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# Effect of intra-operative magnesium sulphate on pain relief and patient comfort after major lumbar orthopaedic surgery

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## Summary

The effects of intra-operative magnesium sulphate on pain relief after major lumbar surgery were investigated in 24 patients. Patients were randomly allocated to receive either an infusion of 50 $mg.kg^{-1}$ magnesium sulphate or an equivalent volume of saline at induction of anaesthesia. Anaesthesia was induced with propofol and remifentanil. Tracheal intubation was facilitated using rocuronium. Maintenance was achieved with remifentanil and sevoflurane in nitrous oxide/oxygen. Intra-operative monitoring included standard equipment and neuromuscular transmission. During surgery, neuromuscular block recovery was longer in the magnesium group. Postoperative opioid consumption and pain scores were lower in the magnesium group. The first night's sleep and the global satisfaction scores were better in the magnesium group. The results of the study support magnesium sulphate as a useful adjuvant for postoperative analgesia after major lumbar surgery.

**Keywords** *Surgery*: orthopaedic, lumbar arthrodesis. *Analgesia*: postoperative. *Patients*: comfort. *Drugs*: opioids, magnesium, piritramide.

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Magnesium, which is the second intracellular ion, has numerous functions in human physiology including activation of enzymes, protein synthesis, regulation of vasomotor tone, neurotransmission and signalling [1]. Magnesium also acts as a non-competitive antagonist of *N*-methyl-D-aspartate (NMDA) glutamate receptors which are involved in pain perception and the persistence of postoperative pain [2, 3].

Magnesium sulphate ($MgSO_4$) is used as a pharmacological agent in a variety of clinical situations: tachyarrythmia, myocardial and neuronal ischaemia, asthma, spasmophilia, pre-eclampsia, tocolysis and postanaesthesia shivering [1]. Since 1990, the effect of magnesium sulphate on postoperative pain relief and its sparing effects on postoperative opioid consumption have been investigated in gynaecological, ophthalmic and arthroscopic knee surgery [4–10]. Our study was designed to investigate the effects of $MgSO_4$ on postoperative pain relief and patient comfort after major lumbar orthopaedic surgery.

## Methods

Following institutional ethics committee approval, 24 ASA status I or II consenting adult patients undergoing routine lumbar arthrodesis were enrolled in this prospective, randomised, double-blind and placebo-controlled study. The patient population included 12 men and 12 women, aged between 26 and 76 years (mean 50 years). Exclusion criteria were impaired renal or hepatic function, intracardiac block, elevated blood pressure, neurological disorders, myopathy, diabetes, drugs or alcohol abuse. Pregnant women and patients treated with calcium channel blockers or magnesium were also not studied.

During the pre-operative visit, patients were extensively informed by the anaesthetist regarding the appropriate use of visual analogue rating scales (VAS) and patient-controlled analgesia (PCA) devices. Patients were randomly assigned to one of two groups: patients in the

magnesium group (group Mg, $n = 12$) received 50 mg.kg$^{-1}$ of $MgSO_4$ in 250 ml of normal saline over 30 min immediately before induction of anaesthesia, whereas patients in the control group (group C, $n = 12$) received the same volume of saline over the same period. Randomisation was performed using a computer randomisation list based on a study identification number and the anaesthetist in charge of the patient received from the chief nurse an infusion bag containing either $MgSO_4$ or normal saline. The anaesthetist was unaware of which solution was administered.

