Journal of Bursa Faculty of Medicine

Volume 1 · Issue 2 · May 2023

e-ISSN: 2980-0218

Available at https://dergipark.org.tr/tr/pub/bursamed

Journal of Bursa Faculty of Medicine

Available at https://dergipark.org.tr/tr/pub/bursamed

PUBLICATION BOARD

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Innovations in the treatment of anemia in chronic kidney failure

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Journal of Bursa Faculty of Medicine
e-ISSN: 2980-0218

Review

Nephrology

Received
December 26, 2022
Accepted
May 09, 2023
Published online
May 29, 2023.

J Bursa Med 2023;1(2) 41-44

ABSTRACT

Chronic kidney disease (CKD) is a chronic inflammatory process. Inflammation, uremic toxins, deficiency of erythropoietin production, iron deficiency, shortening of erythrocyte lifespan, gastrointestinal losses, etc. lead to anemia in CKD. The prevalence of anemia increases as the CKD stage increases. Hepcidin is an important molecule for the use of iron in anemia. Hypoxia-induced factors (HIF) maintain the continuity of erythropoiesis. This molecule is inactivated by prolyl hydroxylase (PH). HIF-PH inhibitors have come into use in the treatment of anemia due to CKD. This review describes anemia in CKD and the use of HIF PH inhibitors.

Keywords: Chronic kidney disease, anemia, hepcidin, HIF-PH inhibitors.

The prevalence of chronic kidney disease increase worldwide. Anemia in CKD may develop due to reasons such as decreased erythropoietin synthesis, inflammation, uremic toxins, iron deficiency, malnutrition, gastrointestinal losses, etc. The incidence of anemia increases as the CKD stage increases (especially after stage 3). In CKD, patients mostly die from cardiovascular causes. Anemia and secondary hyperparathyroidism in CKD associated with mortality. Therefore, anemia should be managed well in the course of the disease [1, 2].

The ARIC study compared patients with and without anemia in CKD patients. Mortality in CKD patients with anemia was 2 times higher than in CKD patients without anemia [3]. Weilner et al. analyzed 2423 CKD patients with and without anemia. All-cause mortality was increased by 65% in patients with anemia. Myocardial infarction (MI), stroke and all-cause mortality were 48% higher in the anemia group [4]. In the presence of anemia in CKD patients, the heart engages compensatory mechanisms to increase oxygen delivery. Left ventricular hypertrophy (LVH) develops. In the presence of anemia and LVH in CKD, the risk of MI, stroke and death increase 4 times, and all-cause mortality increases 3 times [5, 6].

Quality of life in CKD patients with anemia is adversely affected. In patients stage 4 and 5 CKD with anemia, fatigue 79%, respiratory distress 39%, fatigue and weakness 36% and gastrointestinal symptoms 18% were detected. Treating anemia in CKD improves quality of life and reduces mortality [7].

HEPCIDIN and HYPOXIA INDUCIBLE FACTORS (HIF)

Hepcidin is the main regulator of iron metabolism. Hepcidin is an acute phase reactant with protein structure. Iron overload

How to cite this article
Ayar Y. Innovations in the treatment of anemia in chronic kidney failure. J Bursa Med 2023;1(2):41-44

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and inflammation stimulate hepcidin synthesis. Iron deficiency, hypoxia, blood loss, and stimulation of erythropoiesis inhibit hepcidin synthesis. Inflammation shortens erythrocyte lifespan and stimulates their phagocytosis.

Cells that produce erythropoietin (EPO) in hypoxic conditions increase renal EPO output. Hypoxia-inducible factors (HIF) increase gene transcription and erythropoiesis in EPO producing cells. In the presence of HIF (hypoxia, iron deficiency, blood loss, etc.), EPO production and hemoglobin (Hgb) synthesis increase. Hepcidin synthesis is also decreased, iron absorption from the small intestine and iron transport to the plasma and bone marrow for erythropoiesis increase [8, 9].

HIF consists of two structures, HIF α and β. The combination of these two structures (in condtions of hypoxia, anemia, blood loss, etc.) stimulate transcription factors for erythropoiesis. HIF is inhibited by prolyl hydroxylase at normal oxygen levels. Prolyl hydroxylase (PH) is involved in the degradation of HIF. There are three PHs, mainly HIF PH2. HIF PH is inactive in cases of hypoxia, anemia, blood loss, etc. HIF continues its activity and stimulates erythropoiesis [10, 11].

In addition to stimulating erythropoiesis, HIF affects more than 1000 genes such as stimulating angiogenesis, cell migration, glucose metabolism and availability, hormonal and vasomator regulation [12, 13].

CURRENT TREATMENTS

Three treatment options are available for CKD anemia. CKD-associated anemia was described in 1836. Oral iron use is not recommended for CKD patients due to its effectiveness. Oral iron preparations are not recommended for treatment because they have poor gastrointestinal side effects and absorption, and because they interact primarily with phosphorus binders and antacids in CKD. The use of intravenous (IV) iron instead of oral iron preparations was found to be more beneficial and effective in terms of efficacy in CKD patients. IV iron drugs have better bioavailability and rapid action, increase hemoglobin levels and reduc the need for erythropoietin stimulating agents (ESA). The most important side effects of these drugs are anaphylaxis, cytotoxicity, hemosiderosis, bacterial infection, oxidative stress, etc [14-16].

Transfusion directly increases the erythrocyte level. The most important side effects are hemolysis, alloimmunization, anaphylaxis, infections (hepatitis, HIV etc.), fluid overload, hyperkalemia etc [17, 18].

EPO-producing genes identified in the 1950s. Using ESAs started in the 1980s. With the use of ESAs, a decrease in blood transfusions and improve in quality of life have been observed. The most important side effects of ESAs are cardiovascular events, thromboembolism, hypertension and malignancy [17].

High doses of ESA and high hemoglobin levels after using ESA are associated with stroke, MI, and death. The CREATE, CHOIR, and TREAT studies have observed stroke, MI, and cardiovascular events in patients with elevated Hgb following ESA treatment. In a cohort study conducted in Japan, the mortality rate was 13% higher in CKD patients using long-acting ESA. In another study in which stage 3b and 5 non-dialysis patients and patients undergoing dialysis were evaluated, major cardiovascular events was more found as the ESA dose increased, 36% in the non-dialysis group and 60% in the group that undergo dialysis [19-21].

When the effects and side effects of current treatments are evaluated, new searches have increased in the treatment of CKD anemia.

HIF PROLYL HYDROXYLASE INHIBITORS

Since 2008, studies on HIF-PH inhibitors have intensified. The therapeutic use of these drugs started in China, Japan and Europe as of 2018 (Roxadustat and Daprodustat). Vadadustat, Molidustat, Desidustat ve Enarodustat ile ilgili klinik çalışmalar devam etmektedir. HIF-PH inhibitors inhibit HIF-PH reversibly. These drugs prevent HIF α from being hydroxylated by PH at normal oxygen levels, causing stabilization of HIF. As a result, Hepcidin levels decrease, EPO receptors and EPO production increase. The absorption of iron from the intestine and its mobilization from macrophages and transport to the bone marrow are stimulated. The most important advantage of this group of drugs is that they can be taken orally 3 days a week (22, 23).

In studies evaluating stage 3-5 CKD patients not receiving dialysis treatment, when HIF-PH inhibitors were compared with placebo for 52-104 weeks, change in Hgb level from baseline, reaching desired Hgb levels, and maintaining Hgb levels were more significant in those using HIF-PH inhibitors. The need for blood transfusion, IV iron and ESA use were lower in those taking HIF-PH inhibitors. LDL cholesterol

levels were lower in those using HIF-PH inhibitors as a secondary effect. CKD patients receiving ESA therapy who were not on dialysis were similar to achieving the desired Hgb response compared with those receiving HIF-PH inhibitors. IV iron requirement was less in those using HIF-PH inhibitors. LDL cholesterol level was also found to be lower in the same group [24-26].

Achieving and maintaining desired Hgb levels were similar in both groups when compared with patients on new onset (< 4 months) or stable dialysis patients (> 4 months) versus those using HIF-PH inhibitors (52 weeks to 4 years). The need for transfusion and IV iron were less in the group of HIF-PH inhibitors [27, 28].

When the side effect profiles were evaluated, the risk of cardiovascular events were similar in HIF-PH inhibitors compared to the ESA group. Advers effects that developed under treatment were similar to those of the ESA group. The incidences of sepsis, deep vein thrombosis, pulmonary embolism and epilepsy in those using HIF-PH inhibitors were the same as those using ESA [29].

In conclusion, HIF-PH inhibitors will take place as an alternative in the treatment of CKD anemia. It will reduce the need for transfusion and İV iron, and oral use will facilitate patient compliance.

CONCLUSION

Authors' Contribution

Study Conception: YA,; Study Design: YA,; Supervision: YA,; Materials: YA,; Data Collection and/or Processing: YA,; Statistical Analysis and/or Data Interpretation: YA,; Literature Review: YA,; Manuscript Preparation: YA and Critical Review: YA.

Acknowledgements

We are grateful to all treating physicians in our center for collaboration and the data collection.

Financing

There is no source of financial support or funding.

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Analysis of Isolation Precautions in a Tertiary Training and Research Hospital

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Journal of Bursa Faculty of Medicine
e-ISSN: 2980-0218

Original Article

Infectious Diseases and Clinical Microbiology

Received
January 21, 2023
Accepted
April 12, 2023
Published online
May 29, 2023

J Bursa Med 2023;1(2) 45-49

ABSTRACT

Objectives: Isolation precautions are used to take control of pathogen transmission and reduce hospital-acquired infections. The aim of our research is to evaluate all patients for whom isolation is recommended, to determine isolation types, growing microorganisms and isolation compliance.

Methods: All patients isolated within a calendar year were analyzed based on infection control committee records. Of the isolation patients, 14.6% (201/1379) were in the pediatric infection clinic, 14.1% (194/1379) in the pediatric clinics, 11.2% (155/1379) in the general intensive care unit, 8.3% (115/1379) was followed in the urology clinic.

Results: In 2018; 83,750 patients were hospitalized and followed up in our hospital. Isolation was recommended for 1379 (1.6%) of the hospitalized patients. Of the isolation recommended patients, 14.6% (201/1379) were in the pediatric infection clinic, 14.1% (194/1379) in the pediatric clinics, 11.2% (155/1379) in the general intensive care unit, 8.3% (115/1379) was followed in the urology clinic.

