I.V. infusion of magnesium sulphate during spinal anaesthesia improves postoperative analgesia

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Background. In a randomized, double-blind, prospective study, we have evaluated the effect of i.v. infusion of magnesium sulphate during spinal anaesthesia on postoperative analgesia and postoperative analgesic requirements.

Methods. Forty patients undergoing total hip replacement arthroplasty under spinal anaesthesia were included. After the induction of spinal anaesthesia, the magnesium group (Group M) received magnesium sulphate 50 mg kg⁻¹ for 15 min and then 15 mg kg⁻¹ h⁻¹ by continuous i.v. infusion until the end of surgery. The saline group (Group S) received the same volume of isotonic saline over the same period. After surgery, a patient-controlled analgesia (PCA) device containing morphine and ketorolac was provided for the patients. Postoperative pain scores, PCA consumption, and the incidences of shivering, postoperative nausea, and vomiting were evaluated immediately after surgery, and at 30 min, 4, 24, and 48 h after surgery. Serum magnesium concentrations were checked before the induction of anaesthesia, immediately after surgery, and at 1 and 24 h after surgery.

Results. Postoperative pain scores were significantly lower in Group M at 4, 24, and 48 h after surgery (P<0.05). Cumulative postoperative PCA consumptions were also significantly lower in Group M at 4, 24, and 48 h after surgery (P<0.05). Postoperative magnesium concentrations were higher in Group M (P<0.05 at 4, 24, and 48 h after surgery), but no side-effects associated with hypermagnesemia were observed. Haemodynamic variables and the incidences of shivering, nausea, and vomiting were similar in the two groups.

Conclusions. I.V. magnesium sulphate administration during spinal anaesthesia improves postoperative analgesia.

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Total hip replacement arthroplasty is accompanied by moderate to severe pain after surgery and adequate postoperative pain management is important for early rehabilitation and functional recovery.1,2 Magnesium (Mg) has antinociceptive effects due to its antagonistic effect of N-methyl-D-aspartate (NMDA) receptor. Numerous clinical investigations have demonstrated that Mg infusion during general anaesthesia reduced anaesthetic requirement and postoperative analgesic consumption,3–6 whereas other studies suggested that perioperative Mg administration had little effect on postoperative pain.7,8 Relatively few studies have been conducted on the effects of magnesium sulphate administration during regional anaesthesia. A previous study demonstrated that magnesium sulphate infusion started immediately after the induction of spinal anaesthesia and extended for 24 h reduced analgesic consumption without any effect on spinal block.9 However, patients included in this study underwent minor surgical procedures not associated with moderate to severe pain, and postoperative pain scores were similar between the groups other than at 12 h after surgery. Thus, the effects of systemic Mg during spinal
anaesthesia on postoperative analgesia and analgesic consumption have not been fully determined yet. Accordingly, the aim of this study was to evaluate the effect of an i.v. infusion of magnesium sulphate during spinal anaesthesia on postoperative pain and analgesic consumption.

Methods

This study was approved by the Institutional Ethics Committee and written informed consent was obtained from all patients. Forty ASA I and II patients undergoing total hip replacement arthroplasty were enrolled in this study. Exclusion criteria were cardiovascular, hepatic, or renal dysfunction, neuromuscular diseases, opioid or analgesic abuse, and prior treatment with calcium channel blockers. Patients were informed of the study purpose and protocol, and were instructed how to use the visual analogue scale (VAS) and the patient-controlled analgesia (PCA) device during a preoperative visit.

After premedication with i.v. midazolam 0.03 mg kg\(^{-1}\), patients were transferred to the operating theatre. Ringer’s solution 500 ml was given over 15 min, and intraoperative monitoring included non-invasive arterial pressure, ECG, and pulse oximetry.

Spinal anaesthesia was performed through the L3–4 or L4–5 interspace in the lateral decubitus position with the surgical side down. After dural puncture with a 25 G Quincke needle, hyperbaric bupivacaine 0.5% solution (Heavy Marcaine Spinal 0.5%, AstraZeneca AB, Sweden) with fentanyl 20 μg was injected intrathecally. Bupivacaine dose was determined based on height (height \(\leq 155\) cm = 12 mg; \(155–170\) cm = 13 mg; \(170–180\) cm = 14 mg; \(\geq 180\) cm = 15 mg).

Patients were randomly assigned to two groups using closed envelopes chosen by patients before the study. Patients in the magnesium group (Group M, \(n = 20\)) received magnesium sulphate 50 mg kg\(^{-1}\) for 15 min after spinal anaesthesia and then 15 mg kg\(^{-1}\) h\(^{-1}\) by continuous i.v. infusion until the end of surgery. Patients in the saline group (Group S, \(n = 20\)) received the same volume of isotonic saline over the same period. Infusions were prepared in pharmacy and they were administered using the infusion machines identical in appearance. Study data were recorded by an observer unaware of group assignments. The height of spinal block was evaluated for cold sensation 15 min after intrathecal administration of bupivacaine. If the systolic arterial pressure decreased to below 90 mm Hg or if mean arterial pressure decreased >20% from baseline, ephedrine 5 mg was given i.v. If heart rate decreased to <45 beats min\(^{-1}\), i.v. atropine 0.5 mg was administered.

