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CLINICAL ARTICLE - BRAIN TUMORS

Effect of magnesium on functional outcome and paraclinical parameters of patients undergoing supratentorial craniotomy for brain tumors: a randomized controlled trial

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Abstract
Background Several studies have demonstrated that magnesium (Mg) plays an important role in the prevention and treatment of central nervous system (CNS) insults. In this study, we tested the effect of intravenous magnesium sulfate ($MgSO_4$) on the outcome of patients with brain tumors who underwent craniotomy. The outcome was defined clinically as the Barthel index score and paraclinically as blood levels of NSE (neuron-specific enloase) and S100B protein.
Methods Sixty patients were randomly divided into two groups of 30 patients: the treatment and control groups. In the treatment group, 5 g of $MgSO_4$ in normal saline was infused in 6 h 2 days before surgery, and the same dosage was repeated the day before and during surgery. The control group received placebo. Serum S100B and NSE concentrations were measured at baseline before administration of magnesium, before surgery, and on the 2nd postoperative day. The Barthel index score was evaluated and registered before surgery, 3, and 6 months after the operation.
Results The study results showed a significant change in S100B protein levels before and after surgery ($p<0.05$), but we could not find similar results for NSE protein and the Barthel index score. There was a correlation between NSE protein and the Barthel index.
Conclusions The results of this study revealed that administration of intravenous $MgSO_4$ before and during surgery is safe and effective in reducing S100B protein levels in patients undergoing supratentorial craniotomy for brain tumors. Further studies to elucidate the pathophysiology of brain injuries and role of magnesium are warranted.

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Keywords Magnesium sulfate · S100B protein · NSE · Barthel index · Neurosurgery

Introduction

Several studies have demonstrated that magnesium (Mg) plays an important role in the prevention and treatment of central nervous system (CNS) insults [1,2]. Magnesium is the fourth most abundant cation in the body and the second most abundant cation in intracellular fluid. Magnesium is essential for cell functions such as maintenance of smooth muscle tone, regulation of calcium transport, and antagonism of voltage-gated calcium channels [3].

Magnesium is neuroprotective and plays an essential role in many crucial enzyme systems [3]. It is also effective in the treatment of eclampsia [4]. Magnesium enhances neuronal survival by inhibition of excitatory glutamate release, blockade of NMDA glutamate receptors, and regulation of regional cerebral blood flow by vascular smooth muscle relaxation, subsequently increasing cerebral blood flow in the ischemic region [5].

Several studies have documented that the serum magnesium level decreases after traumatic brain injury (TBI) [6,7], and magnesium supplementation, whether given before or shortly after injury, improves the neurological outcome in animals with brain injury and artificially lowered magnesium concentrations [8,9].

S100B is a well-studied biomarker of brain injury. It is a low-molecular-weight calcium-binding protein most abundant in the CNS [10]. Neuron-specific enolase (NSE) is an isoenzyme of enolase in the glycolytic cascade. Together with S100B, NSE is a specific tissue factor of brain injury. The levels of both proteins have been reported to increase after TBI, stroke, and subarachnoid hemorrhage [11]. The increase in serum levels of these proteins has been shown to be related to the intensity of brain injury and clinical outcome [12–15].

In this randomized controlled trial, we tested the effect of intravenous magnesium sulfate on the outcome of patients with brain tumors who underwent craniotomy. The outcome was defined clinically as the Barthel index score and paraclinically as blood levels of NSE and S100B.

Methods

This prospective, parallel randomized, double-blind, and placebo-controlled trial was approved by the Committee of Bioethics of Tehran University of Medical Sciences. The clinical trial registration number is IRCT201204159475N1. Written informed consents were obtained from all patients. The study was carried out between September 2012 and February 2014 at the Department of Neurosurgery, Sina Hospital.

In previous studies, the postcraniotomy level of S100B was reported to be 142 pg/ml with a standard deviation of 84 pg/ml. We used the $n = 2\left(Z_{1-\frac{\alpha}{2}} + Z_{1+\beta}\right)\frac{^2\times SD^2}{d^2}$ formula and considered a 70 pg/ml difference in S100B as the significant endpoint for this study (SD=84, d=70, $Z_{1-\alpha/2}$=1.96 and $Z_{1+\beta}$=1.28). The calculated population size was 30 patients in each arm. Sixty patients older than 18 years of age with brain tumors who were candidates for supratentorial craniotomy were enrolled in this study with an allocation ratio of 1:1. No changes were made in the inclusion criteria throughout the study.