Conclusion: Isolation precautions are very important in protecting both patients and healthcare workers from transmission of infections. It should be aimed to determine the isolation periods in accordance with the criteria determined in the international guidelines and discontinuing the isolation measures as soon as possible when the indication is terminated.

Keywords: Patient isolation, infection control, transmission

Healthcare-associated infections (HAIs) are defined as infections acquired in the hospital settings that are not present at hospital admission [1]. HAIs usually develop 48-72 hours after the patient's hospitalization and within 10 days after discharge. It is of great importance to implementing an effective infection control program has great importance in order to reduce morbidity, mortality and increasing cost associated with hospital infections. Studies on infection control began in the early 1970s with the appointment of the first infection control nurse in England [2]. In our country, the Infection Control Committee was established at Hacettepe University in 1984 and at Istanbul University Istanbul Faculty of Medicine in 1985. In 2005, the Infection

How to cite this article
Asan A, Demir C, Akca MÖ, Gümüş A, Kahrıman A, et al, Analysis of Isolation Precautions in a Tertiary Training and Research Hospital. J Bursa Med 2023;1(2):45-49

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Control Committee became obligatory in hospitals with the "Regulation on the Amendment of the Operating Regulation of Inpatient Treatment Institutions". After the specified date, the Infection Control Committee was established in our hospital and continues to work today. Isolation precautions are used to take control of pathogen transmission and reduce HAIs. The purpose of isolation is to prevent transmission from patient to patient or from patient to healthcare personnel. The aim of our research is to evaluate all patients for whom isolation is recommended, to determine isolation types, growing microorganisms and isolation compliance.

METHODS

All patients who were recommended to be isolated in Health Sciences University Bursa Yüksek İhtisas Training and Research Hospital between January 01, 2018 and December 31, 2018 were examined retrospectively from the infection control committee reports and hospital automation system records. A sample selection method was not used because analysis of all patients was planned. Data analysis was accomplished by IBM SPSS 21.0 statistical program. Descriptive statistics were specified as frequencies and percentages for qualitative data. Chi-square test was used to analyse whether there was a relationship between categorical variables. $P < 0.05$ was considered statistically significant.

RESULTS

In 2018; 83,750 patients were hospitalized and followed up in our hospital. Isolation was recommended for 1379 (1.6%) of the hospitalized patients (Table 1). Of these patients, 601 (43.6%) were male, 788 (56.4%) were female, and the age of the patients ranged from 0 to 104 (42.2 ± 32.2 SD). Of the isolation recommended patients, 14.6% (201/1379) were in the pediatric infection clinic, 14.1% (194/1379) in the pediatric clinics, 11.2% (155/1379) in the general intensive care unit, 8.3% (115/1379) was followed in the urology clinic (Table 2). In terms of isolation methods, contact isolation was recommended for 1041 (75.4%) patients, close contact isolation was recommended for 220 (16.6%) patients, respiratory isolation was recommended for 63 (4.6%) patients, and droplet isolation was recommended for 55 (4.0%) patients. When we look at the microorganisms that are the cause of isolation, extended-spectrum beta-lactamase (ESBL) positive *Escherichia coli* (25.3%), *Klebsiella pneumoniae* (16.8%) and Rotavirus (16.2%) were in the front row (Table 3). When evaluated in terms of isolation compliance, hospital-wide compliance was found to be 96.4%. Compliance with isolation measures was statistically significantly lower in the urology clinic. ($p = 0.001$).

DISCUSSION

Isolation precautions are used to prevent the transmission of microorganisms in healthcare settings to other patients and from patient to healthcare staff and visitors. There are three categories of isolations: contact Precautions, droplet Precautions, and airborne Precautions. In an epidemic study conducted by Jernigan *et al*., it was observed that contact isolation reduces the spread of MRSA by 16 times [3]. How-

Table1. Evaluation of Patients Recommended for Isolation

Number of Inpatients (n)	83.750
Number of Patients in Isolation (%)	1379 (1.6)
Gender M/F (%)	601/788 (43.6/56.4)
Age Mean ± SD (min-max)	42.2 ± 32.2 (0-104)
Insulation Precautions	n (%)
Contact isolation	1261 (92.4)
Respiratory isolation	63 (4.6)
Droplet isolation	55 (4.0)
Compliance to Isolation Precautions	n (%)
Yes	1330 (96.4)
No	49 (3.6)

Table 2. Evaluation of Patients Recommended for Isolation According to Clinics

Klinik	n (%)
Pediatric Infectious Diseases	201 (14.6)
General Intensive Care Unit	199 (14.4)
Child Health and Diseases	194 (14.1)
Urology	115 (8.3)
Internal Medicine	108 (7.8)
Cardiovascular Surgery	74 (5.4)
Palliative	55 (4.0)
Neurology	42 (3.0)
Chest Diseases	42 (3.0)
Pediatric Intensive Care Unit	37 (2.7)
Other Clinics	312 (22.7)

ever, when the patient is isolated; there are problems especially in transfer of patients from intensive care units to clinics, patients waiting for hospitalization in emergency services can not be admitted to the clinics, the hospital bed occupancy rate decreases and this creates a vicious circle [3]. In a study conducted by Morgan *et al*., in a tertiary hospital, when the transfer of a patient colonized with a resistant microorganism was compared with a normal patient transfer; it was concluded that it caused a prolonged waiting period; as 10.9 days and 4.3 days, respectively [4]. Isolation of patients also increases the cost of hospitalization. To manage this condition, it is recommended to place patients colonized and/or infected with the same microorganism in the same room (cohorting patients with the same infection). In addition, there may be an overlooked cost when the patient is isolated, the risk of a decrease in the quality of care of the patient and the occurrence of preventable side effects during the isolation period increases [5-7]. It is obvious that isolation precautions is important to protect other patients from transmission of healthcare associated infections. Patient satisfaction is a measure of the extent to which a patient is content with the health care they received from their health care provider. Patient satisfaction is one of the most important factors to determine the success of a health care facility. It has been shown that isolation precautions significantly reduces the patient's satisfaction with the institution. Patients think that they receive less attention as healthcare professionals enter less rooms, communicate less and have less physical contact against patients who are

Tablo 3. Microorganisms Detected in Patients Recommended for Isolation

Microorganism	n (%)
E. coli	349 (25.3)
Klebsiella pneumoniae	231 (16.8)
Rotavirus	223 (16.2)
Acinetobacter baumannii	203 (14.7)
Pseudomonas aeruginosa	102 (7.4)
Mycobacterium tuberculosis	50 (3.6)
Stafilococcus aureus	45 (3.3)
Adenovirus	38 (2.8)
Enterobacter cloacae	29 (1.8)
Vancomycin resistant enterococci	24 (1.7)
Other	85 (6.1)

isolated. It has been shown that the rate of depression and delirium increases in isolated patients [8-10].

The microorganisms isolated at the forefront in our study were Enterobacteriaceae spp, Rotavirus, *Acinetobacter baumannii*. Similar microorganisms were found in the examinations conducted in Poland between 2010 and 2012. It was concluded that the most prevalent microorganisms in 2012 were Enterobacteriaceae ESBL+, Rotavirus and *Acinetobacter baumanii* in this study [11]. While *C.difficile* was at the forefront in this study, it was quite in the background in our study. The difficulties in accessing screening tests for *C.difficile* infections in our hospital may be contributing to this result.

When the clinics with isolation precautions were evaluated, pediatric clinics and intensive care units were found in the first two lines. Similar clinics have been identified in the literature [11]. When the clinics were evaluated, non-compliance to the isolation precautions in the urology clinic was in the first place with 33%, and this non-compliance was statistically significant (p = 0.001). There is no data in the literature showing that isolation precautions are not followed especially in the urology clinic. Since it is a cross-sectional study, such data was obtained during the analysis period. During the study, no outbreaks occurred in the urology clinic or in other clinics. Estrada *et al*., found that non-compliance to isolation procedures was not due to a deficit of materials, but to individual behaviours [12].

CONCLUSION

In conclusion; Isolation precautions are very important in protecting both patients and healthcare workers from transmission of infections. It should be taken into account that both the physical care and mental state of the isolated patient may be adversely affected. It should be aimed to determine the isolation periods in accordance with the criteria determined in the international guidelines and discontinuing the isolation measures as soon as possible when the indication is terminated.

Limitations of the Study

Since our study was a retrospective, cross-sectional study, the number of isolations and their clinics were evaluated, cost analysis, delayed transfers between services were not analyzed.

Ethical Approval

The protocol of the study was approved by the Medical Ethics Committee of Bursa Yuksek Ihtisas Training and Research Hospital, Bursa, Turkey. (Decision number: 2011-KAEK-25 2019/08-07, date: August 21, 2019).

Authors' Contribution

Authors' Contribution Study Conception: AA,; Study Design: AA, CD, MOA, AG,; Supervision: AA,; Materials: CD, MOA, AG,; Data Collection and/ or Processing: AK, ECG,; Statistical Analysis and/ or Data Interpretation: AA, CD, AG; Literature Review: MOA, AG; Manuscript Preparation: AG, MOA and Critical Review: AA, CD, AG.

Conflict of interest

No potential conflicts of interest relevant to this article were reported.

Acknowledgements

We are grateful to all treating physicians in our center for collaboration and the data collection.

Financing

There is no source of financial support or funding.

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Temperature and holiday impacts on early childhood fracture

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Journal of Bursa Faculty of Medicine

e-ISSN: 2980-0218

Original Article

Orthopedics and Traumatology

Received
March 20, 2023
Accepted
May 21, 2023
Published online
May 29, 2023

J Bursa Med 2023;1(2) 50-56

ABSTRACT

Objectives: Hospitalizations and surgeries of extremity fractures in childhood after emergency admissions have been increasing steadily. One-third of under seventeen-year-old children have at least one fracture; most of them are on the extremity. The relationship between weather conditions and children's fractures is well known. This study aims to reveal the effects of weather conditions and holidays on pre-school and primary school children's (2-12-year-old) extremity fractures.

Methods: All children between 2 and 12-year-old and extremity fractures during the decade of 1 January 2017 and 31 December 2018 were included in the present study. The population was studied in two groups: pre-school and primary school. Monthly meteorological information, the number of holidays, and fracture numbers were compared.

Results: There was a significant relationship between all extremity fractures and monthly average temperature, warm days, and hot days. A negative correlation was detected between cold days and all upper-lower extremity fractures. In both groups, there was a positive correlation between hot days and upper extremity and total fracture numbers. There was no correlation between fracture numbers and monthly holiday numbers in both groups.

