Evaluation of effects of magnesium sulphate in reducing intraoperative anaesthetic requirements

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Background. The present randomized, placebo-controlled, double-blind study was designed to assess the effect of peroperatively administered i.v. magnesium sulphate on anaesthetic and analgesic requirements during total i.v. anaesthesia.

Methods. Eighty-one patients (36 women, 45 men) undergoing elective spinal surgery were included in one of two parallel groups. The magnesium group received magnesium sulphate 30 mg kg⁻¹ as a bolus before induction of anaesthesia and 10 mg kg⁻¹ h⁻¹ by continuous i.v. infusion during the operation period. The same volume of isotonic solution was administered to the control group. Anaesthesia was maintained with propofol (administered according to the bispectral index) and remifentanil (adjusted according to heart rate and arterial blood pressure) infusions.

Results. A significant reduction in hourly propofol consumption was observed with magnesium administration. For example, the mean infusion rate of propofol in the second hour of the operation was 7.09 mg kg⁻¹ h⁻¹ in the control group vs 4.35 mg kg⁻¹ h⁻¹ in the magnesium group (P<0.001). The magnesium group required significantly less remifentanil (P<0.001) and vecuronium (P<0.001). No side-effects were observed with magnesium administration.

Conclusion. The administration of magnesium led to a significant reduction in the requirements for anaesthetic drugs during total i.v. anaesthesia with propofol, remifentanil and vecuronium.

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Magnesium is the fourth most abundant cation in the body and the second most abundant intracellular cation.¹ ² It activates many of the enzyme systems involved in energy metabolism and acts as a natural calcium antagonist by regulating calcium access into the cell.³ Recently, the importance of magnesium in anaesthetic practice has been highlighted.² It has been suggested that magnesium has the potential to treat and prevent pain by acting as an antagonist of N-methyl-D-aspartate (NMDA) receptors.⁴ ⁵ In animals, magnesium suppressed NMDA-induced adverse behavioural reactions and hypersensitivity resulting from nerve injuries.⁵ In a clinical study, the role of magnesium in reducing analgesic requirements during the postoperative period has been demonstrated.⁶ Recently, Koinig and colleagues reported that magnesium administration led to a significant reduction in fentanyl consumption in the peri- and postoperative periods.⁷

At the beginning of the last century, magnesium sulphate was proposed as a general anaesthetic.⁸ ⁹ Although magnesium was regarded as a central nervous system (CNS) depressant, its anaesthetic effect was shown to result from cerebral hypoxia after progressive respiratory and cardiac depression. When respiratory support was maintained, patients showed no CNS depression even at very high serum concentrations of magnesium.¹⁰ On the other hand, a 60% reduction in minimum alveolar concentration of
halothane was demonstrated in magnesium-treated rats. This result was ascribed to a central effect of the ion, but this has not been substantiated.11

The present randomized, placebo-controlled, double-blind study was designed to assess the effect of perioperatively administered i.v. magnesium sulphate on anaesthetic and analgesic requirements during total i.v. anaesthesia with propofol, remifentanil and vecuronium.

**Methods**

The study was approved by the ethics committee of Istanbul Faculty of Medicine and informed consent was obtained from each patient. Eighty-one ASA physical status I–II patients (36 women, 45 men) undergoing elective lumbar discectomy were included in one of two parallel groups (control, n=41; magnesium, n=40).

