery embolism history: An extraordinary myelofibrosis case

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ABSTRACT

The incidence of thrombotic events in patients with prefibrotic primary myelofibrosis (prePMF) is similar to essential thrombocythaemia. Until recently, occult myeloproliferative neoplasm in patients presenting with arterial thrombosis was difficult to diagnose and often overlooked. The co-occurrence of prothrombin gene mutation MTHFR C677T and Factor V Leiden (FVL) mutation is a rare condition that is identified as compound thrombophilia. There are limited data about the risk for arterial thrombosis associated with this condition. A 37-year-old male patient was admitted to the haematology department with leucocytosis, polycythaemia, thrombocytosis and palpable splenomegaly. He had a history of a right popliteal artery embolectomy; FVL, prothrombin G20210A and MTHFR C677T heterozygous mutations were identified before 10 years. He was diagnosed with prePMF based on bone marrow biopsy and JAK2V617F mutation positivity. Hydroxyurea (HU) 500 mg/day was added to the current acetylsalicylic acid treatment. The patient was in a clinically stable condition following the increase in dose of HU to 1000 mg/day.

KEY WORDS: arterial thromboembolism, compound thrombophilia, Factor V Leiden mutation, prefibrotic myelofibrosis

INTRODUCTION

Prefibrotic primary myelofibrosis (prePMF) is a distinct type of chronic myeloproliferative neoplasm (MPN) defined by the revised 2016 WHO classification[1]. Although the clinical features of prePMF patients are heterogeneous, the incidence of thrombotic events is similar to essential thrombocytosis[1]. Until recently, occult MPN in patients presenting with arterial thrombosis was difficult to diagnose and often overlooked. Since the discovery of the JAK2V617F mutation and its high predictive value for the detection of MPN, it has become a routine marker for diagnosing MPN.

Factor V Leiden (FVL) and prothrombin G20210A mutation are the two most common genetic polymorphisms that are known risk factors for venous thromboembolism[2]. The co-occurrence of prothrombin gene mutation, MTHFR C677T and FVL mutation is a rare condition that is identified as compound thrombophilia. Individuals with compound thrombophilia have a significant risk for venous thromboembolism. However, there are limited data on their risk for arterial thrombotic events.

CASE REPORT

A 37-year-old male patient was admitted to the haematology outpatient clinic with leucocytosis, polycythaemia and thrombocytosis without any complaints. He had a history of right popliteal artery embolectomy (2009), ischemic, cyanotic changes, and amputation of his right toes. He also had a 20 pack-year smoking history. There were no significant findings in his family history. Ten years ago, at the time of the popliteal arterial thrombosis, the patient was examined for thrombophilia; FVL heterozygous, prothrombin G20210A heterozygous and MTHFR

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C677T heterozygous mutations were identified. Protein C and S levels were in the normal ranges. In his current examination, only 4 cm of palpable splenomegaly (SM) was detected. His blood work showed the following: white blood cell count of 20,200 μL; haemoglobin level of 18.7 g/dL; and platelet count of 688 × 109/L. His biochemical parameters were normal, except mild elevated lactate dehydrogenase level (294 U/L). His peripheral blood sample was not notable and did not show leucoerythroblastosis, anisopoikilocytosis or dysplasia. Peripheral blood molecular analysis was positive for the JAK2V617F mutation. BCR-ABL mutation and JAK exon 12 mutation studies were unremarkable.

Antiphospholipid syndrome and systemic lupus erythematosus antibodies were not present. The patient's liver structure was normal and the diameter of the portal vein was within normal limits (10 mm). However, portal Doppler ultrasound revealed increased spleen size (164 mm). The patient was considered to have myeloproliferative disease based on the SM, peripheral blood sample image and JAK2V617F mutation.

Bone marrow aspirate examination showed hypercellular marrow with bulbous megakaryocytes, suggestive of MPN and possibly PMF. The myeloid/erythroid ratio was increased[1-4]. He was diagnosed with prePMF based on the bone marrow biopsy. Based on the DIPSS plus score, the patient was classified as low-risk (0 points) patient. Since he had leucocytosis, thrombocytosis, SM and a history of thrombosis, 500 mg/day of hydroxyurea (HU) was added to the current acetylsalicylic acid treatment. Phlebotomy was performed at regular intervals. The HU dose was increased to 1000 mg/day on the first visit period. A follow-up ultrasound, which was performed after three months of HU use, showed that the patient's spleen size had decreased (153 mm). He was advised to quit smoking. The patient has not had a new incident of thrombosis and has been in a clinically stable condition.

DISCUSSION

The clinical features of prePMF range from isolated thrombocytosis to high-risk PMF[3]. Although prefibrotic myelofibrosis is a progressive disease, life expectancy for those with the disease depends not only on its progression but also on thrombotic vascular events. According to a study by Barbui *et al*, major thrombosis affects 1.9% of prePMF patients per year, similar to the percentage of major thrombosis among essential thrombocytosis patients[4]. Only a few studies have specifically evaluated the risk factors for thrombosis in prePMF patients. In a study of 264 patients, leucocytosis at the time of the diagnosis was a significant risk factor for overall (P=0.005, HR 1.15) and arterial thrombosis (P=0.047, HR 1.12)[5].

Information on the co-occurrence of other prothrombotic factors and MPN is limited. Sokolowska *et al* studied 32 JAK2V617F ET patients for the coexistence of other thrombophilic markers[6]. They identified two patients with the FVL mutation. One patient had a protein S deficiency and a history of transient ischemic attack. The other patient had a homozygous MTHFR C677T allele with a history of thrombotic complications. Another case report presented a patient with recurrent splanchnic venous thrombosis who had a protein S deficiency concomitant with MPN[7]. According to a study published in 2012[8], neither MTHFR 677 C>T nor 1298 A>C polymorphism was seen more frequently in patients with MPN than in controls. However, clinical features and life expectancy differences between MPN patients with MTHFR and without MTFHR mutations were not reported in the study.

A study on compound thrombophilia patients reviewed data from 100 patients. In this global, retrospective, multicentre study, 71 individuals had venous thrombosis, four had arterial thrombosis and six had both[9]. Only one of them had a peripheral arterial thrombotic event. The median age at the time of the first arterial thrombotic event was 52.5 years (range: 23-71 years). These cases were much different than our case. In our case, the patient had developed arterial thrombosis at the age of 27. Roach *et al* suggested that the presence of rare compound thrombophilia plays a moderate role in arterial thrombosis than in traditional atherosclerosis[10].

To our knowledge, this is the first case of JAK2V617F-positive prePMF with three co-occurring thrombophilic markers (FVL heterozygous, prothrombin G20210A heterozygous, and MTHFR C677T heterozygous). We hypothesized that the extraordinary concomitance of these factors led to the arterial thrombotic event at an unexpected age with the additive effect of smoking.

CONCLUSION

We believe that thrombophilia should be approached with a wider perspective, especially in patients with atypical thrombosis and that the JAK2V617F mutation should be considered as a thrombotic marker in addition to hereditary thrombophilic factors. Further, prefibrotic myelofibrosis patients with atypical thrombosis should be evaluated for genetic thrombophilic factors. The presence of multiple thrombophilic risk factors not only indicates an increased risk of thrombosis but also changes the treatment approach.

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In the manuscript, the subjects have given his written informed consent to publish their case including publication of images.

Author contribution: Esra Turan Erkek: conception, writer, critical review; Tuba Tahtali: data collection and reporting, literature review

Conflict of interests: None

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Case Report

A case of invasive trichosporonosis in a 4-year-old neutropenic boy with acute myeloid leukemia: a diagnostic dilemma

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ABSTRACT

Trichosporon asahii is an yeast-like fungus which is gaining notoriety as the causative agent of invasive infections in neutropenic children with hematological malignancies. A 4-year-old boy with acute myeloid leukemia was electively admitted for cytotoxic chemotherapy. During chemotherapy, cefepime was administered when a febrile episode occurred. However, he was not neutropenic at this stage and a blood culture was negative for microbial growth. After the completion of chemotherapy, the child became neutropenic and the febrile episodes recurred. Due to persistent fever, meropenem was administered, although blood cultures had been consistently negative. Eleven days post-chemotherapy, the child developed non-pruritic maculopapular cutaneous eruptions and this time, *T. asahii* was isolated from his blood. Conventional amphotericin B and voriconazole were administered as empirical and definitive antimycotic therapies, respectively. Unfortunately, the child developed respiratory distress and succumbed shortly after voriconazole was started.

KEY WORDS: cutaneous eruptions, *Trichosporon asahii*, voriconazole

INTRODUCTION

Where fungemia is concerned, any yeast causative agent that belongs to neither the *Candida* nor *Cryptococcus* genus can be designated as a "rare yeast"[1]. Nevertheless, rare yeasts bring about invasive fungal infections with high mortality rates, and some of them may even be intrinsically resistant to key antimycotics[2]. One such rare yeast genus is *Trichosporon*, which was discovered back in 1865, when it was recognized as the causative agent of a benign hair infection known as white piedra[3]. Today, more than a century later, *T. asahii* (previously known as *T. beigelii*) is regarded as an important opportunistic fungal pathogen in disseminated infections, particularly in the setting of severe neutropenia[4]. We report a rare case of *T. asahii* fungemia, which presented as generalized maculopapular cutaneous eruptions in a neutropenic child who received cytotoxic chemotherapy for acute myeloid leukemia.

CASE REPORT

A 4-year-old boy who was diagnosed with acute myeloid leukemia six months previously was electively admitted to our medical centre for his third course of cytotoxic chemotherapy. On presentation, he was well and had an absolute blood neutrophil count of $4.5\times10^9/\mu L$. The chemotherapy was administered via a peripherally inserted central catheter which had been in situ for less than a month. On the second day of chemotherapy, the child experienced one febrile episode (temperature: 38 °C). He was not neutropenic at this stage, and a blood culture was negative for microbial growth. Despite negative cultures, intravenous (IV) cefepime (dose: 50 mg/kg/q8h) was

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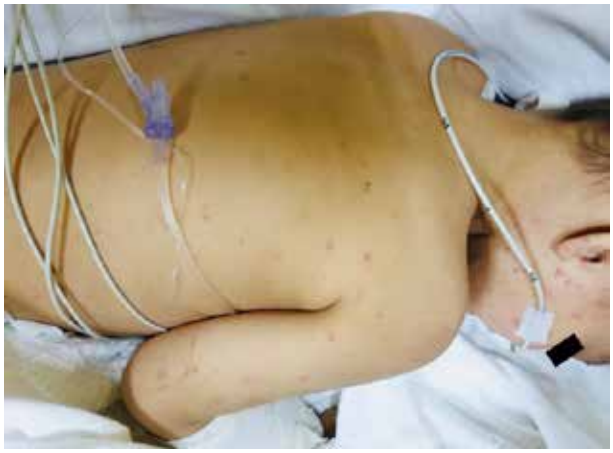

Fig 1: Generalized maculo-papular cutaneous eruptions were seen 11 days post-chemotherapy.

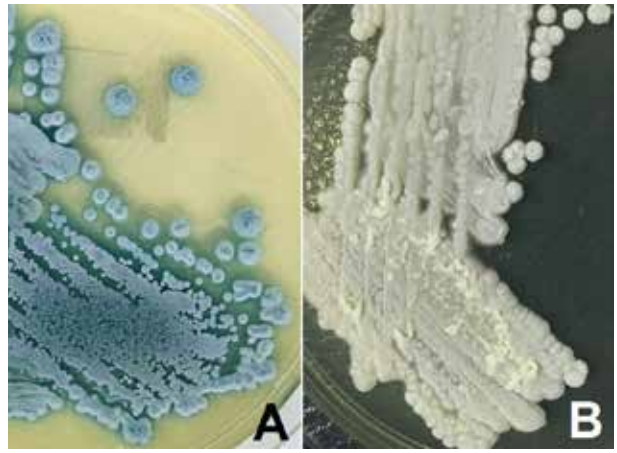

Fig 2: *Trichosporon asahii* colonies on chromogenic agar **(A)** and Sabouraud dextrose agar **(B)** after 48 hours of incubation.

administered for three days. The fever subsided and he managed to complete the full five-day chemotherapy course.

Unfortunately, prior to discharge, his fever recurred and his absolute neutrophil count was now down to $0.8\times10^9/\mu L$. The IV cefepime was restarted, together with IV amikacin (dose: 15 mg/kg/day). After four days on cefepime and amikacin, the child was still febrile. This prompted a change in the antibiotic regime to IV meropenem (dose: 20 mg/kg/q8h). Up to this stage, blood cultures had been persistently negative and there was no apparent source of infection. However, 11 days post-chemotherapy, the mother noticed a non-pruritic maculo-papular skin eruption on her son's body (Fig 1). Another blood culture was sent to the microbiology lab and this time, a yeast was isolated. Once this preliminary finding was conveyed to the paediatric team, the patient was started on IV conventional amphotericin B (dose: 1 mg/kg/day) while awaiting formal fungal identification and antifungal susceptibility testing.

The yeast grew as blue colonies on chromogenic agar and as dry/wrinkled cream-colored colonies on Sabouraud dextrose agar (Fig 2). The wrinkling was particularly pronounced after 48 hours of incubation. The yeast was identified biochemically by the ID 32 C kit (bioMérieux, France) as *Trichosporon asahii*, with an identification percentage of 99.8. The Sensititre YeastOne YO10 colorimetric broth microdilution kit (Thermo Scientific, USA) was used for antifungal susceptibility testing, and the drugs' minimal inhibitory concentration (MIC) values were recorded. By now, the amphotericin B had to be discontinued due to persistent hypokalemia (K^+ level: 2.5-2.9 mmol/L) and since the antifungal agent with the lowest MIC was voriconazole (MIC: 0.06 μg/mL), the patient was given IV voriconazole (dose: 9 mg/kg/q12h). Alas, a few days later, the patient developed respiratory distress which necessitated invasive ventilatory support. He unfortunately succumbed within a few hours of ventilation.

DISCUSSION

Evaluating a child with fever and a cutaneous eruption can be rather taxing because the differential diagnoses are extensive, ranging from self-limiting conditions (*e.g.* roseola) to life-threatening infections (*e.g.* meningococcaemia). Even when the rash can be classified as maculopapular, the most common cause is still a viral exanthem[5]. Also, since our patient was on multiple antibiotics, a cutaneous drug eruption could have also been a possibility[6]. Therefore, attempts to rule out a potentially treatable infectious cause should always be undertaken because the rash may be a red herring and deny the patient from receiving much-needed antimicrobials.

When a systemic mycosis is ultimately responsible, skin rashes are not specific to any fungus, with *Candida*, *Cryptococcus* and *Trichosporon* being implicated in the medical literature as potential rash-causing fungal genera[6-8]. In invasive trichosporonosis, cutaneous involvement is observed in less than a third of cases, with the most common presentation being purpuric papules and nodules with central necrosis or ulceration[6]. However, a maculopapular eruption has also been known to be associated with invasive trichosporonosis, and although a skin biopsy was not performed on our patient, histopathological examination may reveal dermal invasion by fungal structures as well as thromboembolic vasculitis[9]. It is also expected that step sections and a periodic acid-Schiff stain will highlight a small focus of suppurative inflammation, along with periodic acid-Schiff–positive spores and pseudohyphae.

Fungemia attributable to *Trichosporon* spp. generally occurs at a very low rate (<2%) in patients

with haematological malignancies[10]. *Trichosporon* fungemia is also commonly neglected or clinically misdiagnosed as candidemia[4]. Despite its rarity, invasive trichosporonosis has been reported to have a mortality rate of up to 80% among immunocompromised patients[2]. Thus, the importance of accurately diagnosing *Trichosporon* fungemia cannot be overemphasised, and laboratory support is crucial when a patient with a haematological malignancy has certain risk factors. These include neutropenia (60% risk), chemotherapy (58% risk), central venous catheter usage (53% risk), empirical/prophylactic antimycotic therapy (47% risk) and antibiotic therapy (84% risk) [4]. By considering amphotericin B administration as a form of empirical antifungal therapy, our patient had all the predisposing factors for *Trichosporon* fungemia. The availability of molecular techniques (especially direct nucleic acid sequencing) can greatly facilitate an earlier diagnosis and allow pathogen identification to the species level.

Amphotericin B MICs for *T. asahii* are typically above 2 μg/mL, essentially rendering the yeast polyene-resistant[2]. Likewise, MICs to echinocandins are also characteristically elevated, with values surpassing 16 μg/mL[3]. Although our own isolate's amphotericin B MIC was similar, we were unable to ascertain if its echinocandin MICs exceeded 16 μg/mL, due to the inherent MIC range limitations of our broth microdilution kit. Fortuitously, numerous authors have found that *T. asahii* strains respond favourably to voriconazole[2]. Nonetheless, selecting the right drug is only half the battle won, because adequate dosing is also vital. Although the recommended adult dose is 4 mg/kg/q12h, pediatric patients may require 8 mg/kg/q12h to achieve therapeutic drug plasma levels[11]. However, if available, therapeutic drug monitoring should still be undertaken in children due to the wide interpatient pharmacokinetic variation in this age group[11].

CONCLUSION

Invasive trichosporonosis should be ruled out in children with hematological malignancies who develop febrile neutropenia following cytotoxic chemotherapy. The occurrence of a cutaneous maculopapular eruption in such children should be investigated with mycological cultures and if *T. asahii* is isolated, the antimycotic therapy of choice is IV voriconazole. Early detection of trichosporonosis via recognition of clinical, histological and systemic features can aid in rapid treatment and improved outcomes for this rare and fatal infection.

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Conflicts of Interest: None

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Case Report

Campylobacter fetus subsp. fetus meningitis in a 2-month-old child: A case report and mini literature review

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ABSTRACT

There has been a gradual accumulation of reported *Campylobacter fetus* human infections since the first description in 1947. There are only a few case reports of *C. fetus* bacteremia and meningitis in neonates. Nearly all *C. fetus* infections in humans are reported to be caused by *C. fetus* subsp. *fetus*. The few reported cases of *C. fetus* subsp. *venerealis* involved isolates from vaginal discharges. Subspecies identification is rarely performed by human clinical laboratories, and data on the ratio of *C. fetus* subsp *fetus* to *C. fetus* subsp *venerealis* in human isolates are limited. Identification of subspecies is recommended to obtain greater insights into the epidemiology of these infections. In this study, we report a case of *C. fetus* subsp. *fetus* meningitis in a 2-month-old child and conducted a mini literature review.

KEY WORDS: *Campylobacter fetus* subsp. *fetus*, meningitis, neonate

INTRODUCTION

Enteritis caused by *Campylobacter jejuni* and *C.coli* is by far the most frequent clinical entity of *Campylobacter* infection. *C. fetus* subspecies *fetus*, had been considered a pathogen in only cattle and sheep[1]. *C. fetus* subsp. *fetus* is more commonly associated with systemic infections, both *C. jejuni* and *C. fetus* subsp. *fetus* have been reported to cause meningitis and other *Campylobacter* infections, often with no history of diarrhea. The source of infection in these previous cases was usually not identifiable[2].

