Article published online: 2022-07-20

Effects of Magnesium Sulfate on Intraoperative Blood Loss and Anesthetic Requirement in Meningioma Patients Undergoing Craniotomy with Tumor Removal: A Prospective Randomized Study

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J Neuroanaesthesiol Crit Care 2022;9:168–176.

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Abstract

Background Meningioma brain tumor is associated with significant blood loss. Magnesium (Mg), a calcium blocker, can facilitate blood pressure control during surgery. This study aimed to evaluate effects of magnesium on blood loss, anesthetic requirement, and its neuroprotective effect in meningioma patients undergoing craniotomy.

Methods Eighty patients aged between 18 and 70, American Society of Anesthesiologists physical status I and II, diagnosed with meningioma and scheduled for craniotomy tumor removal were randomized into two groups. Group M (Mg) received intravenous magnesium sulfate 40 mg/kg over 30 minutes initiated at skin incision and followed by continuous infusion of 10 mg/kg/h until dura closure. Group N (NSS) received 0.9% NaCl as placebo. Anesthesiologists in charge, surgeons, and patients were all blinded. The assessed outcomes were perioperative blood loss, anesthetic requirement, and pre- and postoperative neurocognitive functions assessed by Montreal Cognitive Assessment (MoCA).

Results Thirty-eight patients in each group were analyzed. In group M, the intraoperative blood losses were 500 (70, 2300) mL, and 510 (100, 1600) mL in group N ($p = 0.315$). Patients who received blood within 24 hours were 39.5% in group M and 47.4% in group N ($p = 0.644$). No differences were observed in anesthetic requirement, intraoperative mean arterial pressure, hypotensive episodes, and vasopressor usages. There were no significant differences in postoperative MoCA score. Magnesium levels did not exceed acceptable levels.

Conclusions Magnesium administration in meningioma patients had no significant effects on blood loss, anesthetic requirement, and postoperative cognitive function.

Keywords
- blood loss
- craniotomy
- magnesium
- meningioma

article published online
July 20, 2022

DOI https://doi.org/10.1055/s-0042-1750692.
ISSN 2348-0548.

Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

Introduction

Meningioma is the most diagnosed primary brain tumors.[1,2] Surgical excision can cause significant blood loss due to a highly vascular tumor, especially in deep-seated meningioma.[3]

Intraoperative bleeding can be reduced by good controlling of blood pressure or preventing hypertensive episodes during various surgical stimuli with various agents such as β-blockers, nitroglycerine, sodium nitroprusside, high doses of potent inhaled anesthetics, α_2 agonists, and magnesium sulfate.[4–8]

Magnesium is a calcium antagonist, acting against calcium inflows of vascular smooth muscle, leading to systemic vasodilation. Magnesium also blocks catecholamine release at adrenergic nerve endings. Magnesium has predominantly an arteriole dilatation, so it is widely used to control blood pressure in preeclampsia and pheochromocytoma.[9,10] At spinal cord and higher brain centers, magnesium antagonizes action of glutaminergic *N*-methyl-D-aspartate receptor, it has antinociceptive activity and prevention of central sensitization. So, it has been used as an adjuvant to reduce anesthetic requirement.[11] Many studies had shown effects of intravenous magnesium sulfate on decreasing intraoperative bleeding, reducing anesthetic, better pain management, less postoperative nausea and vomiting, and providing hemodynamic stability.[12,13] However, its neuroprotective effect was still inconclusive.[14–16]

The primary aim of this study was to study effects of magnesium sulfate on reducing blood loss in adult meningioma patients undergoing craniotomy with tumor removal. The secondary objective was to evaluate its effect on anesthetic requirement and neurocognitive function assessed by Montreal Cognitive Assessment (MoCA).

Materials and Methods

This randomized controlled study was conducted on 80 patients (40 patients in each group) at Siriraj Hospital, Mahidol University, Thailand, from August 2018 to February 2020. The study protocol was approved by the institutional ethics committee (SI 259/2018) and registered on clinical trials.gov (NCT03558516).