Conclusions: We researched the effects of monthly average temperature and the number of holidays on pre-school and primary school children. Results show that there is a close relationship between temperature and fracture numbers. Not only on warm days, as stated in the literature, but also on hot days fracture incidence is increasing. We found no correlation in our study between the number of holidays and the number of fractures.

Keywords: temperature, child, bone fracture, holidays.

Hospitalizations and surgeries of extremity fractures in childhood after emergency admissions are increasing steadily. One of every four children in the United States has urgent medical care, and the rate of fractures in childhood has been reported to be from 12.0 to 36.1/1000 and more than 50,000 in the UK per year [1, 2]. One-third of under seventeen-year-old children have at least one fracture and most of them are on the extremity [3-5]. These common fractures affect the daily life and socio-economic conditions of the parent. The relationship between weather condi-

How to cite this article
Turkmensoy F, Ulusaloglu AC, Çevik N, Akalin Y, Kaya AÖ, et al. Temperature and holiday impacts on early childhood fracture. J Bursa Med 2023;1(2);50-56

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tions and the most common childhood fractures as the supracondylar humerus, femur shaft, and forearm fracture is shown [3, 6, 7].

Children older than two years are generally very active than adults depend on the weather temperatures, and usually, this activity results in an injury. Seasonal variations of child fracture numbers have been demonstrated in many studies using different parameters. Several studies described the relationship between children's fractures and temperature. Daily, weekly, temperatures, monthly minimum and maximum temperatures are used for his descriptions and almost all of these studies have similar results [6, 8-11]. As a general belief, fractures are thought to be associated with holidays, as they peak during the summer months, but results do not support this hypothesis [4].

This study aimed to compare pre-school and school-age children who had fractures to determine how weather affects this cohort. Our hypothesis is that extremity fractures in childhood change upon weather temperature, whether the school is open or not.

METHODS

Ethics committee approval was received from the ethics committee of our hospital (Approval number: 2011-KAEK-25 2020/08-13) to conduct this study. Trauma admissions data were collected from the hospital software system between 1st January 2017 and 31st December 2018 (24 months). International classification of diseases (ICD) codes looked up obtaining all children who had extremity fractures (S42.0-9, S52.0-9, S62.0-8, S72.0-9, S820-9, S92.0-9). Inclusion criteria were (1) children who had fractures between two and 12 years old, (2) performed the surgery or cast, (3) personal trauma lead to fractures that were included in this study. Fractures by influence external forces (e.g., traffic accident and assault), hand phalangeal fractures were excluded because of sharing with the plastic surgery department. Besides the clinical, demographic variables, this study investigated the comparison of the holiday and workdays how they affect the fractures for both groups.

Demographic and clinical data were obtained from patients' records that included gender, age, diagnosis and fractures area (Table 1). We divided the population into two age groups regarding pre-school and school-age. The first group was between two and six years old (pre-school age), and the second group was between 7-12 years old (school age).

Bursa is the fourth biggest city in Turkey and approximately two and a half million people live in the city. The weather temperature of Bursa was obtained from the Turkish State Meteorological Service official website and Bursa international meteorology station (station number: 17116). According to weather daily average temperature (DAT), the cold days (CD), warm days (WD) and hot days (HD) were defined under 15 degrees, between 15 and 22 degrees and over 22 degrees, respectively. We used two years of temperature data to avoid the negative effects of unexpected temperature changes.

We used these formulas for monthly average temperature (C^o) below:

Monthly average temperature (MAT)(C^o)= (Total of daily average temperatures) ÷ (Total days in the same month)

Daily average temperature (DAT)(C^0)= (Total of all temperature measurements(C^0))÷(Number of measurements)

In these two years, we determined cold, warm and hot days for each month. We used heating degree days and cooling degree days on the official meteorology website for cut-off values. (https://mgm.gov.tr/veridegerlendirme/gun-derece.aspx-?g=merkez&m=16-00&y=2019&a=04).

Not only weather conditions but also the number of holidays was calculated monthly. All weekend and bank holidays (e.g., national, religious and weather conditions) were counted in the month they belong to.

Statistical analysis

SPSS 25.0 for Windows was used for statistical analysis. Descriptive statistics; numbers and percentages for categorical data and mean, standard deviation, minimum and maximum values for numerical data were used. Comparisons of numerical variables in two independent groups were made using the Mann-Whitney U test when the normal distribution condition could not be achieved. After the normality test, Kolmogorov-Smirnov and Shapiro-Wilk test, relationships between numerical variables were analyzed using Pearson Correlation Analysis when parametric test condition was met and Spearman Correlation Analysis when parametric test condition was not met. Statistical alpha significance level was accepted as $p < 0.05$.

RESULTS

Five thousand eight hundred twenty-eight fractures were detected in all children. Two thousand one hundred ninety-four fractures were excluded due to that those younger than 2-year-old or older than 12-year-old and who had phalangeal fractures. The fractures by external influences (e.g., road accidents and child abuse) were excluded because they were not related to temperature and repetitive entries were also excluded (Figure 1). In all fractures (2-12-year-old), there was a significant relationship with all (upper-lower) extremity fractures and MAT, WD, HD. A negative correlation was detected between CD and all upper-lower extremity fractures. On the other hand, a positive correlation was detected between only upper extremity fractures and holidays (Table 1).

In the pre-school group, there were 516 boys and 453 girls; the average age was 4,2-year-old. In the school group, there were 1058 boys and 543 girls; the average age was 9,7-year-old. There was no gender dominance in the pre-school group, but in the school group, there was a boy predominance in both upper and lower extremity fractures ($p = 0.001$, $p = 0.013$).

In the pre-school group, there was a negative correlation between CD and upper extremity, lower extremity, and total fractures numbers (p = 0.014, $p = 0.029$ and $p = 0.009$). Also, there was the same negative correlation in the school group ($p = 0.001$, $p = 0.027$ and $p = 0.001$) (Table-2).

In the pre-school group, there was no correlation between WD and upper extremity, lower extremity and total fractures numbers (Table-2). There was a positive correlation between WD and upper extremity, and total fractures numbers in the school group ($p = 0.015$, $p = 0.004$) (Table-2).

In the pre-school group, there was a positive correlation between HD and upper extremity and total fractures numbers ($p = 0.015$, $p = 0.018$). In the school group, there was a positive correlation between HD and upper extremity and total fracture numbers ($p = 0.012$, $p = 0.014$). There was no correlation between lower extremity fracture and HD in the two groups (Table-2).

MAT had a positive effect on the upper extremity, lower extremity, and total fracture numbers in the pre-school group ($p = 0.028$, $p = 0.011$ and $p = 0.010$). Also, in the school group, it had a positive effect on upper extremity and total fracture numbers ($p = 0.001$, $p = 0.001$) (Table-2).

There was no correlation between fracture numbers and monthly holiday numbers in both groups (Table 2).

In addition, particularly the effects of temperature

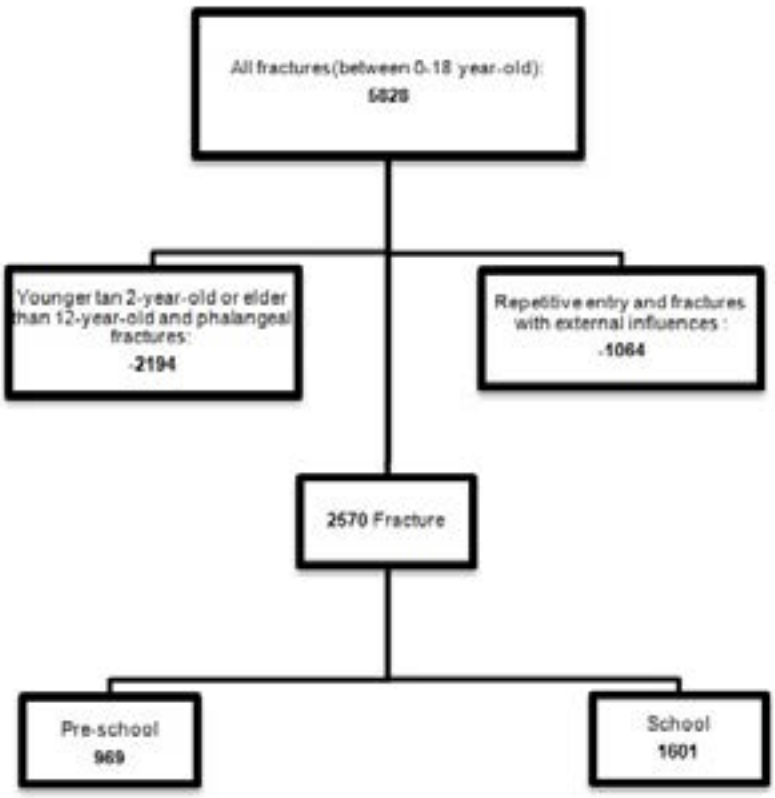

Fig. 1. Flow diagram for inclusion or exclusion of study population

Table 1. **All children's fractures.**

	Monthly Averege Tempterature (°C)		Cold Days (T ≤ 15)		Warm Days (15 < T ≤ 22)		Hot days (T >22)		Holidays	
	r	*p*	r	*p*	r	*p*	r	*p*	r	*p*
Upper Extremity fractures (2195)	0,467	< 0,001	-0,455	< 0,001	0,253	0,013	0,408	< 0,001	0,205	0,045
Lower Extremity fractures (375)	0,342	0,001	-0,336	0,001	0,210	0,040	0,246	0,016	0,100	0,331
Total	0,674	< 0,001	-0,684	< 0,001	0,445	0,029	0,556	0,005	0,203	0,341

and holiday on fractures number, we investigated multivariate effects. We examined how temperature affected when the number of holidays was below fifteen days and fifteen days and more.

In the pre-school group, when the holidays were less than fifteen days, there was no correlation between any fracture site and CD, WD, HD and MAT. However, when the holidays were fifteen days and more, there was a positive correlation between MAT and lower extremity fracture (p = 0.044). In addition, another positive correlation between WD and lower extremity and total fractures (p = 0,010, p = 0,022). In CD, there was a negative correlation between upper extremity and total fracture if there were fifteen or more holidays in a month (p = 0.025, p = 0.025). There was no correlation between WD and any fracture when the holidays are fifteen or more in a month (Table 3).