C.fetus previously classified as *Vibrio fetus* infections in pregnant mother and newborn were first described in 1947[3]. *C. fetus* is a rare cause of meningitis within the pediatric age groups and in particular, among neonates. In premature and newborn babies, infections with *C. fetus* subsp. *fetus* are life-threatening and early diagnosis is of life-saving importance.

Consumption of raw milk and undercooked meat have been reported as a source of infection in meningitis cases of *C. fetus* subsp. *fetus* origin. In addition, catheter use, age, gender and immunocompromised status were evaluated as risk factors[4]. In neonate meningitis, maternal gastroenteritis has been speculated as the source of *C .fetus* subsp. *fetus* infection, which is present in the mother's genital system, and infects the offspring during birth[5-9].

This report documents the meningitis case caused by *C. fetus* subsp. *fetus* in a 2-month-old male child without a history of underlying disease. To our knowledge, no report of neonatal meningitis in this age group due to *C. fetus* subsp. *fetus* have been published.

CASE REPORT

A 2-month-old child was admitted to our clinic with complaints of fever and restlessness. It was learned that his fever was started two days prior, temperature measured at home was 38 °C and he had a decrease in sucking. The patient had no vomiting, diarrhea, cough or additional complaints. The infant had been born at term by spontaneous vaginal delivery and was only fed with breast milk.

Physical examination on admission revealed a temperature of 38 °C, a pulse rate of 108 beat/min,

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respiratory rate 56 breaths/min and blood pressure 75/40mmHg. There were no abnormal findings for the chest or abdomen. Frontal fontanel was 2x2 cm open and abnormality was not observed at neurological examination. His body weight was 5.3 kg (97p), height was 56 cm (97p) and bp of 38cm (12-25p).

Laboratory data were: white blood cells was 13.160/10^9/L, neutrophils were 8.4%, lymphocytes were 62.5%, eosinophils were 12.2%, haemoglobin was 9.2g/dl, platelets were 346000, C-reactive protein was 15.5, and procalcitonin was 0.92.

The results of rotavirus, adenovirus and parasite analysis were negative. The urine, stool and blood samples taken from patient were sent to laboratory. Lumbar puncture was planned with the preliminary diagnosis of possible meningitis in order to illuminate the patient's fever. Lumbar puncture showed a normal pressure and cerebrospinal fluid (CSF) was clear and colorless. CSF revealed a cell count of 500 mm^3 with mononuclear pleocytosis (neutrophils ratio was 20%, lymphocytes 64% and eosinophils 16%), total protein of 259 mg/dl, chlorine of 118 mg/dl and glucose concentration was 27 mg/dl compared with a glucose of 113 mg/dl. Microscopic examination of CSF revealed Gram-negative curved rod-shaped bacteria. The results of serological tests and biochemical parameters revealed no pathology. Culture results of the child's stool and urine obtained at the time of admission to the hospital were found to be negative for specific pathogens.

Empirical antimicrobial therapy consisting of intravenous ceftriaxone 94 mg/kg/day and vancomycin 80mg/kg/day was initiated. By day 2, the patient was apyretic and hemodynamically stable. On the 8th day, there was a positivity for blood culture of the patient, and expanded spectrum beta-lactamase producing *Escherichia coli* was isolated from blood culture. Identification of extended spectrum β-lactamase producing *E.coli* and its antimicrobial susceptibility testing were performed on BD Phoenix 100™ (Beckton Dickinson, USA) automated systems. As *E. coli* was ceftriaxone resistant, treatment was changed to vancomycin+amikacin 40mg 8 hourly. Meanwhile, anaerob culture results of CSF revealed positivity for *Campylobacter* spp. According to results of antibiotic susceptibility testing, in which *Campylobacter* spp. was resistant to amikacin, treatment was switched to vancomycin+meropenem 200mg 8 hourly. Following treatment, there was a significant improvement in the patient's condition.

Lumbar puncture was repeated at the 16th day. The cell count was decreased and the CSF total protein level was 42 mg/dl, chlorine was 125 mg/dl and sugar was 43 mg/dl (CSF: blood glucose ratio 0.56). Questioning of the family revealed no usage of unpasteurized milk or occupational exposure to farm animals. Breast milk and maternal stool samples were taken after 15th day of child infection and examined in terms of *Campylobacter* spp. and found to be negative. However, there was a history of maternal gastroenteritis two weeks before birth.

Identification of the *Campylobacter* spp.

Thioglycollate medium inoculated with CSF was incubated at 37 °C for 48 hours. Microscopic examination from thioglicolate medium revealed Gram-negative curved rod-shaped bacteria. Subcultures made from thioglycollate medium (Beckton Dickinson BBL™, USA) to chocolate agar (Beckton Dickinson BBL™, USA) plates were incubated aerobically, anaerobically and microaerobically at 37 °C for 48-72h. Specific growth was not observed on the aerobic and anaerobic incubated plates at the end of the incubation period. However, the chocolate agar plate incubated microaerobically showed the pure growth of translucent and smooth colonies measuring 1-2 mm in diameter. Two colonies were selected from this plate to obtain pure cultures. Since the automatic identification system could not identify *Campylobacter*, identification of *Camphylobacter* spp. at species level was performed using conventional and molecular methods.

Isolates were then evaluated by using Gram staining, motility, oxidase and catalase activity as described by Kayman *et al*[10]. Based on the results of the phenotypic tests, the isolates were identified as *Campylobacter* spp.

Genomic DNA of the isolates were extracted from pure cultures grown on sheep blood agar via boiling and centrifugation method. *Campylobacter* genus specific polymerase chain reaction was performed using C412F and C1288R primers described by Linton *et al* and the isolates were identified as *Campylobacter* spp. at genus level[11]. In order to identify the species of the isolates, 16S rRNA gene sequencing was performed by using universal primers 27F and 1492R described by Turner *et al.* 16S rRNA sequence analysis revealed that isolates were identified as *C.fetus*[12]. However, BLAST (https://blast.ncbi.nlm.nih.gov/Blast.cgi?PROGRAM=blastn&PAGE_TYPE=BlastSearch&LINK_LOC=blasthome) results showed that 16S rRNA sequencing could not differentiate between *C. fetus* subsp. *fetus* and *C. fetus* subsp. *venerealis*. Since both isolates were identified as *C. fetus* via 16S rRNA sequencing, only one isolate was used after this step. For subspecies level identification of the isolate, the polymerase chain reaction method described by Shulz *et al* was performed with MG3F/MG4R and VenSF/VenSR primers and the isolate was identified as *C. fetus* subsp. *fetus*[13] (Figure 1).

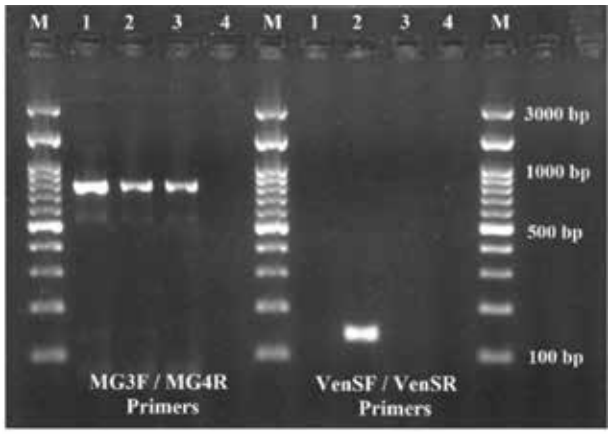

Fig 1. Agarose gel electrophoresis of PCR products obtained by using primer pairs MG3F/MG4R (~750 bp) and VenSF/VenSR (142 bp). **1:** *C. fetus* subsp. *fetus* control strain; **2:** *C. fetus* subsp. *venerealis* control strain; **3:** *C. fetus* subsp. *fetus* isolate recovered from current meningitis case; **4:** Negative control; **M:** Marker, 100bp DNA Ladder H3 RTU, GeneDireX.

In addition, the isolate was found to be tolerant to 1% glycine in the biochemical tolerance test. Then, *Campylobacter fetus* subsp. *fetus* strain obtained from CSF was named as KSU-Cff and the 16S rRNA gene sequence of the strain was deposited in GenBank under accession number MK878407.1.

The antibiotic susceptibility testing was performed using disk diffusion method on Mueller-Hinton agar supplemented with 5% defibrinated sheep blood. While KSU-Cff was susceptible to meropenem, gentamycin, claritromycin, tetracyclin, ampicilin, eritromycin, levofloxacin, azitromycin, ciprofloxacin, klindamycin and amoxicillin/clavulunate, it was found to be resistant to cefotaxime, piperacillin/tazobactam and nalidixic acid. On the 17thday, vancomycin was terminated. According to the results of susceptibility testing, meropenem treatment was continued.

This antibiotic therapy was very effective. The patient was soon afebrile, and gradually all signs and symptoms were resolved. Treatment with meropenem was terminated on 21st day. The child's family provided written informed consent before the study.

The study fulfilled the requirement of the Declaration of Helsinki and ethical approval was obtained from Kahramanmaras Sutcu Imam University Ethics Committee, Turkey (CAAE no.05/05/2019/ 09-03).

DISCUSSION

Meningitis due to *C. fetus* subsp. *fetus* has been reported in both adults[4,13-15] and newborns[5-9,16]. A review of the literature reveals that six cases of *C. fetus* subsp. *fetus* meningitis in the newborn have been reported (Table 1). To our knowledge, the number of meningitis cases from *C. fetus* in neonates is very limited.

The first case of meningitis due to *C. fetus* was reported in a 3-day-old infant and *C. fetus* was isolated from the blood and cerebrospinal fluid of the newborn. The baby recovered with 21-day ampicillin treatment. *C. fetus* was also isolated from stool, cervix and vagina samples of the mother. It was reported that the mother drank raw milk and had diarrhea one week before birth[5]. La Scolea Jr. isolated *C. fetus* from blood and CSF samples of a 3-day-old baby with meningitis[17]. The researcher reported that the mother drank raw milk before birth and had a history of diarrhea and isolated *C. fetus*. Ampicillin, gentamicin and cefotaxime were used in the treatment of the newborn.

Forbes and Scheifele isolated *C. fetus* from the ears, throat and blood of newborn with symptoms of bacteremia and meningitis[6]. In cerebrospinal fluid analysis, leukocyte account was increased and Gram negative spiral shaped rods were detected. *Campylobacter* isolation was performed from the mother's uterus and genital canal and this was interpreted as the source of infection in the newborn. It was also reported that the mother drank raw milk and had abdominal pain and diarrhea lasting for two days three weeks before birth. The newborn was treated with ampicillin and gentamicin for 16 days and recovered.

Morooka *et al* isolated *C. fetus* from four newborns with meningoencephalitis in the neonatal intensive care unit[7]. The investigators reported that *C. fetus* was detected from the 1st baby isolated from blood and cerebrospinal fluid culture and was treated with ampicillin and cefotaxime. *C. fetus* was isolated also

Table 1: Reports of *Campylobacter fetus* subsp. *fetus* meningitis in neonates and source of possible maternal infection.

Reference and year	Age (days)	Possible source	Maternal ıllness	Positive cultures in mother	Treatment of baby	Outcome of baby
Lee, 1985[5]	3	Unpasteurized milk	Diarrhea	Stool, vagina and cervix	Ampi	Survived
La Scolea,1985[17]	3	Unpasteurized milk	Diarrhea	Stool, vagina and cervix	Ampi, genta, ceftx	Survived
Forbes,1987[6]	1	Raw milk	Diarrhea	Endometrium and cervix	Ampi, ceftx	Survived
Morooka,1988[7]	1-3	Not questioned	Not researched	Endometrium cervix and vagina	Not mentioned	Survived
Wong,1990[8]	1-2	Not questioned	Diarrhea	Stool and genital tract	Ampi, ceftx, metr	Survived
Bingham,1992[9]	1	Unpasteurized milk	Diarrhea	Stool and genital tract	Ampi, ceftx, genta	Survived

Ampi: ampicillin; ceftx: cefotaxime; metr; metronidazole

from cervix, vagina and endometrium samples of the mother. *C. fetus* was also isolated from the other three babies. In the study, it was also reported that samples taken from NICU staff and the environment were negative for fetus. Wong *et al* isolated *C. fetus* from a meningitis case in a newborn[8]. Researchers reported that the mother had prenatal enteritis and isolated *C. fetus* from both the feces and genital tract. Ampicillin, cefotaxime and metronidazole were used in the treatment of the newborn[8]. Another case of neonatal meningitis was reported by Bingham *et al*. In this case, *C. fetus* was isolated from newborn cerebrospinal fluid and blood samples[9]. *E.coli* was also isolated from blood culture. It was reported that the mother had a history of drinking raw milk and diarrhea and that the stool sample was positive for *C. fetus*[9]. In these cases reported in newborns, the age of infants varies between 1-3 days.

This study reports the first meningitis case in which *C. fetus* subsp. *fetus* was isolated from a 60 day neonate. In the above cases, it was reported that the mother drank raw milk before birth and had enteritis, and *C. fetus* was isolated from the mother's genital canal. In this case, it was learned that the family did not use unpasteurized milk and there was no history about livestock exposure. However, she had a history of maternal gastroenteritis two weeks before delivery. Mothers' milk and stool samples were also found to be negative for *C. fetus* subsp. *fetus*. The reason for the culture being negative could be due to the sampling time, as we collected and analyzed these samples from the mother 15 days after the child's infection.

Infection usually follows ingestion of improperly handled or cooked food, primarily poultry products. *C. fetus* meningitis associated with eating habits in healthy patients had been reported[13,15]. *Campylobacter* infections are usually self limiting, with full resolution of symptoms. Relapse, chronic infection and carriage state can occur more often in older, debilitated or chronically ill men[5,18]. Neonates may develop meningitis due to *Campylobacter* in the absence of diarrhea[19]. The source of infection could not be clearly determined. It's mode of transmission to humans has not been clearly demonstrated. Direct transmission from person to person is rare[20]. Morooka *et al* reported that *C. fetus* can cause nosocomial meningitis in neonates and asymptomatic carriers may play a role in transmission of the organism[7].

Transplacental spread may result in abortion, stillbirth or early neonatal meningitis. Excretion of organisms has a mean duration of 16 days, when not treated with antibiotics[20]. However, considering the age of the patient, we suppose that transplacental spread did not occur and the infection may be transmitted from the contaminant hand or breast of the mother, who is an asymptomatic carrier. Our experience indicates that *C. fetus* can cause nosocomial meningitis in neonates and asymptomatic carriers may play a role in transmission of the organism.

Early appropriate antibiotic therapy of the neonate is critical. Macrolids are not adequate for the treatment of meningitis. Systemic *C. fetus* infections are generally treated with ampicillin, aminoglycosides, imipenem and chloramphenicol, depending upon the type of infection[11,20].

C. fetus infections often require prolonged paranteral therapy with a single antibiotic or with several antibiotics combined and a minimum of 3-4 weeks of therapy is recommended because of the high risk of relapse after a short course of therapy. Carbapenems were was also successful in treating *Campylobacter fetus* sepsis in a neonate[21]. In this case, a favourable outcome with meropenem was reached.

CONCLUSION

Since *E.coli* is isolated from the blood culture and *C.fetus* subsp. *fetus* from the CSF of a two-month-old baby, detailed examination of samples taken from different sources will be beneficial. Although *Campylobacter* spp. is not isolated from the mother, both bacteria are of gastrointestinal origin, suggesting that the source of transmission is maternal. However, transmission route remains uncertain. Since appropriate initial therapy is important for successful treatment of neonatal *C.fetus* subsp. *fetus* meningitis, carbapenems should be considered as the preferred choice.

ACKNOWLEDGMENTS

Authors' contribution: Filiz Orak presented the idea and devised the project. Hatice Gunes gathered and analyzed data. Filiz Orak and Fuat Aydin searched for relevant data and helped in drafting the manuscript. 16S rRNA sequencing of the isolate and identification at subspecies level were conducted by Fuat Aydin. All authors read, commented and approved the manuscript. The study was funded by study partners.

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Case Report

Optic nerve sheath meningioma with globe invasion

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ABSTRACT

An 82-year-old female presented with painless and progressive visual loss of right eye for two years. Ophthalmological examination revealed choroidal detachment in her right eye. Orbita and brain magnetic resonance imaging showed right optic nerve sheath meningioma with globe invasion.

KEY WORDS: choroidal detachment, globe invasion, magnetic resonance imaging, optic nerve sheath meningioma, ultrasonography

INTRODUCTION

Optic nerve sheath meningiomas (ONSMs) are histopathologically benign tumors. ONSMs grow slowly but they can cause complete vision loss without treatment. ONSMs are usually unilateral and originate from arachnoid cells of the optic nerve sheath. They can be detected from orbit to intracranial space.

ONSMs usually occur in adult women and clinical presentation include progressive visual loss, proptosis, color blindness, and relative afferent pupil defect. In the early stage, papilledema may be seen and it may result in optic atrophy. Mortality risk of ONSMs is null.

Radiological findings are very useful to detect ONSM. First choice scan technique is magnetic resonance imaging (MRI). In MRI, tubular enlargement of the optic nerve, enlarged optic canal, and calcification within the tumor can be seen[1].

In this case, we aimed to present an ONSM patient with intraocular extension and choroidal detachment.

CASE REPORT

The patient was informed about the study and was invited to be a part of it. The patient was also instructed that participation was totally voluntary and not participating in this study would not have any negative effect on her treatment and relationship with their physicians. Before initiating the study, written consent was obtained from the patient. The study conformed to the tenets of the Declaration of Helsinki.

An 82-year-old Turkish female patient presented with a two-year history of progressive visual loss in her right eye. She gave a history of diabetes mellitus, hypertension, and coronary bypass surgery three months ago. Her best-corrected visual acuity on the Snellen chart was 20/400 in the right eye and 10/20 in the left eye. There was a right relative afferent pupillary defect. Bilateral nuclear cataract grade two was detected in anterior segment examination. The intraocular pressure on Goldmann applanation tonometry was 14 mmHg on both eyes. There was no proptosis and restriction of movement in all directions of gaze. A dilated fundus examination of the right eye revealed retinal elevation (Figure 1). In her left eye, chorioretinal atrophy was detected. Orbital ultrasonography examination was performed. The choroidal detachment was detected and there was subretinal tumor suspect (Figure 2). An MRI

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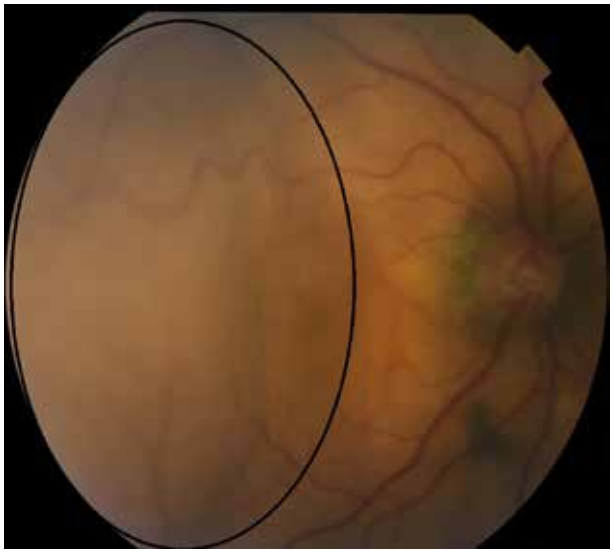

Fig 1: Choroidal detachment in the right eye (black circle).

