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The Relationship of Serum Magnesium Levels with Etiology, Lesion Size, and Localization in Ischemic Stroke

Akut İskemik İnmede Serum Magnezyum Düzeylerinin Etiyoloji, Lezyon Boyutu ve Lokalizasyonla İlişkisi

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ABSTRACT

Objectives: Magnesium is known to have important effects on vascular system and deficiency of magnesium triggers vasoconstriction and facilitates vascular endothelial damage. There were conflicting results in several studies searched for relationship between magnesium levels, etiologic subtypes, and lesion size in ischemic stroke. We aimed to examine relationship between serum magnesium levels and etiology of stroke as well as lesion size and localization.

Methods: A total of 545 patients over the age of 18 years who presented within the first 24 h of acute ischemic stroke and 189 healthy controls were included in the study. Patients were grouped according to TOAST classification and also as anterior and posterior circulation infarcts. Infarct volume was estimated using MRI scan as large (≥5 cm^3) and small (<5 cm^3) infarct. The relationship between serum magnesium levels and etiology, lesion size, and localization was examined.

Results: Serum magnesium level was 1.90±0.23 mg/dL in the patient group and 1.93±0.18 mg/dL in the control group, and no statistically significant difference was found (p=0.11). The mean magnesium level was 1.90±0.2 mg/dL in the atherothrombotic; 1.87±0.2 mg/dL in the cardioembolic; 1.88±0.18 mg/dL in the lacunar; 1.92±0.2 mg/dL in the undetermined; and 1.91±0.2 mg/dL in the other stroke group. There was no statistically significant difference between the magnesium levels according to etiology (p=0.25) and localization (p=0.109).The mean magnesium level was 1.87±0.24 mg/dL and 1.91±0.2 mg/dL in the large and small infarct groups, respectively. An inverse relationship between mean magnesium levels and the infarct size was found (p=0.044, r=−0.087).

Conclusion: Our results suggest that Mg may play a role in the pathophysiology of infarction and relatively high Mg levels may limit the lesion size.

Keywords: Magnesium; ischemic stroke; lesion size; TOAST.

ÖZET

Amaç: Magnezyumun vasküler sistem üzerinde önemli etkileri olduğu ve magnezyum eksikliğinin vazokonstrüksiyonu tetiklediği ve vasküler endotel hasarını kolaylaştırdığı bilinmektedir. İskemik inmede magnezyum düzeyleri, etiyolojik alt tipler ve lezyon boyutu arasındaki ilişkiyi araştıran birçok çalışmada çelişkili sonuçlar bulunmuştur. Bu çalışmada, serum magnezyum düzeyleri ile inme etiyolojisi arasındaki ilişkinin, lezyon boyutunun ve lokalizasyonunun incelenmesi amaçlandı.

Yöntem: Akut iskemik inmenin ilk 24 saati içinde başvuran 18 yaş üstü 545 hasta ve 189 sağlıklı kontrol çalışmaya dahil edildi. Hastalar, TOAST sınıflandırmasına göre ve ayrıca ön ve arka sirkülasyon infarktları açısından gruplandırıldı. İnfarkt hacmi, büyük (≥5 cm^3) ve küçük (<5 cm^3) infarkt olarak manyetik rezonans görüntüleme taraması ile belirlendi. Serum magnezyum seviyeleri ile etiyoloji, lezyon boyutu ve lokalizasyon arasındaki ilişki incelendi.

Bulgular: Serum magnezyum düzeyi hasta grubunda 1,90±0,23 mg/dL, kontrol grubunda 1,93±0,18 mg/dL idi ve istatistiksel olarak anlamlı bir fark bulunmadı (p=0,11). Ortalama magnezyum düzeyi aterotrombotik grupta 1,90±0,2 mg/dL; kardiyoembolik grupta 1,87±0,2 mg/dL; laküner grupta 1,88±0,18 mg/dL; belirlenemeyen grupta 1,92±0,2 mg/dL; diğer inme grubunda 1,91±0,2 mg/dL olarak bulundu. Etiyoloji (p=0,25) ve lokalizasyon (p=0,109) açısından magnezyum düzeyleri arasında istatistiksel olarak anlamlı fark yoktu. Ortalama magnezyum seviyesi büyük ve küçük infarkt gruplarında sırasıyla 1,87±0,24 mg/dL ve 1,91±0,2 mg/dL idi. Ortalama magnezyum seviyeleri ile infarkt boyutu arasında ters bir ilişki bulundu (p=0,044, r=-0,087).