A radiologic assessment by computed tomography (CT) scan prior to enrollment was conducted by independent radiologists, and patients with supratentorial brain tumors were selected for the study. Patients with previous craniotomies (e.g., recurrent tumors), significant organ dysfunctions (e.g., cardiac, respiratory, renal, or liver disorders), severe metabolic diseases, myasthenia gravis, morbid obesity, treatment with calcium channel blockers, or previous usage of magnesium were excluded. Eligibility of the patients for inclusion were assessed by their treating physician (i.e., neurosurgeon). Then, patients were divided into treatment (i.e., received magnesium) and control groups with block randomization by a pharmaco-therapist member of our team, and the neurosurgeons and anesthesiologists were blinded to the allocation. Infusion solutions were prepared by the same pharmacist in similar bottles and given to the physicians and nurses for infusion.

In the treatment group, 5 g of $MgSO_4$ in normal saline was infused in 6 h 2 days before surgery, and the same dosage was repeated the day before and during surgery. In the control group, only normal saline (without $MgSO_4$) was infused at the same intervals. The normal saline bottles with or without magnesium had identical labels to assure the study remained blinded. An infusion pump used for both groups at the rate of 2.7 ml per minute. All surgeries were performed by the same neurosurgery team.

General anesthesia was induced with intravenous fentanyl (2 μg/kg) and midazolam (0.05 mg/kg) followed by propofol (1.5–2 mg/kg) and atracurium (0.5 mg/kg). Maintenance of anesthesia was carried out by continuous infusion of propofol (6–8 mg/kg/h) and fentanyl (1–2 μg/kg/h). Muscle relaxation was kept by repeated dosing of atracurium. An arterial line was fixed to monitor blood pressure and perform blood gas analysis. Hemodynamic parameters, total propofol requirements, blood loss, and duration of anesthesia (i.e., from induction to withdrawal of all anesthetics) were recorded. An electrocardiograph, saturation of oxygen, end-tidal CO_2, and temperature were checked as standard care for all patients. None of the patients received mannitol, and the same nutritional diet was used by all the patients pre- and postoperatively.

Serum S100B and NSE concentrations were measured on three occasions: (1) 2 days before surgery before administration of magnesium, (2) immediately after surgery, and (3) in the morning of the 2nd postoperative day. The concentrations of S100B protein (BioVendor, Laboratornímedicínaa.s.) and NSE (Fujirebio Diagnostics AB) were measured by enzyme-linked immunoassay. The detection limit for S100B protein was 15 pg/ml and for NSE was 1 μg/l. The Barthel index was evaluated and registered before surgery and 3 and 6 months after the operation.

All statistical analyses were performed using SPSS (version 17, Chicago, IL). The independent sample t-test or Mann-Whitney U test was performed to compare continuous variables. The chi-square test was used to compare categorical data. The Kolmogrov-Smirnov test of normal distribution was used, and according to its results, the independent sample

t-test or Mann-Whitney U was utilized for data analysis. Correlation between continuous variables was tested using Pearson or Spearmen rho statistics. The chi-square test was used to compare categorical data. Repeated measures analysis of variance was performed to compare S100B and NSE levels between the control and treatment groups and at different time points. A generalized estimating equation (GEE) approach with an unstructured correlation matrix was used to estimate the correlation between repeated measures of S100B and NSE controlling for the time of measurement. Statistical significance was defined as $p < 0.05$.

The full protocol of the trial is available on the IRCT website at the link below: http://www.irct.ir/index.php

Results

During the study period, 95 patients were assessed for eligibility. Twenty-two patients did not meet the inclusion criteria, and 13 patients declined to participate in the study for various reasons. All patients enrolled in the study completed the study and follow-up period. Sixty patients were divided into two equal groups of 30. Data of the pathology, location, and position of the patients are summarized in Table 1.

There were no differences between the two groups regarding the age, sex, and weight of the patients as well as duration of surgery ($p>0.05$, *t*-test). The mean age of the patients was 52±11 years, and 26 patients were male (43.3 %). The age and sex of the patients showed no significant correlation with the Barthel index score, S100B, and NSE levels ($p>0.05$, Spearman's rho).