Patients were administered alprazolam 1 mg and atropine 0.5 mg given orally 2 h before surgery. Upon arrival in the operating theatre, electrocardiograph, non-invasive blood pressure and pulse oximetry monitoring (Datex AS3®, Helsinki, Finland) were established. Electrodes were applied to the patient's forehead according to the classical bifrontal montage for monitoring the bispectral index (BIS®) of the electroencephalogram (Aspect 2000®, Aspect Medical Systems, Natick, MA). Oesophageal temperature was recorded throughout the study and neuromuscular transmission was monitored at the wrist by accelerography, using train-of-four (TOF) supramaximal stimulations (2 Hz, 50 mA, TOF Watch®, Organon-Teknika). A standardised general anaesthetic was administered using propofol (2 mg.kg$^{-1}$) and remifentanil (0.25 $\mu$g.kg$^{-1}$.min$^{-1}$) for induction. Following loss of the eyelash reflex, rocuronium 0.6 mg.kg$^{-1}$ was administered to facilitate tracheal intubation. No additional dose of muscle relaxant was administered thereafter. Anaesthesia was maintained with remifentanil (constant infusion rate: 0.25 $\mu$g.kg$^{-1}$.min$^{-1}$) and sevoflurane in oxygen/nitrous oxide ($F_{I}O_2 = 0.4$) adjusted to keep the BIS between 40 and 50. Ventilator settings were adjusted to maintain normocapnia (end-tidal carbon dioxide: 30–35 mmHg). Normothermia was maintained with a forced warm air device (Bair Hugger, model 200, Augustine Material, Eden Prairie, MN). Heart rate, systolic, mean and diastolic blood pressures, oxygen saturation, rectal temperature, BIS value, end-tidal carbon dioxide, mean expired sevoflurane concentration (from 30 min after skin incision to the end of surgery) and response to TOF stimulations of the ulnar nerve were recorded at 5-min intervals throughout the surgical procedure. Low arterial blood pressure during surgery was defined as a systolic blood pressure value (SBP) $< 70$ mmHg and was treated by a bolus of 5 mg ephedrine administered intravenously.

Each patient received a bolus of 0.15 mg.kg$^{-1}$ piritramide intravenously at the time of muscle wound closure which was $\approx 15$ min before the end of surgery. Upon emergence, additional boluses of 1 mg piritramide were given on request until patients were pain-free. The time at which patients were pain-free was the start of study period, is noted in the figures as time '0', and is the time from which further VAS pain scores and calculations of piritramide consumption were made. Thereafter, a PCA device (PCA Plus II Infuser®, Abbott Laboratories, Abbott Park, IL) containing piritramide 2 mg.ml$^{-1}$ was provided to all patients using standard setting (1 mg bolus dose, 5 min lockout period, 20 mg maximal dose per 4 h). Episodes of shivering as well as episodes of nausea and vomiting (PONV) were recorded at emergence and thereafter, throughout the study period.

Piritramide consumption was recorded during the first postoperative 24 h. Pain at rest was evaluated using a 0–10 cm VAS at emergence from anaesthesia and 2, 4, 6, 12, and 24 h in the study period. The day after surgery, patients were asked to rate the quality of their first night's sleep using an equivalent VAS (0 = absolute insomnia, to 10 = no insomnia, excellent quality of sleep), which is the inverse VAS described by Kara *et al.* [9]. The patient's global satisfaction regarding comfort was also assessed at the same time using a VAS ranging from 0 (worst discomfort ever experienced in their life) to 10 (totally satisfied by comfort provided during the immediate postoperative period), as described by Tramer *et al.* [4], who used the same VAS but in the inverse order.

Data were analysed using two-tailed unpaired *t*-tests, Yates' corrected Chi-squared tests and Fisher's exact tests and two-way mixed-design ANOVAs as appropriate. Normality of distribution was checked as needed. Values were expressed as counts, percentages or mean (SD). A p-value $< 0.05$ was considered statistically significant. Statistics were computed using DATASIM software (Version 1.1, Drake R. Bradley, Department of Psychology, Bates College, Lewiston, ME, USA). Power estimate calculations were performed using the G-POWER software (Version 2.0, F. Faul and E. Erdfelder, Psychologisches Institut der Universität Bonn, Römerstr. 164, D-53117 Bonn, Germany).

## Results

Patients' characteristics were similar in both groups (Table 1). Systolic blood pressure before induction of anaesthesia was similar in both groups.