Sonuç: Çalışmanın sonuçları, magnezyumun infarkt patofizyolojisinde rol oynayabileceğini ve nispeten yüksek magnezyum seviyelerinin lezyon boyutunu sınırlayabileceğini düşündürmektedir.

Anahtar sözcükler: İskemik inme; serum magnezyum; lezyon büyüklüğü.

Ischemic strokes are caused by occlusion of arteries supplying the brain, either due to a thrombus at the site of occlusion or emboli from another part of the circulation. It constitutes 50–85% of all strokes all over the world.[1] Magnesium (Mg+2) ions have a physiological role in many processes related to ischemia. Magnesium (Mg+2) plays an important role in biological systems and acts as a cofactor in a lot of enzymatic reactions in the body. Numerous evidence suggests that magnesium plays an important role in many disease processes, including blood pressure regulation, oxidative stress, endothelial function, coagulation, and cardiac rhythm disorders.[2] It is an important cofactor for cellular energy metabolism and protein synthesis. In the brain, Mg (2+) ions may decrease the glutamate neurotoxicity by blocking glutamatergic N-methyl-D-aspartate receptors during oxidative stress conditions such as acute ischemic stroke (AIS).[3,4] Low Mg (2+) levels at the time of AIS may decrease penumbral resistance to hypoxic state and result in more severe stroke presentations or progressive neurologic deterioration.[5,6] The correlation of serum magnesium levels with stroke severity, early prognosis, etiologic subtypes, and lesion size in stroke patients has not been extensively studied. Few studies have evaluated the relationship between baseline Mg (2+) levels with prognosis.[5,7,8] The role of serum Mg (2+) or magnesium replacement treatment in ischemic damage, however, remains controversial.[5,7] Some clinical studies have demonstrated the safety of magnesium sulfate ($MgSO_4$) infusion in AIS patients[9] and suggested that $MgSO_4$ administration may provide a therapeutic advantage in these patients.[10] In the present study, we examine the relationship of serum Mg (2+) levels with etiology and lesion size, in patients with AIS at presentation within 24 h.

Methods

Patients with a total number of 683 over the age of 18 years who presented to our clinic within the first 24 h of AIS between January 2015 and January 2017 and 189 healthy controls were examined This study was designed as a retrospective study, so the informed consent of the patients and controls could not be obtained. The Ethical Committee Approval date and number is December 14, 2020/51. The study protocol was in accordance with the Helsinki Declaration. Patients with a history of renal failure, hepatic failure, malignancies, an intracranial mass or central nervous system infection, and ongoing medication with calcium, magnesium, or potassium containing drugs were excluded from the study. Patients of whom blood samples were not taken in the 24 h of initiation of the stroke and control cranial magnetic resonance imaging (MRI) scans were not examined in days 3–7 which were also excluded from the study. Finally, 545 patients suitable to inclusion criteria were included to the study. The control group consisted of 189 individuals who were otherwise healthy; they were examined and their files were analyzed retrospectively. Blood samples were taken for routine biochemical tests and Mg levels within the first 24 h. Atherothrombotic, cardioembolic, lacunar, other causes, and cause of unexplained according to TOAST classification were examined with cranial MRI, carotid-vertebral Doppler USG, and echocardiography. We also classified the stroke groups as anterior and posterior circulation in terms of circulation and also supra and infratentorial infarcts in terms of localization. MRI scan was used to determine the infarct lesion volume at days 3–7. The lesions were grouped into two according to the MRI findings; those ≥5 cm^3 were classified as large infarct lesions and those <5 cm^3 were classified as small infarct lesions.[11] We examined the relationship between serum magnesium levels in groups classified as eti-

ologic subtypes according to TOAST classification and also in groups divided as anterior versus posterior circulation infarcts. We also examined the relationship between serum magnesium levels in infarct lesion size groups estimated using MRI scan.

Statistical Analysis

To determine whether the variables were normally distributed, the Kolmogorov–Smirnov test was used. Mean and standard deviation values were given for variables with normal distribution. For parametric variables with normal distribution, Student's T-test was used. Chi-square test was used for non-parametric non-numeric data. Pearson's test was used as the correlation test. $p<0.05$ was considered statistically significant. Statistical analysis was performed using the 17 version of the Statistical Package for the Social Sciences.

