

## Magnesium Sulfate Does Not Reduce Postoperative Analgesic Requirements

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**Background:** Because magnesium blocks the *N*-methyl-D-aspartate receptor and its associated ion channels, it can prevent central sensitization caused by peripheral nociceptive stimulation. However, transport of magnesium from blood to cerebrospinal fluid (CSF) across the blood-brain barrier is limited in normal humans. The current study was designed to evaluate whether perioperative intravenous magnesium sulfate infusion affects postoperative pain.

**Methods:** Sixty patients undergoing abdominal hysterectomy received 50 mg/kg intravenous magnesium sulfate as a bolus dose followed by a continuous infusion of 15 mg · kg<sup>-1</sup> · h<sup>-1</sup> for 6 h (magnesium group) or the same volume of isotonic saline (control group). At the end of surgery, serum and CSF magnesium concentration were measured in both groups. The cumulative postoperative analgesic consumption was measured to assess the analgesic effect using a patient-controlled epidural analgesia device. Pain intensities at rest and during forced expiration were evaluated at 6, 24, 48, and 72 h postoperatively.

**Results:** At the end of surgery, patients in the magnesium group had significantly greater postoperative serum magnesium concentrations compared with both preoperative and control group values (*P* < 0.001). Despite significantly higher serum magnesium concentrations in the magnesium group, there was no significant difference in magnesium concentration measured in postoperative CSF. Cumulative postoperative analgesic doses were similar in both groups. However, there was observed an inverse relation between cumulative postoperative analgesic consumption and the CSF magnesium concentration in both groups. Visual analog pain scores at rest and during forced expiration were similar and less than 4 in both groups.

**Conclusions:** Perioperative intravenous administration of magnesium sulfate did not increase CSF magnesium concentration and had no effects on postoperative pain. However, an inverse relation between cumulative postoperative analgesic consumption and the CSF magnesium concentration was observed. These results suggest that perioperative intravenous magnesium infusion may not be useful for preventing postoperative pain.

PERIPHERAL tissue injury provokes both peripheral and central sensitization. Peripheral sensitization is a reduction in the threshold of nociceptive afferent peripheral terminals, and central sensitization is an activity dependent increase in the excitability of spinal neurons.<sup>1</sup> Post-

nociceptive central sensitization has been shown to depend on activation of dorsal horn *N*-methyl-D-aspartate (NMDA) receptors by excitatory amino acid transmitters such as glutamate and aspartate.<sup>1-3</sup> Activation of NMDA receptors leads to Ca<sup>2+</sup> entry into the cell and initiates a series of central sensitization such as wind-up and long-term potentiation in the spinal cord of the responses of spinal cells to prolonged stimuli.<sup>1,3</sup> Central sensitization is usually manifested as a postinjury reduction of the pain threshold and hypersensitivity of the withdrawal reflex. Central sensitization is considered to be one of the mechanisms implicated in the persistence of postoperative pain.<sup>4</sup> These data suggest that NMDA receptor antagonists have the potential not only to abolish pain but to prevent or block central hypersensitive states.

Because magnesium acts as an antagonist at the NMDA receptor and its associated ion channels,<sup>5,6</sup> it can prevent central sensitization and abolish such established hypersensitivity. There is considerable evidence that intrathecally administered magnesium has antinociceptive effects in animals.<sup>7-9</sup> Some clinical studies<sup>10,11</sup> have demonstrated antinociceptive effects for systemically administered magnesium sulfate (MgSO<sub>4</sub>) on the assumption that magnesium acts on NMDA receptors located in the spinal cord. However, magnesium transference from blood to cerebrospinal fluid (CSF) across the blood-brain barrier (BBB) is unclear in normal humans. In addition, magnesium given intravenously does not block neuropathic pain,<sup>12</sup> nor does it reduce postoperative pain in patients.<sup>13</sup>

Therefore, the current randomized, double-blind, placebo-controlled study was designed to evaluate whether perioperative intravenous MgSO<sub>4</sub> infusion affects postoperative pain.

### Materials and Methods

Our study was approved by the human investigation committee of Chonbuk National University Hospital, and written, informed consent from each patient was obtained before the study began. Sixty patients with American Society of Anesthesiologists physical status I and II, who were undergoing elective total abdominal hysterectomy with lower midline incision, were enrolled in this study. Exclusion criteria included major hepatic, renal, or cardiovascular dysfunction, especially atrioventricular block; backache; previous treatment with opioids and calcium channel blocker; contraindications to epidural catheter insertion; and inability to use the patient-con-

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trolled analgesia device. Patients were randomly assigned to receive either isotonic saline (control) or 25%  $\text{MgSO}_4$  in a double-blind fashion.

