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# *Intravenous Magnesium Sulfate Administration Reduces Propofol Infusion Requirements during Maintenance of Propofol–$N_2O$ Anesthesia*

## *Part I: Comparing Propofol Requirements According to Hemodynamic Responses*

## *Part II: Comparing Bispectral Index in Control and Magnesium Groups*

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***Background:*** **The authors investigated whether an intravenous administration of magnesium sulfate reduces propofol infusion requirements during maintenance of propofol–$N_2O$ anesthesia.**

***Methods:*** **Part I study: 54 patients undergoing total abdominal hysterectomy were randomly divided into two groups (n = 27 per group). The patients in the control group received 0.9% sodium chloride solution, whereas the patients in the magnesium group received magnesium (50 mg/kg as a bolus, then 8 mg · kg$^{-1}$ · h$^{-1}$). To maintain mean arterial blood pressure (MAP) and heart rate (HR) at baseline value, the propofol infusion rate was changed when the MAP or the HR changed. The amount of propofol infused excluding the bolus dosage was divided by patient's body weight and total infusion time. Part II study: Another 20 patients were randomly divided into two groups (n = 10 per group). When the MAP and HR had been maintained at baseline value and the propofol infusion rate had been maintained at 80 μg · kg$^{-1}$ · min$^{-1}$ (magnesium group) and 160 μg · kg$^{-1}$ · min$^{-1}$ (control group), bispectral index (BIS) values were measured.**

***Results:*** **Part I: The mean propofol infusion rate in the magnesium group (81.81 ± 13.09 μg · kg$^{-1}$ · min$^{-1}$) was significantly less than in the control group (167.57 ± 47.27). Part II: BIS values in the control group (40.70 ± 3.89) were significantly less than those in the magnesium group (57.80 ± 7.32).**

***Conclusion:*** **Intravenous administration of magnesium sulfate reduces propofol infusion requirements. These results suggest that magnesium administration may have an effect on anesthesia or analgesia and may be a useful adjunct to propofol anesthesia.**

THE magnesium ion blocks the ion channel of the *N*-methyl-D-aspartate (NMDA) receptor in a voltage-dependent fashion.[1] Also, increased extracellular magnesium concentrations *in vitro* cause a noncompetitive NMDA blockade.[2] Several studies have shown that intrathecal administration of magnesium sulfate alone produced a small degree of antinociception or no antinociception but resulted in potentiated antinociception when magnesium was coadministered intrathecally with morphine.[3,4] Our recent work has demonstrated that magnesium sulfate potentiated the analgesic effect of bupivacaine when coadministered intrathecally with bupivacaine in rats.[5] Also, some studies have reported that perioperative administration of intravenous magnesium sulfate reduced intra- and postoperative analgesic requirements in patients undergoing arthroscopic knee surgery or elective abdominal hysterectomy.[6,7] In one of the studies, when the propofol infusion rate was held constant and the fentanyl dose was adjusted to hemodynamic endpoints, opioid requirements were reduced.[6] This result suggests that the effect of magnesium on anesthesia should be studied further. Accordingly, we investigated whether intravenous administration of magnesium sulfate reduces propofol infusion requirements during maintenance of propofol–$N_2O$ anesthesia.

## Methods

### *Part I Study*

After approval from our ethics committee and obtaining informed patient consent, 62 patients with an American Society of Anesthesiologists (ASA) physical status of I or II who were undergoing general anesthesia for elective total abdominal hysterectomy were randomly divided into two groups (n = 31 per group). In a double-blind fashion, the patients in the control group received 0.9% sodium chloride solution, whereas the patients in the magnesium group received magnesium sulfate. Exclusion criteria included major organ dysfunction, atrioventricular block, hypertension, obesity, old age, hypnotic or analgesic use, or previous treatment with a calcium channel blocker. Glycopyrrolate, 0.004 mg/kg, was administered as preoperative premedication. When the patients arrived in the operating room, baseline

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

| | Control Group | Magnesium Group | *P* Value |
|---|---|---|---|
| Number (n) | 27 | 27 | |
| Age (yr) | 41.41 ± 3.51 | 43.44 ± 4.31 | 0.0624 |
| Weight (kg) | 57.57 ± 7.03 | 57.84 ± 7.51 | 0.8948 |
| Duration of surgery (min) | 124.19 ± 22.10 | 142.70 ± 21.42 | 0.0029 |
| Intraoperative vecuronium (mg/kg) | 0.15 ± 0.03 | 0.18 ± 0.03 | 0.0009 |