Exclusion criteria included major hepatic, renal or cardiovascular dysfunction, atroventricular block, known allergy to magnesium sulphate or other study drugs, asthma, chronic obstructive pulmonary disease, haematological disorders, obesity, pregnancy and prior treatment with calcium channel blockers, opioids and anticoagulants. The patients were assigned randomly to one of the two groups. The magnesium group received 15% magnesium sulphate and the control group received 0.9% sodium chloride in a double-blind fashion. The solutions were prepared by the coordinator of the study, and the anaesthetist who was in charge of the patients during the operation was unaware of the study medication. Before the induction of anaesthesia, routine monitoring (ECG, pulse oximetry, oesophageal temperature) was started and an i.v. line was sited. An arterial line was inserted to measure systemic blood pressure with a Transpac i.v. system (Abbott Critical Care Systems, Abbott, Sligo, Ireland) on a Datex-Ohmeda AS/3 monitor (Datex-Ohmeda, Bromma, Sweden). Muscle relaxation was monitored with a neurotransmission module (M-NMT) incorporated into the Datex-Ohmeda AS/3 unit. The surface electrodes were positioned over the ulnar nerve at the wrist. The mechanosensor was attached between the thumb and index finger with a piece of tape and the forearm was wrapped in a cotton blanket to minimize cooling. The level of anaesthesia was monitored with the bispectral index (BIS™) method. The BIS electrodes were placed on the forehead and were connected to an A-2000 BIS monitoring system (Aspect Medical Systems, Framingham, MA, USA). A bispectral index of 40–60 was considered the target range for surgical anaesthesia.12

**Study protocol**

Standard recordings of heart rate, systemic pressure [mean arterial pressure (MAP)], arterial oxygen saturation (SpO₂) and BIS values were performed before the induction of anaesthesia. The magnesium group received magnesium sulphate 30 mg kg⁻¹, administered as a slow i.v. bolus before the induction of anaesthesia, and 10 mg kg⁻¹ h⁻¹ by continuous i.v. infusion during the operation. The same volume of isotonic saline was administered to the control group. After preoxygenation of at least 2 min, anaesthesia was induced with fentanyl 1 µg kg⁻¹ and propofol in increments of 20 mg every 5 s until the BIS reached a predetermined value of 60. After induction of anaesthesia, supramaximal train-of-four (TOF) stimulation was measured at 20 s intervals. When a stable twitch response (at least three successive equal responses to TOF stimulation) had been established, vecuronium 10 µg kg⁻¹ was administered via a fast-flowing i.v. infusion over 5 s. The time from the start of anaesthesia induction to reaching a BIS of 60 and the time to 80% (T1=20%) single-twitch depression after administering vecuronium were recorded. Orotracheal intubation was performed after complete (T1=0%) single-twitch depression, then a further set of recordings was made.

Anaesthesia was maintained by propofol and remifentanil infusions. The propofol infusion was started at the rate of 10 mg kg⁻¹ h⁻¹ and titrated to maintain a BIS in the range 45–60. The hourly consumption of propofol was recorded as mg kg⁻¹ h⁻¹. Dose adjustments of remifentanil were based on standard clinical signs and haemodynamic measurements. Signs of inadequate analgesia, defined as an increase in heart rate and mean arterial pressure of more than 20% of baseline, hypertension or hypotension (systolic arterial pressure <90 mm Hg) were to be managed with increased and decreased remifentanil respectively (if BIS was within the recommended range).7 Muscle relaxation was achieved by vecuronium infusion adjusted to provide complete depression of the first twitch after TOF stimulation. Hourly infusion rates of remifentanil and vecuronium were recorded as µg kg⁻¹ h⁻¹.

The lungs of all patients were ventilated mechanically with an oxygen/air mixture to maintain adequate oxygenation and a PaCO₂ level between 35 and 40 mmHg. Normothermia was maintained during the whole procedure. Approximately 30 min before the end of surgery, the vecuronium infusion was discontinued. After discontinuation of the vecuronium infusion, the patients were allowed to recover spontaneously until the return of T1=25%. Then a combination of atropine 0.01 mg kg⁻¹ i.v. and prostigmine 0.02 mg kg⁻¹ was administered to reverse the neuromuscular block. The times for return of T1 to 25% and return of the TOF ratio (T4/T1) to 70% were recorded. Propofol was discontinued on skin closure and the patient was allowed to wake up. Patients were extubated when the BIS reached 80, and the time to BIS=80 was recorded as the recovery period.

Each patient was observed continuously after the termination of anaesthesia and times of events were recorded by the anaesthetist. After transfer to the recovery area, patients were assessed neurologically for any sign of hypermagnesaemia. Any adverse events or side-effects were recorded during the perioperative and postoperative periods.