We explained how to use the visual analog scale (0 = no pain, 10 = worst pain imaginable) for pain rating and the operational aspect of the patient-controlled analgesia pump (Walkmed; Medex, Duluth, GA) to each patient during a preoperative visit on the day before surgery. In addition, baseline values of forced vital capacity and forced expiratory volume in 1 s were obtained with a portable pulmonary function test device (Microlab 3000 series; Micro Medical Ltd., Rochester, United Kingdom). The anesthetic procedure was standardized. Three minutes before anesthesia induction, patients received 0.01 mg/kg vecuronium to prevent muscle fasciculation by succinylcholine. General anesthesia was induced with 5 mg/kg thiopental, 0.5 mg/kg esmolol, and 1.5 mg/kg succinylcholine. After anesthesia induction, preoperative serum magnesium concentration in both groups was measured by chlorophosphonazo 3 method (Cobas Integra 700; Roche, Basel, Switzerland). Magnesium concentrations are expressed in milligrams per deciliter. The normal serum magnesium range in the adult population from our laboratory is 1.7–2.2 mg/dl. Thereafter, the patients received intravenously either 25%  $\text{MgSO}_4$  (magnesium group) or the same volume of isotonic saline (control group). In magnesium group, 50 mg/kg  $\text{MgSO}_4$  as a bolus dose was followed by a continuous intravenous infusion of  $15 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$  with a syringe pump for 6 h. Standard magnesium initial bolus and maintenance doses used in the treatment of preeclamptic patients are 4–6 g and 2 g/h. Our magnesium regimen was 50–70% of that used in the preeclamptic patients. These doses were chosen in our pilot study, in which the doses adequate to keep serum magnesium concentration 200% of normal at the end of infusion were determined. The current study design of preoperative administration and a 6-h continuous infusion of magnesium was chosen to achieve preemptive effect and to cover the main period of nociceptive surgical stimulation. Anesthesia was maintained with isoflurane, and the lungs were mechanically ventilated with oxygen–air (end-tidal carbon dioxide, 34–38 mmHg). The presence of intraoperative pain was defined as an increase in heart rate and mean arterial pressure of more than 20% from preanesthetic values. In both groups, isoflurane concentration was adjusted to maintain the heart rate and mean arterial pressure within 20% of preinduction baseline values. Muscle paralysis was achieved with 0.05 mg/kg vecuronium. Because of possible enhancement of neuromuscular blockade by magnesium administration, muscle relaxation was monitored by train-of-four stimulation using a peripheral nerve stimulator (Relaxogram; Datex, Helsinki, Finland). Adequate muscle relaxation, defined as 0–2 responses of train-of-four stimulation, was maintained with additional doses of 0.01 mg/kg vecuronium.

At the end of surgery, serum magnesium concentration was measured in both groups. A 17-gauge Touhy needle (Epidural catheterization set; Arrow, Reading, PA) was introduced into the epidural space at the L3–L4 interspace using the loss-of-resistance technique with the patient in right lateral position. Through the epidural needle, a long 27-gauge Whitacre pencil point spinal needle (119 mm; Becton Dickinson, Singapore) was introduced into the subarachnoid space. After obtaining a free flow of clear CSF, a 1-ml sample was collected for measurement of magnesium concentration, and the spinal needle was then withdrawn. A 19-gauge epidural catheter was inserted 4–5 cm into the epidural space *via* the epidural needle, which was subsequently removed. Intravascular or subarachnoid placement of the epidural catheter was ruled out by confirming that no blood or CSF was aspirated. After surgery, antagonism of neuromuscular blockade was achieved with 10–15 mg pyridostigmine and 0.4 mg glycopyrrolate.

When the patients complained of pain in the postanesthesia care unit, an epidural test dose of 6 ml of 1% lidocaine containing 5  $\mu\text{g/ml}$  epinephrine (1:200,000) was injected through the epidural catheter. Thereafter, each patient was equipped with a patient-controlled analgesia device for 72 h. An analgesic solution of 0.05% bupivacaine and 5  $\mu\text{g/ml}$  fentanyl was given to all patients. Initial patient-controlled epidural analgesia settings were a demand bolus dose of 4 ml with no background infusion and lockout interval of 10 min. All patients were transferred from the postanesthesia care unit to the surgical ward 6 h after surgery.