In the school group, when the holiday was less than fifteen days (< 15), there was a positive correlation between MAT and upper –total extremity fractures (p = 0.004 and p = 0.001). A negative correlation between CD and total fracture number (p = -0.024) and a positive correlation between WD and upper –total extremity fractures was detected (p = 0.023 and p = 0.010). There was a positive correlation between HD and lower extremity fractures (p = 0.045). In the same group, when the holiday was fifteen days and more (≥ 15), we detected negative correlations with CD and upper-lower extremity and total fractures (p = 0.025, p

Table 2. **Pre-school and school group fractures.**

	Monthly Averege Tempterature (°C)		Cold Days (T ≤ 15)		Warm Days (15 < T ≤ 22)		Hot Days (T > 22)		Holidays	
Pre-school group	r	*p*	r	*p*	r	*p*	r	*p*	r	*p*
Upper Extremity fractures (796)	0,448	0,028	-0,495	0,014	0,185	0,387	0,491	0,015	0,240	0,259
Lower Extremity fractures (173)	0,511	0,011	-0,445	0,029	0,100	0,641	0,390	0,060	0,393	0,057
Total (969)	0,517	0,010	-0,521	0,009	0,211	0,323	0,480	0,018	0,241	0,257
School group										
Upper Extremity fractures (1399)	0,651	0,001	-0,641	0,001	0,490	0,015	0,504	0,012	0,233	0,274
Lower Extremity fractures (202)	0,298	0,157	-0,450	0,027	0,404	0,050	0,322	0,125	-0,007	0,974
Total (1601)	0,650	0,001	-0,660	< 0,001	0,560	0,004	0,493	0,014	0,149	0,487

Table 3. Multivariate analaysis of holiday and temperatures.

Upper Extremity fractures			
Group		**Holiday**	***p***
pre-school group	< 15	HD	0,058
	15 ≤	HD	0,072
school group	< 15	WD	0,008
	15 ≤	WD	0,004
		HD	0,001
Lower Extremity fractures			
Group	**Holiday**		***p***
pre-school group	< 15	WD	0,031
		HD	0,069
	15 ≤	HD	0,040
school group	< 15	HD	0,009
	15 ≤	CD	0,011
Total fracture			
Group		**Holiday**	***p***
pre-school group	< 15	HD	0,138
	15 ≤	HD	0,036
school group	< 15	WD	0,004
	15 ≤	MAT	0,066
		CD	0,002

= 0.022 and $p = 0.025$). There was no correlation with MAT, WD, HD and extremity fractures (Table 3).

DISCUSSION

This study showed that weather temperature influences the frequency of the extremity fracture at 2-12 years old. The monthly number of fractures increased in MAT, but typically, they decreased in CD. The changes were clearly observed in the school-age group, in which upper and total extremity fractures increased in WD and HD. All fractures in the pre-school group only increased in HD.

There is a significant correlation between the number of fractures and increased temperature. We thought the main reason for this correlation is related to outdoor physical activities these days. A previous study has shown that children are exhibit less sedentary behaviors and more increased physical activities with warm and windless weather conditions [9]. Unfortunately, children are more likely to fall and cause extremity fractures. Our study showed the linear proportion between the number of the lower extremity fractures and MAT in the pre-school group (who are muscle straight and balance are still developing), but unlikely in the primary school group. It would be appropriate to expect an increase in child fractures in trauma centers in the months when monthly average temperatures increase and plan resources to meet these expectations.

Childhood fractures were classified by whether temperature and showed that the number of fractures was observed on warm days (15Co < T ≤ 25-28 Co), but it was not significantly related to hot days temperature [3, 4, 6-8, 11-14]. The pre-school group who

had fractures was not significantly related to warm days. However, in the same group, upper total extremity fractures were significantly related to hot days.

Our study showed that the number of holidays was not a risk factor for the pre-school and school-age groups. The number of holidays greater than 15 days, correlated to lower and total fractures during increased MAT. Additional lower extremity-not total fracture number- fractures were significantly related to the number of holidays less than fifteen days in a month in the primary school group.

Loder *et al*. has reported that the reason for increasing fracture is spent more time in outdoor activities [7]. In many studies, fractures generally occurred on rainless and warm days and suggested that outdoor activities influenced the increased number of fractures [3, 7, 13].

This study has some limitations. First, data were collected retrospectively and several types of fracture were included. Second, we only looked at the temperature variable from the weather conditions, besides, variables such as rain and wind speed can prevent children's outdoor activities, especially. Finally, childhood fractures occur due to multi-factorial causes, and we examined limited variables in this study.

CONCLUSION

In conclusion, there is a close relationship between child extremity fractures and temperature. Extremity fractures in children decrease when the number of cold days in a month increases but increases when the number of warm and hot days increases. Contrary to expectations, the monthly number of fractures is not affected by the number of vacation days per month.

Ethical Approval

The protocol of the study was approved by the Medical Ethics Committee of Bursa Yuksek Ihtisas Training and Research Hospital, Bursa, Turkey. (Decision number: 2011-KAEK-25 2019/04-33, date: April 10, 2019).

Authors' Contribution

Study Conception: NÇ,; Study Design: FT,; Supervision: AÖ,; Materials: NÇ,; Data Collection and/or Processing: YM, UI, HS, TU,; Statistical Analysis and/or Data Interpretation: AÖK,; Literature Review: YA,; Manuscript Preparation: FT and Critical Review: AÖ.

Conflict of interest

No potential conflicts of interest relevant to this article were reported.

Acknowledgements

We are grateful to all treating physicians in our center for collaboration and the data collection.

Financing

There is no source of financial support or funding.

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Journal of Bursa
Faculty of Medicine
e-ISSN: 2980-0218

The effects of intravenous magnesium sulfate infusion on perioperative hemodynamics, postoperative recovery, and analgesia in arthroscopic knee surgery during spinal anesthesia.

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Original Article

Anesthesiology and Reanimatio

Received
May 09, 2023
Accepted
May 15, 2023
Published online
May 29, 2029

J Bursa Med 2023;1(2) 57-64

ABSTRACT

Objectives: Magnesium sulphate infusion after general anesthesia reduces post-operative analgesic consumption. Numerous clinical investigations have demonstrated that magnesium infusion during general anesthesia reduced anesthetic requirement and post-operative analgesic consumption. This study was planned and executed to assess the effects of intravenous magnesium sulfate infusion on perioperative hemodynamics and post-operative analgesic consumption in patients undergoing spinal anesthesia for arthroscopic knee surgery.

Methods: ASA I and II patients, aged 18-65 years, undergoing spinal anesthesia for arthroscopic knee surgery were enrolled in this study. The patients were assigned to two groups according to presence of magnesium sulfate infusion. Patients in the magnesium group (Group M) received magnesium sulphate 40 mg kg-1 for 15 min after spinal anesthesia and then 20 mg kg-1 h-1 by continuous i.v. infusion until the end of surgery. Patients in the saline group (Group I) received the same volume of isotonic saline over the same period. For each case, a patient-controlled analgesia (PCA) device containing tramadol hydrochloride was connected i.v. at the end of surgery. Postoperative pain score, analgesic consumption and hemodynamics were recorded at 4., 8., 12. and 24. h after surgery. The incidences of postoperative nausea, vomiting and headache were recorded. Blood samples for serum Mg concentration were obtained in Group M before surgery, and 30 minutes and 24 hours after surgery.

Results: Fourty patients were included in our study. Postoperative pain score and analgesic consumption in Group M patients were significantly less in comparison with Group I. There was no significant difference in hemodynamic variables and side effects during the intra- or postoperative period. Postoperative serum Mg concentration in Group M was significantly higher than that in Group I at 30. minutes after surgery; however no significant side effect was observed.

Keywords: pain, magnesium, patient controlled analgesia, postoperative, tramadolol

How to cite this article
Ersal M, Altan A. The effects of intravenous magnesium sulfate infusion on perioperative hemodynamics, postoperative recovery, and analgesia in arthroscopic knee surgery during spinal anesthesia. J Bursa Med 2023;1(2):57-64

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Day care surgery procedures are increasingly gaining ground in anesthesia practice nowadays. In this regard, the role of technological support that ensures less traumatic surgical procedures, as well as drugs with shorter but less side effect profiles entering modern anesthesia practice, is significant. Day surgery procedures are preferred due to their lower cost, shorter hospital stay, reduced expenses, decreased incidence of nosocomial infections, and reduced patient anxiety [1].

Joint arthroscopies are generally day surgery procedures. Spinal anesthesia is an optimal and cost-effective option in arthroscopic surgery. The advantages of spinal anesthesia include minimal nausea and vomiting, patient wakefulness, no airway problems, rapid onset of anesthesia, excellent surgical conditions, no orientation problems for the patient, minimal postoperative care, and a smooth transition to postoperative analgesia [1-3]. However, there are also disadvantages to spinal anesthesia, such as prolonged ambulation time after surgery, increased incidence of headache and back pain after spinal anesthesia, and prolonged urination.

Postoperative pain is an acute type of pain that begins with surgical trauma and ends with tissue healing. This pain not only causes discomfort, depression, and anxiety in the patient but also leads to significant physiopathological changes in the body's organ systems. Eliminating this pain is not only about eliminating an uncomfortable sensation but is also essential for the organism's homeostasis.

Various agents and methods are used to provide pain relief after arthroscopic surgery. According to some studies intravenous magnesium sulphate (MgSO4) improves postoperative analgesia without affecting the onset and recovery from spinal anesthesia [4]. Intravenous infusion of either dexmedetomidine or MgSO4 with spinal anesthesia effectively improves the quality of spinal anesthesia and prolongs the duration of postoperative analgesia and decreases the 24-hour postoperative morphine consumption [5]. In our study, the effects of intravenous (i.v.) magnesium sulfate infusion administered during spinal anesthesia on perioperative hemodynamics and postoperative analgesia in arthroscopic knee surgery and the effects of magnesium sulfate on pain relief and tramadol consumption were investigated.

METHODS

This is a prospective controlled study conducted at the Okmeydanı Education and Research Hospital's Orthopedics and Traumatology operating room. The study included 40 patients of both genders, between the ages of 18-65, with ASA class I-II, who under-

Table 1. Comparison of the Clinical and Anesthesia-Related Characteristics of the Groups.

		Group				Test Statistics	Sig. (p)
		Serum Sale (Serum Physiological) Group		Magnesium Group			
		f	%	f	%		
ASA	**ASA1 (No systemic pathology)**	15	75,0	14	70,0	0,125 (χ^2)	0,723
	ASA2 (There is systemic pathology that does not affect daily activity)	5	25,0	6	30,0		
Spinal Block level	**T3**	0	0,0	3	15,0	5,762 (χ^2)	0,450
	T4	4	20,0	3	15,0		
	T5	5	25,0	7	35,0		
	T6	3	15,0	3	15,0		
	T7	5	25,0	2	10,0		
	T8	2	10,0	2	10,0		
	T10	1	5,0	0	0,0		
Motor Block Time (min.)		186,500	2,101	188,950	3,118	-0,652 (t)	0,519
Time to First Analgesic Need (min.)		225,650	3,070	246,250	10,641	-1,860 (t)	0,071

went elective arthroscopic knee surgery. Patients with cardiovascular, hepatic, or renal disorders, neuromuscular diseases, drug addiction, coagulopathy, and psychiatric problems were excluded from the study.

