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ORIGINAL ARTICLE

Magnesium Deficiency and its Relationship with the Prognosis of Sepsis in Intensive Care Unit

Yoğun Bakımdaki Sepsisli Hastalarda Magnezyum Eksikliği ile Prognoz İlişkisi

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Abstract

Introduction: Magnesium plays an important role in more than 600 metabolic reactions. The frequency of magnesium deficiency may be as high as 60%, especially in patients hospitalized in the intensive care unit (ICU). In this study, the relationship between magnesium deficiency and mortality, clinical course and outcomes in patients who developed sepsis in the ICU is examined.

Methods: This retrospective study was carried out in the ICU of a university hospital between January 2020 and December 2021. Patients were divided into two groups based on magnesium levels. Between groups, patients' demographics, physical examination, culture, and laboratory data were compared. All-cause mortality data in the first 28 days after admission to ICU were inspected.

Results: In 27 (33.7%) of all participants, magnesium deficiency was documented. Magnesium deficiency was more frequent in females (48.5%, p=0.013). Diabetes mellitus was more frequent in the hypomagnesemia group, compared with the group with normal magnesium levels (p=0.028). Platelet counts were higher in the magnesium deficiency group (p=0.036). The mortality rate of whole study groups after 28 days of admission to the ICU was 56.2% and was similar in study groups.

Discussion and Conclusion: Between groups, clinical courses, the length of stay in the ICU, and mortality rates were similar. To understand the relationship between magnesium levels and sepsis, further studies in prospective design that contain a larger number of participants and inspect intracellular magnesium levels will be beneficial.

Keywords: Magnesium deficiency; Sepsis; Platelet count; Mortality; Intensive care unit

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Magnesium plays an important role in more than 600 metabolic reactions. It is an important mineral, which has numerous physiological functions within the body. Magnesium, also known as "the forgotten ion," is the second most abundant intracellular cation.[1]

In hospitalized patients, when compared with the general population, magnesium deficiency is more frequently observed. Especially in patients hospitalized in the intensive care unit (ICU), the frequency of magnesium deficiency may be as high as 60%. Thus, magnesium levels in all patients admitted to ICU must be checked.[2,3] Reportedly, magnesium deficiency can promote progression of infections.[4] The relationship between magnesium deficiency and length of hospital stay, development of sepsis and lactic acidosis, and mortality were reported in patients admitted to the ICU.[5,6] Considering that deficiency of magnesium does not have pathognomonic symptoms, the diagnosis may easily be missed in patients who are admitted to a hospital.[7]

Sepsis is a life-threatening condition in which an impaired immune response to causative infectious agents exists, which results in multi-organ failure, and is an important reason for mortality in the ICU.[8,9] The deficiency of magnesium was more frequent in patients who developed sepsis.[10] However, the relationship between the deficiency of magnesium and the prognosis of sepsis is unclear.[11]

This study aimed to examine the relationship between magnesium deficiency and mortality, clinical course, and outcomes in patients who developed sepsis after being admitted to the ICU.

Material and Methods

This retrospective study was carried out in the ICU (which had 51 beds) of Lokman Hekim University Ankara Hospital between January 2020 and December 2021. The Ethics Committee of the Lokman Hekim University approved this study (App. No: 2022058, 18.04.2022), which was conducted in accordance with good clinical practices and Helsinki Declaration directives. No form of artificial intelligence or assisted technologies were utilized in the production of this submitted work.

The patients who developed sepsis after admission to the ICU participated in this study. Those who were under 18 years old, who developed sepsis before admission to the ICU, who were admitted to the ICU in the previous 6 months, and who were hospitalized after trauma or surgery were excluded. Additionally, those with hypermagnesemia (levels higher than 2.4 mg/dL) were excluded.

Patients were divided into two groups based on magnesium levels. Magnesium levels below 1.6 mg/dL were accepted as hypomagnesemia. Sepsis diagnosis was confirmed based on Sepsis-3 diagnostic criteria.[8] The body height and weight data, smoking status, accompanying diseases, blood gas inspection parameters, Glasgow coma scale scores (GCS), Acute Physiology and Chronic Health Evaluation II (APACHE-II) scores, the need for mechanic ventilation and inotropic agents, mean arterial pressure, lactate levels, whole blood count parameters, calcium, magnesium, creatinine, C-reactive protein (CRP), procalcitonin, albumin, sodium, and potassium levels of participants were recorded after being diagnosed to have sepsis. Blood, urine, and sputum cultures were obtained on the first day of ICU admission and prior to the beginning of the antimicrobial therapy for each patient, in order to specify the etiologic infectious agent. All-cause mortality data in the first 28 days after admission to the ICU were recorded from the hospital computer database.

Whole blood count parameters were studied in Sysmex XN-1000 analyzer (USA). Albumin, sodium, potassium, CRP, calcium, and magnesium parameters were studied in the Roche Hitachi Cobas 501 analyzer (Switzerland). Procalcitonin levels were studied in the Roche Hitachi Cobas 601 analyzer (Switzerland). Lactate levels and blood gas parameters were evaluated using an ABL 800 FLEX (Radiometer, Denmark) blood gas analyzer. Samples for culture were obtained based on international standards and were cultured in 5% sheep blood agar and eosin methylene blue agar. Identification of isolates was made using a BD Phoenix 100 (USA) device.