We enrolled patients aged between 18 and 70 years, American Society of Anesthesiologists grade I and II, diagnosed with supratentorial meningioma and undergoing elective craniotomy to remove the tumor. The exclusion criteria included the following conditions; preoperatively unstable hemodynamics, heart disease, liver disease with Child Pugh Score C, renal insufficiency, or an estimated glomerular filtration rate less than 60 mL/min/1.73 m^2, allergy to magnesium or any drug used in the study protocol, use of calcium channel blocker, pregnancy, having received magnesium sulfate for other conditions, a baseline serum magnesium level of more than 2.6 mg/dL, body mass index$>$ 30 kg/m^2, and impending herniation.

The patients were randomized into two groups in blocks of four by computer-generated numbers. The sequence numbers and groups were placed inside concealed envelopes, which were opened by the researchers who did not participate in patient care. On the day before surgery, informed consent was obtained and baseline neurocognitive function was measured by MoCA test by the researchers.

At the operating room, standard monitorings were used. General anesthesia was induced with propofol 1.5 to 2.0 mg/kg, fentanyl 1 to 2 μg/kg, and then cis-atracurium 0.15 mg/kg. Then, the large bore intravenous lines were accessed and the radial artery was cannulated for continuous arterial pressure monitoring. A baseline blood sampling for magnesium level was obtained (►**Fig. 1**).

Anesthesia was maintained with sevoflurane not exceeding 1 minimal alveolar concentration (MAC) with supplemental of intermittent fentanyl 0.5 to 1 μg/kg, and continuous infusion of cis-atracurium 0.06 to 0.1 mg/kg/h. If the depth of anesthesia seemed not adequate (in charge anesthesiologist's discretion) or needed brain relaxation, continuous infusion of propofol 1 to 6 mg/kg/h was administered (dose adjusted by attending anesthesiologists). Intraoperative blood pressure was kept within 20% of baseline and the vasopressors (norepinephrine and/or ephedrine) or vasodilators (nicardipine and/or labetalol) were used to control blood pressure. Ventilator was set with fraction of inspired oxygen 0.5, tidal volume 8 mL/kg with positive end expiratory pressure 5 cmH_2O, and respiratory rate was adjusted to maintain end tidal CO_2 30 to 35 mm Hg or partial pressure of carbon dioxide 35 to 40 mm Hg. Mannitol (0.5–1.0 g/kg) was given in all cases for brain relaxation. Experienced surgeons (more than 10 years) and surgical trainees worked together in all cases. In charge anesthesiologists and surgeons were blinded to patients' group allocation. Medications affecting the clotting mechanism were not used. Blood components such as fresh frozen plasma or platelets could be given if massive blood loss occurred.

Patients in group M (study group) received loading dose of 40 mg/kg of magnesium sulfate (magnesium sulfate 50%, 1 g/2 mL, Atlantic Pharmaceutical company, Hong Kong) infused in 30 minutes starting at incision followed by a continuous drip of 10 mg/kg/h until dura was sealed. The dose of magnesium came from the systematic review[13] that most studies used 30 to 50 mg/kg of Mg. Meanwhile, patients in group N (control group) received normal saline with the same amount for loading and continuous infusion. Identical infusion syringes of magnesium (Mg) and placebo were prepared and labeled by research staff who did not participate in patient's care.

Hematocrit levels were measured every 2 to 3 hours and packed red cell was transfused when hematocrit decreased below 27%. Magnesium levels were measured at the beginning and 4 hours. If magnesium level was more than 4 mg/dL, the study drug would be stopped. Intraoperative bleeding was measured by fluid in suction bottle, drapes, and soaked gauzes subtracting the amount of irrigating fluid. Fluid was administered according to good clinical practice with the aid of pulse pressure variation from invasive arterial pressure.