Pain intensities at rest and during the forced expiration were evaluated using a visual analog scale at 6, 24, 48, and 72 h postoperatively. The number of analgesic demands and cumulative postoperative analgesic consumption were checked to assess the analgesic effect. Postoperative percentage recovery of forced vital capacity and forced expiratory volume in 1 s were assessed at each time point using a portable pulmonary function test device. Side effects such as hypotension, bradycardia, nausea, vomiting, urinary retention, pruritus, somnolence, postdural puncture headache, and respiratory depression were recorded.

#### *Statistical Analysis*

We conducted a double-blind pilot study of patient-controlled epidural analgesia using identical settings and analgesic solution concentration. With regard to this study after power analysis, a sample size of 29 patients per group was needed to detect a minimum 20% difference in analgesic consumption. Differences between groups were analyzed using a Student *t* test for comparisons of continuous variables such as demographic data, magnesium concentrations, and analgesic consumption. Linear regression was used to determine the relation between CSF magnesium concentration and cumulative

**Table 1. Demographic Data for the Two Groups**

	Control Group	Magnesium Group
Number (n)	29	29
Age (yr)	42.9 ± 4.8	44.2 ± 6.3
Height (cm)	156.5 ± 5.1	155.7 ± 5.2
Weight (kg)	58.4 ± 6.7	56.7 ± 7.2
Duration of surgery (min)	113.0 ± 21.1	109.3 ± 23.2
Intraoperative isoflurane concentration (vol%)	2.0 ± 0.3	2.0 ± 0.2
Time from initial magnesium administration to skin incision	10.1 ± 4.6	11.3 ± 4.3
Intraoperative vecuronium (mg/kg)	0.11 ± 0.02	0.08 ± 0.01*

Values are mean ± SD.

\*  $P < 0.05$  versus control group.

analgesic consumption. Difference between regression lines was analyzed using a  $z$  test. Ordinal data, like visual analog scale scores, were analyzed using the Mann-Whitney U test at each time period. Values are expressed as mean ± SD. A  $P$  value  $< 0.05$  was considered statistically significant.

## Results

Sixty women were enrolled in the study. Data from two patients were not included in the analysis. One patient in the magnesium group complained of an allergic reaction to the adhesive tape on her skin and required withdrawal of the epidural catheter. In the other patient in the control group, the epidural catheter was accidentally withdrawn. The two groups with the remaining 58 patients completed the 72-h follow-up data with adequate pain relief. Patient characteristics, duration of surgery, time from the initial magnesium administration until the start of operation, and intraoperatively administered isoflurane concentration were similar in the two groups. However, analysis of intraoperative doses of vecuronium revealed that patients in the magnesium group used significantly ( $P < 0.01$ ) less than those in the control group (table 1), and no patients had difficulty in reversal of neuromuscular blockade at the end of the operation. In the magnesium group, the mean magnesium dosage was  $8,038 \pm 925$  mg.

Preoperative magnesium serum concentrations were similar in both groups. At the end of surgery, patients from the control group significantly decreased serum magnesium concentrations compared with preoperative values ( $P < 0.001$ ). In the magnesium group, the patients had significantly greater serum magnesium concentrations after surgery compared with preoperative and control group values ( $P < 0.001$ ). All patients in the magnesium group showed an increase in serum magnesium, and all had a value greater than the upper limit of the normal range. Despite the serum magnesium con-