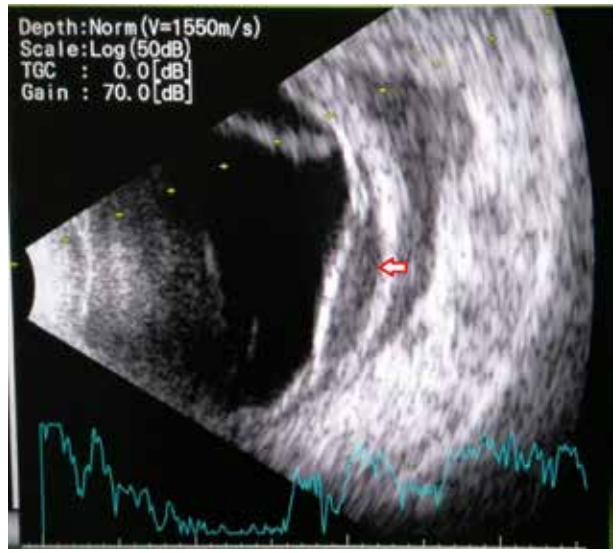

Fig 2: Orbita ultrasonography (red arrow shows choroidal detachment).

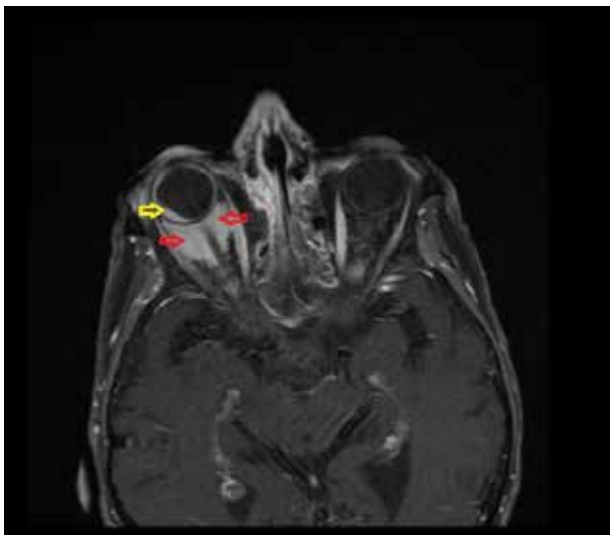

Fig 3: The axial T1-weighted fat suppressed with gadolinium contrast MRI scan of optic nerve sheath meningioma (red arrow) and globe invasion (yellow arrow).

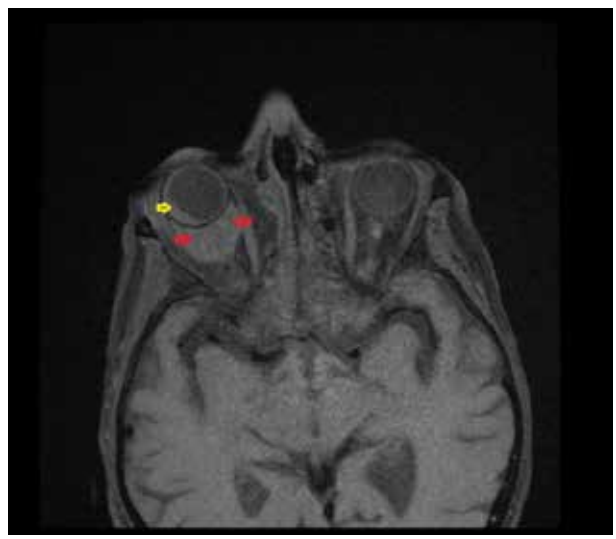

Fig 4: The axial T1-fat suppressed without gadolinium contrast MRI scan of optic nerve sheath meningioma (red arrow) and globe invasion (yellow arrow).

(gadolinium contrast) scan of the brain and orbits were performed and post-contrast T1-weighted axial MRI with fat saturation and the axial T1-fat suppressed without gadolinium contrast MRI scan showed diffuse enlargement and contrast enhancement of the right intraorbital optic nerve sheath, and intrabulbar extension was detected (Figures 3-6). In the coronal T2 scan, we detected hyperintense lesion which was around the optic nerve (Figure 5). The coronal T1 weighted fat suppressed with gadolinium contrast MRI scan showed us intense contrast-enhancing lesion around the optic nerve (Figure 6). The patient was referred to the neurosurgery department with a prediagnosis of right ONSM. They confirmed the diagnosis and planned surgery but the surgical intervention was not a good choice because of age and cardiovascular disease. Patient took a total dose of 50 Gy fractionated stereotactic radiotherapy over the course of eight weeks.

DISCUSSION

ONSMs constitute about 2% of all orbital tumors and 1-2% of all meningiomas[2]. After gliomas, ONSMs are the second most common optic nerve tumor. Middle-aged women are the most affected population in the world, but ONSMs may occur in childhood, especially those who have neurofibromatosis type 2[3]. The typical clinical symptom is progressive

visual loss. The tumor grows around the optic nerve and makes compression so that clinical findings are usually seen in optic disc. Clinical findings include optic nerve head edema, optic atrophy, optociliary collateral vessels, relative afferent pupillary defect, dyschromatopsia, and proptosis.

In the past decades, MRI (especially with gadolinium-enhanced fat-suppression sequences) has become a gold standard scanning technique for diagnosis of ONSMs. The other scanning technique is high-resolution computed tomography. Nowadays, the most popular treatment method is radiotherapy, especially in early and progressing stage. Some authors suggest surgery if tumors invade to the intracranial space[4,5]. The other treatment options are surgery, radiotherapy, and simply follow-up observation.

Our case is atypical because she had an intrabulbar extension and choroidal detachment. ONSM may apply mechanical pressure to the choroid. Also, ONSM may compress the retinal and choroidal veins. When these veins are chronically compressed, venous pressure in the eye rises. Venous stasis occurs. These conditions may cause ONSM choroidal detachment.

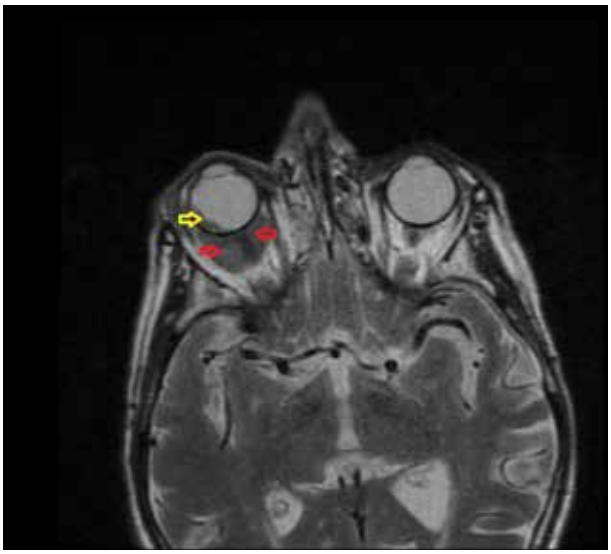

Fig 5: The axial T2 MRI scan of optic nerve sheath meningioma (red arrow) and globe invasion (yellow arrow).

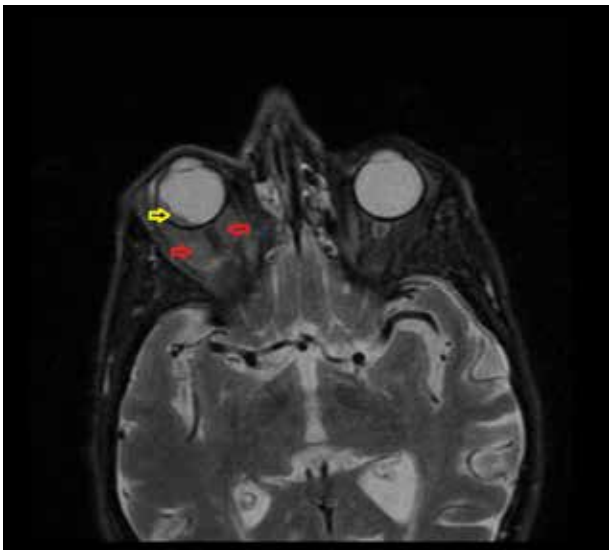

Fig 6: The axial T2-weighted fat suppressed MRI scan of optic nerve sheath meningioma (red arrow) and globe invasion (yellow arrow).

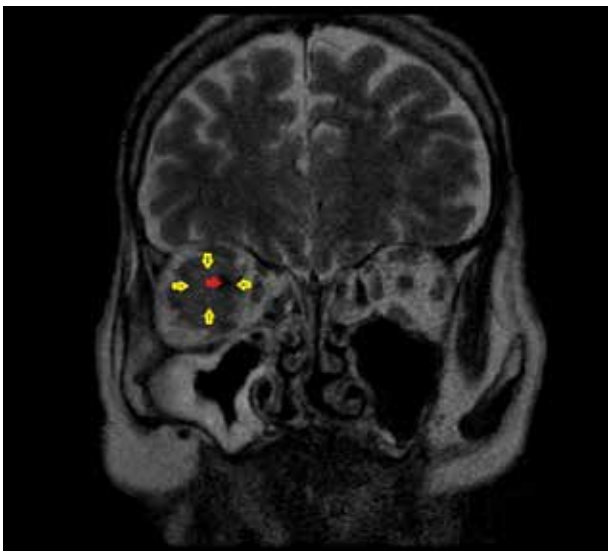

Fig 7: The coronal T2 MRI scan of optic nerve sheath meningioma (yellow arrow) and optic nerve (red arrow).

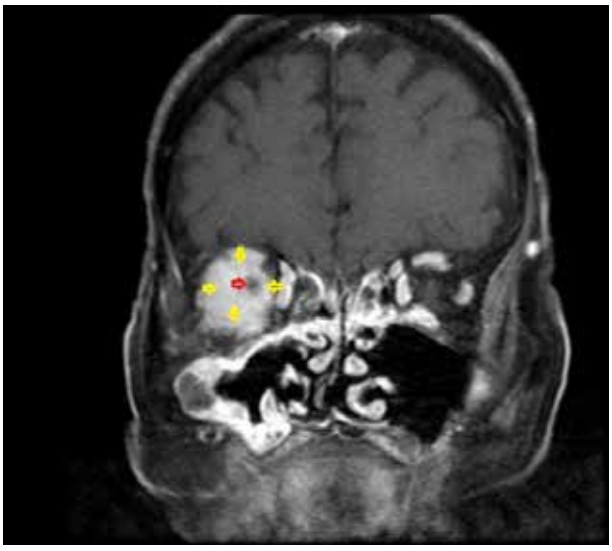

Fig 8: The coronal T1 weighted fat suppressed with gadolinium contrast MRI scan of optic nerve sheath meningioma (yellow arrow) and optic nerve (red arrow).

In our case, orbital involvement in the axial MR image is well seen. We thought that the reason for the choroidal detachment was an orbital invasion. In the literature, the intraocular extension of the ONSMs are very rare. In a review of 5000 orbital meningiomas, Dutton reported that intraocular extension rate was 3.8%[6]. He detected that tumor may invade optic disc, sclera, choroid and retina. Schittkowski *et al* presented a patient with an intraocular spread of ONSM in 1999[7]. Some authors described the choroidal invasion. Schatz *et al* reported a patient who had ONSM and choroidal neovascular membrane, but this patient had age-related macular degeneration in both eyes[8]. Tirkey *et al* reported a similar case who had ONSM and choroidal neovascular membrane, but they said that there was no predisposing factor[9]. Sekeryapan *et al* showed choroidal folds in a patient with ONSM and they thought that the choroidal fold formation was probably due to stretching of the optic nerve[10]. In our patient, we detected choroidal detachment. Due to the intraocular invasion seen in MRI, we thought that the reason for the choroidal detachment was ONSM.

CONCLUSION

ONSM should be considered in a patient with progressive visual loss, and intraocular invasion possibility of the ONSM should be kept in mind.

ACKNOWLEDGMENTS

Authors contributions: Selim Cevher: design of the work, acquisition, analysis, interpretation of data, drafting and writing of the manuscript; Cihan Simsek and Tayfun Sahin wrote the manuscript and acquisition.

Conflict of interest: None

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Case Report

A novel technique of endoscopic intervention for pancreatic pseudocyst; Percutaneous endoscopic cyst gastrostomy with anterior gastropexy: Case report

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ABSTRACT

Surgical cystogastrostomy has been largely replaced by endoscopic drainage techniques. However, this technique requires both advanced skill and medical equipment such as endoscopic ultrasound and it cannot be effectively performed at all institutions in clinical practice.

Here, we reported one case with pancreatic pseudocyst that was successfully treated with percutaneous endoscopic cystogastrostomy with anterior gastropexy.

A 52-year-old man was admitted with early satiety, epigastric pain and jaundice. He was diagnosed as symptomatic pancreatic pseudocyst accompanied with obstruction of gastric outlet and bile duct.

Under general anesthesia, we fixed the stomach to the abdomen wall by anterior gastropexy. A 5mm trocar was percutaneously inserted into the pseudocyst through the anterior and posterior wall of stomach. Then, double pigtail stent was introduced via trocar to evacuate pseudocyst content.

Pancreatic pseudocyst could also be treated with percutaneous endoscopic cystogastrostomy with anterior gastropexy.

KEY WORDS: anterior gastropexy, endoscopic intervention, pancreatic pseudocyst

INTRODUCTION

A pancreatic pseudocyst represents the mature encapsulated acute peripancreatic fluid collection that develops usually at least 4 weeks after onset of necrotizing acute pancreatitis. Although it has visible capsule, it is distinguished pathologically from walled off pancreatic necrosis (WOPN) containing solid debris[1].

Current approaches only consider treatment for pseudocysts that cause symptoms (abdominal pain, early satiety), complications (infection, bleeding, rupture) or obstruction of a surrounding hollow viscous (gastric, duodenal or biliary obstruction).

Since endoscopic intervention for pancreatic pseudocyst is highly successful unlike WOPN, surgical treatment (surgical cystogastrostomy, surgical cystoduodenostomy) has been largely replaced by endoscopic drainage techniques. Many reports have documented a high degree of success using endoscopic cystgastrostomy, suggesting its efficacy and minimal invasiveness[2-4].

However, this novel technique has also limitations; first, it must be accomplished in special center with modern endoscopic equipment. Secondly, it highly depends on interventionist's technique and experience. Moreover, it requires endoscopic ultrasound guidance.

Here, we report the first case with symptomatic pseudocyst that was successfully treated with percutaneous endoscopic cystogastrostomy with anterior gastropexy.

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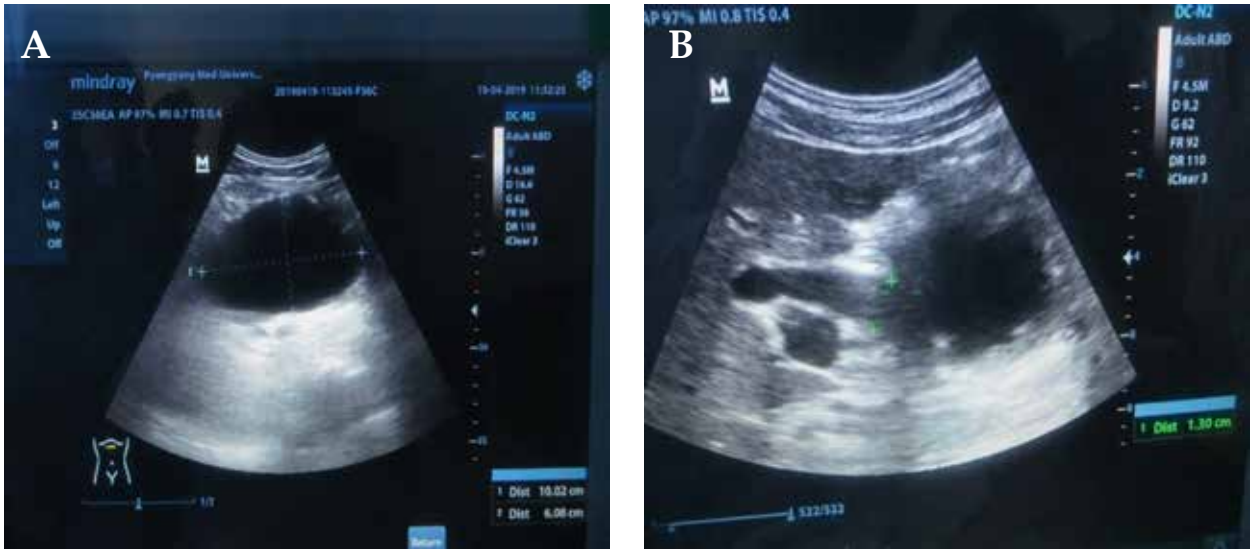

Fig 1: (a) Pancreatic pseudocyst adjacent to the head of pancreas; (b) common bile duct is dilated by compression of pseudocyst

CASE REPORT

A 52-year-old man was admitted presenting with early satiety, epigastric pain and jaundice. Two years ago, he underwent a laparotomy following a diagnosis of traumatic hemoperitoneum. He had previous history of acute necrotizing pancreatitis four months ago.

Blood test, transabdominal ultrasonography and contrast enhanced computer tomography were performed initially. He had high level of serum bilirubin (total bilirubin 74.0μmol/L, direct bilirubin 45.0μmol/L, indirect bilirubin 29.0μmol/L) and aminotransferases (aspartate aminotransferase 96IU/L, alanine aminotransferase 93IU/L).

Abdominal ultrasonography showed fluid collection (10.02cm×6.08cm), dilated common bile duct (1.3cm) and enlargement of gall bladder (9.05cm×3.48cm; Fig 1a & Fig 1b).

Contrast enhanced computer tomography demonstrated oval fluid collection with a thick wall located in the head of pancreas and there was no evidence of solid or non-fluid contents. Fine needle aspiration proved it contained pure liquid involving rich pancreatic juice.

Thus, he was diagnosed as symptomatic pseudocyst (obstruction of gastric outlet and bile duct) associated with necrotizing pancreatitis.

At 3rd day of admission, we performed percutaneous endoscopic cysto-gastrostomy. Endoscope was placed within the stomach in supine position under general anesthesia. Appropriate sites were selected relying on the combination of transillumination and finger palpation of the abdominal wall with the endoscope in the stomach. We chose two sites to fix the stomach into the abdominal wall, which was different from percutaneous endoscopic gastrostomy (PEG). Once appropriate sites were chosen, the abdominal wall is cleaned with an iodine-based solution and lidocaine was injected at the site.

Anterior gastropexy was achieved as follows. An 18-gauge spinal needle in which the two ends of 3-0 prolene suture were placed was introduced into the gastric cavity by percutaneous puncture through the anterior abdominal wall and anterior gastric wall (Fig 2a). It was then withdrawn backwards keeping 3-0 prolene suture remained in the stomach cavity (Fig 2b).