After the uneventful operations, the patients were extubated and transferred to the neurosurgical intensive care

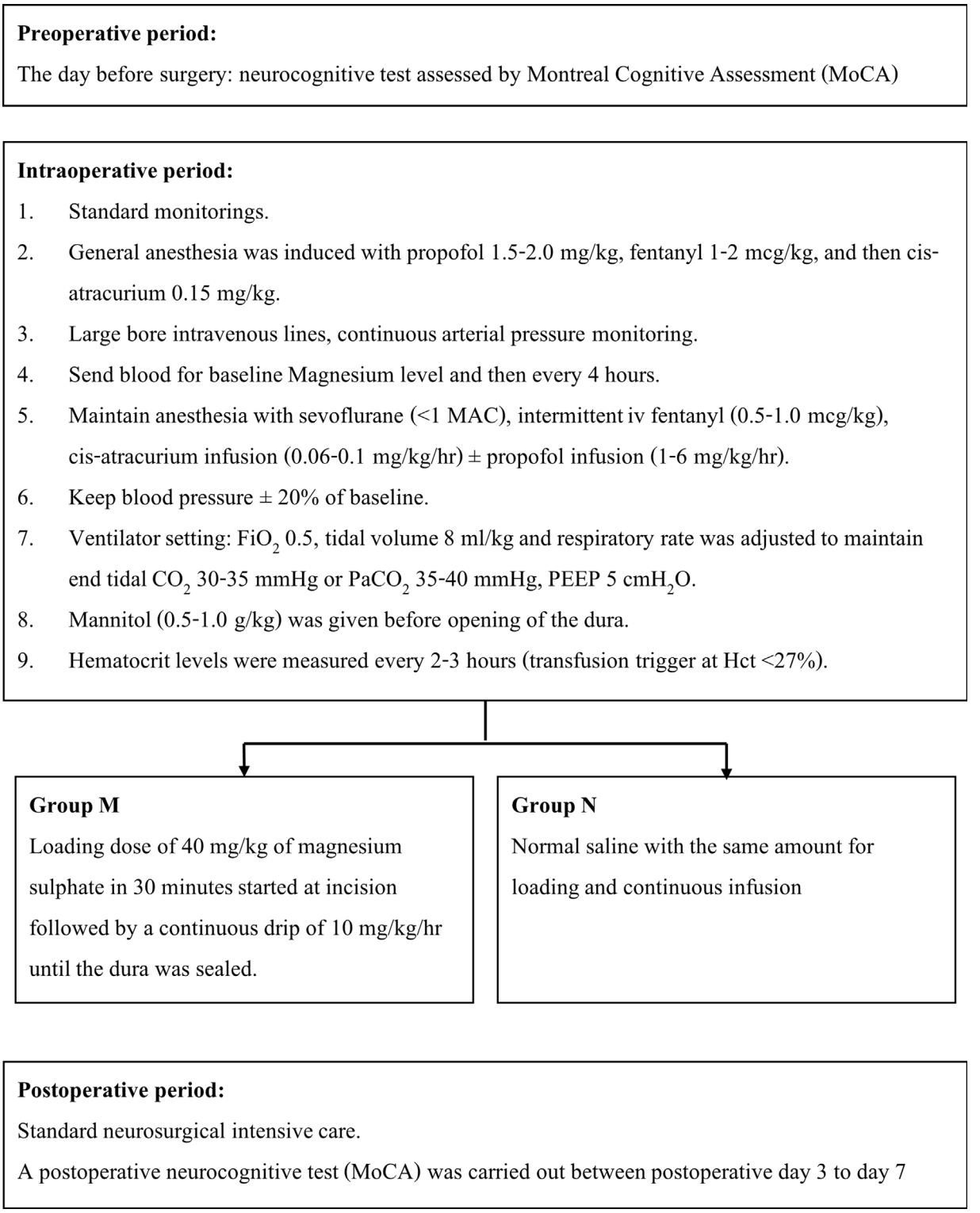

Fig. 1 Flowchart of research protocol. FiO_2, fraction of inspired oxygen; Hct, hematocrit; MAC, minimum alveolar concentration; $PaCO_2$, partial pressure of carbon dioxide; PEEP, positive end expiratory pressure.

unit. Some patients remained intubated and ventilated and the reason(s) for remaining intubation was noted.