During surgery, the mean end-tidal concentration of sevoflurane was not significantly different in the two groups [1.07 (0.12)% in group Mg and 1.23 (0.15)% in group C]. The time to obtain four clinical responses to TOF stimulation was significantly longer in group Mg than in group C [56.6 (12.1) min vs. 35.8 (5.5) min].

**Table 1** Demographic data. Data are shown as mean (SD) or as counts.

| | Group Mg ($n = 12$) | Group C ($n = 12$) |
|---|---|---|
| Age; years | 55 (16) | 46 (19) |
| Weight; kg | 72 (13) | 81 (20) |
| ASA; I/II | 4/8 | 2/10 |
| Gender; male/female | 4/8 | 7/5 |
| Duration of surgery; min | 191 (42) | 183 (33) |

**Table 2** Side effects and mean end-tidal concentration of sevoflurane during surgery for both groups.

| | Group Mg ($n = 12$) | Group C ($n = 12$) |
|---|---|---|
| End-tidal etsevo; %, [mean (SD)] | 1.07 (0.12) | 1.23 (0.15) |
| Side effects | | |
| SBP < 70 mmHg | 8 | 6 |
| PONV | 0 | 1 |
| Shivering | 3 | 3 |
| Time to four responses to TOF stimulation; min [mean (SD)] | 56.6 (12.1) | 35.8 (5.5) |

The incidence of side-effects associated to the administration of $MgSO_4$ is summarised in Table 2. There was no difference in the incidence of systemic hypotension between the groups. Shivering at emergence was observed in three patients from each group. PONV was observed in only one patient from the control group.

Cumulative piritramide consumption over the 24 h study period was lower in the group Mg than in group C. The difference was statistically significant from 6 h and remained so until 24 h (Fig. 1). The number of patients who required additional piritramide boluses upon emergence was lower in group Mg than in group C (2 vs. 6 patients, respectively) but the difference was not statistically significant (Fig. 2). A two-way mixed-design ANOVA allowed us to conclude that the rate of piritramide consumption per hour during the study period was significantly lower in group Mg than in group C. When considering the 24 patients together, the piritramide consumption was highest between 4 and 6 h and significantly higher during this period than between 6 and 12 h, and between 12 and 24 h. The VAS pain scores were significantly higher in group C than in group Mg when considering the whole study period. In the entire group of patients ($n = 24$) VAS pain scores were significantly lower after recovery than at 2, 4 and 6 h, in both groups of patients. The global satisfaction VAS scores and quality of the first night's sleep scores were significantly higher in group Mg than in group C (Fig. 3).

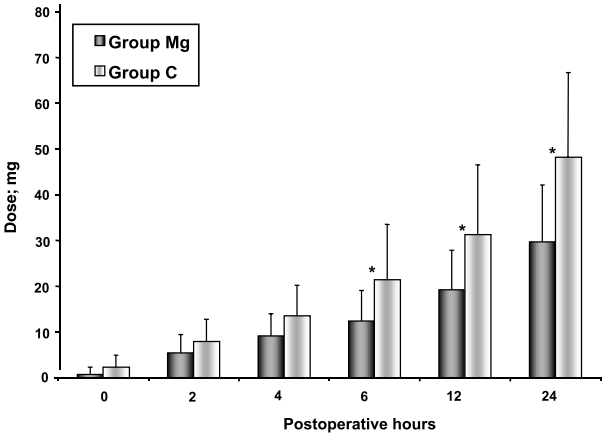


**Figure 1** Mean cumulative piritramide consumption (mg) (SD) after patients were pain-free in recovery and at 2, 4, 6, 12 and 24 h thereafter. Cumulative piritramide consumption was significantly higher in group C than in group Mg at 6, 12 and 24 h. *$p < 0.05$.