Table 1 Tumor characteristics in the treatment and control groups

		Control group	Treatment group
Tumor pathology	GBM/AA	7	6
	LGG	8	8
	Metastasis	2	1
	Meningioma	10	13
	Other pathologies	3	2
Tumor location	Frontal	9	8
	Temporal	3	5
	Parietal	7	9
	Occipital	6	5
	Skull base	5	3
Patient position	Supine	19	22
	Prone	4	3
	Lateral	7	5
Tumor largest diameter (mean ± SD)		39.1±11.8	41.8±17.7

AA Anaplastic astrocytoma; *GBM* glioblastoma multiforme; *LGG* low-grade glioma; *SD* standard deviation

Variables including age, sex, Barthel index score, S100B, NSE, blood loss, duration of hospitalization, and surgery time are shown in Table 2. Again, age and sex showed no correlations with duration of surgery, bleeding volume, and hospital stay ($p>0.05$, Spearman's rho). Mean arterial pressure ($p<0.05$), heart rate ($p<0.05$), bleeding volume ($p<0.01$), and required dose of propofol ($p<0.01$) were significantly lower in the treatment group (*t*-test).

S100B levels were significantly different among various time points ($p<0.01$, Friedman test), and there was an interaction effect between S100B and the groups during the time; in other words, the groups were changing over time but were changing at significantly different rates ($p=0.005$, Mann-Whitney *U* test). S100B had a higher elevation in the control group after surgery ($p<0.003$, Mann-Whitney *U* test) (Fig. 1). NSE levels increased over time in all patients ($p<0.05$, Friedman test), but no significant differences were found between the control and treatment group levels at each time point ($p>0.05$, Mann-Whitney *U* test) (Fig. 2). The Barthel score decreased over time in all patients ($p<0.05$, Friedman test), but there was no significant difference between the control and treatment groups ($p<0.05$, Mann-Whitney *U* test) (Fig. 3).

NSE and S100B were positively correlated (beta = 3.238, $SE=0.667$, $p<0.001$, Spearman's rho). Statistical analysis showed that each unit increase of NSE increased S100B by 3.238 units (GEE). NSE levels after surgery showed a significant correlation with duration of hospital stay ($r=0.249$, $p<0.05$, Spearman's rho). Duration of hospital stay did not have any correlations with duration of surgery and bleeding volume ($p>0.05$, Spearman's rho). S100B levels did not show any significant correlation with duration of hospital stay ($p>0.05$, Spearman's rho), but postoperative levels had a positive correlation with duration of surgery ($r=0.318$, $p<0.05$, Spearman's rho) and bleeding volume ($r=0.320$, $p<0.05$, Spearman's rho). S100B did not have any correlation with the Barthel score ($p>0.05$, Spearman's rho), but the NSE level showed a negative correlation with the Bartehl score at different time points (p value < 0.05, Spearman's rho). The Barthel index showed no correlation with the duration of surgery or bleeding volume ($p>0.05$, Spearman's rho).

Discussion

The aim of this study was to investigate the neuroprotective effect of Mg on surgically induced brain injury. The study results showed a significant change in S100B protein levels before and after surgery, but we could not find similar results with NSE protein and the Barthel index, while there was a correlation between NSE protein and the Barthel index. This might be explained by the fact that neurological injuries

Table 2 Patient characteristics and outcomes

Factor	Total	Intervention	Placebo	*P*-value
Male/female	26/34	14/15	12/19	0.655
Age (years)	52±11	47±10	49±08	0.676
S100B2, mean (SD, range) pg/ml	214 (135, 76–816)	208 (130, 76–816)	220 (143, 83–670)	0.888
S100B3, mean (SD, range) pg/ml	404 (185, 162–982)	339 (162, 162–880)	468 (186, 166–982)	0.006
NSE2, mean (SD, range) μg/l	32.3 (22.4, 7.3–106.7)	30.2 (23.2, 7.3–106.7)	34.5 (21.6, 8.5–96.9)	0.458
NSE3, mean (SD, range) μg/l	43.5 (33.7, 7.8–162.8)	39.8 (35.4, 11–162.8)	47.3 (32, 7.8–144.2)	0.394
Barthel2, mean (SD, range)	76 (16, 20–100)	78 (14, 20–100)	74 (18, 30–100)	0.413
Barthel3, mean (SD, range)	68 (16, 30–100)	70 (12, 30–95)	68 (19, 35–100)	0.515
Surgery time, median (range) h	4 (2–7)	5 (2–7)	4 (3–7)	0.244
Hospitalization, mean days (SD, range)	5 (2, 2–9)	5 (2, 2–9)	5 (2, 2–9)	0.573
Bleeding, median, (range) ml	500 (100–1,000)	300 (100–500)	550 (300–1,500)	<0.001