G-power version 3.1[12] software was utilized to determine the estimated participant numbers. To achieve a power of 80% with an alpha error of 5% and an effect size of 65%, 78 patients were needed to participate in the study. Continuous variables were reported as mean±standard deviation. Categorical data were reported as numbers and percentages. Categorical and continuous variables were compared with the chi-square test and Student's t-test for the study groups determined based on magnesium levels. A p-value <0.05 was accepted to be significant. All data were analyzed using SPSS Version 21.0 (Armonk, NY, USA) statistical computer software.

Results

A total of 80 patients, 45 male (56.2%) and 35 female (43.8%), were examined. The mean age was 71.96±15.18 (males, 72.22±13.26; females, 71.66±17.15; p=0.875). In 27 (33.7%) of all participants, magnesium deficiency was documented.

Table 1. Demographic characteristics and laboratory parameters of patients with sepsis who had hypomagnesemia and normal magnesium levels

Parameter	Low magnesium	Normal magnesium	p*
Age, years	72.56±12.74	71.66±16.38	0.805
Male, n (%)	10 (37)	35 (66)	**0.013**
Height (cm)	164.04±9.73	166.64±15.44	0.427
Weight (kg)	71.11±14.51	70.70±15.57	0.909
Smoking status	22.2%	28.3%	0.559
Accompanying diseases			
Diabetes mellitus	55.6%	30.2%	**0.028**
Hypertension	44.4%	45.3%	0.943
Chronic obstructive pulmonary disease	22.2%	13.2%	0.301
Coronary artery disease	44.4%	32.1%	0.277
Malignancy	18.5%	18.9%	0.970
Chronic kidney disease	7.4%	20.8%	0.126
Dementia	22.2%	24.5%	0.819
Cerebrovascular disease	22.2%	28.3%	0.559
Platelet counts ($\times10^9$/L)	273.70±146.59	205.51±128.86	**0.036**
Leukocyte counts ($\times10^9$/L)	15.78±8.53	17.64±13.51	0.517
Albumin (mmol/L)	0.42±0.11	0.41±0.09	0.726
C-reactive protein (mg/L)	228.58±94.63	222.85±108.37	0.816
Procalcitonin (µg/L)	24.95±31.95	34.34±42.04	0.318
Lactate (mmol/L)	3.25±4.21	4.59±6.29	0.530
Sodium (mmol/L)	139.04±5.71	139.98±8.59	0.608
Potassium (mmol/L)	3.90±1.09	4.20±0.90	0.188
Calcium (mmol/L)	1.96±0.30	2.02±0.24	0.354
pH (blood gas analysis)	7.37±0.14	7.35±0.10	0.424
Mean arterial pressure	77.78±15.25	76.21±18.11	0.701
Urine output (ml/day)	1079.98±652.98	1159.43±1018.01	0.714
Partial oxygen pressure	69.70±25.10	100.30±100.10	0.116
Fractional oxygen concentration	0.40±0.13	0.41±0.17	0.861
Glasgow coma scale	10.48±3.20	8.83±4.02	0.067
APACHE-II score	21.81±5.67	25.40±8.97	0.063
Need for mechanical ventilation	66.7%	64.1%	0.823
Need for inotropic drug	66.7%	66.1%	0.999
Length of hospital stay (days)	15.07±13.38	14.66±10.64	0.881
Mortality rate	63%	52.9%	0.388

*: Categorical variables were evaluated using the chi-square test and continuous variables were evaluated using Student's t-test.

Magnesium deficiency was more frequent in females (48.5%, p=0.013). Diabetes mellitus was more frequent accompanying disease in the group with hypomagnesemia (p=0.028). Additionally, platelet counts were higher in the magnesium deficiency group (p=0.036). The mortality rate after 28 days of admission to the ICU was 56.2% and was higher in the group with magnesium deficiency, but this was not significant (63% vs. 52.9%, p=0.388). Table 1 shows the comparison of demographics, physical examination, and laboratory data.

Considering all the participants, the most frequent accompanying diseases were hypertension, diabetes mellitus, and coronary artery disease (45.0%, 38.7%, and 36.3%, respectively).

Positive culture results were documented in 14 (51.8%) of the hypomagnesemia group and in 26 (49.1%) of patients in the group with normal magnesium levels (p=0.818). The most frequent infection was in the urinary system (57.5%). Table 2 presents the etiologic agents detected in cultures. The most frequent agents were Klebsiella pneumoniae and Escherichia coli (35.4% and 22.9%, respectively).