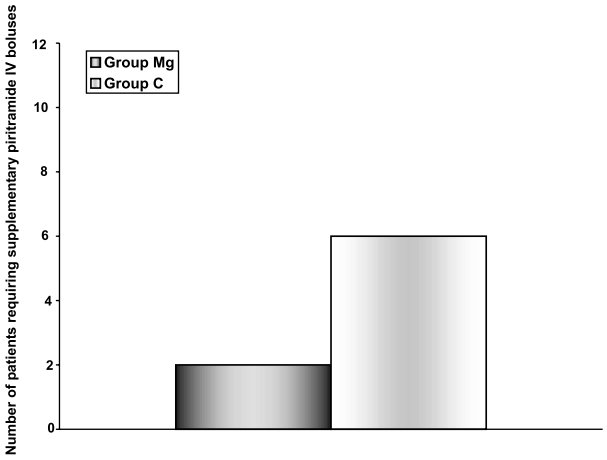


**Figure 2** Number of patients requiring additional piritramide boluses upon emergence from anaesthesia in group Mg and group C (Fisher's exact test, n.s.).

## Discussion

The results of this study demonstrate that 50 $mg.kg^{-1}$ magnesium sulphate given as a bolus at induction of anaesthesia significantly reduces opioid consumption and improves patient comfort after major lumbar surgery.

The treatment of postoperative pain is increasingly based on a multimodal approach and although opioids remain the drug of choice, they are often used in combination with other analgesics (paracetamol, cyclo-oxygenase inhibitors or non-steroidal anti-inflammatory drugs) and co-analgesic agents (clonidine and anti-NMDA such as ketamine or $MgSO_4$). The rationale for

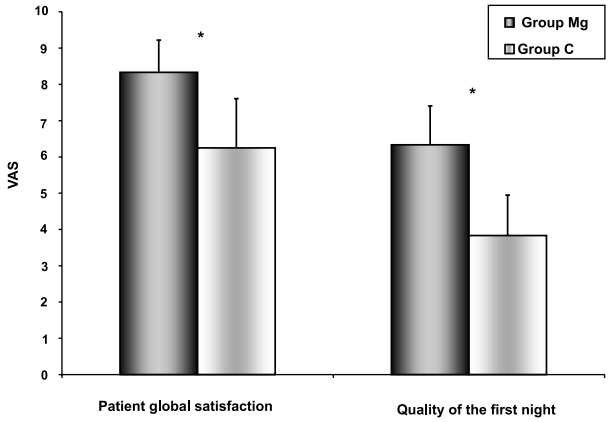


**Figure 3** Global satisfaction of patients and quality of their first night as assessed using a 0–10 cm visual analogue scale (VAS). *$p < 0.05$.

a combined analgesia is to achieve additive or synergistic analgesic properties while decreasing the incidence of side effects by reducing the dose of each agent. Nociceptive stimuli are known to activate the release of the excitatory amino acid glutamate in the dorsal horn of the spinal cord. The resultant activation of NMDA receptors causes calcium entry into the cell and triggers central sensitisation. This mechanism is involved in the perception of pain and mainly accounts for its persistence during the postoperative period. Magnesium produces a voltage-dependent block of NMDA receptors and has been reported to have analgesic properties that might be related to this inhibiting property [4, 5].

Previous studies investigating the analgesic efficacy of $MgSO_4$ have shown conflicting results. After hysterectomy, reduced analgesic requirements, reduced discomfort and better sleep quality have been reported by some investigators, whereas others failed to find any improvement in postoperative analgesia, or any reduction in postoperative analgesic consumption [4, 7, 8]. Although NMDA receptors are not involved in the mechanism of analgesia provided by local anaesthetics, the authors observed an inverse relationship between the cumulative postoperative analgesic consumption and the magnesium concentration in the cerebrospinal fluid. In arthroscopic knee surgery, as well as in ophthalmic surgery, the perioperative administration of magnesium has been reported to reduce intra- and postoperative analgesic requirements [5, 7].