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Statistical analyses
Comparisons between the control and the study groups were conducted using Student’s t test, analysis of variance (ANOVA) or repeated measures ANOVA, as appropriate. The analysis was conducted on an intention-to-treat basis. Data for missing values were evaluated by the last observation carried forward (LOCF) method. For LOCF analysis, the last measurement was carried forward into all subsequent time slots for which actual measurements were not available. A P value below 0.05 was considered significant.

Results
The groups were comparable with respect to age, weight, ASA status and duration of surgery. All patients underwent the same type of surgery (discectomy), performed by the same group of surgeons. The numbers of cases in the control and magnesium groups respectively, according to operation duration, were as follows: 1–5 h, 27 and 27; up to 6 h, 3 and 6; up to 7 h, 5 and 2; up to 8 h, 4 and 3; up to 9 h, 2 and 2 patients.

In neither measurement period was there any statistically significant difference in heart rate or arterial blood pressure between the two groups. No haemodynamic instability was observed with magnesium perfusion during the observation period.

Induction of anaesthesia (BIS=60) was achieved in 55.4 (SD 10.6) s in the magnesium group and in 81.2 (13.6) s in the control group (P<0.0001). The recovery time was shorter in the control group (7.19 vs 9.60 min, P<0.0001). The baseline mean BIS before induction was above 90% for both the study and the control group. After induction, the mean BIS value, calculated from the lowest of the BIS values that were recorded every hour during the operational period, was not different between the two groups (Fig. 1). The times from the cessation of vecuronium to T1=25% (48.08 vs 38.73 min, P<0.001) and T4/T1≥70% (51.70 vs 41.59 min, P<0.001) were significantly longer in the magnesium group compared with the control group.

The mean anaesthetic requirements, measured every hour and evaluated by the LOCF method, are given in Table 1. Significantly lower propofol, remifentanil and vecuronium requirements were recorded during each measurement period in the magnesium group. When the hourly consumption rates of each drug were evaluated within the groups, significant reductions were observed in the second and third hours for propofol and remifentanil consumption in both groups. For vecuronium, a significant dose reduction was only apparent in the magnesium group.

Discussion
We studied the possible effects of magnesium sulphate in reducing the anaesthetic requirements during total i.v. anaesthesia with propofol, remifentanil and vecuronium. Our results demonstrate a significant reduction in the consumption of each drug used for balanced anaesthesia with magnesium administration. To our knowledge, this is the first study evaluating the potentiating interaction of magnesium with a combination of analgesic, hypnotic and muscle relaxant.

Importantly, we used an objective, quantitative measure of the anaesthetic state (BIS) to guide anaesthetic requirements and to determine end-points. Induction of anaesthesia with propofol was more rapid in the presence of magnesium, but recovery was slower. The effects of magnesium on propofol consumption could be related to a sedative effect of magnesium, but evidence for such an effect is conflicting. Magnesium has been reported to produce general anaesthesia and enhance the activity of local anaesthetic agents.17 18 In these studies, depressant effects on the CNS of animals injected with magnesium salts were reported. A narcotic state in human beings undergoing surgical operations was achieved in a study by Peck and Meltzer, who reported three patients undergoing hernioraphy under attempted anaesthesia by magnesium sulphate infusion.9 However, Aldrete and colleagues suggested that this anaesthetic state was actually a sleep-like state caused by cerebral hypoxia from progressive respiratory and cardiac depression.19 When ventilation was maintained, even very high levels of serum magnesium produced no CNS depression.11 In healthy volunteers, i.v. magnesium failed to induce sleep even at magnesium concentrations 10 times higher than normal. The subjects felt and heard everything happening up to when the magnesium level exceeded 7 mmol litre-1. There were no signs of anaesthesia, but the hand-grip force was markedly reduced.10 On the contrary, increasing the magnesium dose was found to be associated with reductions in halothane
MAC in rats. With these data, Thomson and colleagues suggested that anaesthetics be titrated carefully in patients with high serum magnesium concentrations and patients receiving magnesium.