The brain relaxation score was not applied in this study; however, the brain edema was observed and recorded.

The standard neurosurgical intensive care was applied for all cases that included vital signs measurement, neurological assessment, pain, and fluid management. In addition, routine laboratory investigations such as complete blood counts, electrolytes (Mg included), blood glucose, chest X-ray, and electrocardiography were performed on the first postoperative day. The patients were taken care of by neurosurgeons and neurointensive care nurses.

A postoperative cognitive function test (MoCA) was performed between postoperative day 3 to day 7 when the patient had the least amount of pain and was comfortable for testing.

The measured outcomes were intraoperative blood loss, mean arterial blood pressure, incidences of hypotension (systolic blood pressure [SBP] < 90 mm Hg), severe hypotension (SBP < 80 mm Hg), anesthetic requirement, perioperative complications, and MoCA score.

Sample Size Calculation

From previous studies, the intracranial meningioma resection had mean estimated blood loss at 965.2 ± 356 mL.[5] We

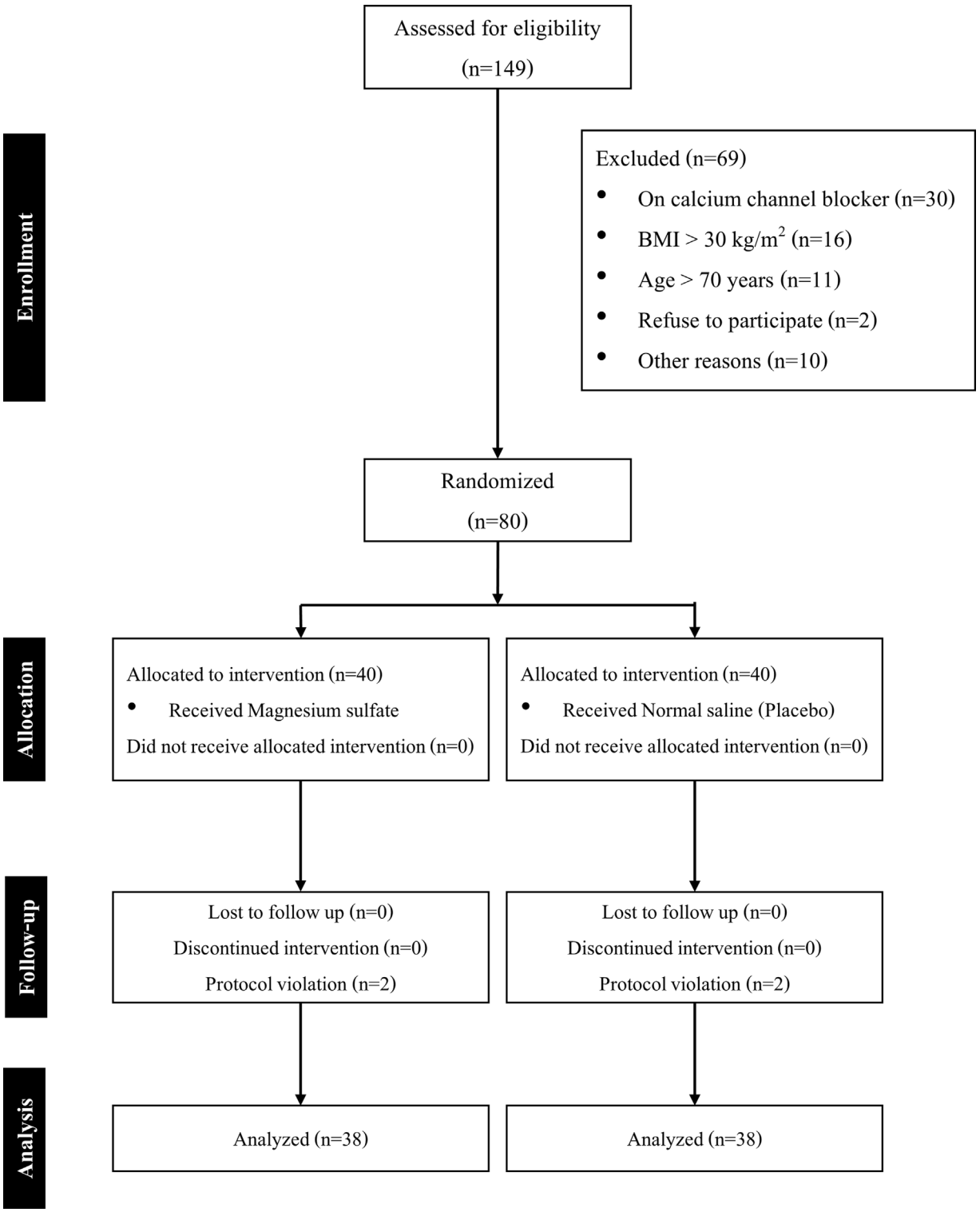

Fig. 2 Consort diagram of the study. BMI, body mass index.

expected that magnesium could reduce blood loss approximately 25% or 724 ± 356 mL, which was considered clinically significant. The sample size was calculated by nQuery program (two independent means) with α error 0.05 and study power of 80% and study population was 35 patients per group. We estimated a dropout rate of 10%, so 40 patients per group were adopted.

The collected data were analyzed by Statistical Package for the Social Sciences (SPSS) software version 18.0 (SPSS Inc., Chicago, Illinois, United States). Data were described in terms of frequencies (number and percent of cases), mean ± standard deviation, median (min, max) when appropriate. Chi-squared or Fisher's exact test was used for comparing categorical data. Student's *t*-test was used for comparing continuous data with normal distribution. Comparison of nonparametric variables was done using Mann–Whitney test. The p-value < 0.05 were considered statistically significant.