In our study, patients in the control group had more pain than those in the Mg group despite the use of a PCA device. Moreover, the cumulative piritramide consumption was significantly lower in group Mg at 6, 12 and 24 h. These observations support both the co-analgesic properties and opioid-sparing effect of magnesium administered at induction of anaesthesia. In the entire group of patients ($n = 24$), the piritramide consumption rate was highest 6 h after the end of surgery. Such a delay is consistent with the duration of action of the boluses of piritramide administered before completion of surgery. Finally, the global patient satisfaction score and the first night's sleep score were significantly higher in the Mg group, which is in agreement with previous studies [4, 5, 7, 9]. It is worth noting that, even provided with a PCA device, patients still had a moderate level of pain, as mean VAS scores approached 5 throughout the first 24 postoperative hours, except during the immediate recovery period. This indicates that this kind of surgery is painful and that postoperative analgesia might still be improved.

Shulz-Stubner *et al.* [7] and Kara *et al.* [9] demonstrated a significant decrease in intra-operative opioid consumption for patients who received magnesium. In our protocol, as maintenance of anaesthesia was achieved using a constant remifentanil infusion, one might have expected to observe a significant sparing effect of $MgSO_4$ on the sole varying anaesthetic agent during surgery, i.e. sevoflurane. Although this was not the objective of our study, we were not able to demonstrate such an effect of $MgSO_4$ on sevoflurane requirements. The mean end-tidal sevoflurane concentration was only slightly lower in group Mg than in group C. However, we cannot conclude that there is actually no sparing effect of $MgSO_4$ on sevoflurane requirements given that the power of our study, in that respect, is 88% if a difference between means of 0.2%, a standard deviation of 0.15% and an p-value of 0.05 are considered. Therefore, there remains a 12% chance of erroneously considering $MgSO_4$ as a nonsparing sevoflurane medication. Our sample should be enlarged to at least two groups of 16 patients each in order to achieve a 95% power of detecting a significant difference.

According to Tramer *et al.* [4], the hypotensive effect of magnesium could be explained by its direct vasodilatory effect through a calcium channel blockade. A larger series of patients would have been necessary to examine the hypotensive effect of magnesium, a tendency that has been observed by other authors [4, 7]. Two groups of 57 patients each would be necessary to reach a power of $> 95\%$ and thus reduce the risk of type II error to 5%. In our patient population, episodes of arterial hypotension were of short duration and easily treated by ephedrine.

The rocuronium-induced neuromuscular block was significantly prolonged in patients who received $MgSO_4$, as described elsewhere [11]. Indeed, magnesium is known to decrease acetylcholine release at the presynaptic level of the neuromuscular junction and its muscle-relaxant properties have been known for a long time. The

potentiating effect of magnesium on neuromuscular block has already been reported with vecuronium and succinylcholine in several studies [1]. In our study, the delay to recover four responses to TOF stimulation was increased by ≈ 20 min in group Mg. As no further rocuronium was administered after the induction of anaesthesia and the duration of surgery exceeded 50 min, this delay had no consequence on the emergence conditions.

In this study, $MgSO_4$ was administered intravenously at induction of anaesthesia as a bolus dose of 50 $mg.kg^{-1}$ administered over 30 min without any subsequent continuous infusion. Such a dose has already been reported in several studies to be devoid of adverse effects. Lower bolus doses have not been shown to improve postoperative analgesia [6]. Hence, a continuous infusion of $MgSO_4$ seems to have no benefit compared with a single bolus dose of 50 $mg.kg^{-1}$. It has been suggested that NMDA blocking agents should be administered before the beginning of nociceptive stimulation to inhibit the process of central sensitisation [8, 9].

In conclusion, a 50 $mg.kg^{-1}$ bolus of $MgSO_4$ given at induction of anaesthesia results in a significant reduction in postoperative opioid consumption, a better satisfaction score and a more satisfactory first night's sleep in patients undergoing major lumbar orthopaedic surgery. It can be recommended as a useful adjunct for postoperative analgesia provided attention is paid to its effect on neuromuscular transmission.

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