Table 2. Etiologic agents detected in cultures*

Etiologic agent	Urine		Blood		Sputum		Total
	Hyp.	NM	Hyp.	NM	Hyp.	NM	
Klebsiella pneumoniae	3	5	–	4	1	4	17
Escherichia coli	3	5	–	–	–	3	11
Candida species	2	3	–	–	–	–	5
Enterobacter species	–	1	1	1	1	1	5
Staphylococcus aureus	–	–	1	4	–	–	5
Acinetobacter baumannii	–	–	–	1	1	1	3
Cedeceala pagei	1	–	–	–	–	–	1
MRSA†	–	–	–	1	–	–	1
Culture negative	18	39	25	42	24	44	

*: Some patients had more than one positive culture result; Hyp.: Hypomagnesemia; NM: Normal magnesium; †: MRSA: Methicillin-resistant *Staphylococcus aureus*.

Discussion

The results of this study reveal that there were no relationships between magnesium levels and mortality, the length of ICU stay, GCS, and APACHE-II scores in patients with sepsis. Magnesium deficiency was more frequent in females and in people with diabetes. Platelet counts were higher in patients with hypomagnesemia.

The studies that inspect magnesium deficiency and mortality in ICU reveal conflicting results. In a study from India, the relationship between mortality and magnesium deficiency was significant.[13] In some meta-analyses, magnesium deficiency was reported to increase the length of stay in the ICU and mortality.[6,14] Contrarily, a study from China reported that there was no relationship between magnesium levels and the length of hospital stay and mortality in 974 patients admitted to the ICU, although the mortality rate was reported to be increased six times in patients with increased magnesium levels. As mentioned, hypermagnesemia may cause malignant arrhythmias, lowers blood pressure, and may cause hypoventilation via its effects on respiratory muscles.[15] Moreover, in a study from Türkiye that involved 329 patients, mortality was similar in patients in the ICU, irrespective of magnesium levels.[16] Some studies also reported no relationship between magnesium levels and mortality in patients with sepsis.[17–19] Congruously, this reported study also documented no relationship between magnesium deficiency and the length of ICU stay and mortality.

Magnesium, as a cofactor in numerous enzymatic reactions in the body, is related to macrophage activation and activity against bacteria, and migration of lymphocytes, and production of cytokines.[20] Therefore, magnesium was stated to play an important role in the etiopathogenesis of sepsis.[5] However, many studies, including this reported study, were unable to endorse this statement. Magnesium is mainly intracellular; extracellular magnesium constitutes only 1% of total body magnesium. Magnesium deficiency should reflect the decrease in total body magnesium levels, but it is difficult to measure actual intracellular magnesium levels. Thus, a statement for low magnesium levels should be carefully made.[21,22] This may be an explanation for irrelevant results regarding the role of magnesium levels in patients with sepsis. Alternative methods are utilized to measure magnesium levels. In a study, although ionized magnesium levels measured at the time of ICU admission were found to be related to clinical course and outcomes, serum magnesium levels were found to be unrelated.[23] A study inspecting geriatric patients reported normal magnesium levels in all participants, whereas 57% of them had low erythrocyte magnesium levels.[21] This may be the reason why this reported study was unable to reveal a relationship between magnesium levels and mortality. Additionally, this study did not evaluate cytokine levels that are direct indicators of immune activation, such as interleukins and tumor necrosis alpha. However, besides this fact, procalcitonin, CRP, leukocyte counts, and serum albumin levels, as indirect indicators of immune activation, were compared in patient groups who had low and normal magnesium levels and were found to be similar.

Hypomagnesemia was more frequent in patients with diabetes than in the normal population.[24] Reportedly, this might be a result of decreased intake of magnesium and increased loss of magnesium by urine in patients with diabetes.[25] This study reports lower magnesium levels in patients with diabetes than in those without, harmoniously.

Magnesium deficiency was more frequent in females than in males.[26] This is stated to be due to lower consumption

of magnesium in the female population.[27] Moreover, in this study, low magnesium levels are revealed in the female gender, concordantly.

A positive correlation between magnesium levels and platelet counts was documented in patients undergoing hemodialysis.[28] Furthermore, decrease in platelet counts was reported in patients developing sepsis. In sepsis, the coagulation cascade was more frequently activated in patients with hypomagnesemia than in those who had normal magnesium levels. Thus, prothrombin times were found to be prolonged and the levels of fibrinogen and platelets were found to be decreased.[11] Congruent with the aforementioned studies, the current study also revealed a relationship between platelet counts and magnesium levels.

This study has numerous limitations. Magnesium levels were only studied at the time of diagnosis of sepsis, but follow-up magnesium levels were not achieved; thus, changes in magnesium levels and clinical course and outcomes could not be compared. To come in agreement with previous studies, patients with higher magnesium levels were not included in the study.[19,29] The magnesium levels of the participants were measured only in serum samples but not in erythrocytes, and this is another limitation of this study.

Conclusion

Clinical course, the length of ICU stay, and mortality rates were similar in patients who had hypomagnesemia and those who had normal magnesium levels at the time of diagnosis of sepsis. Further studies in prospective design, containing a larger number of participants and inspecting intracellular magnesium levels, will be beneficial for the understanding of the relationship between magnesium levels and sepsis.

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