Results

A total of 545 patients with acute ischemic stroke and 189 control patients were included in the study. The mean age of the patients and controls was 69.23±12.95 and 67.67±14.34, respectively. Male to female (M/F) percentages of patients (n=286/259) and the control group (n=94/95) were 52.5/47.5 and 49.4/50.6, respectively, and there was no statistically significant difference in terms of gender and age both in the patient and control groups ($p>0.05$). Serum magnesium level was found to be 1.90±0.23 mg/dL in the patient group and 1.93±0.18 mg/dL in the control group, and no statistically significant difference was found ($p=0.11$) (Table 1 and Fig. 1). The mean magnesium level was 1.90±0.2 mg/dL in the atherothrombotic stroke group (n=195), 1.87±0.2 mg/dL in the cardioembolic stroke group (n=146), 1.88±0.18 mg/dL in the lacunar stroke group (n=18), 1.92±0.2 mg/dL in the undetermined stroke group (n=35), and 1.91±0.2 mg/dL in the other stroke group (n=151). There was no statistically significant difference between the magnesium levels in terms of stroke groups ($p=0.25$) (Table 2 and Fig. 2). The mean magnesium level was 1.89±0.23 mg/dL in anterior circulation group (n=365) and was 1.91±0.22 mg/dL in posterior circulation group (n=180), and there was no statistically significant difference between two groups ($p=0.35$). Furthermore, there was no significant difference between magnesium levels in supratentorial (n=449) (1.89±0.24 mg/dL) and infratentorial (n=96) (1.93±0.20 mg/dL) groups ($p=0.109$) (Table 3, Figs. 3 and 4).

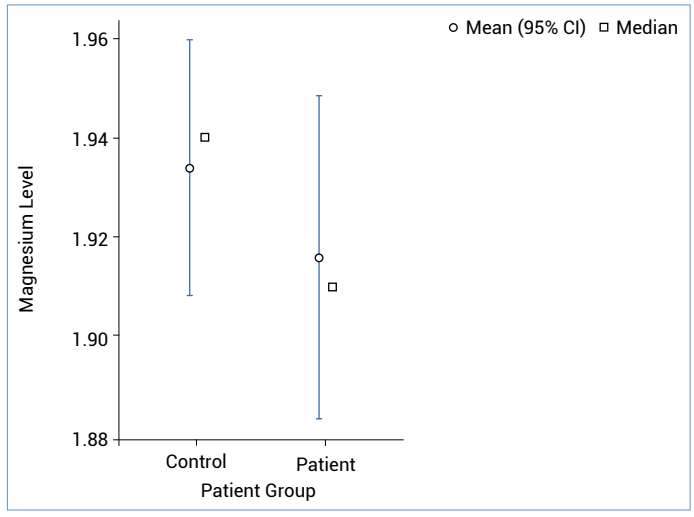

Figure 1. Mean magnesium level.

The mean magnesium level in the large infarct group (≥5 cm^3) (n=243) was 1.87±0.24 mg/dL, and the mean magnesium level in the small infarct group (<5 cm^3) (n=302) was 1.91±0.2 mg/dL. There was statistically significant difference between the magnesium levels in terms of infarct size

Table 1. Demographic data and mean magnesium level

Variables	AIS patients, n=545	Control group, n=189	p
Gender ratio (female/male) (n)	0.90	1.01	0.21
	F: 259	F: 95	
	M: 286	M: 94	
Age (years)	69.23±12.95	67.67±14.34	0.18
Magnesium level (mg/dL)	1.90±0.23	1.93±0.18	0.11
Median	1.91	1.94	
Minimum	0.7	1.23	
Maximum	2.8	2.4	

AIS: Acute ischemic stroke.

Table 2. Mean magnesium level according to the stroke types

Variables	Atherothrombotic group, n=195	Cardioembolic group, n=146	Lacunar, n=18	Undetermined, n=35	Other, n=151	p
Magnesium level (mg/dL)	1.91±0.2	1.86±0.3	1.88±0.2	1.9±0.2	1.97±0.6	0.25