Results

Eighty patients were recruited and randomized into two groups as shown in the consort diagram (►**Fig. 2**). Two patients from each group were excluded due to protocol violation. Female patients accounted for the majority of the group (89.5%), and the mean age was around 50 years. ►**Table 1** shows that there were no differences regarding demographic data. The preoperative MoCA test was conducted in only 21 (55.3%) and 26 (68.4%) patients in group N and group M, respectively. The missing patients were attributed to visual, hearing, or writing problems. MoCA score ranges from zero to 30, and a score of 26 or higher was considered normal. In both groups, meningioma patients had mild cognitive impairment.

Intraoperative data are displayed in ►**Table 2** and it shows that surgical duration and anesthetic duration were comparable in both groups. The median (min, max) of intraoperative blood loss was 500 (70, 2300) in group M and 510 (100, 1600) in group N ($p = 0.315$).

The intraoperative mean arterial pressures (MAP) before, during, and after study drug infusion was 81 ± 11, 78 ± 8, and 82 ± 10 mm Hg in group M and 83 ± 13, 79 ± 9, and 83 ± 10 mm Hg in group N ($p = 0.469$, 0.495, 0.479), respectively. The intraoperative MAP did not differ between groups. The hypotensive, severe hypotensive episodes, use of vasopressor and vasodilators were not different. There were no significant differences regarding the total dose of propofol, cis-atracurium, fentanyl, average MAC of sevoflurane. One-third of the patients needed propofol infusion to provide brain relaxation.

The reasons for remaining intubation were severe brain edema (7.9% in each group), unstable hemodynamics (5.3% in group M and 2.6% in group N), prolonged surgery (2.6% in group M and 7.9% in group N), delayed emergence (2.6% in each group), and subdural hemorrhage (2.6% in group N). Some patients had more than one reasons for remaining intubation.