In the present study, the aim was not to evaluate magnesium as an anaesthetic agent but to find out if magnesium could reduce propofol requirements during general anaesthesia. It is hard to speculate on the exact mechanism of magnesium’s contribution to anaesthesia in our study. Theoretically, magnesium could modulate anaesthesia by several mechanisms. Magnesium antagonizes NMDA receptors in the CNS. Another mechanism could involve the reduction of catecholamine release through sympathetic stimulation, by which magnesium might decrease peripheral nociceptor sensitization or the stress response to surgery. However, these mechanisms do not explain the reduction in propofol requirements independently of the reduction in requirements for remifentanil. Clearly, further studies of the interaction between magnesium and propofol as a sole agent are needed.

Our data demonstrated a significant reduction in remifentanil and vecuronium consumption during i.v. anaesthesia with continuous magnesium administration. The effect on vecuronium consumption is not surprising as the effects of magnesium ions at the neuromuscular junction are well known. The analgesic effect of magnesium has been demonstrated in several animal and human studies. The effect of magnesium on perioperative analgesic requirements was first evaluated by Koenig and colleagues. Their data demonstrated that magnesium can be an adjuvant to perioperative analgesic management by lowering the fentanyl requirement. Recently, in a study by Shulz-Stübner and colleagues, magnesium sulphate given as a bolus after induction produced a significant reduction in remifentanil and mivacurium consumption during general anaesthesia.

In our study, as in previous reports, the remifentanil requirement was adjusted according to haemodynamic changes as surrogate measures of intraoperative nociception. This might be considered a limitation of the study, as heart rate and MAP could change for many other reasons. Also, magnesium inhibits the release of catecholamines and might blunt the haemodynamic responses to inadequate analgesia. These anti-adrenergic actions have led to the use of magnesium during surgery for phaeochromocytoma and to evaluation of its efficacy in attenuating the response to endotracheal intubation. However, the doses used in these studies, either as a bolus or as a perfusion, were twice as high as the dose we used in our study. As a matter of fact, our study population was ASA I–II patients in whom heart rate and MAP increases are probably caused by pain perception.

Unfortunately, we did not measure serum magnesium concentrations. However, it is known that the plasma magnesium concentration does not represent the magnesium content of the tissues. The lack of correlation between plasma magnesium and total body magnesium content in healthy subjects is also well recognized. Arnold and colleagues showed that the measurement of intra- and extracellular magnesium concentrations does not predict magnesium levels in other body tissues accurately. Doses of magnesium similar to ours were shown to produce reductions in analgesic requirements both during and after surgical interventions. The dose–response relationship for magnesium with respect to its potentiating effect during anaesthesia needs to be evaluated further.

In conclusion, the administration of magnesium led to a significant reduction in the amounts of anaesthetic drugs used during total i.v. anaesthesia.

References

Table 1 Propofol, remifentanil and vecuronium consumption during maintenance of total i.v. anaesthesia. P values were determined by comparing control and magnesium groups. *Significant difference within group (P<0.05)

<table>
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<th>Hours</th>
<th>1</th>
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<tr>
<td>Propofol (mg kg⁻¹ h⁻¹)</td>
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<tr>
<td>Control (n=41)</td>
<td>8.91 (0.84)</td>
<td>7.09 (1.19)*</td>
<td>6.88 (0.99)</td>
<td>7.04 (0.66)</td>
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<td>4.35 (0.64)*</td>
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<td>3.59 (0.29)</td>
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<td>Remifentanil (µg kg⁻¹ h⁻¹)</td>
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<tr>
<td>Control (n=41)</td>
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<td>6.33 (1.39)*</td>
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<td>5.58 (0.89)</td>
<td>5.90 (0.77)</td>
<td>5.68 (0.57)</td>
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<td>Vecuronium (µg kg⁻¹ h⁻¹)</td>
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<tr>
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