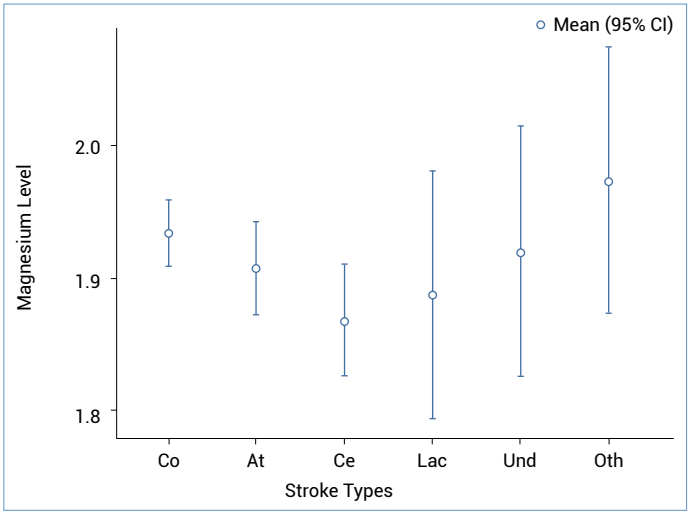

Figure 2. Mean magnesium level according to the stroke types.

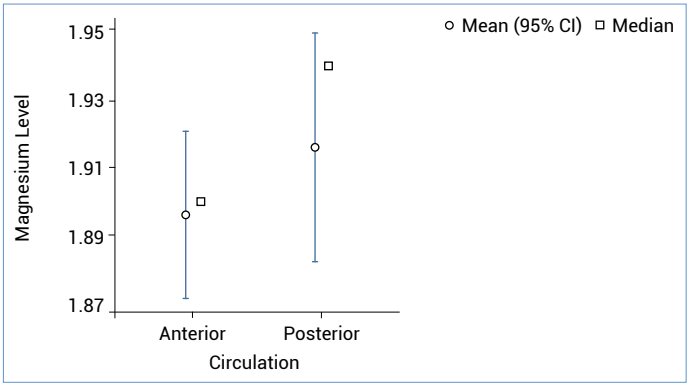

Figure 3. Mean magnesium level according to the circulation.

(p=0.044). The inverse relationship between mean magnesium levels and the infarct size was found (p=0.044, r:–0.087) (Table 3 and Fig. 5).

Discussion

The response to a lack of oxygen and nutrients (i.e., ischemia) by the brain includes a local release of chemicals that can damage brain cells, in addition to ischemic damage.[12-16] Perhaps, the most neurotoxic of these chemicals is glutamate, which is an important neurotransmitter in normal brain tissue. During AIS, however, the massive amount of glutamate released, causes calcium influx inside brain cells, which, in turn, causes them to die prematurely. Magnesium is thought to have the ability to prevent calcium influx inside the cells by blocking glutamate and thus protecting them from premature death.[13,17-23] Magnesium plays well-known roles in our bodies such as vasodilatation, increasing cardiac output, and prolonging bleeding time. Magnesium has been used in a long time in eclampsia to prevent seizures and as an antiarrhythmic agent in cardiology.[13,14,17,18,20,24-27] Magnesium concentration in cerebrospinal fluid (CSF) is maintained at levels higher than serum levels using the active transport system. With intravenous administration, magnesium concentration in CSF can reach to a peak level in 4 h.[28-30]

Table 3. Mean magnesium level according to the lesion localization and size

Variables	Anterior circulation, n:365	Posterior circulation, n:180	p
Magnesium level (mg/dL)	1.89±0.23	1.91±0.22	0.35
	Supratentorial, n:449	**Infratentorial, n:96**	
Magnesium level (mg/dL)	1.89±0.24	1.93±0.20	0.109
Lesion size	**Large infarcts (≥5 cm^3), n: 243**	**Small infarcts (<5 cm^3), n: 302**	
Magnesium level (mg/dL)	1.87±0.24	1.91±0.22	0.044*[b]

[a]Mann–Whitney U-test. [b]Student's t-test.

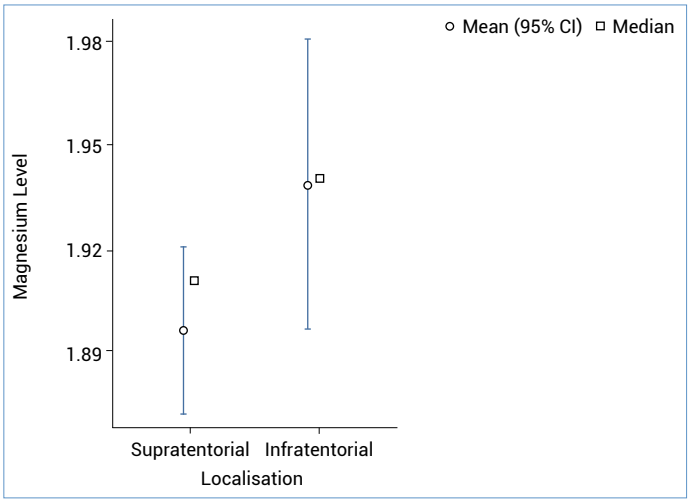

Figure 4. Mean magnesium level according to the localization.