Postoperative ventilator support, neurointensive care length of stay, and hospital stay showed no differences (►**Table 3**). Most patients needed only overnight ventilator support and stayed in neurosurgical intensive care unit only 1 day. Group M had higher magnesium levels but did not reach toxic levels. No patient in this study showed signs of magnesium toxicity.

Table 1 Demographic data

Parameter	Group N ($n = 38$)	Group M ($n = 38$)	p-Value
Age (y)	52 ± 9.6	47 ± 11.0	0.051
Female	34 (89.5%)	34 (89.5%)	1.000
BMI (kg/m^2)	23.8 ± 3.6	23.3 ± 3.2	0.505
ASA I/II	25/13	22/16	0.479
Hemoglobin (g/dL)	13 ± 1.5	13 ± 1.2	0.996
Platelet count (1 × 10^3)	289 ± 63	301 ± 77	0.445
PT (sec)	11.4 ± 0.8	11.7 ± 2.5	0.393
aPTT(sec)	24.4 ± 3.0	23.6 ± 3.4	0.263
Hypertension	1 (2.6%)	7 (18.4%)	0.056
MAP baseline at ward (mm Hg)	95 ± 12	93 ± 10	0.438
Single/multiple tumor Tumor size: largest diameter (cm)	34/4 4.6 ± 2.0	33/5 3.8 ± 1.7	1.000 0.090
Recraniotomy	8 (21.1%)	10 (26.3%)	0.589
Baseline MoCA scores	21 (14, 28) ($n = 21$)	23 (11, 28) ($n = 26$)	0.120

Abbreviations: aPTT, activated partial thromboplastin time; ASA, American Society of Anesthesiologists; BMI, body mass index; MAP, mean arterial pressure; MoCA, Montreal Cognitive assessment MoCA (a score of 26 and higher considered normal); PT, prothrombin time; SD, standard deviation. Data are presented as mean ± SD, median (min, max) or number (%).

Table 2 Intraoperative data

Parameter	Group N ($n = 38$)	Group M ($n = 38$)	*p*-Value
Surgical duration (h)	4.5 ± 2.0	4.3 ± 1.5	0.640
Anesthetic duration (h)	5.9 ± 2.1	5.7 ± 1.6	0.668
Baseline magnesium level (mg/dL)	1.9 ± 0.17	2.0 ± 0.20	0.081
Magnesium level at 4 hours (mmol/L)	0.85 ± 0.11	1.45 ± 0.18	<0.001[a]
Intraoperative blood loss (mL)	510 (100, 1600)	500 (70, 2300)	0.315
Patient received PRC	10 (26.3%)	7 (18.4%)	0.409
PRC transfusion (unit)	2 (1, 4)	1 (1, 3)	0.270
Intraoperative crystalloid use (mL)	2,350 (170, 6500)	2,325 (650, 5000)	0.934
Intraoperative colloid use (mL)	0 (0, 1000)	0 (0, 500)	0.370
Urine output	2,060 ± 945	2,130 ± 714	0.718
Hypotensive episodes (times)	1.5 (0, 13)	1 (0, 9)	0.484
Severe hypotensive episodes (times)	0 (0, 4)	0 (0, 7)	0.716
Patients needed vasopressors (*n*, %)	19 (50%)	20 (52.6%)	1.000
Patients needed vasodilators (*n*, %)	12 (31.6%)	9 (23.7%)	0.609
Patient received propofol for maintenance	14 (36.8%)	12 (31.6%)	0.809
Propofol use for maintenance (mg/kg/h)	1.49 (0.4, 5.4)	1.31 (0.3, 7.2)	0.820
Sevoflurane (average MAC)	0.65 ± 0.12	0.66 ± 0.17	0.764
Fentanyl use (mcg/kg/h)	0.65 ± 0.19	0.60 ± 0.18	0.199
Cisatracurium(mg/kg/h)	0.08 ± 0.02	0.08 ± 0.01	0.828
Intraoperative brain edema	3 (7.9%)	3 (7.9%)	1.000
Extubation time (minutes)	7 (5, 15)	5 (1, 27)	0.167
Remained intubation	7 (18.4%)	5 (13.2%)	0.529

Abbreviations: MAC, minimum alveolar concentration; PRC, paced red cell; SD, standard deviation.
Data are presented as mean ± SD, median (min, max) or number (%).
[a]*p*-Value <0.05.