SD Standard deviation

during our operations were not severe enough, so the protective effects of Mg could not be displayed.

Clinical studies on Mg showed conflicting results [1,5,16]. One of the caveats to using magnesium as a neuroprotective agent is its bioavailability in the brain. One study on preecclampitc women showed that Mg infusion increased the ionized magnesium level in the CNS [17]. The authors related this increase to stress-induced changes of the blood-brain barrier properties. It has been shown that stress during neurosurgery also exerts the same effects [18]. Therefore, lower levels of S100B protein in the treatment group can be explained by Mg's effects on the CNS.

It is believed that hypotension is associated with higher mortality after TBI [19,20]. Hypotension leads to CNS hypoperfusion and subsequent hypoxia. In a study by Temkin and colleagues on TBI patients, hypotensive episodes were reported in 26–36 % of the patients treated with Mg and associated with higher mortality [5]. In our study, although the treatment group had significantly lower mean arterial pressure during surgery, it was not associated with increased mortality or morbidity.

Female patients have reportedly lower morbidity and mortality after TBI due to female sex hormones' neuroprotective effects on TBI [21]. On the other hand, in a multicenter trial of

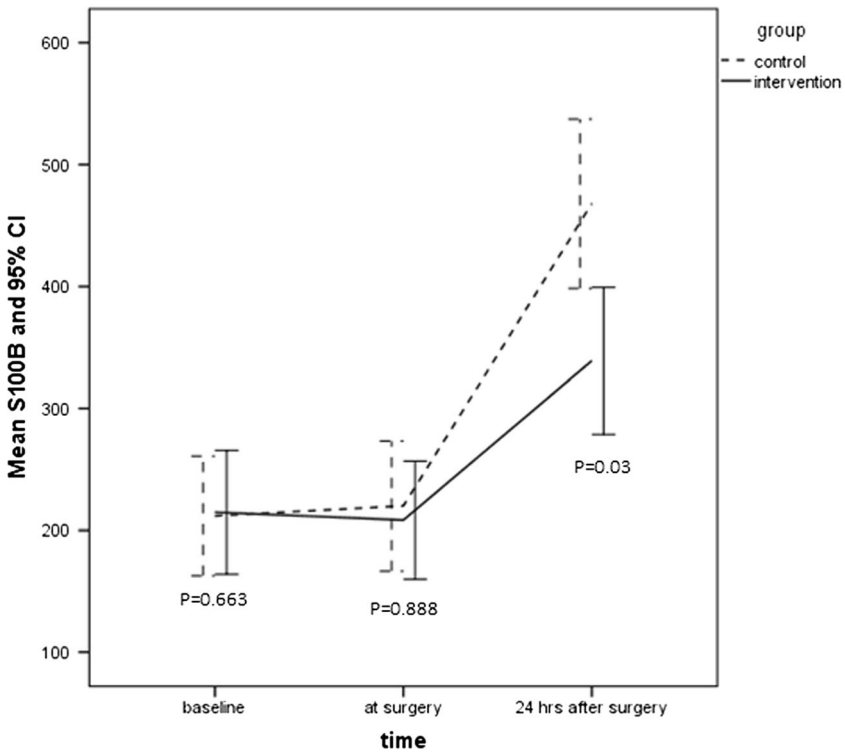

Fig. 1 S100B level measured at three time points: (1) Before magnesium injection, (2) immediately before surgery, and (3) 2 days after surgery. Please refer to the text for detailed comparison of the control and treatment groups over time