The needle with two ends of another 3-0 prolene suture was inserted again at the same site of the skin. The latter suture was passed through the snare of the first prolene suture, which was pulled outside with the ends of second suture. The second suture was tied to fix the stomach to the abdominal wall. In the same way, another anterior gastropexy was performed beside 2cm away (Fig 2c). After anterior gastropexy, a 5 mm skin incision was made between these two sites to insert a 5mm trocar percutaneously into the stomach (Fig 2d). Then, the trocar was continued to move towards posterior wall of stomach under the endoscopic view to puncture pancreatic pseudocyst (Fig 2e). Pseudocystal collection was removed through the trocar with suction tube and guide-wire was introduced into the cyst through the trocar (Fig 2f). Pigtail stent was placed into the cystal cavity via guide-wire (Fig 2g).

The trocar and a guide-wire were removed, ensuring correct position of pigtail under endoscope (Fig 2h). Finally, the trocar site was closed with the stitches of 1-0 non-absorbable suture through abdominal wall and anterior gastric wall. The procedure time was 40 minutes.

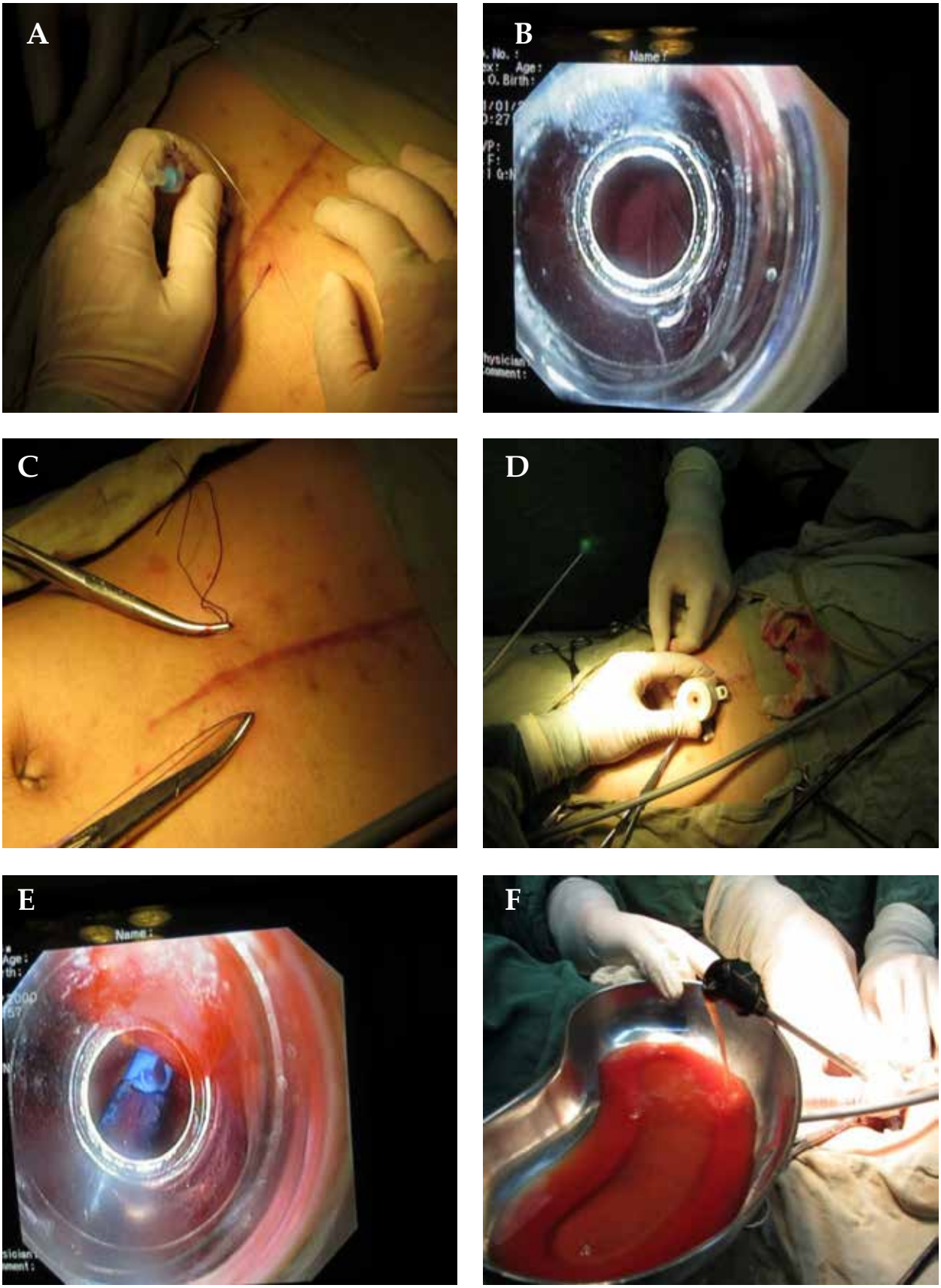

Fig 2: (a, b, c) Fixing stomach to the anterior abdominal wall at 2 sites; (d) percutaneous endoscopic insertion of trocar under endoscopic view; (e) trocar inserted into the cyst; (f) pancreatic pseudocyst being drained out via trocar-loaded catheter.

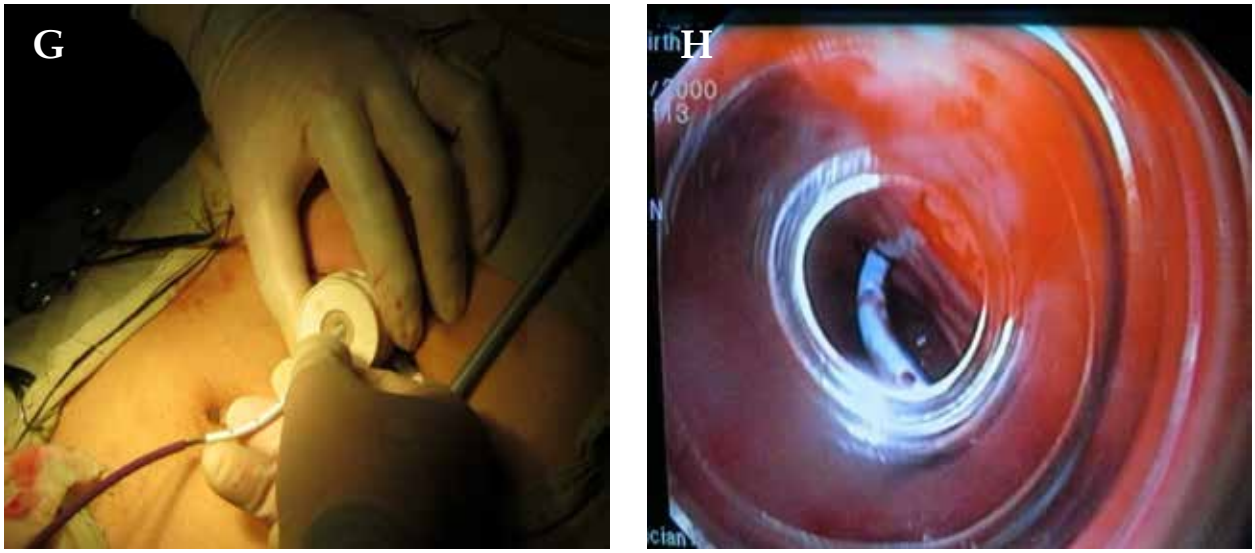

Fig 2: (g) trocar-loaded pigtail insertion; (h) pigtail stent placed into the cyst through posterior wall of stomach

On the 3rd day of procedure, ultrasonography revealed decrease in pseudocyst size (4.04×2.09cm; Figure 3). There was no evidence of pseudocyst and dilated bile duct, and gall bladder decreased to normal range at 7th day. At 11th day, serum bilirubin was back to normal and the patient discharged without any clinical symptoms.

This study was approved by Pyongyang University of Medicine Hospital ethic review committee.

DISCUSSION

We developed a new technique-percutaneous endoscopic cystogastrostomy with anterior gastropexy for management of pancreatic pseudocyst. Development of minimally invasive approaches has largely changed management of acute pancreatitis and its complications. Endoscopic intervention is believed to be associated with fewer complications.

Fig 3: Ultrasound image of pancreatic pseudocyst at 3rd day of procedure (white arrow indicates decreased pseudocyst)

During the last few decades, percutaneous drainage has been largely replaced by an endoscopic approach due to higher morbidity, longer hospital stays and long duration of indwelling drains. In an observational study of 164 patients with pseudocyst and WOPN that included both pseudocysts and WOPN, treatment success was higher in patients managed endoscopically compared with percutaneous drainage (70% vs 31%)[5]. The endoscopic approach was also associated with a lower rate of surgery (4% vs 11%).

Endoscopic cytogastrostomy has technical and treatment success rates of 89%-100% and 82%-100% respectively, and a mortality rate of less than 1%[2-4,6-9]. However, this technique requires both advanced skill and medical equipment (endoscopic ultrasound) and it cannot be effectively performed at all institutions in clinical practice, despite strong clinical evidence.

Our approach only required an endoscope and was less invasive than surgical cytogastrostomy. This procedure with anterior gastropexy also inserted double pigtail stent into pancreatic pseudocyst through gastric walls via trocars under the endoscopic visualization as in the endoscopic cystogastrostomy.

Our patient had previous laparotomy and he might have adhesions prone to complications. Thus, we have marked safe points for insertion of trocars with ultrasound before operation to avoid it. These points were then checked up with endoscope during the procedure in order to avoid incidental complications.

As well-known, PEG is a typical percutaneous approach for the inner stomach procedures and its safety has been already approved worldwide. PEG is also possible and safe when prior abdominal surgery has been done[10]. We have used PEG method as the approach into the stomach in this case.

Of course, there is a possibility that adhesions and previous operations make percutaneous approach prone to complications. However, the stomach is situated in the epigastric region and there is a new fear that other organs such as large and small intestine could be situated on this region, especially between the stomach and abdominal wall. Previous operations especially make the stomach adhere to the incision. That is why percutaneous approach is likely to be as safe as much as PEG. Adhesions on this region would also be likely to prevent incidental complications, contrary to what others would think.

However, we propose that every approach should be individualized according to the findings approved before procedure.

CONCLUSION

Pancreatic pseudocyst could be also managed with percutaneous endoscopic cystogastrostomy with anterior gastropexy.

ACKNOWLEDGMENT

Author contribution: Sung-Il Rim designed the concept, defined the intellectual content, data analysis, statistical analysis and reviewed the manuscript. Won-Ho Kim defined the intellectual content and reviewed the manuscript. Hye-Song Kim searched the literature, did clinical studies, acquired data of experimental studies and the statistical analysis.

Conflict of Interest: None

Financial Support: None

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Case Report

Wolff-Parkinson-White syndrome with Cor Triatriatum Sinister - a rare association

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ABSTRACT

Cor triatriatum is a rare congenital anomaly, and it is diagnosed in 0.4% and 0.1% in autopsy series and clinically respectively. It is frequently accompanied by secundum type atrial septal defect and pulmonary venous return anomaly. We report a case of a 67-year-old female patient admitted to hospital with complaints of palpitation which occurs approximately 3-4 times in a month. Wolf Parkinson White (WPW) syndrome was detected in the electrocardiogram (ECG) and transthoracic echocardiogram showed features of cor triatriatum sinister (CTS), mild mitral regurgitation and left atrial dilatation. She was asymptomatic from CTS pathology. Although there was no documented tachycardia, because of intermittent palpitation, preexitation features in the ECG, left atrial dilatation and a potential for dangerous atrial fibrillation, we performed electrophysiological study. The accessory pathway was detected in the posterior mitral annulus and ablated successfully. Since she was asymptomatic, surgical treatment for CTS was not recommended. Although the concomitant CTS with other congenital heart diseases has been reported, to the best of our knowledge, there is only one previous case report in the literature regarding association of CTS with WPW syndrome.

KEY WORDS: ablation, accessory pathway, fibro-muscular septa

INTRODUCTION

Cor triatriatum is a rare congenital anomaly and it is diagnosed in 0.4% and 0.1% of autopsy series and clinically respectively[1].

Cor triatriatum sinister (CTS) is generally diagnosed in the pediatric period and 80% of cases are accompanied by other cardiac anomalies. It is frequently accompanied by secundum type atrial septal defect and pulmonary venous return anomaly[1]. Although there are several classifications of CTS, the most useful classification is based on the size and number of fenestrations in the fibro-muscular membrane in the left atrium proposed by Loeffler in 1949[2]. According to this classification, the fibro-muscular membrane is intact in the first group, there are one or more small openings in the second group, and there is a single and a large opening through which the accessory and true left atrium are connected in the third group. There are other modern classifications as well, including association of pulmonary venous connection.

CASE REPORT

A 67-year-old female patient with no known disease was admitted to our clinic with complaints of palpitation which occurs approximately 3-4 times a month. Patient didn't seek medical help because of short duration of palpitation attacks. She reported that heart rate was 187/min on a digital blood pressure monitor at home. Features of pre-excitation - Wolf Parkinson White (WPW) syndrome- were detected in the electrocardiogram (ECG, Figure 1). Transthoracic echocardiogram showed a fibro-muscular septum in the left atrium indicative of CTS, mild mitral regurgitation and left atrial dilatation (Figure 2). The

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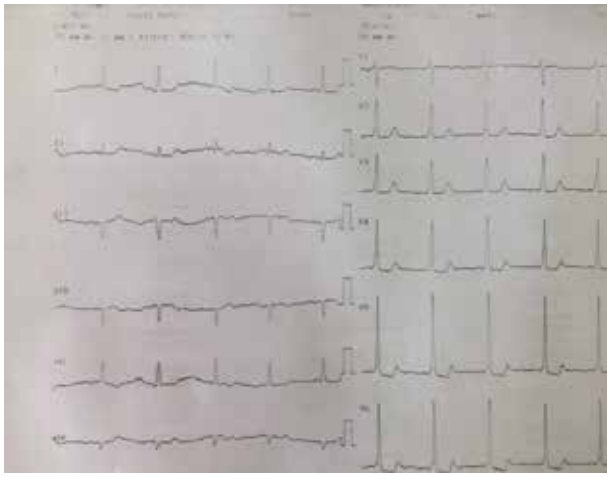

Fig 1: ECG with pre-excitation, showing short PR interval and delta waves.

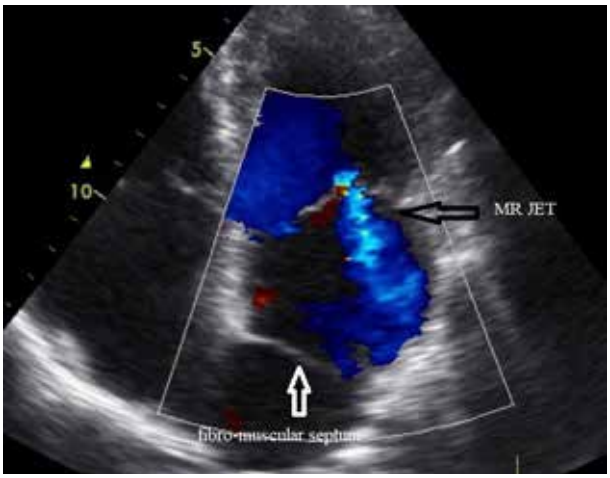

Fig 2: 2D echocardiography, showing mitral regurgitation.

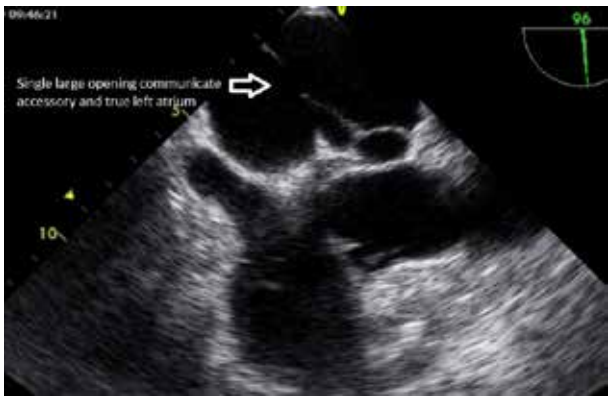

Fig 3: TEE in bicaval view showing fibromuscular septum in the left atrium with large opening.

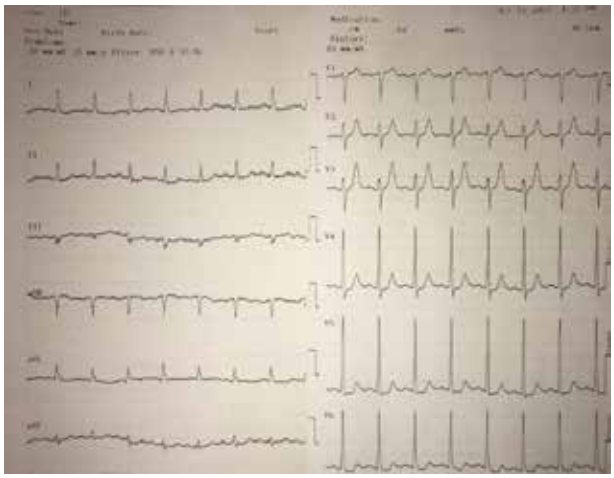

Fig 4: ECG after ablation, showing disappearance of delta waves and PR interval becoming normal.

accessory atrium drained via a single wide orifice to the true atrium without significant gradient (Figure 3). The systolic pulmonary artery pressure measured via minimal tricuspid regurgitation jet was normal (27 mmHg).

She was not symptomatic from CTS pathology. Although there was no documented tachycardia, because of intermittent palpitation, pre-excitation features in the ECG, left atrial dilatation, and a potential for atrial fibrillation, we did electro-physiological study. HRA, His and CS catheters were placed and basal measurements were taken (BCL: 870 msec, AH: 80 msec, HV: 21 msec). The antegrade and retrograde ERP of the accessory pathway measured 260 msec. The accessory pathway was located in the posterior mitral annulus. Dual pathway physiology was observed with programmed stimulation from the right atrium and then atypical AVNRT induced (TCL: 315 msec, tachycardia VA: 100 msec, VpVA-tachycardia VA: 140 msec). Junctional beats were observed with two RF applications in the slow path region and slow path conduction was eliminated. Although an accessory pathway-mediated tachycardia was not induced, since the ERP was 260 msec, the risk of atrial fibrillation was considered and accessory pathway ablation was initiated.

The left ventricle was reached by retrograde transaortic route and mitral annulus mapping was performed with the ENSITE system. A tacticath irrigated sensor enabled ablation catheter was positioned in the posterior mitral annulus where there was a continuous AV and VA relationship with sinus rhythm and ventricular pace. Ablation was started and accessory pathway conduction disappeared within the first 5 seconds and ablation was continued in the same region for 90 seconds. Accessory pathway conduction did not return during the 45 min waiting period after the procedure and no tachycardia was induced by

programmed stimulations from the right atrium and right ventricle.The ECG was normal at the first month follow-up (ECG , Figure 4) and the patient stated that she had no complaints.