Postoperative complications such as hypocalcemia, hypokalemia, infection, and neurological complication were not significantly different between groups either. The neurological complications are shown in ►**Table 3**.

Discussion

Magnesium and Blood Loss

Permissive hypotension has long been used to reduce intraoperative blood loss, improve quality of surgical field, and facilitate surgery of various types such as spine surgery, endoscopic sinus surgery, middle ear surgery, and meningioma resection.[17] However, this method can potentially cause cerebral and other end-organ ischemia and might contribute to worse outcomes. On the contrary, controlling blood pressure according to the patient's baseline blood pressure is very crucial. Magnesium sulfate has been chosen to facilitate blood pressure control because of its vasodilatory effect, and its attenuating sympathetic stimulation.[9,10]

In this study, administration of intravenous magnesium sulfate during craniotomy did not show any significant reduction of intraoperative blood loss. Our result was concordant with a study by Juibari et al,[18] who compared magnesium sulfate with placebo in patients undergoing bimaxillary orthognathic surgery and found that magnesium sulfate had no significant effect on blood loss. On the contrary, Göral et al[12] demonstrated that the use of magnesium sulfate during microscopic lumbar discectomy could decrease blood loss. Another study by Elsharnouby and Elsharnouby,[4] which used magnesium during endoscopic sinus surgery, showed that blood loss was significantly reduced. The different results were probably due to the other anesthetic agents and vasoactive drugs being used to maintain blood pressure with the same acceptable levels.

Magnesium and Anesthetic Requirement

Rodríguez-Rubio et al[13] performed a systematic review and meta-analysis of 20 clinical trials to uncover the influence of magnesium sulfate on intravenous anesthetic requirements. It found that magnesium sulfate reduced the requirement of propofol, nondepolarizing neuromuscular blocking agents, and fentanyl. More recently, Walia et al[19] evaluated the propofol sparing effect of dexmedetomidine and magnesium sulfate during bispectral index targeted anesthesia. They

Table 3 Postoperative data

Parameter	Group NSS ($n = 38$)	Group Mg ($n = 38$)	*p*-Value
Ventilator support (h)	13 (2, 19)	12 (3, 86)	0.876
ICU stay (d)	0.9 (0.6, 4.8)	0.9 (0.7, 5.6)	0.655
Hospital stay (d)	8 (5, 35)	8 (4, 33)	0.417
Hemoglobin (g/dL)	11.1 ± 1.5	11.3 ± 1.4	0.685
Magnesium level (mmol/L)	0.85 ± 0.10	1.35 ± 0.15	<0.001[a]
Total patients received PRC	18 (47.4%)	15 (39.5%)	0.644
Total PRC transfusion (unit)	1 (1, 4)	1 (1, 4)	0.630
MoCA scores	22.5 (15, 28) ($n = 16$)	25 (8, 30) ($n = 21$)	0.239
MoCA differences	1.5 (−3, 5) ($n = 16$)	2 (−5, 7) ($n = 21$)	0.752
Neurological complication	10 (26.3%)	12 (31.6%)	0.613
Seizure	2 (5.3%)	0 (0%)	
Cranial nerve palsy	5 (13.2%)	3 (7.9%)	
Delirium	0 (0%)	2 (5.3%)	
Hemiparesis	2 (5.3%)	3 (7.9%)	
CSF leakage	0 (0%)	1 (2.6%)	
Diabetes insipidus	1 (2.6%)	3 (7.9%)	

Abbreviations: MoCA differences = postoperative MoCA – preoperative MoCA scores; CSF, cerebrospinal fluid; MoCA, Montreal Cognitive Assessment (a score of 26 and higher considered normal); ICU; intensive care unit, PRC, paced red cell; SD, standard deviation.
Note: Data are presented as mean ± SD, median (min, max) or number (%).
[a]*p*-Value <0.05.