Values are mean ± SD.

mean arterial blood pressure (MAP) and heart rate (HR) were measured before anesthesia induction and thereafter every 5 min. Before propofol administration, the patients in both groups received 1 mg/kg lidocaine, 1%, intravenously. Lidocaine was administered to reduce pain caused by the injection of propofol and stimuli during orotracheal intubation. Before intubation, patients in both groups received 2 mg/kg propofol as a bolus followed by continuous infusion of 8 $mg \cdot kg^{-1} \cdot h^{-1}$. After the induction of anesthesia with propofol, the magnesium group received 50 mg/kg magnesium sulfate slowly administered intravenously as a bolus (before intubation) and magnesium infused continuously at the rate of 8 $mg \cdot kg^{-1} \cdot h^{-1}$ during the entire anesthesia period.[6] In the control group, 0.9% sodium chloride solution was administered instead of magnesium sulfate, and the volume administered in the control group was the same as the magnesium group. After orotracheal intubation with the help of 0.1 mg/kg vecuronium, anesthesia was maintained with 40% $O_2$–60% $N_2O$–propofol. During anesthesia, noninvasive arterial pressure monitoring, finger pulse oximetry, electrocardiography, end-tidal carbon dioxide concentration, concentrations of end-tidal anesthetic gases, and train-of-four responses were monitored. An increase of the MAP and HR was interpreted as an intraoperative pain sensation.[6] To maintain the MAP and HR at a baseline value, the propofol infusion rate was increased when the MAP and HR increased more than 10% of baseline. The propofol infusion rate was decreased when the MAP decreased to more than 10% of baseline. If the MAP and HR were not controlled by the aforementioned methods or if the systolic pressure sharply increased to more than 200 mmHg, diltiazem or hydralazine was administered. Patients who received the antihypertensive agents were excluded from this study. The amount of propofol infused excluding the bolus dosage was divided by the patient's body weight and total propofol infusion time. In each patient, $\mu g \cdot kg^{-1} \cdot min^{-1}$ indicates unit of mean propofol infusion rate during the entire infusion period. In the intraoperative period, baseline intravenous infusion rate of lactated Ringer's solution was set at 6 $ml \cdot kg^{-1} \cdot h^{-1}$ in both groups, but additional solutions were infused if required (requirements were set at urine output of less than 1 $ml \cdot kg^{-1} \cdot h^{-1}$ or blood loss). Blood samples for determination of serum magnesium concentration were obtained before administering the study drug and in the postanesthesia care unit (when patients arrived in the postanesthesia care unit) for patients in both groups. Muscle relaxation was monitored by train-of-four stimulation. When train-of-four responses were more than two responses of train-of-four stimulation or muscle relaxation was inadequate for surgery, an additional bolus of 0.01 mg/kg vecuronium was administered until closure of the peritoneum.

*Part II Study*

As the Part I study was performed solely according to hemodynamic responses, after completing the Part I study, we decided to determine whether different mean propofol infusion rates obtained from both groups in the Part I study resulted in identical or different bispectral index (BIS) values. Another 20 patients not included in the Part I study were randomly divided into two groups (n = 10 per group). Methods used were identical to the Part I study. After the onset of the operation, when the MAP and HR had been maintained at baseline value and the propofol infusion rate had been maintained at 80 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (for magnesium group) and 160 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (for control group) for more than 10 min (80, 160: approximate mean values obtained from each group in the Part I study), the BIS values were measured.

*Statistical Analysis*

Statistical analysis using Student *t* test and paired *t* test (Part I study) and the Wilcoxon signed-rank test (Part II study) was done with the SAS statistical package (version 6.12; SAS Institute, Cary, NC) . An overall *P* value of less than 0.05 was considered significant.

## Results

*Part I Study*

Because of exclusion of 4 patients who received the antihypertensive agents in each group, 54 patients (n = 27 in each group) were included in the study. Age and body weight did not differ between the two groups. Duration of surgery for the control group was shorter than for the magnesium group (table 1). Preoperative serum magnesium concentrations were compared with postoperative serum magnesium concentrations (24 pa-

tients in each group; 3 patients in each group were excluded because of a technical problem in sampling the blood). In the control group, serum magnesium concentrations significantly decreased from 2.48 ± 0.30 to 2.10 ± 0.48 (mean ± SD) mg/dl (normal serum magnesium concentration, 1.9–3.1 mg/dl). In the magnesium group, serum magnesium concentrations significantly increased from 2.44 ± 0.24 to 3.30 ± 0.39 mg/dl.