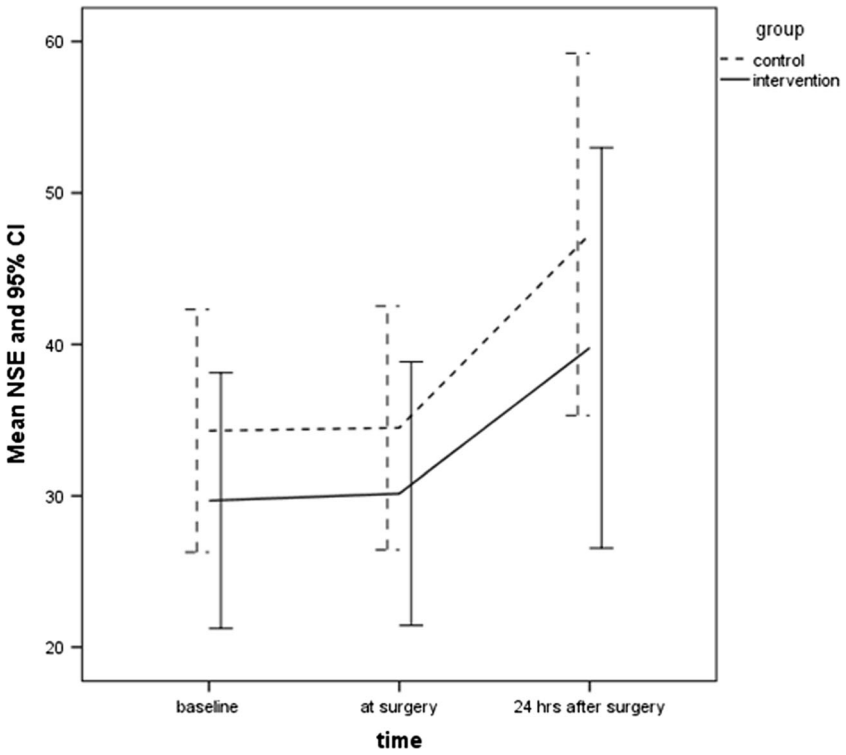

Fig. 2 Neuron-specific enolase (NSE) measured at three time points: (1) before magnesium injection, (2) immediately before surgery, and (3) 2 days after surgery. Please refer to the text for detailed comparison of the control and treatment groups over time

236 TBI patients, a correlation between age and outcome was reported [22]. However, in this study, no relations between age, sex, and injury biomarkers were found.

The half-life of the S100B biomarker was reported to be less than 60 min in previous studies. Therefore, we considered the first 24 h after surgery to be a logical time limit for

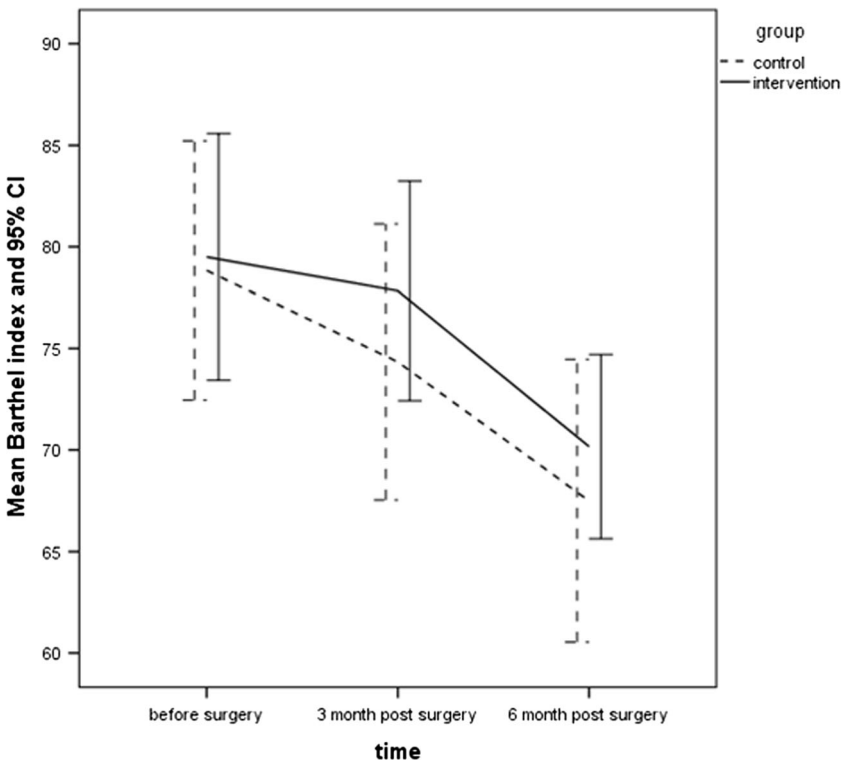

Fig. 3 Barthel index measured at three time points: (1) Before surgery, (2) 3 months after surgery, and (3) 6 months after surgery. Please refer to the text for detailed comparison of the control and treatment groups over time