**Table 2. Magnesium Concentration in Serum and Cerebrospinal Fluid (CSF)**

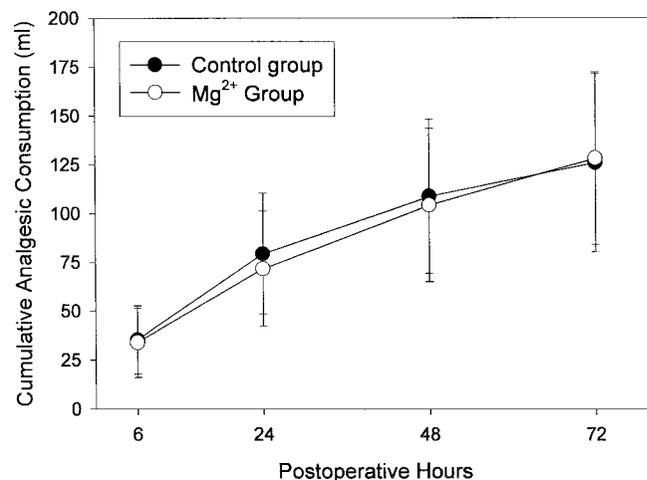
	Control Group	Magnesium Group
Pretreatment serum magnesium concentration (mg/dl)	1.91 ± 0.26	1.96 ± 0.20
Posttreatment serum magnesium concentration (mg/dl)	1.65 ± 0.26*	3.51 ± 0.42*†
Posttreatment CSF magnesium concentration (mg/dl)	2.67 ± 0.44	2.79 ± 0.43

Values are mean ± SD.

\*  $P < 0.001$  versus pretreatment value. †  $P < 0.001$  versus control group.

centrations of the magnesium group being significantly higher than the control group, there was no significant difference in the magnesium concentration measured in the CSF at the end of the operations (table 2). The average heart rates in the control and magnesium groups at preinduction, during operation, and in the recovery room were  $74.8 \pm 5.5$  versus  $73.3 \pm 5.6$ ,  $76.1 \pm 10.3$  versus  $74.2 \pm 10.6$ , and  $76.1 \pm 11.3$  versus  $75.1 \pm 8.5$  beats/min, respectively. The average mean arterial pressure in the control and magnesium groups were  $93.4 \pm 8.0$  versus  $91.3 \pm 7.6$ ,  $95.9 \pm 12.5$  versus  $94.4 \pm 10.4$ , and  $95.0 \pm 8.6$  versus  $94.1 \pm 6.9$  mmHg, respectively. There was no significant difference in average heart rate and mean arterial pressure between the two groups in each period.

Cumulative postoperative analgesic doses were similar in both groups (fig. 1). We observed an inverse relation between cumulative postoperative analgesic consumption and the CSF magnesium concentration in the control ( $y = 231 - 43 \times x$ ,  $r = 0.372$ ,  $P < 0.05$ ) and



**Fig. 1.** Cumulative patient-controlled epidural analgesic consumption (mean ± SD) in patients with abdominal hysterectomy 6, 24, 48, and 72 h after surgery. "Cumulative" represents the sum of the mean volumes of analgesic consumption for each group over time. Patients in the Mg<sup>2+</sup> group received 50 mg/kg intravenous MgSO<sub>4</sub> as a bolus dose followed by a continuous infusion of 15 mg · kg<sup>-1</sup> · h<sup>-1</sup> for 6 h, and patients in the control group received the same volume of isotonic saline. There was no significant difference in both groups at each time.

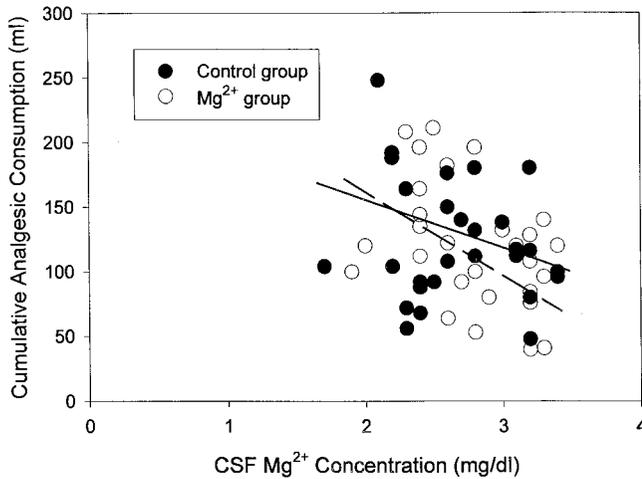


Fig. 2. The relation between cumulative postoperative analgesic consumption and cerebrospinal fluid (CSF) magnesium concentrations in both groups. There is an inverse relation between cumulative postoperative analgesic consumption and the CSF magnesium concentration in the control (solid line) and magnesium (dashed line) groups (control group:  $y = 231 - 43 \times x$ ,  $r = 0.372$ ,  $P < 0.05$ ; magnesium group:  $y = 289 - 64 \times x$ ,  $r = 0.651$ ,  $P < 0.05$ ). There was no significant difference between regression lines in both groups.