The patients were given premedication with 0.03 mg/kg intravenous midazolam and were then taken to the operating room. Before the operation, a 500 ml ringer lactate solution was administered for 15 minutes. The patients were monitored during the procedure using non-invasive arterial monitoring, pulse oximetry, and electrocardiography (ECG).

The patients were given spinal anesthesia via a 22G spinal needle at the L3-4 or L4-5 intervertebral space with a 0.5% bupivacaine solution (Marcaine® Spinal Heavy) adjusted according to the patient's height. After the procedure, the patients were placed in the supine position.

The patients were randomly divided into two groups: the magnesium group (group M, n: 20) and the saline group (group S, n:20). Patients in the magnesium group received a 15-minute infusion of 40 mg/kg/min magnesium sulfate after spinal anesthesia and then an infusion of 20 mg/kg/h until the end of the surgery. Patients in the saline group were given the same volume of isotonic saline during the same period.

The spinal block level was evaluated 15 minutes after intrathecal bupivacaine injection using a cold sensation test. Efedrin (Efedrin Hidroklorur 0.05 gr/ml Biosel®) was administered when systolic arterial pressure dropped below 80 mmHg or mean arterial pressure dropped below 20%. Atropine was administered when heart rate dropped below 50 bpm. Postoperatively, 10 mg metoclopramide (Metpamid® ampoule 10 mg) was administered intravenously to prevent nausea.

Both groups received 150 ml of serum saline containing 450 mg of tramadol (Contramal® 100 mg/2 ml ampoule) via Patient-Controlled Analgesia (PCA) device (CADD legacy PCA) after surgery. The PCA device was set to administer 10 mg boluses every 10 minutes (lock out time). Systolic blood pressure, diastolic blood pressure, heart rate (HR), tramadol consumption, and pain scores were recorded at postoperative 30 minutes, 4 hours, 8 hours, 12 hours, and 24 hours. If postoperative pain was severe (Visuel analog scala > 7), 75 mg diclofenac sodium was given intramuscular as a rescue analgesic.

Statistical analysis

The data collected in the study was analyzed using the SPSS 18.0 statistical package program. Variables were described with descriptive statistics (mean, standard error of the mean, minimum, maximum values) for the data. Two independent group t-tests were used to compare the means of the variables between the saline and magnesium groups. χ^2 (Chi-square) independence tests were used to compare data of variables that could not be averaged between the two groups. The significance level in the study was chosen as 0.05.

RESULTS

The study included 40 patients between the ages of 18 and 65, classified as ASA class I-II, undergoing arthroscopic knee surgery under spinal anesthesia. 10 male and 10 female patients were assigned to the saline group, while 9 male and 11 female patients were assigned to the magnesium group. There was no statistically significant difference between the groups in terms of gender, age, height, and weight (*p* values were 0.752, 0.466, 0.642, 0.843, respectively).

The preoperative mean magnesium levels of the patients in the magnesium group were 2.010 ± 0.051 mg/dl (ranging from 1.7 to 2.4 mg/dl). After the operation, the magnesium levels ranged from 2.3 to 4 mg/dl, with an average of 3.055 ± 0.102 mg/dl per patient at 30 minutes post-operation, and ranged from 1.8 to 3 mg/dl, with an average of 2.385 ± 0.060 mg/dl per patient at 24 hours post-operation.

There was no statistically significant difference between the groups in terms of all clinical and anesthe-

Table 2. Comparison of patients' pain scores according to groups.

	Groups		Test Statistic (t)	Sig. (*p*)
	Serum Sale (Serum Physiological) Group	Magnesium Group		
4 Hours After the Operation	5,550 ± 0,276	2,050 ± 0,276	8,966	**0,000***
8 Hours After the Operation	5,500 ± 0,303	2,800 ± 0,268	6,674	**0,000***
12 Hours After the Operation	5,250 ± 0,239	2,600 ± 0,255	7,571	**0,000***
24 Hours After the Operation	1,200 ± 0,296	0,350 ± 0,109	2,697	**0,010***

sia-related characteristics ($p > 0.05$) (Table 1).

The majority of patients in the saline group, accounting for 75%, and also in the magnesium group, accounting for 70%. Meanwhile, 25% of patients in the saline group and 30% of patients in the magnesium group were ASA II patients.

In terms of the spinal block heights achieved by patients in the saline and magnesium groups, it was found that 25% of patients in the saline group were at T5, 25% were at T7, 20% were at T4, 15% were at T6, 10% were at T8, and 5% were at T10. As for the magnesium group, 35% were at T5, 15% were at T4, 15% were at T6, 15% were at T3, 10% were at T7, and 10% were at T8.

The mean motor block duration for patients in the saline group was determined to be 186,500 ± 2,101 minutes, while the mean motor block duration for patients in the magnesium group was 188,950 ± 3,118 minutes.

The average time until the first analgesic requirement for patients in the saline group was found to be 225,650 ± 3,070 minutes, while the average time until the first analgesic requirement for patients in the magnesium group was 246,250 ± 10,641 minutes.

Systolic arterial pressure levels were observed to be higher in the saline group than in the magnesium group at the start of the operation, after spinal anesthesia, 15 minutes after the start of the operation, 30 minutes after the start of the operation, 45 minutes after the start of the operation, at the end of the operation, and 4 hours after the operation. However, at any time, there was no statistically significant difference between the systolic arterial pressure levels measured in the saline and magnesium groups ($p > 0.05$). Therefore, systolic arterial pressure levels did not differ based on whether patients were given saline or magnesium. Findings showed that the diastolic arterial blood pressure levels measured 30 minutes and 12 hours after the operation were statistically significantly different ($p < 0.05$) between the serum physiologic and magnesium groups. In both time periods, the average diastolic arterial blood pressure levels per patient in the magnesium group were statistically significantly higher than those in the serum physiologic group. Although there was no statistically significant difference between the groups, the time periods in which the average diastolic arterial blood pressure levels per patient were higher in the magnesium group than in the serum physiologic group were as follows: 15 minutes after the operation started, 45 minutes after the operation started, at the end of the operation, 4 hours after the operation, 8 hours after the operation, and 24 hours after the operation.

Heart rate levels were observed to be higher in the serum physiologic group in the measurements taken 4 hours, 12 hours, and 24 hours after the operation, whereas the potassium, magnesium, and calcium (PMC) levels were higher in the magnesium group in the measurements taken at the start of the operation, after spinal anesthesia, 15 minutes after the operation started, 30 minutes after the operation started, 45 minutes after the operation started, at the end of the operation, 30 minutes after the operation ended, and 8 hours after the operation. However, there was no statistically significant difference ($p > 0.05$) in the PMC levels measured at any time between the serum physiologic and magnesium groups.

The study examined whether the evaluation of pain levels based on the Visual Analog Scale (VAS) at specific intervals after the operation differed according to whether the cases in the sample group were in the magnesium or serum physiologic group (Table 2). VAS evaluation scores patients' pain levels from 0-10, with 0 representing no pain and 10 representing severe pain. It was determined that the VAS values of patients were statistically significantly different ($p < 0.05$) between the serum physiologic and magnesium groups in the evaluations performed 4 hours, 8 hours, 12 hours, and 24 hours after the operation. Thus, administering magnesium to patients was more effective

Table 3. Comparison of the painkiller levels given by PCA according to the groups.

	Grup		Test Statistic (t)	Sig. (*p*)
	Serum Sale (Serum Physiological) Group	Magnesium Group		
4 Hours After the Operation	64,000 ± 6,341	16,000 ± 4,554	6,148	**0,000***
8 Hours After the Operation	112,000 ± 10,428	50,000 ± 4,867	5,388	**0,000***
12 Hours After the Operation	160,500 ± 12,407	72,500 ± 4,914	6,594	**0,000***
24 Hours After the Operation	205,000 ± 15,703	85,000 ± 4,730	7,317	**0,000***

in reducing pain compared to administering serum physiologic. In addition, while the perceived average pain level of patients in the serum physiologic group decreased as time passed after the operation, the perceived average pain level in the magnesium group was higher 8 hours after the operation than 4 hours after the operation, and the pain level began to decrease after 8 hours.

Statistically significant differences ($p < 0.05$) were found in the levels of analgesic administered with PCA (patient-controlled analgesia) to patients four hours, eight hours, twelve hours, and twenty-four hours after surgery between the group receiving saline and the group receiving magnesium. This difference may have been caused by the fact that patients in the saline group were administered analgesic at statistically significantly higher doses compared to those in the magnesium group. In both groups, the need for analgesic and the level of analgesic administered to patients increased over time following the surgery.

DISCUSSION

This study demonstrated that intravenous magnesium sulfate infusion during surgery under spinal anesthesia reduced postoperative pain and analgesic consumption without any significant complications. As it is expected that analgesic adjunct drugs will not affect motor block duration and sedation, and will increase the side effect profile while reducing the dose, our findings show that magnesium sulfate infusion meets these.

According to Frassanito *et al*s.' study, they concluded that iv perioperative administration of Mg did not influence postoperative pain control and analgesic consumption after total knee arthroplasty. They adviced that more studies should be performed with different intra and postoperative pain protocols to enhance the potential anti-nociceptive effect of Mg [6]. Developments in understanding pain mechanisms have led to the administration of analgesics before exposure to pain stimuli to prevent central sensitization and postoperative pain amplification. Magnesium sulfate is used in obstetric and cardiac patients. Magnesium reduces the release of acetylcholine from motor nerve terminals and, at lower levels, reduces the sensitivity of motor nerve fibers by lowering the stimulation threshold [7]. Additionally, it has been shown that magnesium ions inhibit postjunctional potentials, reducing muscle fiber excitability [8]. In their study, Akutagawa *et al*. [9] demonstrated that the nerve block of some local anesthetics could be increased by altering the magnesium concentration in the nerve fiber bath depending on its physical properties. However, while the basic mechanism of Mg's analgesic effect is unclear, it is estimated that its NMDA receptor antagonism prevents central sensitization induction due to peripheral nociceptive stimulation and eliminates hypersensitivity. Calcium channel blockers also show antinociceptive effects in animals and enhance the effect of morphine in chronic pain patients.