sampling. On the other hand, as we wanted to find an early predictor of long-term complications of craniotomy, we used a limited time frame for biomarker sampling. The difference between results of NSE and S100B in this study may be due to differences between the time to rise of NSE and S100B protein levels after trauma. Mehta et al. reported a slower increase of NSE in comparison with S100B protein in closed head injury patients [23]. This could be related to the type of cell from which the biomarker originated: damage to the glial cells that S100B protein has been derived from occurs more extensively and rapidly than in the neuronal cells, which release NSE. As mentioned before, edema and ischemia are considered two major complications of surgically induced brain injury, in contrast to direct trauma. The previous studies on brain ischemia showed that there is an earlier increase in NSE contrasted with a delayed increase in S100B. The delayed increase in NSE supports the influence of direct trauma in surgically induced brain injury [9].

Although S100B levels were not correlated with the Barthel index in our study, there are some reports indicating their correlation [24]. On the other hand, there was a relation between the NSE levels and Barthel index, which is in agreement with the trial conducted by Wunderlich and colleagues [25]. S100B protein has more sensitivity and specificity in comparison with NSE [10,12,15]. However, it seems that the NSE level is a better predictor of long-term outcome in surgically induced brain injury.

The limitations of the study were the small sample size and limited time frame for biomarker sampling. The pathophysiology of brain injury is evolving and not completely understood. Using a single agent for neuroprotection may not be sufficient, and multiple pharmacological and physiological interventions might be needed to affect the complex pathology of brain injury.

Conclusion

This study showed the effect of magnesium on surgically induced brain injury. It seems that intravenous $MgSO_4$ before and during surgery is safe and effective in reducing S100B protein levels in patients undergoing supratentorial craniotomy for brain tumors. Further studies to elucidate the pathophysiology of brain injuries and role of magnesium are warranted.

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Conflicts of interest None.

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Comment

Magnesium is an essential electrolyte involved in several basic cellular processes including preservation of membrane integrity, protein synthesis, energy metabolism, maintenance of ionic gradients, and regulation of calcium transport. The neuroprotective effect of magnesium sulfate has been attributed to the noncompetitive NMDA receptor antagonist activity of magnesium. In addition, magnesium modulates the ischemic brain injury cascade at other levels. These include the abilities to inhibit neurotransmitter release and cerebral vasospasm, to antagonize voltage-gated calcium ion channels, and to attenuate production of reactive oxygen species. Results on the use of magnesium sulfate (MgSO4) are however controversial: magnesium administration has been demonstrated to be safe and to improve short-term postoperative neurologic function after cardiac surgery, particularly in preserving short-term memory and cortical control over brainstem functions [1]. On the other hand, even though pilot studies have suggested the possible beneficial effects of MgSO4 infusion in treating patients with aneurysmal subarachnoid hemorrhage (SAH), an up-to-date systematic review and meta-analysis showed that MgSO4 administration does not reduce delayed ischemic deficits or improve neurological outcomes [2]. This same meta-analysis of six eligible studies with 875 patients suggests that a beneficial effect cannot, however, be ruled out because of sample size limitation.

In conclusion, although MgSO4 is a promising neuroprotective drug, studies involving hundreds of patients seem necessary to unequivocally demonstrate its clinical efficacy.

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In this prospective, randomized, double-blind and placebo-controlled study, Mirrahimi and colleagues assessed the effect of intravenous magnesium administration on the functional outcome and other parameters, such as the Barthel index score or duration of hospitalization, in 60 patients undergoing supratentorial brain tumor surgery. They found that the mean arterial pressure, heart rate, bleeding volume, and required dose of propofol were significantly lower in the treatment group.

Even though there are some limitations of the study, also seen by the authors themselves, in my opinion the study design warrants publication, and the results should encourage further studies.

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