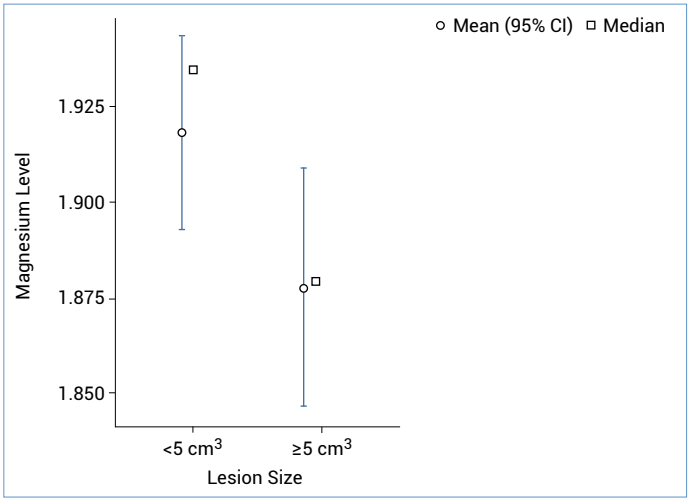

Figure 5. Mean magnesium level according to the lesion size.

The effectiveness of magnesium in acute stroke has been demonstrated in animal studies. Studies using rats and mice showed that if given at high concentrations, magnesium can decrease the area of the ischemic brain damage. A meta-analysis of four studies in which magnesium was administered to patients with AIS stroke showed an 8% reduction in the risk of death or dependence after 3–6 months from the onset.[12] The results of a large randomized study, in which magnesium was administered intravenously <12 h (median, 7 h) from symptom onset, was frustrating. Magnesium not only failed to show any beneficial effect on mortality and morbidity at 3 months but also it slightly increased mortality.[13] In this study, the investigators only found a beneficial effect in a subgroup of patients with lacunar strokes and also in patients with a mean arterial blood pressure that was higher than the median.[13] Intravenous magnesium sulfate administration during the hyperacute phase of stroke was shown to be safe in an open-label study. Dramatic early recovery was achieved in 42% of patients, and good functional outcome (modified Rankin scale ≤ 2) at 90 days was achieved by 69% of all patients.[28]

We did not detect any statistical difference in serum Mg (2+) levels between patient and control groups (p=0.11). We also did not detect any significant difference between serum Mg (2+) levels and etiologic stroke subtypes classified according to the TOAST as atherothrombotic, cardioembolic, lacunar, undetermined, and other (p=0.25); stroke groups classified as anterior and posterior circulation and also supra and infratentorial infarcts (p=0.35 and p=0.109, respectively). Due to lesion size classified as small (<5 cm^3) and large (≥5 cm^3) infarcts, there was statistically significant difference between the magnesium levels in terms of infarct size and the inverse relationship between mean magnesium levels and the infarct size was found (p=0.044, r=–0.087). Because of the postulated vasodilating and neuroprotective effects mentioned above, the relatively high median Mg levels found in small infarct group and may have been played a role by limiting the lesion size. However, we did not find any literature knowledge for supporting our comment.

Conclusion

Serum magnesium levels were not found to be statistically different between patients and control group and were not found to be associated with any groups classified as according to etiology, circulation, and localization. We only found an inverse relationship between mean magnesium levels and infarct lesion size and suggested that Mg may play a role in the pathophysiology of infarction and relatively high Mg levels may limit the lesion size. However, the current state of knowledge from the literature does not allow for the practical use of magnesium in acute ischemic human stroke, some data are promising and require further evaluation in randomized, large-scale studies.

Disclosures

Ethics Committee Approval: The Ethical Committee Approval date and number is December 14, 2020/51. The study protocol was in accordance with the Helsinki Declaration.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – M.Ü.; Design – M.Ü.; Supervision – F.D.; Materials – T.T.; Data collection &/or processing – M.D., R.K.; Analysis and/or interpretation – M.D.; Literature search – M.Ü.; Writing – M.Ü.; Critical review – F.D.

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