magnesium groups ( $y = 289 - 64 \times x$ ,  $r = 0.651$ ,  $P < 0.05$ ) (fig. 2). However, there was no correlation between pain scores and CSF magnesium concentrations in both groups. The numbers of valid and invalid (analgesic was not delivered) demands for the total study period were  $31.5 \pm 11.3$  and  $44.4 \pm 53.2$  in the control group and  $31.5 \pm 12.0$  and  $42.9 \pm 73.5$  in the magnesium group, respectively. Visual analog pain scores at rest and during forced expiration were similar and less than 4 in both groups during the time of each examination (fig. 3). The percentage recovery of pulmonary function as determined by forced vital capacity and forced expiratory volume in 1 s showed no significant differences in both groups at each measurement (fig. 4).

Eight patients, two in the control group and six in the magnesium group, complained of nausea during the 24 h after surgery, and one patient from each group vomited. This was treated with 10 mg metoclopramide. Four patients in the control group and three in the magnesium group complained of lower back pain. Urinary retention after removal of the urinary catheter at postoperative 24 h was observed in one patient in the magnesium group. No patients complained of neurologic complications and developed pruritus, postdural puncture headache, hypotension (systolic blood pressure  $< 25\%$  below the preoperative value), bradycardia (heart rate  $< 60$  beats/min), or respiratory depression (respiratory rate  $< 8$  breaths/min).

## Discussion

The principal findings of this investigation are that the perioperative intravenous administration of  $MgSO_4$  did

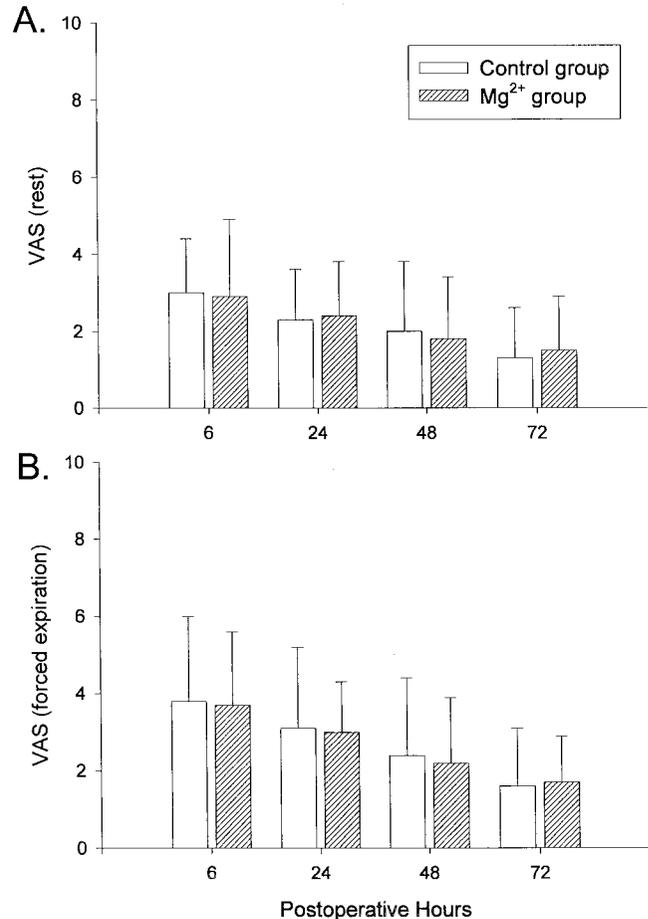


Fig. 3. Pain scores at rest (A) and during forced expiration (B) as determined using a visual analog scale (VAS). Pain scores are presented as mean  $\pm$  SD. Pain scores at rest and during forced expiration were similar and less than 4 in both groups at the time of each examination, indicating that patients from both groups self-administered a dosage to achieve a subjectively comfortable level of analgesia with the patient-controlled epidural analgesia device.

not increase CSF magnesium concentration and had no effect on postoperative pain, and that an inverse relation exists between CSF magnesium concentration and cumulative postoperative analgesic consumption. This is the first clinical report to show the relation between CSF magnesium concentration and postoperative analgesic requirement.