The effects of magnesium sulfate-induced neuromuscular blockade were investigated in electromyogram and mechanogram in pigs. It was observed that the single stimulation at 0.1 Hz decreased, and the mechanogram was more suppressed than the electromyogram. The absence of fade signs after quadruple stimulation at 2 Hz and the increase in contraction force for 5 seconds after tetanic stimulation at 50 Hz indicate magnesium's presynaptic effects [10]. Magnesium causes dose-dependent desensitization in isolated frog muscle preparations. This effect can be reversed by reducing carbamylcholine concentration or increasing potassium concentration [11]. Our findings are partially consistent with those obtained in a previous study [12]. In this study, after spinal block, patients were given a bolus of 5 mg/kg magnesium sulfate, followed by 500 mg/hour infusion or saline for 24 hours, and significant reduction in postoperative analgesic consumption was observed in the mg group. However, the VAS values of the two groups were similar during the first 24 hours after surgery, except for the first 12 hours, and therefore, it is thought that the magnesium sulfate dosage used was insufficient for postoperative analgesia. Sufficient bolus and infusion doses of magnesium sulfate are important for effective analgesia.

In a recent clinical study, the intravenous infusion of magnesium sulfate did not affect the magnesium concentration in cerebrospinal fluid [13]. On the contrary, when magnesium sulfate was given intrathecally, the magnesium concentration in cerebrospinal fluid increased while plasma levels were unaffected, suggesting that the blood-brain barrier is impermeable to this cation. These results explain why motor block duration did not change after spinal anesthesia in another study [14, 15]. However, the analgesic effect observed in our study is more pronounced.

Activation of small-diameter primary afferent nerves can affect the stimulation of nerves in the spinal cord for a long time, causing the response to

change in different directions and central sensitivity. Woolf *et al*. [16] showed that NMDA antagonists can increase the excitability of the spinal cord while not affecting the reflex response in rats using mustard oil. It has been shown that magnesium sulfate injection reduces nociceptive behavior in experimental peripheral nerve injuries [17]. In this study, it can be considered that the analgesic effects of magnesium sulfate infusion are due to a reduction in sensitivity caused by calcium or the effect of an NMDA antagonist. In the rat postoperative pain model, the antiallodynic effect produced by intrathecal gabapentin is reduced by NMDA antagonists magnesium chloride and ruthenium red. It has been shown that the alpha (2) delta subunit of voltage-gated calcium channels is partly responsible for pain, and magnesium has an affinity for this receptor [18]. Intrathecal injection of isoosmolar magnesium sulfate has been observed to cause long-lasting spinal anesthesia and general sedation in rats and humans [19]. Repeated intrathecal administration has been reported to not cause neurotoxicity in animal studies [20]. The fact that intrathecal magnesium enhances the analgesic effects of spinal opioids (fentanyl) in childbirth analgesia suggests that intrathecal administration of NMDA antagonists may have a role in pain modulation [21].

Magnesium has been shown to significantly reduce the requirements of propofol, remifentanil, and vecuronium in patients undergoing elective spinal surgery with total intravenous anesthesia [22]. Tramer *et al*. [23] have shown in their studies that magnesium sulfate infusion reduces morphine consumption with patient-controlled analgesia (PCA) and provides better sleep scores and comfort in patients undergoing abdominal hysterectomy under general anesthesia. The effects of intravenous drugs such as fentanyl, ketamine, and magnesium sulfate on pain threshold, sensitivity, and opioid consumption were investigated after abdominal hysterectomy surgery. While the effects of the drugs on pain threshold varied, the pain scores and morphine consumption were similar, and all drugs reduced spinal sensitivity after surgery [24]. In addition, in a study conducted in the same surgical group, bolus and infusion administration reduced analgesic requirements without side effects during the perioperative period [25]. However, Zarausa *et al*. [24] reported that the application of oral nifedipine, intravenous nimodipine, and magnesium sulfate during colorectal surgery did not affect perioperative morphine consumption. These unfavorable results can be explained by the number of study groups, the route of administration, the type of calcium channel blocker used, and the mechanism of pain. Recently, Ko *et al*. [13] have shown in their studies that intravenously administered magnesium sulfate infusion during surgery has no positive effect on postoperative pain. The main difference between their study and ours is that the PCA device used to reduce pain was connected to an epidural catheter. Thus, the additive effects of magnesium sulfate and morphine administered by different routes may not have been observed.

In gynecology patients who were administered a bolus dose of 50 mg/kg and maintenance dose of 15 mg/kg/hour of magnesium sulfate before and during surgery, the requirement for rocuronium was reduced and the quality of postoperative analgesia was improved without any significant adverse effects [12,26]. Therefore, in our study, we applied a bolus dose of 40 mg/kg and a maintenance dose of 20 mg/kg/hour.

Postoperative VAS scores and cumulative PCA consumption were significantly lower at 4, 8, 12, and 24 hours. This difference may be due to the fact that the average pain levels perceived by patients in the magnesium group were statistically significantly lower than those in the saline group. Thus, administering magnesium to patients is more effective in reducing pain than administering saline. There was no significant difference in postoperative pain and analgesic use immediately after surgery and at 30 minutes. We attributed this to the residual effect of spinal anesthesia.

However, in previous studies evaluating the effects of Mg on postoperative analgesia, different VAS values were observed between the control and Mg groups, even though PCA was used during the postoperative period [27,28]. Possible explanations include: PCA use can reduce the pain seen after surgery, but cannot eliminate it completely. PCAs are used with or without ketorolac and opioids, which have dose-related side effects such as nausea and vomiting that can limit the use of unlimited PCAs. Additionally, PCA settings include locking times to prevent overdose, and patients may not be able to take as much analgesic as they want.

Magnesium sulfate administration during general anesthesia may have other benefits, such as increasing the strength of neuromuscular blockade [12, 28]. The mechanisms involved include a decrease in the amount of acetylcholine released from motor nerve terminals and a decrease in the depolarization effect of acetylcholine at the endplate or in the excitability of the muscle fiber membrane. Therefore, i.v. magnesium

administration during spinal anesthesia may facilitate muscle relaxation and surgical procedures requiring extensive joint rotation. However, more studies are needed to confirm this hypothesis.

Adjuvant medications such as magnesium sulfate can provide greater pain relief and reduce analgesic consumption in postoperative patients using PCA. Theoretically, mild side effects such as flushing, nausea, and headache are expected at serum Mg levels above 2 mmol/L, and potentially life-threatening complications primarily involving the cardiovascular and neuromuscular systems are observed when serum Mg concentrations exceed 5 mmol/L. In our study, an average magnesium value of 2,010 ± 0.051 mg/dL was obtained in the Magnesium group before surgery. Two patients reported short-lived hot flashes during surgery. The same patients had an average magnesium value of 3,055±0.102 mg/dL 30 minutes after surgery and an average value of 2,385±0.060 mg/dL 24 hours after surgery. None of the patients exceeded 5 mg/dL. Magnesium causes dose-dependent negative inotropic effects, and hemodynamic studies have shown that magnesium has a peripheral (primarily arteriolar) vasodilatory effect in humans [29]. A rapid infusion of 3-4 mg of magnesium sulfate led to a decrease in systemic arterial pressure associated with low systemic vascular resistance [30]. In this study, prehydration was performed with 500 mL of lactated Ringer's solution and magnesium bolus dose infusion was given, likely explaining why significant hypotension was not encountered after the magnesium bolus dose was given and no significant difference was observed between the groups during surgery.

CONCLUSION

Postoperative analgesia is important for the comfort of patients. In today's world where outpatient surgical approaches are becoming more common, the main goal is to minimize the postoperative pain and analgesic consumption during the postoperative period.

In conclusion, it was found that administering intravenous magnesium sulfate during spinal anesthesia reduces postoperative pain and analgesic consumption in knee surgery. Especially in cases where the use of opioids and non-steroidal anti-inflammatory drugs (NSAIDs) needs to be reduced or is contraindicated, this alternative approach can be considered.

Ethics Approval and Consent to Participate

This study titled "The Effects of Intravenous Magnesium Sulfate Infusion on Perioperative Hemodynamics, Postoperative Recovery, and Analgesia in Arthroscopic Knee Surgery During Spinal Anesthesia" was conducted at the Okmeydanı Education and Research Hospital's Orthopedics and Traumatology operating room between 2010 and 2011. Ethics Approval was not required at the time of the study. This study was conducted under the supervision of Associate Professor Aysel Altan at the Okmeydanı Education and Research Hospital.

Authors' Contribution

Study Conception: Study Conception: ME, AA; Study Design: ME, AA; Supervision: AA; Materials: ME, AA; Data Collection and/or Processing: ME, AA; Statistical Analysis and/or Data Interpretation: ME, AA; Literature Review: ME, AA; Manuscript Preparation: ME; and Critical Review: ME, AA.

Conflict of interest

No potential conflicts of interest relevant to this article were reported.

Acknowledgements

We are grateful to all treating physicians in our center for collaboration and the data collection.

Financing

There is no source of financial support or funding.

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Journal of Bursa Faculty of Medicine
e-ISSN:

Case Report

Obstetrics and Gynecology

Received
December 18, 2022
Accepted
December 18, 2022
Published online
May 29, 2023

J Bursa Med 2023;1(1) 65-68

Ovarian hyperstimulation syndrome developed in a patient who underwent neovagen with the diagnosis of Müllerian agenesis and was a candidate for uterine transplantation: Case Report

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ABSTRACT

We aimed to present OHSS that developed after OPU in a patient who underwent neovagen 10 years ago with the diagnosis of Müllerian agenesis and was awaiting uterine transplant. We wanted to draw attention to successful approaches in such groups of patients with Müllerian agenesis.

A 35-year-old sexually active patient who applied to the Gynecology and Obstetrics Emergency Service of our institution with the complaint of abdominal pain had zero gravida. In her anamnesis, a 15-year-old patient who applied to the obstetrics clinic with the complaint of primary amenorrhea was diagnosed with MRKH syndrome in an external center. Neovagen was performed by laparoscopic method due to vaginal agenesis of the patient in an external center in 2012. The patient was informed and admitted to the gynecology service for follow-up with the diagnosis of mild OHSS.

The patient was informed and admitted to the gynecology service for follow-up with the diagnosis of mild OHSS. During the follow-up period, waist circumference and weight did not increase, the follow-up was balanced, no free fluid was observed in the abdomen in the ultrasonography, there was no electrolyte imbalance, there was no deterioration in liver-kidney functions and hemoconcentration did not develop. The patient was discharged on the 3rd day of hospitalization due to the regression of abdominal pain.