noticed significantly lower propofol dose requirements compared with placebo. We did not use processed electroencephalography (EEG) to monitor depth of anesthesia. In our hospital, we do not routinely use processed EEG for meningioma resection because this brain tumor is extra-axial type and the operation is supratentorial craniotomy. For supratentorial craniotomy, sometimes the processed EEG electrodes lose their contact with the brain after scalp elevation. However, contralateral or modified position for processed EEG could have been used. Anesthesia was maintained with volatile agent base. The depth of anesthesia was easily adjusted by using end-tidal anesthetic gas and clinical monitorings. All patients were taken care of by experienced neuroanesthesiologists.

Magnesium and Neuroprotective Effect

Studies about the use of magnesium sulfate for neuroprotective effects remain controversial. For example, Mack et al[14] studied the effects of magnesium by using neuropsychometric testing in carotid endarterectomy and found less postoperative neurocognitive impairment in patients treated with low dose of magnesium therapy. However, Mathew et al[15] did not notice any significant reduction in postoperative cognitive dysfunction in patients who received magnesium intravenously during cardiac surgery. Mirrahimi et al[16] demonstrated that the biomarker of brain injuries had a significant change in the magnesium group. However, the functional clinical score was not significantly different. In this study, the MoCA score was slightly higher in the postoperative period in both groups. However, sample size was too small to draw a conclusion regarding the neuroprotective effect of magnesium. We did not use brain biomarkers because functional outcomes are more important.

Magnesium and Safety Concern

Despite the diuretic effect of mannitol, after loading dose and continuous infusion, the Mg levels were still higher than normal. These levels were lower than the suggested therapeutic range in preeclampsia women.[20,21] A recent systematic review[22] reported the patients receiving Mg as an adjuvant anesthetic had higher serum magnesium levels and no patient documented any adverse effects to magnesium.

The effects of magnesium sulfate on cerebral blood flow are controversial. However, some studies[23,24] in preeclampsia patients found a vasodilatory effect on intracerebral blood vessels after magnesium sulfate treatment. Hatab et al[25] revealed no significant difference on cerebral blood flow between pre- and postmagnesium sulfate treatment in 12 preeclampsia women. Similarly, Wong et al[26] found that magnesium sulfate administration did not have any impact on cerebral blood flow among 12 subarachnoid hemorrhage patients. There are some concerns about the vasodilating

effect of magnesium, which may result in brain swelling during operation. In our study, patients with intraoperative brain swelling or delayed emergence were similar in both groups.

Limitations

There were some limitations of this study. Postoperative management at intensive care unit was managed by neurosurgeons and blood was transfused without rigid criteria. Because of a strict research protocol, in charge anesthesiologists infrequently adjusted the doses of anesthetic agents, so the anesthetics were similar. Since we did not use processed EEG to monitor depth of anesthesia, two groups might have different depths of anesthesia. Finally, the MoCA test could not be conducted in several patients and with a relatively small sample size, we could not demonstrate the role of magnesium in preventing postoperative cognitive impairment.

Conclusions

In summary, the administration of intravenous magnesium sulfate in meningioma patients undergoing craniotomy with tumor removal could not demonstrate significant effects on intraoperative blood loss, anesthetic requirement, and postoperative cognitive dysfunction. However, there was no significant adverse event of magnesium sulfate reported in this study.

Funding
This study is supported by grant funds from Siriraj Research Development Fund, Faculty of Medicine, Siriraj Hospital, Mahidol University (R016131045). The funders had no role in study design, data collection, and analysis, decision to publish, or preparation of the manuscript.

Conflict of Interest
None declared.

Acknowledgments
The authors would like to thank Miss Julaporn Pooliam and Miss Nerisa Thornsri for statistical analysis and Miss Nichapat Thongkaew and Miss Chusana Rungjindamai for their help with administrative work.

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