Intense or repeated noxious stimulation causes release of excitatory amino acids such as glutamate and aspartate in the dorsal horn. The actions of the excitatory amino acids are mediated by NMDA and non-NMDA receptors.<sup>1-3</sup> Activation of NMDA receptor leads to  $Ca^{2+}$  entry into the cell and initiates a series of central sensitization such as wind-up and long-term potentiation in the spinal cord in the responses of cells to prolonged stimuli.<sup>1,3</sup> Central sensitization has an important role for pain perception and is considered to be one of the mechanisms implicated in the persistence of postoperative pain.<sup>4</sup> NMDA antagonists such as ketamine<sup>12,14,15</sup>

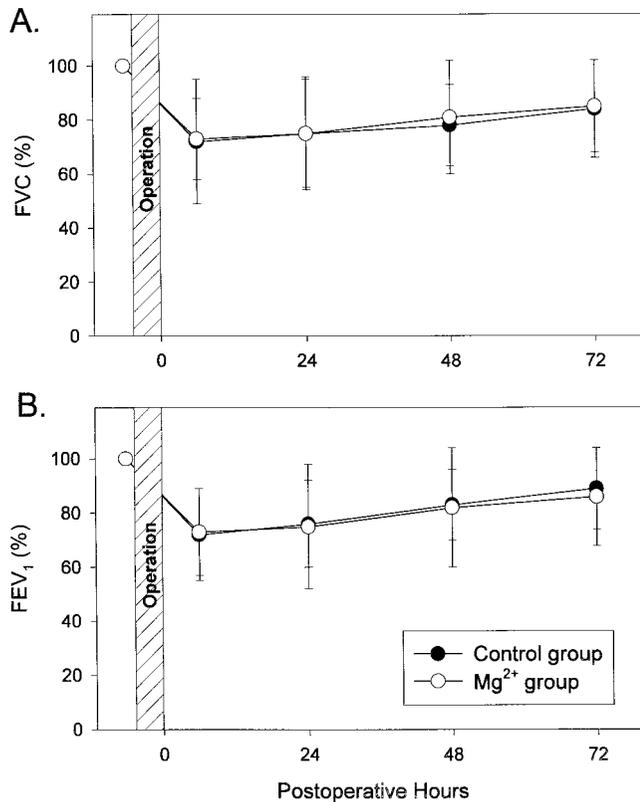


Fig. 4. Percentage recovery of pulmonary function as determined by forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV<sub>1</sub>). There were no significant differences between the two groups at each time.

and MK801<sup>16,17</sup> have the potential to prevent the induction and maintenance of central sensitization. Magnesium acts as an antagonist at the NMDA receptor and its associated ion channels.<sup>5,6</sup> Therefore, theoretically, magnesium could modulate postoperative pain by preventing nociception-associated central sensitization *via* blockade of NMDA-receptor calcium inophore. However, the results regarding intraoperative and postoperative analgesia after magnesium supplementation are contradictory. Although some investigators<sup>10,11</sup> could observe a decreased analgesic requirement after perioperative MgSO<sub>4</sub> administration, others,<sup>13</sup> including us, could not confirm this observation.

Two earlier clinical studies<sup>10,11</sup> showed the results that perioperative magnesium administration led to a significant reduction of analgesic consumption. In these studies, however, fentanyl was given for intraoperative analgesia, unlike our study. Although the exact mechanism of the interaction between the NMDA receptor complex and opioid antinociception has not been fully elucidated, magnesium supplement potentiated the analgesic effect of opioids and delayed the development of tolerance.<sup>7,9</sup> In addition, antinociceptive effects of magnesium in these studies were minimal at early postoperative periods compared with other NMDA antagonists such as ketamine.<sup>14,15</sup> In addition, these studies did not measure

magnesium concentration in CSF despite antinociceptive effects of magnesium, assuming that intravenously administered magnesium blocked the NMDA receptor in the spinal cord.

Magnesium concentration in CSF was significantly greater than in plasma, and CSF magnesium concentrations tended to remain stable in the face of changing plasma concentration.<sup>18,19</sup> Although serum magnesium concentration was significantly reduced in the control group and the serum magnesium concentration of the magnesium group was more than 200% greater than that of the control group, the CSF magnesium concentrations were similar between the two groups. This result suggests that intravenously administered magnesium cannot pass to CSF through the BBB even though CSF magnesium concentrations were not compared from dependent samples in each group.