DISCUSSION

As unrestrictive cortriatriatum remains asymptomatic, it is usually diagnosed incidentally in adulthood[2]. As a matter of fact, our case was asymptomatic until the age of 67 as it was not obstructive, and hence we did not recommend surgical resection of the cortriatrial diaphragm.

The association of WPW syndrome with other congenital cardiac anomalies is well known[3]. But, to the best of our knowledge, there is only one case report in the literature regarding the association with manifest accessory pathway[4]. In our case, accessory pathway was found in the mitral annulus, but unlike our case, it was found laterally rather than posteriorly in the reported case. In our case, because of the congenital anomaly and potentially complicated transseptal puncture, the transaortic retrograde approach was applied for ablation of the accessary pathway.

CONCLUSION

We are reporting a rare association of WPW syndrome and CTS, which we believe is the second case reported in the literature. Associated CTS posed problem for trans septal approach for ablasion of accessory pathway, which was done through tranaortic retrograde approach successfully.

ACKNOWLEDGMENT

Authors have no conflict of interest. Writing and correction were done by Kamal Isgandarov, transthoracic echocardiogram was performed by Gurbet Ozge Mert, and electrophysiological study procedure was performed by Kamal Isgandarov and Ozcan Yucel.

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Short Communication

COVID-19: Impact on the cornea in two years

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INTRODUCTION

In December 2019 China sent to the World Health Organization (WHO) an alert on unusual pneumonia cases, first recognized in Wuhan, the capital of Hubei Province.

Later, on the 30th of January 2020, WHO announced the outbreak of the highly transmissible novel coronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), representing "a public health emergency of international concern"[1]. It has now been seen worldwide.

The ophthalmologist Dr. Li Wenliang raised an early concern about the coronavirus and regrettably died from COVID-19 after contamination from an asymptomatic glaucoma patient examined in his clinic.

This tragic circumstance highlights a need to raise the awareness of medical professionals about possible COVID-19 related ocular manifestations. An attempt was made to collect the most up-to-date information on COVID-19 impact on the cornea as a resource for identifying symptoms and disorders, and mitigating contamination and transmission.

Initially, cases of eye redness and irritation in COVID-19 patients were documented only in 0.8% of hospitalized patients from 30 provinces in China from December 2019 through January 2020.

Now, recent studies put to light a higher frequency of ocular manifestations in COVID illness. As was estimated in a meta-analysis by Nasiri *et al*[2], a pooled prevalence of total eye disorders reached 11.03%, with conjunctivitis as the most frequent ocular disease (88.8%).

Currently, available findings indicate that "ocular manifestations may be non-specific and present as the initial symptoms of infection"[3]. The cases are shown variability of presentations. The illness could manifest by ocular symptoms followed by systemic symptoms in a time range of 3 hours to 5 days in 13% of patients. At the same time, more severe systemic illness could correspond to ocular findings.

It has been two years since the WHO declared the COVID-19 pandemic, and the evidence of ocular manifestation in COVID-19 patients is gradually accumulating.

At present it was documented that angiotensin-converting enzyme 2 (ACE2), wide spread in the body, including the eye, represent a target for SARS-CoV-2 virus, which often causes multiple organ and system damaging manifestations. The eye in general[4], and in particular the cornea and the ocular surface could also serve as an "entrance gate" for the coronavirus, since it contains ACE2 receptors and transmembrane protease serine 2 (TMPRSS2) proteins on stem cells of the corneal limbus. The researchers revealed highly expressed ACE2 in limbal, peripheral corneal epithelium and superficial central corneal epithelium. Genomic and subgenomic RNA of SARS-CoV-2 virus was also detected in the corneas of patients with severe COVID illness[5]. The highest frequency of SARS-CoV-2 RNA was evidenced in the posterior corneal endothelial surface in cadaveral study of the cornea.

Taking all this into account, it is possible that COVID-19 may be responsible for corneal manifestations. This is quite concerning, given the fact that the ophthalmologists are on the front line, and it is recommended to protect the professionals' eyes during the patient examination.

It is of utmost importance to determine COVID-related corneal manifestations.

Keratoconjunctivitis

SARS-CoV-2 can be involved in the cornea as well as in the conjunctiva. Several keratoconjunctivitis cases were documented, some with relapsing pattern[6]. Among them, it was a case of a 29-year-old female complaining about ocular discomfort, watery

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discharge and photophobia without any systemic symptoms of COVID-19, but tested positively in a nasopharyngeal swab and weakly positive in the conjunctival swab. The patient initially presents with herpes-like pseudo dendrites and epithelial infiltrates, causing deterioration of vision. All reported cases pointed that keratoconjunctivitis could be an initial COVID-19 illness presentation without any sign of viral infection.

Keratitis

Stromal keratitis as an early manifestation could follow the loss of smell and taste, fatigue, as was verified by Cano-Ortiz *et al*[7] in a 25-year-old female case with a positive polymerase chain reaction test.

Exposure keratopathy and corneal abrasion could cause a sight-threatening condition in patients with severe illness, who are on ventilators or respiratory masks in the Intensive Care Units.

COVID has an impact on the cornea not only in the early phase of disease, but also in long COVID, as was shown by the latest research[8]. The case is named long COVID if the symptoms persist longer than 12 weeks after infection and are unexplained by another cause. Such cases revealed in 1 from 10 patients with COVID.

Corneal neuropathy

The latest studies have uncovered corneal nerve fiber loss and increased dendritic cells[8]. The corneal subbasal plexus changes and neuropathy were evidenced in 91.31% of the patients within a 10-month period after recovering from COVID illness, indicating the chronic course of neuropathy[8].

Corneal graft rejection

Currently available findings indicate that COVID-19 is impacting not only a healthy cornea, but also a donor one, causing a graft rejection, specifically an endothelial graft rejection[9]. A similar issue was raised by several researchers in relation with COVID-19 vaccine[10]. Shah *et al*[10] presented acute corneal transplant rejection cases in penetrating keratoplasty, Descemet membrane endothelial keratoplasty and Descemet stripping automated endothelial keratoplasty. The investigators evidenced a success of aggressive topical steroid therapy in all cases.

CONCLUSION

Summarizing, the cases of COVID-19 are exponentially growing, and it is well documented that SARS-CoV-2 causes ocular complications. The eye, and in particular the cornea, is not the primary target of SARS-CoV-2, but the cornea shows alterations in asymptomatic, early, late and long COVID-19, some of which can be sight threatening. Taking all this into account, it is an urgent need to raise an ocular vigilance on COVID-19 related corneal manifestations.

ACKNOWLEDGMENT

Conflict of interest: None

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Selected Abstracts of Articles Published Elsewhere by Authors in Kuwait

Kuwait Medical Journal 2022; 54 (3): 430 - 433

Neurodevelopmental outcomes of infants born to mothers with SARS-CoV-2 infections during pregnancy: a national prospective study in Kuwait

Mariam Ayed[1], Alia Embaireeg[1], Mais Kartam[2], Kiran More[3], Mafaza Alqallaf[4], Abdullah AlNafisi[5], Zainab Alsaffar[2], Zainab Bahzad[2], Yasmeen Buhamad[2], Haneen Alsayegh[6], Wadha Al-Fouzan[7], Hessa Alkandari[8]

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BMC Pediatr 2022 May 319:(1)22;30. doi: 10.1186/s12887-022-03359-2.

BACKGROUND
An increasing proportion of women are infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) during pregnancy. Intrauterine viral infections induce an increase in the levels of proinflammatory cytokines, which inhibit the proliferation of neuronal precursor cells and stimulate oligodendrocyte cell death, leading to abnormal neurodevelopment. Whether a maternal cytokine storm can affect neonatal brain development is unclear. The objective of the present study was to assess neurodevelopmental outcomes in neonates born to mothers with SARS-CoV-2 infections during pregnancy.

METHODS
In this prospective cohort study, the neurodevelopmental status of infants (N = 298) born to women with SARS-CoV-2 infections during pregnancy was assessed at 10-12 months post-discharge using the Ages and Stages Questionnaire, 3rd edition (ASQ-3). The ASQ-3 scores were classified into developmental delays (cutoff scores ≤ 2 standard deviations (SDs) below the population mean) and no delays (scores > 2 SDs above the population mean).

RESULTS
The majority (90%) of the infants born to mothers with SARS-CoV-2 infections during pregnancy had favorable outcomes and only 10% showed developmental delays. Two of the 298 infants tested positive for SARS-CoV-2, and both had normal ASQ-3 scores. The majority of the pregnant women had SARS-CoV-2 infections during their third trimester. The risk of developmental delays among infants was higher in those whose mothers had SARS-CoV-2 infections during the first (P = 0.039) and second trimesters (P = 0.001) than in those whose mothers had SARS-CoV-2 infections during the third trimester.

CONCLUSION
The neurodevelopmental outcomes of infants born to mothers with SARS-CoV-2 infections seem favorable. However, more studies with larger sample sizes and longer follow-up periods are required.

Case report: Nasopharyngeal mucormycosis, atypical presentation in a seventy-year-old diabetic lady

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Int J Surg Case Rep. 2022 Jun 10;96:107297. doi: 10.1016/j.ijscr.2022.107297. Online ahead of print.

INTRODUCTION AND IMPORTANCE
Mucormycosis is rare type of infection yet, it is common in patient with Diabetes Mellitus and immune deficiencies. Mucormycosis mostly target the rhino-orbito-cerebral region, hence the common presenting symptoms are nasal symptoms followed by orbito-cerebral symptoms.

CASE PRESENTATION
Here, we present a diabetic lady with unusual presentation of mucormycosis. This old lady present with long history of left dull ear pain and decrease in hearing, nasopharyngeal exam revealed a mild bulging in the fossa of Rosenmuller region. The mild bulging reported as left nasopharyngeal heterogonous soft tissue mass extending to the left external auditory canal and skull base by CT scan. Excisional biopsy was taken and found to be nasopharyngeal mucormycosis.

CONCLUSION
Mucormycosis is a fatal infection which require early diagnosis and emergent intervention.

Ocular Myasthenia: Clinical Course and the Diagnostic Utility of Assaying Acetylcholine Receptor Antibodies

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Neuroophthalmology. 2022 Mar 15;46(4):220-226. doi: 01658107.2022.2037662/10.1080. eCollection 2022.

Myasthenia gravis (MG) is an autoimmune disease that causes neuromuscular junction transmission defect and has a predilection for the with neuromuscular junction transmission defect and predilection for extra-ocular and eyelid muscles. Most cases of ocular MG (OMG) convert later to generalised MG (GMG). Assaying acetylcholine receptor antibodies (AchRA) has been used to diagnose MG, but the reported sensitivity in OMG is lower (50%) than in GMG. We report the clinical course and the diagnostic yield of assaying AchRA in a Kuwaiti cohort of patients with OMG. We carried out a retrospective review of 47 patients diagnosed with OMG who were tested for AchRA. Ancillary tests included the ice test, single-fibre electromyography (SFMEG), and repetitive nerve stimulation electromyography (RNS). Progression to GMG occurred in 51% of OMG patients with a mean time to progression of 12.1 months (range 4 to 20 months). AchRAs were positive in 46 of 47 cases (98%), while SFEMG was positive in 31 of 34 cases (91.1%). Older age (44.25 years versus 38 years, $p < .05$) and higher AchRA titre (2.0 nmol/L versus 1.27 nmol/L, $p < .05$) were significantly associated with conversion to GMG. We have found a high rate of AchRA seropositivity in relatively younger subjects of OMG. Higher AchRA titres and older age were associated with conversion to GMG, usually within the first 2 years.

Extracorporeal Membrane Oxygenation in Pregnant Women With COVID-19

Omar Mohammed Bamasood, Mohammed Shamsah, Huda Alfoudri, Zouheir Bitar, Farah R Al Shammari, Jayakumar Jagadeesan, Vimal Raj Pandian, Yasser Elkenany, Abdalaziz H Alsarraf, Abdullatif Almutawa, Turki KH Abdullah, Mohamed Mahmoud Ibrahim Mahmoud
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ASAIO J. 2022 Apr 1;68(4):471-477. doi: 10.1097/MAT.0000000000001646.

Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and lung involvement is common. Patients with COVID-19 may progress to acute respiratory distress syndrome (ARDS) for which they may require mechanical ventilation. When conventional ventilation strategies are unable to achieve the desired oxygenation and gas exchange, extracorporeal membrane oxygenation (ECMO) might be an option in selected patients. The literature on the use of ECMO in peripartum women with COVID-19 is limited. We present a series of ten cases involving pregnant and recently pregnant women who rapidly developed ARDS after the onset of COVID-19 for which they received ECMO. Nine of the 10 patients survived intensive care unit discharge after a gradual recovery of their pulmonary function and weaning from mechanical ventilation and ECMO. In addition, 9 out of the 10 delivered neonates survived neonatal intensive care unit discharge.

Post-dural puncture headache: a prospective study on incidence, risk factors, and clinical characterization of 285 consecutive procedures

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BMC Neurol. 2022 Jul 14;22(1):261. doi: 10.1186/s0-02785-022-12883.

BACKGROUND
Lumbar puncture (LP) is a common and relatively safe neurological procedure. It can be complicated by post-dural puncture headache (PDPH) after both diagnostic and therapeutic procedures. The aim of this study is to identify the incidence, risk factors and clinical characterization of PDPH in the inpatient setting of the main tertiary neurology hospital in Kuwait.

METHODS
We conducted a prospective observational cohort study that included patients who were admitted to neurology department at Ibn Sina hospital, Kuwait, from January 1, 2019 to December 31, 2020, on whom, LP was performed for diagnostic and/or therapeutic reasons. Multivariate logistic regression analysis was performed to evaluate the association between PDPH and different clinical parameters.

RESULTS
A total of 285 patients were included; 225 females (78.9%), mean age of 32.9 ± 11.7 years. PDPH was reported by 84 patients (29.5%), with mean headache onset of 1.7 ± 0.8 days, and mean duration of 2.4 ± 2.1 days. The commonest headache type was dull aching in 49 patients (58.3%). Headache severity was mild to moderate in 64 patients (76.2%), with mean NRS of 4.1 ± 0.9. Most PDPH (99.3%) resolved with conservative

medical management, with only 2 patients (0.7%) requiring epidural blood patch. In multivariate logistic regression model, there was a statistically significant correlation between development of PDPH and young age ($p = 0.001$), female gender ($p = 0 .001$), low BMI ($p < 0 .001$), pre-LP headache ($p = 0.001$), history of previous PDPH ($p = 0.001$), and number of LP attempts ($p < 0.001$). PDPH was statistically significantly higher in patients with optic neuritis ($p = 0.009$), and cerebral venous thrombosis ($p = 0.007$), and lower in patients with peripheral neuropathy ($p = 0.011$) and spinal muscular atrophy ($p = 0.042$).

CONCLUSIONS

Findings from clinical practice in the main tertiary neurology hospital in Kuwait were in line with literature findings. Younger age, female gender, lower BMI, pre-procedural headache, previous history of PDPH, and number of LP attempts were found to be independent risk factors for developing PDPH. To our knowledge, this study represents the first comprehensive description of PDPH in a population from the Arabian Gulf Region.

Forthcoming Conferences and Meetings

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Vineetha Elizabeth Mammen

Kuwait Medical Journal 2022; 54 (3): 434 - 441

1362nd International Conference on **Medical, Biological and Pharmaceutical Sciences** (ICMBPS)
Sep 01, 2022
Ireland, Dublin
Email: info@iastem.org
Event Website: http://iastem.org/Conference2022/Ireland/1/ICMBPS/

1391st International Conference on Recent Advances in **Medical Science** (ICRAMS)
Sep 01, 2022
United Arab Emirates, Dubai
Email: info@theiier.org
Event Website: http://theiier.org/Conference2022/UAE/6/ICRAMS/

International Conference on **Medical and Health Sciences** (ICMHS)
Sep 02, 2022
United Kingdom, Glasgow
Email: papers.scienceplus@gmail.com
Event Website: http://scienceplus.us/Conference/20740/ICMHS/

World **Disability & Rehabilitation** Conference
Sep 04, 2022
India, Karnataka, Bengaluru
Email: papers.asar@gmail.com
Event Website: http://asar.org.in/Conference/32252/WDRC/

International Conference on **Medical and Health Sciences** (ICMHS)
Sep 05, 2022
United States, Boston
Email: papers.scienceplus@gmail.com
Event Website: http://scienceplus.us/Conference/21323/ICMHS/

1214th International Conference on **Pharma and Food** (ICPAF)
Sep 06, 2022
New Zealand, Hamilton
Email: info@academicsera.com
Event Website: http://academicsera.com/Conference2022/NewZealand/3/ICPAF/

International Conference on **Medical, Pharmaceutical and Health Sciences** (ICMPH)
Sep 07, 2022
Japan, Osaka
Email: info.gsrd@gmail.com
Event Website: http://gsrd.co/Conference2022/9/Japan/2/ICMPH/

International Conference on **Healthcare and Clinical Gerontology** (ICHCG)
Sep 08, 2022
New Zealand, Christchurch
Email: info.sciencefora@gmail.com
Event Website: http://sciencefora.org/Conference/12933/ICHCG/

International Conference on **Medical, Pharmaceutical and Health Sciences** (ICMPH)
Sep 09, 2022
Qatar, Doha
Email: info.gsrd@gmail.com
Event Website: http://gsrd.co/Conference2022/9/Qatar/ICMPH/

International Conference on **Cell and Tissue Science** (ICCTS)
Sep 09, 2022
United States, San Jose
Email: info@conferencefora.org
Event Website: http://conferencefora.org/Conference/33607/ICCTS/

1398th International Conference on Recent Advances in **Medical Science** (ICRAMS)
Sep 12, 2022
France, Paris
Email: info@theiier.org
Event Website: http://theiier.org/Conference2022/France/3/ICRAMS/

International Conference on Advances in **Health and Medical Science** (ICAHMS)
Sep 13, 2022
United Arab Emirates, Dubai
Email: info.saard.org@gmail.com
Event Website: http://saard.org/Conference2022/9/UAE/1/ICAHMS/

International Conference on Recent Advances in **Medical Science** (ICRAMS)
Sep 15, 2022
United States, Massachusetts
Email: info@theiier.org
Event Website: http://theiier.org/Conference2022/US/82/ICRAMS/

International Conference on **Medical and Biological Engineering**
Sep 15, 2022
Japan, Tokyo
Email: papers.techno@gmail.com
Event Website: http://technoarete.com/Conference/7904/ICMBE/

International Conference on Recent Advances in **Medical Science** (ICRAMS)
Sep 16, 2022
United States, Honolulu
Email: info@theiier.org
Event Website: http://theiier.org/Conference2022/US/83/ICRAMS/

International Conference on Recent Advancement in **Medical Education, Nursing, and Health Sciences** (ICRAMNH)
Sep 16, 2022
Australia, Melbourne
Email: info.irfconference@gmail.com
Event Website: http://irfconference.org/Conference/14613/ICRAMNH/