OHSS may be one of the difficulties experienced by all Müllerian agenesis patients who decide to become a real family. These patients should be given up-to-date information about neovagen production, IVF processes and uterine transplantation by all obstetricians. Considering all of these approaches will raise awareness in this patient population, which faces a variety of lifelong challenges in starting a family.

Keywords: ohss, neovagen, müllerian agenesis, uterine transplatation

Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome is a congenital disorder characterized by agenesis of the müllerian ducts (uterus, cervix, and upper two-thirds of the vagina).

The external genitalia and secondary sex

How to cite this article

Bilgin Yüce E, Gumus Satici Y, Koca E, Yenigul NN. Ovarian hyperstimulation syndrome developed in a patient who underwent neovagen with the diagnosis of Müllerian agenesis and was a candidate for uterine transplantation: Case Report J Bursa Med 2023;1(2):65-68

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characteristics of these 46, XX women are normal [1]. MRKH syndrome occurs in approximately one in 4500 live births and is the second most common cause of primary amenorrhea after gonadal dysgenesis [2]. It has been reported to affect approximately 10% of women with primary amenorrhea. [2-3]. It may be associated with renal, cardiac, skeletal and other anomalies. These patients have been able to become sexually active for many years thanks to neovagen operations. Especially with the developments in endoscopic surgery, neovagen techniques have been advanced and this has given hope to women with this diagnosis.

Until recently, legal adoption was the only option for women with MRKH syndrome. Uterine transplantation gave hope to these women. Uterine transplantation performed on a patient with mullerian agenesis performed by Ozkan and friends in 2013 changed a lot [4]. Now these women have the chance to have their own children with embryo transfer after uterine transplant.

Pharmacological ovarian stimulation has been used as the gold standard since the beginning of in vitro fertilization (IVF). Ovarian Hyperstimulation Syndrome (OHSS), which was defined in the 1930s; It is a syndrome that can develop during ovulation induction or rarely in the natural cycle, is characterized by massive ovarian growth and multiple ovarian cysts, and progresses with electrolyte disturbance and protein loss as a result of excessive steroid hormone and capillary permeability [5]. Of those who develop OHSS, the incidence of which has increased in recent years, clinically significant ones are 2-3%, but milder forms of OHSS develop in 20-30% of all IVF patients [6]. Agents such as clomiphene citrate (CC), human menopausal gonadotropin (hMG), follicle stimulating hormone (FSH), gonadotropin-releasing hormone (GnRH), GnRH analogs, human chorionic gonadotropin (hCG), which are used for ovulation induction, are held responsible for the development of OHSS.

In this article, we aimed to present OHSS that developed after oocyte pick up (OPU) in a patient who underwent neovagen 10 years ago with the diagnosis of Müllerian agenesis and was awaiting uterine transplant. We wanted to draw attention to successful approaches in such groups of patients with Müllerian agenesis.

CASE

A 35-year-old sexually active patient who applied to the Gynecology and Obstetrics Emergency Service of our institution with the complaint of abdominal pain had zero gravida. In her anamnesis, a 15-year-old patient who applied to the obstetrics clinic with the complaint of primary amenorrhea was diagnosed with MRKH syndrome in an external center. Neovagen was performed by laparoscopic method due to vaginal agenesis of the patient in an external center in 2012. In her anamnesis, it was learned that oocyte pick-up was performed in an external center 4 days ago, 20 oocytes were collected and the patient was during uterine transplantation in another center.

The vulva and vagina examination performed by us was normal. Vaginal length was 3 centimeter (cm), cervix was not observed. Bilateral ovarian dimensions were slightly increased in transvaginal ultrasonography (right ovary 82 millimeter (mm) (Figure 1), left ovary 72 mm (Figure 2)), and no uterus was observed. There was no free fluid in the abdomen. There was no sign of acute abdomen in the physical examination. The patient's weight was 67 weight (kg) and waist

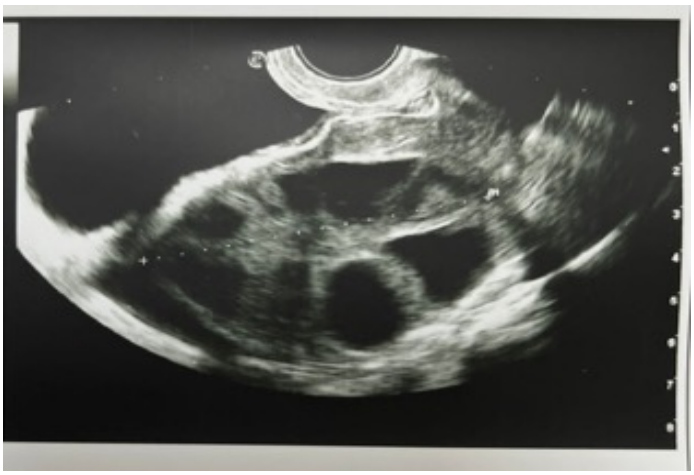

Figure 1. Right ovary

Figure 2. Left ovary

circumference was 71 cm. In the pelvic MRI of the patient, a suspicious appearance of uterine tissue (rudimentary uterus?) measuring 15x8 mm was observed at the level of the uterine lodge. In addition, bilateral kidneys were normally located and no accompanying renal anomaly was observed. In the blood tests studied from the patient, hemogram 13.1 g/dl, leukocyte 14.680/mcl, hematocrit 38.6%, beta hcg 10.9 mIU/l, creatinine 0.6 mg/dl, AST 13 U/l, ALT 9 U/ l and it was observed that there was no electrolyte imbalance.

The patient was informed and admitted to the gynecology service for follow-up with the diagnosis of mild OHSS. Daily waist circumference, weight, ultrasonography, complete blood count, liver-kidney function test, electrolytes and intake and output were followed up. Thromboprophylaxis was administered during hospitalization. During the follow-up period, waist circumference and weight did not increase, the follow-up was balanced, no free fluid was observed in the abdomen in the ultrasonography, there was no electrolyte imbalance, there was no deterioration in liver-kidney functions and hemoconcentration did not develop. The patient was discharged on the 3rd day of hospitalization due to the regression of abdominal pain. The examinations and tests performed on the 3rd, 10th and 15th days after discharge were found to be normal.

DISCUSSION

OHSS is the most serious complication of controlled ovarian hyperstimulation. Exogenous human chorionic gonadotropin (hCG) administration plays an important role in the pathogenesis of OHSS. Regardless of the degree of ovarian response to gonadotropin stimulation, OHSS does not occur unless an ovulatory dose of hCG is administered [7,8]. Exogenous hCG induces intense luteinization of granulosa cells leading to the production of vasoactive substances such as VEGF that increase vascular permeability. Such massive luteinization is not usually observed when the final steps of oocyte maturation are achieved with drugs other than hCG (eg, gonadotropin-releasing hormone (GnRH) agonists) [9].

The diagnosis of OHSS is made by clinical history and transvaginal ultrasound. There should be a history of ovarian stimulation after hCG administration. Early OHSS is usually mild to moderate and begins four to seven days after a human hCG dose to induce ovulation [10]. To the best of our research, we could not find a case in the literature who had undergone neovagen surgery due to mullerian agenesis and was diagnosed with OHSS while waiting for the uterine transplant. We think that this case report, which is a first in this sense, is important to draw attention to uterine transplantation. The effect of the presence of the uterus or the presence of a rudimentary horn on the occurrence or course of OHSS is unknown. With the increase in transplant success in these patient groups, IVF cycles may increase over time and clearer data can be generated.

As a result of problems such as inability to have sexual intercourse and absolute uterine infertility seen in patients with MRKH syndrome; It is stated that psychosocial problems such as low self-esteem, lack of self-confidence, feeling of worthlessness, and fear of rejection by the opposite sex occur [11, 12]. Studies have shown that patients diagnosed with MRKH Syndrome experience negative emotions such as reactive depression, shock, and suicidal thoughts [13], and they feel different and incomplete than other women who experience sexual identity threat and loss of sexual and social roles in the future [14]. Therefore, the psychological and medical approach to patients with Müllerian agenesis has become more important in recent years. Thanks to assisted reproductive techniques before uterine transplantation that can be performed in patients with Müllerian agenesis, with the developing technology and new treatment methods, oocyte collection and embryo freezing has become a new hope for the fertility of these patients.

It is a very difficult process for these patients with absolute uterine factor infertility to decide on uterine transplantation [15]. These patients, on the one hand, come under a very serious financial burden with this decision, and on the other hand, they take the decision to create their own families by taking serious personal risks. In this sense, they should receive serious training and know the risks that may occur in detail [15]. Recent studies have shown that despite all the difficulties, women in this patient group will want to prefer uterine transplantation as an alternative to surrogacy or adoption [15, 16].

This case report reveals that OHSS may be one of the difficulties experienced by all Müllerian agenesis patients who decide to become a real family. These patients should be given up-to-date information about neovagen production, IVF processes and uterine transplantation by all obstetricians. Considering all of these approaches will raise awareness in this patient population, which faces a variety of lifelong challeng-

es in starting a family.

CONCLUSION

Authors' Contribution

Study Conception: NNY,; Study Design: NNY,; Supervision: NNY,; Materials: EK,; Data Collection and/or Processing: YSG,; Statistical Analysis and/or Data Interpretation: EYB,; Literature Review: YSG,; Manuscript Preparation: EYB and Critical Review: EK

Conflict of interest

No potential conflicts of interest relevant to this article were reported.

Financing

There is no source of financial support or funding.

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Congenital Syphilis as A Cause of Hydrops Fetalis: A Case Report

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Journal of Bursa Faculty of Medicine
e-ISSN: 2980-0218

Case Report

Pediatrics

Received
December 21, 2023
Accepted
January 05, 2023
Published online
May 29, 2023

J Bursa Med 2023;1(2) 69-72

ABSTRACT

Congenital syphilis remains a significant public health problem worldwide and there is a global rise in frequency. It also remains one of the leading causes of fetal and neonatal death globally. Affected newborn infants may be asymptomatic or present with the involvement of many different organs. Non-immune hydrops fetalis is also one of the clinical manifestations. In this article, a case diagnosed with congenital syphilis, which was examined for non-immune hydrops fetalis, was published to share its rarity and difficulties in its management.

Keywords: Congenital syphilis, hydrops fetalis, newborn

Congenital syphilis (CS) is an important public health problem that occurs when *Treponema pallidum*, a spirochete, infects the fetus. Despite CS being well known and optimal prevention strategies, it remains one of the main causes of fetal and neonatal death globally [1]. CS can result in preterm delivery, organ dysfunction, hydrops fetalis, or a wide variety of clinical manifestations. Most cases occur because women of childbearing age are not screened, or treated effectively for syphilis before or during pregnancy [2].