Cerebral and spinal cord ischemia can result in excessive amino acid neurotransmitter release such as glutamate and aspartate.<sup>20-23</sup> The NMDA receptor, when stimulated by these excitatory amino acid neurotransmitters, opens the voltage-operated calcium channel, thereby allowing massive influx of calcium ions into the cell.<sup>24,25</sup> Because magnesium not only blocks NMDA receptor and calcium channels but also enhances buffering of intracellular calcium ions, magnesium may act as a neuroprotective agent. Magnesium has been reported to improve neurologic outcome in a variety of experimental models of brain<sup>26,27</sup> and spinal cord injury.<sup>28,29</sup> Many studies<sup>26-28,30-32</sup> suggested increased plasma magnesium passes the BBB and acts on the central nervous system. In addition, a small amount of magnesium crosses the BBB in patients with preeclampsia undergoing magnesium therapy.<sup>33</sup> However, we believe that increased plasma magnesium is easily transferred to the CSF because the BBB of patients with CNS injuries or preeclampsia may be impaired. The BBB of normal humans may be different from patients with CNS injuries or preeclampsia.

Despite the prolonged duration of the magnesium infusion in our study, no clinical analgesic effects were observed. We think there are three main possible causes that magnesium had no antinociceptive effect. First, the lack of effect may have been caused by insufficient magnesium dosage even though the serum magnesium concentration measured in this study was higher than 200% of normal range. Dose-response studies for intravenous magnesium and its possible increment on CSF magnesium concentration are rare in normal humans. If greater doses are administered intravenously, does CSF magnesium concentration increase? Currently, the answer for this question is unknown. However, although magnesium was known as a central nervous system depressant, intravenous MgSO<sub>4</sub> failed to induce sleep in healthy volunteers even when administered at magnesium serum concentrations 10 times higher than nor-

mal.<sup>34</sup> It is suggested that magnesium penetrates the BBB poorly despite serum concentration being much higher than normal, and its concentration in the CSF is well controlled.<sup>18,19</sup> Problems could occur perioperatively after an increase in serum magnesium concentrations, such as an intensified action of muscle relaxants, vasodilatation, cardiac conductivity disorders, or gastric hypomotility. Therefore, although magnesium may have antinociceptive effects, the use of large doses of magnesium as an analgesic is limited by serious side effects. The second possible cause of no clinical analgesic effects being observed is the effect of NMDA receptor antagonists on postoperative pain. Recently, studies in an animal model of postoperative pain<sup>35,36</sup> showed that NMDA antagonists did not modify nociception and suggested that NMDA receptors do not play an important role in the maintenance of postoperative pain. These studies<sup>35,36</sup> have indicated that the receptor mechanism involved in postoperative hyperalgesia related more to the non-NMDA receptor than the NMDA receptor. As the investigators mention,<sup>36</sup> however, further studies may be necessary to discover why NMDA receptor antagonism did not affect postoperative pain in an animal model.

There are limitations to our study design. First, we performed lumbar puncture and epidural catheterization during general anesthesia, which increases the potential for nerve injury because of patients' inability to complain about pain from needle trauma or intraneural injection. Lumbar puncture and epidural catheterization were performed by one expert anesthesiologist, and no patients complained of neurologic complications related to lumbar puncture and epidural catheterization. Second, magnesium concentration in the CSF was measured only once at end of surgery because frequent CSF sampling by lumbar puncture or intrathecal catheterization is more invasive. Therefore, we did not compare CSF magnesium concentration in dependent samples in each group. Third, analgesic consumption and pain scores were used as measures of postoperative central sensitization mediated by the NMDA receptor. Analgesic consumption and pain score at rest were correlated with primary hyperalgesia caused by increased responsiveness of primary afferent nociceptors (peripheral sensitization).<sup>37</sup> Pain score during forced expiration was measured as a movement-related pain, which might be more sensitive to altered sensory processing, although this is speculative. However, the role of hyperalgesia in postoperative pain is not fully understood.

In summary, perioperative intravenous administration of MgSO<sub>4</sub> in our dose did not increase CSF magnesium concentration and had no effects on postoperative pain. However, there was an inverse relation between cumulative postoperative analgesic consumption and CSF magnesium concentration. These results suggest that the CSF magnesium concentration affects postoperative

pain, but perioperative intravenous magnesium administration had no analgesic effects. To fully explore these results concerning postoperative pain and clinical outcomes, further studies about the relation between CSF magnesium concentration and serum magnesium concentration and the relation between CSF magnesium concentration and antinociceptive effects of magnesium are needed.

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