International Conference on **Cell and Tissue Science** (ICCTS)
Sep 17, 2022
Spain, Málaga
Email: info@conferencefora.org
Event Website: http://conferencefora.org/Conference/33871/ICCTS/

International Conference on **Healthcare and Clinical Gerontology** (ICHCG)
Sep 17, 2022
United States, Kansas City
Email: info.sciencefora@gmail.com
Event Website: http://sciencefora.org/Conference/13166/ICHCG/

International Conference on **Medical Ethics and Professionalism** (ICMEP)
Sep 18, 2022
Korea (*South*), Daegu
Email: info.sciencefora@gmail.com
Event Website: http://sciencefora.org/Conference/13214/ICMEP/

International Conference on **Cell and Tissue Science** (ICCTS)
Sep 19, 2022
Romania, Brasov
Email: info@conferencefora.org
Event Website: http://conferencefora.org/Conference/33955/ICCTS/

1374th International Conference on **Medical, Biological and Pharmaceutical Sciences** (ICMBPS)
Sep 20, 2022
Turkey, Istanbul
Email: info@iastem.org
Event Website: http://iastem.org/Conference2022/Turkey/4/ICMBPS/

International Conference on **Medical and Health Sciences** (ICMHS)
Sep 20, 2022
United Kingdom, Cambridge
Email: papers.scienceplus@gmail.com
Event Website: http://scienceplus.us/Conference/20780/ICMHS/

1405th International Conference on Recent Advances in **Medical Science** (ICRAMS)
Sep 23, 2022
Spain, Barcelona
Email: info@theiier.org
Event Website: http://theiier.org/Conference2022/Spain/4/ICRAMS/

International Conference on **Science, Health and Medicine** (ICSHM)
Sep 24, 2022
Canada, Quebec City
Email: info@iser.co
Event Website: http://iser.co/Conference2022/Canada/45/ICSHM/

1393rd International Conferences on **Medical and Health Science** (ICMHS)
Sep 25, 2022
Austria, Vienna
Email: info@theires.org
Event Website: http://theires.org/Conference2022/Austria/1/ICMHS/

International Conference on **Medical and Health Sciences** (ICMHS)
Sep 25, 2022
United Arab Emirates, Dubai
Email: papers.academicsconference@gmail.com
Event Website: http://academicsconference.com/Conference/22357/ICMHS/

International Conference on **Obesity, Weight Management and Nutrition Research** (ICOBWN)
Sep 25, 2022
India, Kerala, Kochi
Email: info.irfsr@gmail.com
Event Website: http://irfsr.com/Conference/2184/international-conference-on-obesity-weight-management-and-nutrition-research/

1407th International Conference on Recent Advances in **Medical Science** (ICRAMS)
Sep 26, 2022
Italy, Milan
Email: info@theiier.org
Event Website: http://theiier.org/Conference2022/Italy/6/ICRAMS/

International Conference on Recent Advancement in **Medical Education, Nursing, and Health Sciences** (ICRAMNH)
Sep 26, 2022
United Arab Emirates, Dubai
Email: info.irfconference@gmail.com
Event Website: http://irfconference.org/Conference/14655/ICRAMNH/

International Video Conference on **Healthcare** (IVCH)
Sep 28, 2022
Turkey, Istanbul
Email: info.conferenceonline@gmail.com
Event Website: http://www.conferenceonline.net/Conference/407/IVCH/

International Conference on **Medical and Biological Engineering** (ICMBE)
Sep 28, 2022
Indonesia, Bali
Email: papers.techno@gmail.com
Event Website: http://technoarete.com/Conference/7892/ICMBE/

World **Disability & Rehabilitation** Conference (WDRC)
Sep 15, 2022
Canada, Montreal
Email: papers.asar@gmail.com
Event Website: http://asar.org.in/Conference/29506/WDRC/

International Conference on **Medical Ethics and Professionalism** (ICMEP)
Sep 30, 2022
China, Nanjing
Email: info.sciencefora@gmail.com
Event Website: http://sciencefora.org/Conference/13469/ICMEP/

1373rd International Conference on **Medical and Biosciences** (ICMBS)
Oct 01, 2022
United Arab Emirates, Dubai
Email: info@researchworld.org
Event Website: http://researchworld.org/Conference2022/UAE/7/ICMBS/

1376th International Conference on Recent Advances in **Medical and Health Sciences** (ICRAMHS)
Oct 02, 2022
United Arab Emirates, Abu Dhabi
Email: info@academicsworld.org
Event Website: http://academicsworld.org/Conference2022/UAE/7/ICRAMHS/

International Conference on **Healthcare and Clinical Gerontology** (ICHCG)
Oct 02, 2022
United Arab Emirates, Dubai
Email: info.sciencefora@gmail.com
Event Website: http://sciencefora.org/Conference/14490/ICHCG/

International Conference on Recent Advances in **Medical, Medicine and Health Sciences** (ICRAMMHS)
Oct 03, 2022
United States, Texas, Houston
Email: contact.wrfer@gmail.com
Event Website: http://wrfer.org/Conference/21648/ICRAMMHS/

International Conference on **Medical, Pharmaceutical and Health Sciences** (ICMPH)
Oct 04, 2022
Germany, Berlin
Email: info.gsrd@gmail.com
Event Website: http://gsrd.co/Conference2022/10/Germany/ICMPH/

International Conference on **Medical and Health Sciences** (ICMHS)
Oct 04, 2022
London, United Kingdom
Email: papers.scienceplus@gmail.com
Event Website: http://scienceplus.us/Conference/21242/ICMHS/

1412th International Conference on Recent Advances in **Medical Science** (ICRAMS)
Oct 06, 2022
Australia, Melbourne
Email: info@theiier.org
Event Website: http://theiier.org/Conference2022/Australia/7/ICRAMS/

World **Disability & Rehabilitation** Conference (WDRC)
Oct 06, 2022
Vietnam, Hanoi
Email: papers.asar@gmail.com
Event Website: http://asar.org.in/Conference/29635/WDRC/

World **Disability & Rehabilitation** Conference (WDRC)
Oct 08, 2022
Thailand, Bangkok
Email: papers.asar@gmail.com
Event Website: http://asar.org.in/Conference/29697/WDRC/

International Conference on **Cardiology and Diabetes** (ICCD)
Oct 11, 2022
United Arab Emirates, Dubai
Email: info.iared.org@gmail.com
Event Website: http://iared.org/Conference/198/ICCD/

International Conference on Recent Advances in **Medical, Medicine and Health Sciences** (ICRAMMHS)
Oct 12, 2022
Qatar, Doha
Email: contact.wrfer@gmail.com
Event Website: http://wrfer.org/Conference/21676/ICRAMMHS/

International Conference on **Obesity, Weight Management and Nutrition Research** (ICOBWN)
Oct 13, 2022
India, Karnataka, Bengaluru
Email: info.irfsr@gmail.com
Event Website: http://irfsr.com/Conference/2226/international-conference-on-obesity-weight-management-and-nutrition-research/

1370th International Conference on **Science, Health and Medicine** (ICSHM)
Oct 15, 2022
Denmark, Copenhagen
Email: info@iser.co
Event Website: http://iser.co/Conference2022/Denmark/2/ICSHM/

International Conference on **Healthcare and Clinical Gerontology** (ICHCG)
Oct 15, 2022
Switzerland, Bern
Email: info.sciencefora@gmail.com
Event Website: http://sciencefora.org/Conference/14647/ICHCG/

1386th International Conference on Recent Advances in **Medical and Health Sciences** (ICRAMHS)
Oct 17, 2022
United States, Orlando
Email: info@academicsworld.org
Event Website: http://academicsworld.org/Conference2022/USA/15/ICRAMHS/

International Conference on Advances in **Health and Medical Science** (ICAHMS)
Oct 19, 2022
Singapore, Singapore
Email: info.saard.org@gmail.com
Event Website: http://saard.org/Conference2022/10/Singapore/2/ICAHMS/

2nd Edition of **International Vaccines Congress**
Oct 19, 2022
United States, Orlando, Florida
Email: vaccines@magnusconference.com
Event Website: https://vaccinescongress.com/

International Conference on **Medical and Biological Engineering** (ICMBE)
Oct 20, 2022
United Kingdom, Edinburgh
Email: papers.techno@gmail.com
Event Website: http://technoarete.com/Conference/7862/ICMBE/

International Conference on **Cell and Tissue Science** (ICCTS)
Oct 21, 2022
Scotland, Dundee
Email: info@conferencefora.org
Event Website: http://conferencefora.org/Conference/33896/ICCTS/

International Conference on **Science, Health and Medicine** (ICSHM)
Oct 23, 2022
Canada, Calgary
Email: info@iser.co
Event Website: http://iser.co/Conference2022/Canada/49/ICSHM/

International Video Conference on **Healthcare** (IVCH)
Oct 23, 2022
Thailand, Phuket
Email: info.conferenceonline@gmail.com
Event Website: http://www.conferenceonline.net/Conference/426/IVCH/

1245th International Conference on **Sports Nutrition and Supplements** (ICSNS)
Oct 24, 2022
South Africa, Cape Town
Email: info@academicsera.com
Event Website: http://academicsera.com/Conference2022/SouthAfrica/3/ICSNS/

International Conference on **Cardiology and Diabetes** (ICCD)
Oct 24, 2022
Germany, Berlin
Email: info.iared.org@gmail.com
Event Website: http://iared.org/Conference/206/ICCD/

1209th International Conference on **Medical & Health Science** (ICMHS)
Oct 25, 2022
France, Paris
Email: info@researchfora.com
Event Website: http://researchfora.com/Conference2022/France/5/ICMHS/

1378th International Conference on **Science, Health and Medicine** (ICSHM)
Oct 26, 2022
Japan, Tokyo
Email: info@iser.co
Event Website: http://iser.co/Conference2022/Japan/10/ICSHM/

1413th International Conferences on **Medical and Health Science** (ICMHS)
Oct 27, 2022
Canada, Ottawa
Email: info@theires.org
Event Website: http://theires.org/Conference2022/Canada/5/ICMHS/

1379th International Conference on **Science, Health and Medicine** (ICSHM)
Oct 28, 2022
Saudi Arabia, Riyadh
Email: info@iser.co
Event Website: http://iser.co/Conference2022/SaudiArabia/7/ICSHM/

National Conference on **Medical and Health Sciences** (NCMHS)
Oct 30, 2022
India, Pune, Maharashtra
Email: papers.nrf@gmail.com
Event Website: http://nationalconference.org.in/Conference/9785/national-conference-on-medical-and-health-sciences/

World **Disability & Rehabilitation** Conference (WDRC)
Nov 02, 2022
China, Beijing
Email: papers.asar@gmail.com
Event Website: http://asar.org.in/Conference/29588/WDRC/

International Conference on **Medical Ethics and Professionalism** (ICMEP)
Nov 02, 2022
United Arab Emirates, Dubai
Email: info.sciencefora@gmail.com
Event Website: http://sciencefora.org/Conference/13828/ICMEP/

International Conference on **Medical Health Science, Pharmacology & Bio Technology** (ICMPB)
Nov 05, 2022
India, Chhattisgarh, Bilaspur
Email: papers.issrd@gmail.com
Event Website: http://issrd.org/Conference/16367/international-conference-on-medical-health-science-pharmacology--bio-technology/

1253rd International Conference on **Pharma and Food** (ICPAF)
Nov 06, 2022
Lebanon, Beirut
Email: info@academicsera.com
Event Website: http://academicsera.com/Conference2022/Lebanon/2/ICPAF/

1385th International Conference on **Science, Health and Medicine** (ICSHM)
Nov 07, 2022
New Zealand, Wellington
Email: info@iser.co
Event Website: http://iser.co/Conference2022/NewZealand/4/ICSHM/

International Conference on **Medical and Biological Engineering**
Nov 08, 2022
Singapore, Singapore
Email: papers.techno@gmail.com
Event Website: http://technoarete.com/Conference/7844/ICMBE/

International Conference on **Medical, Pharmaceutical and Health Sciences** (ICMPH)
Nov 08, 2022
United Kingdom, Manchester
Email: info.gsrd@gmail.com
Event Website: http://gsrd.co/Conference/9238/ICMPH/

1407th International Conference on **Medical, Biological and Pharmaceutical Sciences** (ICMBPS)
Nov 10, 2022
Russian Federation, Moscow
Email: info@iastem.org
Event Website: http://iastem.org/Conference2022/Russia/3/ICMBPS/

International Conference on **Medical, Pharmaceutical and Health Sciences** (ICMPH)
Nov 11, 2022
Hungary, Budapest
Email: info.gsrd@gmail.com
Event Website: http://gsrd.co/Conference2022/11/Hungary/ICMPH/

1399th International Conference on **Medical and Biosciences** (ICMBS)
Nov 13, 2022
Saudi Arabia, Riyadh
Email: info@researchworld.org
Event Website: http://researchworld.org/Conference2022/SaudiArabia/7/ICMBS/

International Research Conference on Covid-19 and its Impact on **Mental Health** (IRCCIMH)
Nov 14, 2022
India, Goa
Email: info.researchconferences@gmail.com
Event Website: http://researchconferences.in/Conference/2864/international-research-conference-on-covid-19-and-its-impact-on-mental-health/

1260th International Conference on **Pharma and Food** (ICPAF)
Nov 17, 2022
Finland, Helsinki
Email: info@academicsera.com
Event Website: http://academicsera.com/Conference2022/Finland/2/ICPAF/

International Conference on **Healthcare and Clinical Gerontology** (ICHCG)
Nov 20, 2022
Malaysia, Kuala Lumpur
Email: info.sciencefora@gmail.com
Event Website: http://sciencefora.org/Conference/14268/ICHCG/

1409th International Conference on Recent Advances in **Medical and Health Sciences** (ICRAMHS)
Nov 23, 2022
Romania, Bucharest
Email: info@academicsworld.org
Event Website: http://academicsworld.org/Conference2022/Romania/2/ICRAMHS/

International Conference on Recent advancement in **Medical Education, Nursing, and Health Sciences** (ICRAMNH)
Nov 23, 2022
India, Maharashtra, Mumbai
Email: info.irfconference@gmail.com
Event Website: http://irfconference.org/Conference/16377/international-conference-on-recent-advancement-in-medical-education-nursing-and-health-sciences/

International Conference on **Medical Health Science, Pharmacology & Bio Technology** (ICMPB)
Nov 24, 2022
Italy, Rome
Email: papers.issrd@gmail.com
Event Website: http://issrd.org/Conference/14486/international-conference-on-medical-health-science-pharmacology--bio-technology/

1410th International Conference on Recent Advances in **Medical and Health Sciences** (ICRAMHS)
Nov 25, 2022
France, Paris
Email: info@academicsworld.org
Event Website: http://academicsworld.org/Conference2022/France/5/ICRAMHS/

World Conference on **Pharma Industry and Medical Devices**
Nov 25, 2022
United Arab Emirates, Sharjah
Email: info.iferp@gmail.com
Event Website: http://iferp.org/Conference/6807/WCPIMD/

International Conference on **Medical, Medicine and Health Sciences** (ICMMH)
Nov 26, 2022
Greece, Crete
Email: contact.iierd@gmail.com
Event Website: http://iierd.com/Conference/2092/ICMMH/

1445th International Conference on Recent Advances in **Medical Science** (ICRAMS)
Nov 27, 2022
Canada, Ottawa
Email: info@theiier.org
Event Website: http://theiier.org/Conference2022/Canada/5/ICRAMS/

International Conference on **Oncolytic Virus Therapeutics** (ICOVT)
Nov 27, 2022
United States, New York
Email: info.conferenceonline@gmail.com
Event Website: http://www.conferenceonline.net/Conference/432/ICOVT/

1400th International Conference on **Science, Health and Medicine** (ICSHM)
Nov 29, 2022
China, Shanghai
Email: info@iser.co
Event Website: http://iser.co/Conference2022/China/12/ICSHM/

International Conference on Recent Advances in **Medical, Medicine and Health Sciences** (ICRAMMHS)
Nov 30, 2022
Indonesia, Jakarta
Email: contact.wrfer@gmail.com
Event Website: http://wrfer.org/Conference/21513/ICRAMMHS/

International Conference on Recent Advances in **Medical, Medicine and Health Sciences**
Dec 03, 2022
United States, Texas, Houston
Email: contact.wrfer@gmail.com
Event Website: http://wrfer.org/Conference/21277/ICRAMMHS/

International Conference on Recent Advances in **Medical, Medicine and Health Sciences** (ICRAMMHS)
Dec 04, 2022
Switzerland, Geneva
Email: contact.wrfer@gmail.com
Event Website: http://wrfer.org/Conference/20990/ICRAMMHS/

1272nd International Conference on **Pharma and Food** (ICPAF)
Dec 05, 2022
Sweden, Stockholm
Email: info@academicsera.com
Event Website: http://academicsera.com/Conference2022/Sweden/2/ICPAF/

International Conference on **Medical Health Science, Pharmacology & Bio Technology** (ICMPB)
Dec 07, 2022
India, Maharashtra, Thane
Email: papers.issrd@gmail.com
Event Website: http://issrd.org/Conference/16773/international-conference-on-medical-health-science-pharmacology--bio-technology/

12th Global Conference on **Pharma Industry and Medical Devices**
Dec 08, 2022
Hong Kong, Hong Kong
Email: info@igrnet.org
Event Website: http://www.gcpimd.igrnet.org/254/hong-kong/

International Conference on **Medical and Biological Engineering**
Dec 09, 2022
India, Chhattisgarh, Bhilai
Email: papers.techno@gmail.com
Event Website: http://technoarete.com/Conference/7802/ICMBE/

1452nd International Conference on Recent Advances in **Medical Science** (ICRAMS)
Dec 10, 2022
Qatar, Doha
Email: info@theiier.org
Event Website: http://theiier.org/Conference2022/Qatar/2/ICRAMS/

1416th International Conference on **Medical and Biosciences**
Dec 10, 2022
Bahrain, Manama
Email: info@researchworld.org
Event Website: http://researchworld.org/Conference2022/Bahrain/2/ICMBS/

1440th International Conferences on **Medical and Health Science** (ICMHS)
Dec 12, 2022
Morocco, Marrakesh
Email: info@theires.org
Event Website: http://theires.org/Conference2022/Morocco/3/ICMHS/

1408th International Conference on **Science, Health and Medicine** (ICSHM)
Dec 13, 2022
France, Cannes
Email: info@iser.com
Event Website: http://iser.co/Conference2022/France/4/ICSHM/

World Conference on **Pharma Industry and Medical Devices**
Dec 19, 2022
Turkey, Antalya
Email: info.iferp@gmail.com
Event Website: http://iferp.org/Conference/6729/WCPIMD/

1435th International Conference on **Medical and Health Sciences** (ICMHS)
Dec 20, 2022
Italy, Rome
Email: info@iserd.co
Event Website: http://iserd.co/Conference2022/Italy/7/ICMHS/

International Virtual Conference on **Covid-19 and its Effect** (IVCCE)
Dec 23, 2022
Japan, Tokyo
Email: info.conferenceonline@gmail.com
Event Website: http://www.conferenceonline.net/Conference/449/IVCCE/

International Conference on Recent Advances in **Medical, Medicine and Health Sciences** (ICRAMMHS)
Dec 23, 2022
Spain, Barcelona
Email: contact.wrfer@gmail.com
Event Website: http://wrfer.org/Conference/21203/ICRAMMHS/

1448th International Conferences on **Medical and Health Science** (ICMHS)
Dec 24, 2022
South Africa, Cape Town
Email: info@theires.org
Event Website: http://theires.org/Conference2022/SouthAfrica/3/ICMHS/

1416th International Conference on **Science, Health and Medicine** (ICSHM)
Dec 25, 2022
France, Paris
Email: info@iser.co
Event Website: http://iser.co/Conference2022/France/5/ICSHM/

1430th International Conference on Recent Advances in **Medical and Health Sciences** (ICRAMHS)
Dec 26, 2022
Italy, Milan
Email: info@academicsworld.org
Event Website: http://academicsworld.org/Conference2022/Italy/9/ICRAMHS/

1450th International Conferences on **Medical and Health Science** (ICMHS)
Dec 28, 2022
Kuwait, Kuwait City
Email: info@theires.org
Event Website: http://theires.org/Conference2022/Kuwait/2/ICMHS/

International Conference on **Obesity, Weight Management and Nutrition Research** (ICOBWN)
Dec 30, 2022
India, Haryana, Gurugram
Email: info.irfsr@gmail.com
Event Website: http://irfsr.com/Conference/1956/international-conference-on-obesity-weight-management-and-nutrition-research/

WHO-Facts Sheet

1. Chagas disease
2. Epilepsy
3. Health-care waste
4. Lassa fever
5. Parkinson disease

Compiled and edited by
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1. Chagas disease

KEY FACTS

- About 6–7 million people worldwide, mostly in Latin America, are estimated to be infected with Trypanosoma cruzi, the parasite that causes Chagas disease.
- It is transmitted by the triatomine bug (vector-borne), as well as orally (food-borne), through blood/blood products, mother-to-child (congenital) transmission, organ transplantation and laboratory accidents.
- Trypanosoma cruzi infection is curable if treatment is initiated soon after infection. In chronic patients, antiparasitic treatment can potentially prevent or curb disease progression and prevent transmission, for instance, mother-to-child infection.
- Up to 30% of chronically infected people develop cardiac alterations and up to 10% develop digestive, neurological or mixed alterations which may require specific treatment.
- Vector control and other strategies are key methods to prevent Chagas disease in Latin America.
- Blood screening is vital to prevent infection through transfusion and organ transplantation all over the world.
- Detection and treatment of girls and women of child-bearing age is essential, together with the screening of newborns and siblings of infected mothers without previous antiparasitic treatment.