The propofol infusion rate for the control group was 167.57 ± 47.27 $\mu g \cdot kg^{-1} \cdot min^{-1}$, whereas the propofol infusion rate for the magnesium group was 81.81 ± 13.09 $\mu g \cdot kg^{-1} \cdot min^{-1}$. The mean propofol infusion rate for the magnesium group was significantly less than for the control group.

The amount of vecuronium administered for the control group was significantly less than for the magnesium group (table 1).

*Part II Study*

The demographic data did not differ between the two groups (age [yr], 43.70 ± 6.48 [control group] *vs.* 44.90 ± 7.20 [magnesium group]; body weight [kg], 59.95 ± 6.44 [control group] *vs.* 57.50 ± 5.28 [magnesium group]). The BIS values in the control group were 40.70 ± 3.89, whereas the values in the magnesium group were 57.80 ± 7.32. BIS values in the control group were significantly less than those in the magnesium group.

## Discussion

*Part I Study*

Magnesium sulfate is an antagonist of the NMDA receptor. When tested by tail clamp technique, intravenous administration of magnesium in rats reduces halothane minimum alveolar concentration in a dose-dependent manner.[8] Many NMDA antagonists (ketamine, phencyclidine, MK-801/dizolcipine, CGS19755, D-CPP-ene) also reduce the minimum alveolar concentration for other anesthetic agents (halothane, isoflurane, and others) *in vivo*.[9] The exact mechanism of propofol action has not yet been fully elucidated. But, evidence suggests that the action of propofol is to promote the function of the $\beta_1$ subunit of γ-aminobutyric acid (GABA) through activation of the chloride channel and thereby enhance the inhibitory synaptic transmission. Propofol also inhibits the NMDA subtype of the glutamate receptor. This action may also contribute to the inhibition of the excitatory synaptic transmission. Inhibition of NMDA-mediated excitatory neurotransmission may contribute to the anesthetic, amnesic, and anticonvulsant properties of propofol.[10] Therefore, the aforementioned action mechanisms suggest that magnesium sulfate when coadministered with propofol potentiates anesthetic effects and NMDA antagonism of propofol.

One study has reported that when magnesium sulfate was administered intravenously to preeclamptic gravid women (6 g loading dose followed by a 2 g/h maintenance dose), cerebrospinal fluid magnesium concentrations were highly correlated with serum magnesium concentrations. These results suggest that a small amount of magnesium sulfate crosses the blood-brain barrier.[11] Another study has showed that a bolus of 60 mg/kg $MgSO_4$ in neurosurgical patients leads to a significant increase in the cerebrospinal fluid magnesium concentration at least 90 min after the bolus injection. In that study, 4 of 20 patients included underwent resection of microadenoma of the pituitary gland, an extradural pathology not affecting blood-brain barrier function. In these patients, an increase in cerebrospinal fluid magnesium concentration was similar to that observed in the remaining 16 patients.[12] Serum magnesium concentrations decrease after major surgery.[13] In our present study, serum magnesium concentrations also decreased after surgery in the control group. These results suggest that magnesium administration may exert an antinociceptive effect *via* blockade of the NMDA receptor complex or a nonspecific effect *via* prevention of hypomagnesemia.

In rats, painful natural stimulus (when the tissue is squeezed rapidly with a large needle holder with force that is intense enough to crush metatarsal and tarsal bones in the hind paw) induces an immediate and highly significant increase in arterial blood pressure and HR despite full surgical anesthesia.[14] In rats, intrathecal administration of the NMDA receptor antagonist [D-AP5 (D(-)-2-amino-5-phosphonovaleric acid)] inhibits the nociceptive input and reduces the increase of the blood pressure during tetanus in surgical anesthesia.[15] The MAP and HR can be used as indicators of pain in full surgical anesthesia. In anesthesia practice, anesthesiologists interpret increases of the MAP and HR as the onset of pain.[16,17] In our present study, therefore, increases in the MAP and HR were interpreted as intraoperative pain sensation.[6] But, because the MAP and HR can change for other reasons (for example, hypertension), only patients with an ASA physical status of I or II were included in the study sample. Patients with hypertension were excluded.