Hydrops fetalis is a clinical condition characterized by fluid accumulation in at least two of the serous spaces such as the peritoneum, pleura and pericardium, accompanied by diffuse skin edema. It may occur due to an immune cause as a result of alloimmunization of red blood cells, or non-immune causes. The causes of non-immune hydrops fetalis include congenital heart diseases, arrhythmias, chromosomal anomalies, syndromes, metabolic and other hematological diseases and infections [3]. In this article, a case diagnosed with congenital syphilis, which was examined for non-immune hydrops fetalis, was published to share its rarity and difficulties in its management.

CASE

Twenty-seven years old pregnant woman was referred to the perinatology clinic due to hydrops fetalis at 32nd gestational week. Her Venereal Disease Research Laboratory (VDRL) test performed at the 25th gestational week was positive. However, she had not been medicated. Her indirect coombs test was negative. Her serological tests for parvovirus, TORCH, human immunodeficiency virus, hepatitis B and hepatitis C viruses were also negative. No structural or rhythm anomaly was detected in fetal cardiological examination. *Treponema pallidum* hemagglutination (TPHA) test of the moth-

How to cite this article
Şenocak Z, Dorum BA, Bozdemir ŞE. Congenital Syphilis as A Cause of Hydrops Fetalis: A Case Report. J Bursa Med 2023;1(2);69-72

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er was reactive as 1/5120. VDRL negative detected.

Following her first pregnancy she delivered a baby boy at 32 weeks' gestation via cesarean section with Apgar scores of 5 and 7 in the first and fifth minutes, respectively. His birth weight was 1800 g (50-90th percentile), length was 41 cm (< 10th percentile), and head circumference was 27 cm (10–50th percentile). The baby with generalized skin edema was admitted to the neonatal intensive care unit with non-invasive respiratory support. He had massive ascites, and hepatosplenomegaly (Figure 1).

Laboratory tests revealed anemia (hemoglobin 9 g/dL), thrombocytopenia (17000/µL), conjugated hyperbilirubinemia (1.35 mg/dL), and high C-reactive protein level (40 mg/L). His direct coombs test was negative. Pleural effusion on chest x-ray, pericardial fluid accumulation on echocardiographic examination, diffuse ascites and hepatosplenomegaly on abdominal ultrasonography were detected. The VDRL test was positive and the TPHA test was 1/320 reactive. Cerebrospinal fluid examination revealed 1/128 positive syphilis indirect hemagglutination (IHA) and VDRL positive. The patient's CSF protein level was high (230 mg/dL) and he was diagnosed as neurosyphilis. In other tests for non-immune hydrops fetalis, TORCH and parvovirus antibodies, metabolic tests (Tandem, blood amino acids and urine organic acids) were normal. Cranial magnetic resonance imaging was evaluated as normal.

The patient was started on benzylpenicillin and

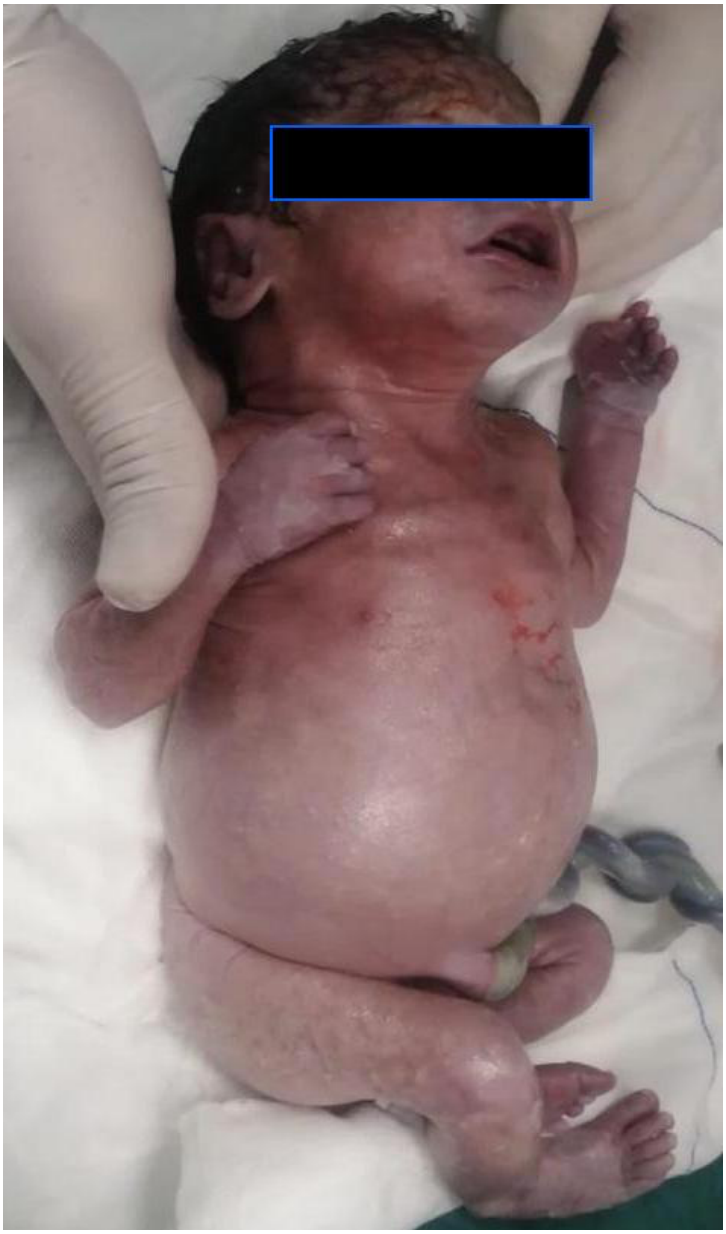

Figure 1. The appearance of the baby immediately after birth, significant abdominal distension due to ascites draws attention

gentamicin treatments. He underwent erythrocyte and thrombocyte transfusion. Paracentesis was performed because massive acid increased respiratory distress. Caffeine treatment was started for apnea.

During the follow-up of the patient, maculopapular rashes were observed. Repeated transfusions and paracentesis were required. He needed intubation for 3 days, and non-invasive respiratory support for 23 days. Penicillin treatment was continued for 30 days. The hepatosplenomegaly regressed. The patient was discharged on the 40th day with oral feeding and weighing 2290 g. He is being followed up in the neurology and infection outpatient clinics.

DISCUSSION

In this article, a case of congenital syphilis who was delivered at 32 weeks of gestation due to the development of heart failure and fetal stress after non-immune hydrops fetalis and was discharged after a successful neonatal management is shared.

CS remains a public health problem around the world. There are even publications stating that its frequency has increased in recent years [2, 4, 5]. According to CDC data, neonatal mortality rate was reported as 1.16% [6]. It has also been reported that most of these deaths occurred among infants born to mothers with untreated or inadequately treated syphilis. In our patient, VDRL test for syphilis was detected positive at 25th gestational week, but no adequate treatment protocol was applied to his mother.

Intrauterine infection occurs after maternal spirochetemia. It has been reported that *T. pallidum* is detected in fetal fluids in 74% of pregnant women with early syphilis [7]. Although the risk of intrauterine infection increases as the gestational week increases, it can occur at any time of pregnancy [2].

In infants with prenatal clinical suspicion, the diagnosis of CS can be made by IgM increase in fetal serums and the demonstration of *T. pallidum* in amniotic fluid [2]. In addition, making the diagnosis of CS by RNA gene sequencing in amniotic fluid is another prenatal diagnosis method [8].

Affected newborn infants may be asymptomatic or present with the involvement of many different organs. In the series reported by Liu *et al*, the most common clinical and laboratory abnormalities were reported as anemia (75%), hepatomegaly (72%), thrombocytopenia (58%), abnormal CSF findings (81%), rash (55%), splenomegaly (52%), and elevated CRP (68%) [9]. In our patient, anemia requiring transfusion, thrombocytopenia, hepatosplenomegaly, liver function disorders, rash that developed in the follow-up, and protein elevation in CSF were observed. In addition, as in our patient, prematurity and related complications are common in newborn cases with CS reported in the literature. Deall H *et al*. reported a case born to a seronegative mother during pregnancy with atypical liver lesions [10].

Aleem *et al*. reported that CS may be associated with hypoxic-ischemic encephalopathy, persistent pulmonary hypertension, and disseminated intravascular coagulation [4]. They reported that all 7 babies with CS were intubated at birth, and one baby was born with hydrops fetalis and died in the delivery room [4].

In cases diagnosed after the neonatal period, pathological findings on long bone radiographs, long-term results of CNS involvement, rhagades, teeth, and eye findings occur, apart from the findings mentioned [11].

Although congenital syphilis can lead to pregnancy loss or life-threatening organ dysfunction, it is a preventable and treatable disease. Pregnant women with syphilis should treat with the penicillin regimen. Screening pregnant women for syphilis is important for the prevention of CS and its complications. With successful screening and treatment of pregnant women in the UK, only 17 CS newborn cases were detected between 2010 and 2015 [12]. However, the prozone phenomenon is an important problem for screening. It may cause false negative results in the tests performed during pregnancy [13]. The same is true for the diagnosis of postnatal babies [5, 14].

Our patient was successfully treated with benzylpenicillin for 4 weeks. While 10 days of penicillin treatment is usually sufficient, treatment can be applied for up to 3-4 weeks in infants with continuing clinical and serological findings. In addition, *T. Pallidum* is also sensitive to other beta-lactam antibiotics, so cefotaxime can be used successfully in the treatment [10].

CONCLUSION

Since clinical findings are nonspecific, congenital syphilis should be considered in the differential diagnosis in cases of unexplained hydrops fetalis. For the prevention of CS, screening of pregnant women for T. pallidum and appropriate treatment if necessary is the most important precaution to be taken.

Authors' Contribution

Study Conception: BAD, ZS, SEB,; Study Design: BAD, ZS, SEB,; Supervision: SEB,; Materials: ZS, BAD,; Data Collection and/or Processing: ZS, BAD,; Statistical Analysis and/or Data Interpretation: SEB,; Literature Review: ZS, BAD,; Manuscript Preparation: ZS, BAD and Critical Review: SEB.

Conflict of interest

No potential conflicts of interest relevant to this article were reported.

Acknowledgements

We are grateful to all treating physicians in our center for collaboration and the data collection.

Financing

There is no source of financial support or funding.

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