Overview

Chagas disease, also known as American trypanosomiasis, is a potentially life-threatening illness caused by the protozoan parasite *Trypanosoma cruzi.* About 6–7 million people worldwide are estimated to be infected with *T. cruzi*. The disease is found mainly in endemic areas of 21 continental Latin American countries *(1)*, where it has been mostly transmitted to humans and other mammals by contact with faeces or urine of triatomine bugs (vector-borne), known as kissing bugs, among many other popular names, depending on the geographical area.

Chagas disease is named after Carlos Ribeiro Justiniano Chagas, a Brazilian physician and researcher who discovered the disease in 1909.

Distribution

Chagas disease was once entirely confined to continental rural areas of the Region of the Americas (excluding the Caribbean islands). Due to increased population mobility over previous decades, most infected people now live in urban settings and the infection has been increasingly detected in the United States of America, Canada, and many European and some African, Eastern Mediterranean and Western Pacific countries.

Transmission

In Latin America, *T. cruzi* parasites are mainly transmitted by contact with faeces/urine of infected blood-sucking triatomine bugs. These bugs typically live in the wall or roof cracks of homes and peridomiciliary structures, such as chicken coops, pens and warehouses, in rural or suburban areas. Normally they hide during the day and become active at night when they feed on animal blood, including human blood. They usually bite an exposed area of skin such as the face (hence its common name, kissing bug), and the bug defecates or urinates close to the

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bite. The parasites enter the body when the person instinctively smears the bug's faeces or urine into the bite, other skin breaks, the eyes or the mouth.

T. cruzi can also be transmitted by:

- consumption of food or beverages contaminated with *T. cruzi* through, for example, contact with faeces or urine of infected triatomine bugs or marsupials. This kind of transmission typically causes outbreaks;
- passage from an infected mother to her newborn during pregnancy or childbirth;
- blood or blood product transfusion from infected donors;
- some organ transplants using organs from infected donors; and
- laboratory accidents.

Signs and symptoms

Chagas disease presents in two phases. The initial acute phase lasts for about two months after infection. During the acute phase, a high number of parasites circulate in the blood, but in most cases symptoms are absent or mild and unspecific. In less than 50% of people bitten by a triatomine bug, characteristic first visible signs can be a skin lesion or a purplish swelling of the lids of one eye. Additionally, they can present fever, headache, enlarged lymph glands, pallor, muscle pain, difficulty in breathing, swelling, and abdominal or chest pain.

During the chronic phase, the parasites are hidden mainly in the heart and digestive muscle. One to three decades later, up to 30% of patients suffer from cardiac disorders and up to 10% suffer from digestive (typically enlargement of the oesophagus or colon), neurological or mixed alterations. In later years the infection in those patients can cause the destruction of the heart muscle and nervous system, consequent cardiac arrhythmias or progressive heart failure and sudden death.

Treatment

To kill the parasite, Chagas disease can be treated with benznidazole or nifurtimox. Both medicines are nearly 100% effective in curing the disease if given soon after infection at the onset of the acute phase, including the cases of congenital transmission. The efficacy of both diminishes, however, the longer a person has been infected and the adverse reactions are more frequent at older age. Treatment is also indicated for those in whom infection has been reactivated (for example, due to immunosuppression), and for patients during the early chronic phase, including girls and women of childbearing age (before or after pregnancy) to prevent congenital transmission.

Infected adults, especially those with no symptoms, should be offered treatment because antiparasitic treatment can also prevent or curb disease progression. In other cases, the potential benefits of medication in preventing or delaying the development of Chagas disease should be weighed against the duration of treatment (up to 2 months) and possible adverse reactions (occurring in up to 40% of treated adult patients). Benznidazole and nifurtimox should not be taken by pregnant women or by people with kidney or liver failure. Nifurtimox is also contraindicated for people with a background of neurological or psychiatric disorders. Additionally, specific treatment for cardiac, or digestive or neurological manifestations may be required.

Control and prevention

The large reservoir of *T. cruzi* parasites in wild animals of the Americas means that the infection cannot be eradicated. Instead, the control targets are elimination of the transmission to humans and early health-care access of the infected people.

There is no vaccine to prevent Chagas disease. *T. cruzi* can infect many species of triatomine bugs, the majority of which are found in the Americas. Vector control has been the most effective method of prevention in Latin America. Blood screening is necessary to prevent infection through transfusion and organ transplantation and to increase detection and care of the affected population all over the world.

Depending on the geographical area, WHO recommends the following approaches to prevention and control:

- spraying of dwellings and surrounding areas with residual insecticides;
- house improvements and house cleanliness to prevent vector infestation;
- personal preventive measures such as bednets, good hygiene practices in food preparation, transportation, storage and consumption;
- development of contextualized information, education and communication activities for different actors and scenarios about preventative measures and surveillance tools;
- screening of blood donors;
- testing of organ, tissue or cell donors and receivers;
- access to diagnosis and treatment of people with medical indication or recommendation to do antiparasitic treatment, especially children and women of child-bearing age before pregnancy; and
- screening of newborns and other children of infected mothers without previous antiparasitic treatment to do early diagnosis and provide treatment.

Themedical care cost of patients with chronic

cardiac, digestive, neurologic or mixed forms of the disease has been calculated to be >80% higher than the cost of spraying residual insecticide to control vectors and prevent infection.

WHO response

Since the 1990s there have been important successes in parasite and vector control in the Americas, leading to a substantial reduction in transmission and increased access to diagnosis and antiparasitic treatment. The risk of transmission by blood transfusion decreased sharply through the universal screening in all blood banks of the continental Latin American countries, and some in other regions.

WHO recognized Chagas disease as a neglected tropical disease (NTD) in 2005. This facilitated a greater recognition of the disease as a public health problem on the international scene and facilitated the fight against misinformation, the lack of social demand and the weak political commitment to solve the problems related with Chagas disease, as well as insufficient scientific research and development related with prevention, detection and comprehensive care, including diagnosis, treatment, medicine presentations, social aspects, information, education and communication tools. In May 2019, following a decision by the 72 World Health Assembly, the World Chagas Disease Day was established to be celebrated on 14 April (the date in 1909 when Carlos Chagas diagnosed the first human case of the disease, a two-year-old girl called Berenice).

The NTD road map includes five Chagas disease objectives:

1. verification of the interruption of vectorial domiciliary transmission;
2. verification of interruption of transfusion transmission;
3. verification of the interruption of transmission by organ transplants;
4. elimination of congenital Chagas disease; and
5. 75% coverage of antiparasitic treatment of the eligible population.

To attain the goal of elimination of Chagas disease transmission and provide health care for infected or people suffering from the disease both in endemic and non-endemic territories, WHO aims to increase networking at the global level and reinforce regional and national capacities.

1. Argentina, Belize, Bolivia (Plurinational State of), Brazil, Chile, Colombia, Costa Rica, Ecuador, El Salvador, French Guiana, Guatemala, Guyana, Honduras, Mexico, Nicaragua, Panama, Paraguay, Peru, Suriname, Uruguay, and Venezuela (Bolivarian Republic of).

2. Epilepsy

KEY FACTS

- Epilepsy is a chronic noncommunicable disease of the brain that affects people of all ages.
- Around 50 million people worldwide have epilepsy, making it one of the most common neurological diseases globally.
- Nearly 80% of people with epilepsy live in low- and middle-income countries.
- It is estimated that up to 70% of people living with epilepsy could live seizure- free if properly diagnosed and treated.
- The risk of premature death in people with epilepsy is up to three times higher than for the general population.
- Three quarters of people with epilepsy living in low-income countries do not get the treatment they need.
- In many parts of the world, people with epilepsy and their families suffer from stigma and discrimination.

Epilepsy is a chronic noncommunicable disease of the brain that affects around 50 million people worldwide. It is characterized by recurrent seizures, which are brief episodes of involuntary movement that may involve a part of the body (partial) or the entire body (generalized) and are sometimes accompanied by loss of consciousness and control of bowel or bladder function.

Seizure episodes are a result of excessive electrical discharges in a group of brain cells. Different parts of the brain can be the site of such discharges. Seizures can vary from the briefest lapses of attention or muscle jerks to severe and prolonged convulsions. Seizures can also vary in frequency, from less than one per year to several per day.

One seizure does not signify epilepsy (up to 10% of people worldwide have one seizure during their lifetime). Epilepsy is defined as having two or more unprovoked seizures. Epilepsy is one of the world's oldest recognized conditions, with written records dating back to 4000 BCE. Fear, misunderstanding, discrimination and social stigma have surrounded epilepsy for centuries. This stigma continues in many countries today and can impact on the quality of life for people with the disease and their families.

Signs and symptoms

Characteristics of seizures vary and depend on where in the brain the disturbance first starts, and how far it spreads. Temporary symptoms occur, such as loss of awareness or consciousness, and disturbances of movement, sensation (including vision, hearing and taste), mood, or other cognitive functions.

People with epilepsy tend to have more physical problems (such as fractures and bruising from injuries related to seizures), as well as higher rates of psychological conditions, including anxiety and depression. Similarly, the risk of premature death in people with epilepsy is up to three times higher than in the general population, with the highest rates of premature mortality found in low- and middle-income countries and in rural areas.

A great proportion of the causes of death related to epilepsy, especially in low- and middle-income countries, are potentially preventable, such as falls, drowning, burns and prolonged seizures.

Rates of disease

Epilepsy accounts for a significant proportion of the world's disease burden, affecting around 50 million people worldwide. The estimated proportion of the general population with active epilepsy (i.e. continuing seizures or with the need for treatment) at a given time is between 4 and 10 per 1000 people.

Globally, an estimated 5 million people are diagnosed with epilepsy each year. In high-income countries, there are estimated to be 49 per 100 000 people diagnosed with epilepsy each year. In low- and middle-income countries, this figure can be as high as 139 per 100 000. This is likely due to the increased risk of endemic conditions such as malaria or neurocysticercosis; the higher incidence of road traffic injuries; birth-related injuries; and variations in medical infrastructure, the availability of preventive health programmes and accessible care. Close to 80% of people with epilepsy live in low- and middle-income countries.

Causes

Epilepsy is not contagious. Although many underlying disease mechanisms can lead to epilepsy, the cause of the disease is still unknown in about 50% of cases globally. The causes of epilepsy are divided into the following categories: structural, genetic, infectious, metabolic, immune and unknown. Examples include:

- brain damage from prenatal or perinatal causes (e.g. a loss of oxygen or trauma during birth, low birth weight);
- congenital abnormalities or genetic conditions with associated brain malformations;
- a severe head injury;
- a stroke that restricts the amount of oxygen to the brain;
- an infection of the brain such as meningitis, encephalitis or neurocysticercosis,
- certain genetic syndromes; and
- a brain tumour.

Treatment

Seizures can be controlled. Up to 70% of people living with epilepsy could become seizure free with appropriate use of antiseizure medicines. Discontinuing anti-seizure medicine can be considered after 2 years without seizures and should take into account relevant clinical, social and personal factors. A documented etiology of the seizure and an abnormal electroencephalography (EEG) pattern are the two most consistent predictors of seizure recurrence.

- In low-income countries, about three quarters of people with epilepsy may not receive the treatment they need. This is called the "treatment gap".
- In many low- and middle-income countries, there is low availability of antiseizure medication. A recent study found the average availability of generic antiseizure medicines in the public sector of low- and middle-income countries to be less than 50%. This may act as a barrier to accessing treatment.
- It is possible to diagnose and treat most people with epilepsy at the primary health-care level without the use of sophisticated equipment.
- WHO pilot projects have indicated that training primary health-care providers to diagnose and treat epilepsy can effectively reduce the epilepsy treatment gap.
- Surgery might be beneficial to patients who respond poorly to drug treatments.

Prevention

An estimated 25% of epilepsy cases are preventable.

- Preventing head injury is the most effective way to prevent post-traumatic epilepsy.
- Adequate perinatal care can reduce new cases of epilepsy caused by birth injury.
- The use of drugs and other methods to lower the body temperature of a feverish child can reduce the chance of febrile seizures.
- The prevention of epilepsy associated with stroke is focused on cardiovascular risk factor reduction, e.g. measures to prevent or control high blood pressure, diabetes and obesity, and the avoidance of tobacco and excessive alcohol use.
- Central nervous system infections are common causes of epilepsy in tropical areas, where many low- and middle-income countries are concentrated. Elimination of parasites in these environments and education on how to avoid infections can be effective ways to reduce epilepsy worldwide, for example those cases due to neurocysticercosis.

Social and economic impacts

Epilepsy accounts for more than 0.5% of the global burden of disease, a time-based measure that combines years of life lost due to premature mortality and time

lived in less than full health. Epilepsy has significant economic implications in terms of health-care needs, premature death and lost work productivity.

The economic impact of epilepsy varies significantly depending on the duration and severity of the condition, response to treatment, and the health-care setting. Out-of-pocket costs and productivity losses create substantial burdens on households. An economic study from India estimated that public financing for both first- and second-line therapy and other medical costs alleviates the financial burden from epilepsy and is cost-effective.

Although the social effects vary from country to country, the stigma and discrimination that surround epilepsy worldwide are often more difficult to overcome than the seizures themselves. People living with epilepsy can be targets of prejudice. The stigma of the disease can discourage people from seeking treatment, to avoid becoming identified with the disease.

Human rights

People with epilepsy can experience reduced access to educational opportunities, a withholding of the opportunity to obtain a driving licence, barriers to enter particular occupations, and reduced access to health and life insurance. In many countries legislation reflects centuries of misunderstanding about epilepsy, for example, laws which permit the annulment of a marriage on the grounds of epilepsy and laws that deny people with seizures access to restaurants, theatres, recreational centres and other public buildings.

Legislation based on internationally-accepted human rights standards can prevent discrimination and rights violations, improve access to health-care services, and raise the quality of life for people with epilepsy.

WHO response

WHO and its partners recognize that epilepsy is a major public health concern. WHO, the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE) led the Global Campaign Against Epilepsy to bring the disease "out of the shadows" to provide better information and raise awareness about epilepsy and to strengthen public and private efforts to improve care and reduce the disease's impact.

These efforts have contributed to the prioritization of epilepsy in many countries, which resulted in regional declarations in all 6 WHO regions. The WHO Region of the Americas endorsed the Strategy and Plan of Action on epilepsy in 2011 and the World Health Assembly (WHA) resolution on the global burden of epilepsy (WHA68.20) was approved in 2015. The Resolution urges Member States to take coordinated action against epilepsy and its consequences.

Projects have been carried out in many countries to reduce the treatment gap and morbidity of people with epilepsy, to train and educate health professionals, to dispel stigma, to identify potential prevention strategies, and to develop models integrating epilepsy care into local health systems. Combining several innovative strategies, these projects have shown that there are simple, cost-effective ways to treat epilepsy in low-resource settings.

The WHO Programme on reducing the epilepsy treatment gap and the mental health Gap Action Programme (mhGAP) achieved these goals in Ghana, Mozambique, Myanmar and Viet Nam. These projects focused on expanding the skills of primary care and nonspecialist health providers at the community level to diagnose, treat and follow up people with epilepsy. These 4 pilot programmes have led to a considerable increase in access, such that 6.5 million more people have access to treatment for epilepsy should they need it.

3. Health-care waste

KEY FACTS

- Of the total amount of waste generated by health-care activities, about 85% is general, non-hazardous waste.
- The remaining 15% is considered hazardous material that may be infectious, toxic or radioactive.
- Every year an estimated 16 billion injections are administered worldwide, but not all of the needles and syringes are properly disposed of afterwards.
- Open burning and incineration of health care wastes can, under some circumstances, result in the emission of dioxins, furans, and particulate matter.
- Measures to ensure the safe and environmentally sound management of health care wastes can prevent adverse health and environmental impacts from such waste including the unintended release of chemical or biological hazards, including drug-resistant microorganisms, into the environment thus protecting the health of patients, health workers, and the general public.

Health-care activities protect and restore health and save lives. But what about the waste and by-products they generate?

Of the total amount of waste generated by health-care activities, about 85% is general, non-hazardous waste comparable to domestic waste. The remaining 15% is considered hazardous material that may be infectious, chemical or radioactive.