The amount of vecuronium administered for the control group was significantly less than for the magnesium group. This may be the result of a lower mean infusion rate of propofol in the magnesium group. Because of short duration of surgery in three patients in the control group (74, 95, and 95 min) and long duration of surgery in three patients in the magnesium group (177, 180, and 192 min), there was a difference in duration of surgery between the two groups. When these six patients were excluded from the data analysis of this study, no significant difference was found between the two groups for duration of surgery. When these six patients were excluded from the analysis, the amount of vecuronium

administered for the control group (0.16 ± 0.03) was significantly less than for the magnesium group (0.18 ± 0.04). Also with the exclusion of these six patients, the propofol infusion rate in the control group was 168.41 ± 39.82 $\mu g \cdot kg^{-1} \cdot min^{-1}$, whereas the propofol infusion rate in the magnesium group was 83.33 ± 13.05 $\mu g \cdot kg^{-1} \cdot min^{-1}$. These results do not differ from results obtained when these six patients were included.

Recognition of the multietiologic nature of pain suggests that no ideal analgesic for all types of pain is likely to be found. For some types of pain, where the efficacy of existing therapies is relatively high (*e.g.*, opioids for perioperative pain or nonsteroidal antiinflammatory drugs for inflammatory pain), the need for new drugs is dictated by side-effect liabilities.[18] If magnesium sulfate potentiates the anesthetic or analgesic effect of other anesthetic or analgesic agents when coadministered intravenously, the administration of magnesium sulfate may reduce the amount of other anesthetic or analgesic drugs required.

*Part II Study*

There are at least two components to a satisfactory anesthetic state in the paralyzed patient. The first component is amnesia. The second component is the attenuation of autonomic responses to noxious stimulation.[19] We think that the anesthesia depth in our experiment satisfied these two components. According to a previous study,[20] at the mean BIS values of 57 observed in magnesium group and 40 in control group of our study, there is a very low probability of recall or consciousness. When more than 6 h after magnesium administration had passed and the patients' mental state was alert, they were asked to tell if they had any memory about events from induction of anesthesia to emergence. In all patients, there was no memory about events after induction of anesthesia up until emergence; however, a mean BIS value of 40 in the control group implies that to suppress hemodynamic responses during a total abdominal hysterectomy, the propofol has to be infused to a level that induces deep hypnosis.

We cannot ascertain the general anesthetic depth with hypnosis or BIS alone.[21] Some anesthetic agents do not have an effect on BIS. One study has reported that $N_2O$ alone did not change the BIS.[22] Previous study with ketamine, another NMDA antagonist, has revealed that ketamine, in analgesic dosages, did not have a significant influence on the BIS measures of propofol sedation.[23] Doses of ketamine that produced unconsciousness cause a paradoxical increase in the BIS values.[24] Also, during propofol–fentanyl anesthesia, administration of ketamine significantly increased the BIS.[25] Further, with ketamine supplementation of propofol, the clinical endpoints of hypnosis have been achieved at a higher BIS. These results suggest that the paradoxically higher BIS at the hypnotic endpoints may be the result of lower propofol requirements or no effect of ketamine on the electroencephalogram variables.[26] We could not find any study testing the effect of magnesium on BIS, but similar to ketamine, magnesium (NMDA antagonist) may increase BIS or may not have an influence on the BIS of propofol. Further, these make the analysis of BIS results difficult. In our study, the magnesium administration reduced propofol infusion requirements during maintenance of propofol–$N_2O$ anesthesia. Therefore, we think that magnesium administration increases the BIS as an effect of the magnesium itself or because of lower propofol requirements or no effect of magnesium on the BIS values.

It may be that the hypotensive effects of magnesium caused lower propofol infusion requirements in the magnesium group. However, one study has reported that patients treated with magnesium did not show any hemodynamic difference compared with control patients in the intraoperative and postoperative period. The dosage of magnesium used in that study (3 g bolus, 0.5 g/h for the next 20 h) was similar to that used in our present study.[7] Another study has showed that a bolus of 4 g magnesium sulfate resulted in a rapid but transient decrease in arterial pressure in hypertensive patients, whereas normotensive patients did not have any appreciable change in blood pressure.[27] Nevertheless, it cannot be precluded that the dosage of magnesium used in this study had hypotensive effects and potentiated the hypotensive effects of propofol.

In conclusion, the reasons that intravenous magnesium sulfate administration decreases propofol infusion requirements and increases BIS may be as follows: (1) the probability that magnesium potentiates anesthetic effects and the NMDA antagonism of propofol; (2) the possibility that magnesium has a hypotensive effect and magnesium potentiates hypotensive effects of propofol; and (3) the possibility that magnesium has an anesthetic and analgesic effect. These results suggest that intravenous magnesium sulfate administration may have an effect on anesthesia or analgesia and may be a useful adjunct to intravenous propofol anesthesia. Further studies are needed to clarify these mechanisms.

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