Types of waste

Waste and by-products cover a diverse range of materials, as the following list illustrates:

· Infectious waste: waste contaminated with blood and other bodily fluids (e.g. from discarded diagnostic samples), cultures and stocks of infectious agents from laboratory work (e.g. waste from autopsies and infected animals from laboratories), or waste from patients with infections (e.g. swabs, bandages and disposable medical devices);

- **Pathological waste:** human tissues, organs or fluids, body parts and contaminated animal carcasses;
- **Sharps waste:** syringes, needles, disposable scalpels and blades, etc.;
- **Chemical waste:** for example solvents and reagents used for laboratory preparations, disinfectants, sterilants and heavy metals contained in medical devices (e.g. mercury in broken thermometers) and batteries;
- **Pharmaceutical waste:** expired, unused and contaminated drugs and vaccines;
- **Cytotoxic waste:** waste containing substances with genotoxic properties (i.e. highly hazardous substances that are, mutagenic, teratogenic or carcinogenic), such as cytotoxic drugs used in cancer treatment and their metabolites;
- **Radioactive waste:** such as products contaminated by radionuclides including radioactive diagnostic material or radiotherapeutic materials; and
- **Non-hazardous or general waste:** waste that does not pose any particular biological, chemical, radioactive or physical hazard.

The major sources of health-care waste are:

- hospitals and other health facilities
- laboratories and research centres
- mortuary and autopsy centres
- animal research and testing laboratories
- blood banks and collection services
- nursing homes for the elderly

High-income countries generate on average up to 0.5 kg of hazardous waste per hospital bed per day; while low-income countries generate on average 0.2 kg. However, health-care waste is often not separated into hazardous or non-hazardous wastes in low-income countries making the real quantity of hazardous waste much higher.

Health risks

Health-care waste contains potentially harmful microorganisms that can infect hospital patients, health workers and the general public. Other potential hazards may include drug-resistant microorganisms which spread from health facilities into the environment.

Adverse health outcomes associated with health care waste and by-products also include:

- sharps-inflicted injuries;
- toxic exposure to pharmaceutical products, in particular, antibiotics and cytotoxic drugs released into the surrounding environment, and to substances such as mercury or dioxins, during the handling or incineration of health care wastes;
- chemical burns arising in the context of disinfection, sterilization or waste treatment activities;
- air pollution arising as a result of the release of particulate matter during medical waste incineration;
- thermal injuries occurring in conjunction with open burning and the operation of medical waste incinerators; and
- radiation burns.

Sharps-related

Worldwide, an estimated 16 billion injections are administered every year. Not all needles and syringes are disposed of safely, creating a risk of injury and infection and opportunities for reuse.

Injections with contaminated needles and syringes in low- and middle-income countries have reduced substantially in recent years, partly due to efforts to reduce reuse of injection devices. Despite this progress, in 2010, unsafe injections were still responsible for as many as 33 800 new HIV infections, 1.7 million hepatitis B infections and 315 000 hepatitis C infections **(1)**.

A person who experiences one needle stick injury from a needle used on an infected source patient has risks of 30%, 1.8%, and 0.3% respectively of becoming infected with HBV, HCV and HIV.

Additional hazards occur from scavenging at waste disposal sites and during the handling and manual sorting of hazardous waste from health-care facilities. These practices are common in many regions of the world, especially in low- and middle-income countries. The waste handlers are at immediate risk of needle-stick injuries and exposure to toxic or infectious materials.

In 2015, a joint WHO/UNICEF assessment found that just over half (58%) of sampled facilities from 24 countries had adequate systems in place for the safe disposal of health care waste **(2)**.

Environmental Impact

Treatment and disposal of healthcare waste may pose health risks indirectly through the release of pathogens and toxic pollutants into the environment.

- The disposal of untreated health care wastes in landfills can lead to the contamination of drinking, surface, and ground waters if those landfills are not properly constructed.

- The treatment of health care wastes with chemical disinfectants can result in the release of chemical substances into the environment if those substances are not handled, stored and disposed in an environmentally sound manner.
- Incineration of waste has been widely practised, but inadequate incineration or the incineration of unsuitable materials results in the release of pollutants into the air and in the generation of ash residue. Incinerated materials containing or treated with chlorine can generate dioxins and furans, which are human carcinogens and have been associated with a range of adverse health effects. Incineration of heavy metals or materials with high metal content (in particular lead, mercury and cadmium) can lead to the spread of toxic metals in the environment.
- Only modern incinerators operating at 850-1100 °C and fitted with special gas-cleaning equipment are able to comply with the international emission standards for dioxins and furans.
- Alternatives to incineration such as autoclaving, microwaving, steam treatment integrated with internal mixing, which minimize the formation and release of chemicals or hazardous emissions should be given consideration in settings where there are sufficient resources to operate and maintain such systems and dispose of the treated waste.

Waste management: reasons for failure

Lack of awareness about the health hazards related to health-care waste, inadequate training in proper waste management, absence of waste management and disposal systems, insufficient financial and human resources and the low priority given to the topic are the most common problems connected with health-care waste. Many countries either do not have appropriate regulations, or do not enforce them.

The way forward

The management of health-care waste requires increased attention and diligence to avoid adverse health outcomes associated with poor practice, including exposure to infectious agents and toxic substances.

Key elements in improving health-care waste management are:

- promoting practices that reduce the volume of wastes generated and ensure proposer waste segregation;
- developing strategies and systems along with strong oversight and regulation to incrementally improve waste segregation, destruction and disposal practices with the ultimate aim of meeting national and international standards;
- where feasible, favouring the safe and environmentally sound treatment of hazardous health care wastes (e,g, by autoclaving, microwaving, steam treatment integrated with internal mixing, and chemical treatment) over medical waste incineration;
- building a comprehensive system, addressing responsibilities, resource allocation, handling and disposal. This is a long-term process, sustained by gradual improvements;
- raising awareness of the risks related to health-care waste, and of safe practices; and
- selecting safe and environmentally-friendly management options, to protect people from hazards when collecting, handling, storing, transporting, treating or disposing of waste.

Government commitment and support is needed for universal, long-term improvement, although immediate action can be taken locally.

WHO response

WHO developed the first global and comprehensive guidance document, Safe management of wastes from health-care activities, now in its second edition and more recently a short guide that summarizes the key elements.

- Safe management of wastes from health-care activities

The guide addresses aspects such as regulatory framework, planning issues, waste minimization and recycling, handling, storage and transportation, treatment and disposal options, and training. The document is aimed at managers of hospitals and other health-care facilities, policy makers, public health professionals and managers involved in waste management. In addition, as part of monitoring Sustainable Development Goal 6 on safely managed water and sanitation, the WHO/UNICEF Joint Monitoring Programme will regularly report on safe management of health care waste as part of wider monitoring efforts on water and sanitation in health care facilities.

In collaboration with other partners, WHO also developed a series of training modules on good practices in health-care waste management covering all aspects of waste management activities from identification and classification of wastes to considerations guiding their safe disposal using both non-incineration or incineration strategies.

WHO guidance documents on health-care waste are also available including:

- a monitoring tool;
- a cost assessment tool;
- a rapid assessment tool;
- a policy paper;

- guidance to develop national plans;
- management of waste from injection activities;
- management of waste at primary health care centres;
- management of waste from mass immunization activities; and
- management of waste in emergencies.

In addition, WHO and UNICEF together with partners in 2015 launched a global initiative to ensure that all health care facilities have adequate water, sanitation and hygiene services. This includes addressing health care waste.

1. Pépin J, Abou Chakra CN, Pépin E, Nault V, Valiquette L. Evolution of the global burden of viral infections from unsafe medical injections, 2000-2010.PLoSOne. 2014 Jun 9;9(6):e99677. **(2)** WHO/UNICEF,2015. Water, sanitation and hygiene in health care facilities: status in low- and middle-income countries. World Health Organization, Geneva.

4. Lassa fever

KEY FACTS

- Lassa fever is an acute viral haemorrhagic illness of 2-21 days duration that occurs in West Africa.
- The Lassa virus is transmitted to humans via contact with food or household items contaminated with rodent urine or faeces.
- Person-to-person infections and laboratory transmission can also occur, particularly in hospitals lacking adequate infection prevention and control measures.
- Lassa fever is known to be endemic in Benin, Ghana, Guinea, Liberia, Mali, Sierra Leone, and Nigeria, but probably exists in other West African countries as well.
- The overall case-fatality rate is 1%. Observed case-fatality rate among patients hospitalized with severe cases of Lassa fever is 15%.
- Early supportive care with rehydration and symptomatic treatment improves survival.

Background

Though first described in the 1950s, the virus causing Lassa disease was not identified until 1969. The virus is a single-stranded RNA virus belonging to the virus family *Arenaviridae*.

About 80% of people who become infected with Lassa virus have no symptoms. 1 in 5 infections result in severe disease, where the virus affects several organs such as the liver, spleen and kidneys.

Lassa fever is a zoonotic disease, meaning that humans become infected from contact with infected animals. The animal reservoir, or host, of Lassa virus is a rodent of the genus *Mastomys*, commonly known as the "multimammate rat." *Mastomys* rats infected with Lassa virus do not become ill, but they can shed the virus in their urine and faeces.

Because the clinical course of the disease is so variable, detection of the disease in affected patients has been difficult. When presence of the disease is confirmed in a community, however, prompt isolation of affected patients, good infection prevention and control practices, and rigorous contact tracing can stop outbreaks.

Lassa fever is known to be endemic in Benin (where it was diagnosed for the first time in November 2014), Ghana (diagnosed for the first time in October 2011), Guinea, Liberia, Mali (diagnosed for the first time in February 2009), Sierra Leone, and Nigeria, but probably exists in other West African countries as well.

Symptoms of Lassa fever

The incubation period of Lassa fever ranges from 6–21 days. The onset of the disease, when it is symptomatic, is usually gradual, starting with fever, general weakness, and malaise. After a few days, headache, sore throat, muscle pain, chest pain, nausea, vomiting, diarrhoea, cough, and abdominal pain may follow. In severe cases facial swelling, fluid in the lung cavity, bleeding from the mouth, nose, vagina or gastrointestinal tract and low blood pressure may develop.

Protein may be noted in the urine. Shock, seizures, tremor, disorientation, and coma may be seen in the later stages. Deafness occurs in 25% of patients who survive the disease. In half of these cases, hearing returns partially after 1–3 months. Transient hair loss and gait disturbance may occur during recovery.

Death usually occurs within 14 days of onset in fatal cases. The disease is especially severe late in pregnancy, with maternal death and/or fetal loss occurring in more than 80% of cases during the third trimester.

Transmission

Humans usually become infected with Lassa virus from exposure to urine or faeces of infected *Mastomys* rats. Lassa virus may also be spread between humans through direct contact with the blood, urine, faeces, or other bodily secretions of a person infected with Lassa fever. There is no epidemiological evidence supporting airborne spread between humans. Person-to-person transmission occurs in both community and health-care settings, where the virus may be spread by contaminated medical equipment, such as re-used needles. Sexual transmission of Lassa virus has been reported.

Lassa fever occurs in all age groups and both sexes. Persons at greatest risk are those living in rural areas where *Mastomys* are usually found, especially in communities with poor sanitation or crowded living conditions. Health workers are at risk if caring for Lassa fever patients in the absence of proper barrier nursing and infection prevention and control practices.

Diagnosis

Because the symptoms of Lassa fever are so varied and non-specific, clinical diagnosis is often difficult, especially early in the course of the disease. Lassa fever is difficult to distinguish from other viral haemorrhagic fevers such as Ebola virus disease as well as other diseases that cause fever, including malaria, shigellosis, typhoid fever and yellow fever.

Definitive diagnosis requires testing that is available only in reference laboratories. Laboratory specimens may be hazardous and must be handled with extreme care. Lassa virus infections can only be diagnosed definitively in the laboratory using the following tests:

- reverse transcriptase polymerase chain reaction (RT-PCR) assay
- antibody enzyme-linked immunosorbent assay (ELISA)
- antigen detection tests
- virus isolation by cell culture.

Treatment and prophylaxis

The antiviral drug ribavirin seems to be an effective treatment for Lassa fever if given early on in the course of clinical illness. There is no evidence to support the role of ribavirin as post-exposure prophylactic treatment for Lassa fever.

There is currently no vaccine that protects against Lassa fever.

Prevention and control

Prevention of Lassa fever relies on promoting good "community hygiene" to discourage rodents from entering homes. Effective measures include storing grain and other foodstuffs in rodent-proof containers, disposing of garbage far from the home, maintaining clean households and keeping cats. Because *Mastomys* are so abundant in endemic areas, it is not possible to completely eliminate them from the environment. Family members should always be careful to avoid contact with blood and body fluids while caring for sick persons.

In health-care settings, staff should always apply standard infection prevention and control precautions when caring for patients, regardless of their presumed diagnosis. These include basic hand hygiene, respiratory hygiene, use of personal protective equipment (to block splashes or other contact with infected materials), safe injection practices and safe burial practices.

Health-care workers caring for patients with suspected or confirmed Lassa fever should apply extra infection control measures to prevent contact with the patient's blood and body fluids and contaminated surfaces or materials such as clothing and bedding. When in close contact (within 1 metre) of patients with Lassa fever, health-care workers should wear face protection (a face shield or a medical mask and goggles), a clean, non-sterile long-sleeved gown, and gloves (sterile gloves for some procedures).

Laboratory workers are also at risk. Samples taken from humans and animals for investigation of Lassa virus infection should be handled by trained staff and processed in suitably equipped laboratories under maximum biological containment conditions.

On rare occasions, travellers from areas where Lassa fever is endemic export the disease to other countries. Although malaria, typhoid fever, and many other tropical infections are much more common, the diagnosis of Lassa fever should be considered in febrile patients returning from West Africa, especially if they have had exposures in rural areas or hospitals in countries where Lassa fever is known to be endemic. Health-care workers seeing a patient suspected to have Lassa fever should immediately contact local and national experts for advice and to arrange for laboratory testing.

WHO response

The Ministries of Health of Guinea, Liberia and Sierra Leone, WHO, the Office of United States Foreign Disaster Assistance, the United Nations, and other partners have worked together to establish the Mano River Union Lassa Fever Network. The programme supports these 3 countries in developing national prevention strategies and enhancing laboratory diagnostics for Lassa fever and other dangerous diseases. Training in laboratory diagnosis, clinical management, and environmental control is also included.

5. Parkinson disease

KEY FACTS

- Parkinson disease (PD) is a degenerative condition of the brain associated with motor symptoms (slow movement, tremor, rigidity and imbalance) and other complications including cognitive impairment, mental health disorders, sleep disorders and pain and sensory disturbances.
- Globally, disability and death due to PD are increasing faster than for any other neurological disorder.

- Clinical diagnosis of PD by trained non-specialized health-care workers and simplified treatment guidelines offer better management in primary care settings.
- Levodopa/carbidopa, the most effective medicine for improving symptoms, functioning and quality of life is not accessible, available or affordable everywhere, particularly in low- and middle-income countries.
- Rehabilitation can help improve functioning and quality of life for people with PD.

Overview

Parkinson disease (PD) is a degenerative condition of the brain associated with motor symptoms (slow movement, tremor, rigidity, walking and imbalance) and a wide variety of non-motor complications (cognitive impairment, mental health disorders, sleep disorders and pain and other sensory disturbances). Motor impairments, such as dyskinesias (involuntary movements) and dystonias (painful involuntary muscle contractions) contribute to limitations in speech, mobility and restrictions in many life areas. Progression of these symptoms results in high rates of disability and care requirements. Many people with PD also develop dementia during the course of their disease.

While PD is the most common movement disorder, other movement disorders exist such as multiple system atrophy, progressive supranuclear palsy, chorea, ataxia and dystonia. Some movement disorders have similar symptoms to PD such as tremor, slow movement and rigidity. All movement disorders share the same challenges as PD regarding diagnostic and treatment gaps and access to medication, particularly in low- and middle-income countries (LMIC).

Risk factors for PD include increasing age, although younger people can be affected as well. Men are more affected than women. A number of studies have shown that environmental factors, including pesticides, air pollution and industrial solvents could increase the risk of PD.

The cause for PD is not known but is thought to arise from a complex interaction between genetic factors and exposure to environmental factors such as pesticides, solvents and air pollution throughout life.

Epidemiology

Globally, disability and death due to PD are increasing faster than for any other neurological disorder. The prevalence of PD has doubled in the past 25 years. Global estimates in 2019 showed over 8.5 million individuals with PD. Current estimates suggest that, in 2019, PD resulted in 5.8 million disability-adjusted life years, an increase of 81% since 2000, and caused 329 000 deaths, an increase of over 100% since 2000.

Assessment and care

PD is a clinical diagnosis that not only can be made by neurologists but also by trained non-specialist health-care workers. Assessment and management of PD by trained non-specialized health-care workers in primary care is particularly important in areas where specialist neurological services are unavailable, such as in some LMIC.

Although there is no cure, medicines, surgical treatment and other therapies can treat the symptoms of PD. Levodopa/carbidopa remains the most common and effective medication and is on the WHO Model List of Essential Medicines. Other medications, such as anticholinergics, or therapies such as deep brain stimulation can also treat symptoms of PD, especially tremors as well as to reduce medicine intake. However, many medications and surgical resources are not accessible, available or affordable everywhere.

As with many degenerative neurologic disorders, nonpharmacological management such as rehabilitation can offer relief. Specific types of physiotherapy including strength training, gait and balance training, and hydrotherapy can help improve functioning and quality of life for people with PD and other movement disorders. They can also reduce the strain on carers.

Telemedicine can also be used to increase the access to care for people with PD.

Impact on families and carers

Informal carers (i.e. most commonly family members and friends) spend many hours daily providing care for people living with PD. This can be overwhelming. Physical, emotional and financial pressures can cause great stress to families and carers, and support is required from the health, social, financial and legal systems. Useful support resources from other conditions can be drawn upon, such as WHO's iSupport programme for dementia.

Human rights

People with PD are often subject to stigma and discrimination, including unjust discrimination within the workplace and lack of opportunities to engage and participate in their communities.

People with PD require accessible health services for general health-care needs like the rest of the population, including medicine access, promotive and preventive services and prompt diagnosis, treatment and care. A common barrier is created by health-care

providers' inadequate knowledge and understanding of PD and myths that PD is a contagious illness or a normal part of aging.

WHO response

In May 2022, the World Health Assembly endorsed the Intersectoral global action plan on epilepsy and other neurological disorders 2022–2031. The action plan will address the challenges and gaps in providing care and services for people with epilepsy and other neurological disorders such as PD that exist worldwide and ensure a comprehensive, coordinated response across sectors. This includes raising policy prioritization and strengthening governance, providing effective, timely and responsive diagnosis, treatment and care, implementing strategies for promotion and prevention, fostering research and innovation and strengthening information systems.

A WHO technical brief entitled Parkinson disease: a public health approach is available for policy-makers, health programme managers and planners, health-care providers, researchers, people with PD, carers and other stakeholders. It outlines the important action areas for intervention in PD including global health policies focused on prevention and risk reduction, education and awareness and access to treatment and care at various levels of the health system.

WHO's iSupport, a knowledge and skills training programme for carers of people living with dementia is available as an online course and a hardcopy manual. iSupport Lite includes easy-to-read posters and a brief video that can act as a quick reference or a refresher, reinforcing previously acquired caregiving skills and knowledge.