In each case, a PCA device containing morphine 70 mg and ketorolac 150 mg in normal saline in a total volume of 100 ml was connected i.v. at the end of surgery. This was set to deliver a 1 ml bolus dose with a 10 min lockout period. After surgery, patients were transferred to the post-anesthetic room. Postoperative PCA consumption and pain scores were recorded immediately after surgery, at 30 min, and 4, 24, and 48 h after surgery. If necessary, ketorolac 30 mg was i.v. administered as rescue analgesia during the postoperative period.

Pain scores were evaluated using a 0–100 mm VAS (0, no pain, to 100, worst pain imaginable). The incidences of shivering and postoperative nausea and vomiting (PONV) were recorded at 30 min, and 4, 24, and 48 h after surgery. Blood samples for serum Mg concentration were obtained immediately after surgery, and 1 and 24 h after surgery (normal range at our centre 0.75–1.0 mmol litre\(^{-1}\)). Patients’ overall satisfaction levels were assessed using a five-point scale (1, very unsatisfactory; 5, excellent).

The primary outcome of this study was postoperative PCA drug consumption. On the basis of pilot data, 20 patients per group were required to detect a significant difference in the postoperative PCA consumption at a significance level of 95% with a power of 80%. Power Analysis and Sample Size software (2005, NCSS, USA) was used for this calculation. Values were expressed as mean (SD) or median (inter-quartile ranges). The SPSS software (version 12.0; SPSS Inc., Chicago, IL, USA) was used for statistical analysis. The Mann–Whitney test was used to analyse quantitative data (weight, height, age, VAS pain scores, PCA consumptions, and satisfaction score), and the \(\chi^2\) test was used for qualitative data (gender). Repeated-measures ANOVA was used to analyse haemodynamic variables over time between two groups. Statistical significance was accepted for a \(P\)-value of <0.05.

Results

No significant difference was found between the two groups in terms of age, weight, height, gender, or anaesthetic time (Table 1). No technical failure related to spinal anaesthesia occurred and all surgery proceeded without difficulty. The two groups were similar in terms of height of spinal block, mean time to first pain, and administered dose of bupivacaine (Table 2).
Postoperative serum Mg concentrations in Group M were significantly higher than those in Group S ($P<0.001$ immediately after surgery, and at 1 and 24 h after surgery, Table 3). However, all patients in Group M had a serum Mg concentration in the normal range 24 h after surgery.

There was no significant difference in haemodynamic variables (mean arterial pressure and heart rate) during the intra- or postoperative period (Figs 1 and 2). Six patients in Group M and three patients in Group S developed hypotension, and two patients in Group M and one patient in Group S experienced bradycardia during surgery. In accordance with the study protocol, ephedrine 5 mg and atropine 0.5 mg were administered in each event, and in all cases, arterial pressure and heart rate were normalized.

Postoperative VAS scores were markedly lower in Group M at 4, 24, and 48 h after surgery (all $P<0.001$, Table 4). Furthermore, cumulative postoperative PCA consumptions were markedly lower in Group M ($P<0.001$ at 4, 24, and 48 h after surgery, Fig. 3), and fewer patients in Group M required additional rescue analgesia during the postoperative period ($2 \text{ vs } 6$ patients), but this was not statistically significant ($P=0.079$).

The incidences of PONV and shivering after surgery were similar in the two groups. However, global satisfaction scores were significantly higher in Group M [3.4 (0.6) vs 2.6 (0.5), $P<0.05$].

### Discussion

This study showed that i.v. magnesium sulphate infusion during surgery under spinal anaesthesia reduced postoperative pain and analgesic consumption without any notable complications. Total hip replacement arthroplasty is usually associated with moderate to severe postoperative pain, which disturbs early rehabilitation and functional recovery. Accordingly, a number of strategies for pain management have been introduced during the postoperative period. Regional anaesthesia is preferred to general anaesthesia during the perioperative period and patient-
controlled epidural analgesia or nerve blocks have also been used in some patients. Improvements in understanding the mechanism of pain have resulted in the administration of analgesics before exposure to pain stimuli to prevent the central sensitization and the amplification of postoperative pain.12

Magnesium sulphate has been used in obstetric and cardiac patients. Its use as an adjuvant for perioperative analgesia is based on the properties of NMDA receptor antagonist and calcium channel blocker. However, although the basic mechanism of analgesic effect of Mg is unclear, it is presumed that its antagonism of NMDA receptor prevents the induction of central sensitization due to peripheral nociceptive stimulation and abolishes hypersensitivity. In addition, calcium channel blockers have shown antinociceptive effects in animals and morphine potentiation in patients with chronic pain.10

Our findings are partly in line with those in a previous study,9 where, immediately after spinal block, patients received a 5 mg kg\(^{-1}\) bolus of magnesium sulphate followed by a 500 mg h\(^{-1}\) infusion or saline in the same volumes for 24 h, and postoperative analgesic consumption was significantly lower in the Mg group. However, VAS scores in the two groups during the first 24 h after surgery were similar except at 12 h after surgery, and thus, it is assumed that the dosage of magnesium sulphate used was insufficient for postoperative analgesia.

Adequate bolus and infusion doses of magnesium sulphate are important for effective analgesia. In a comparison of the effects of three different dose regimens of Mg on postoperative morphine consumption,11 a single bolus injection at 40 mg kg\(^{-1}\) was found to reduce postoperative morphine consumption, and when this was followed by a maintenance infusion of 10 mg kg\(^{-1}\) h\(^{-1}\), the effect was enhanced. Moreover, increasing the maintenance infusion to 20 mg kg\(^{-1}\) h\(^{-1}\) provided no additional advantage and induced unwarranted haemodynamic effects. Pre- and intraoperative administration of magnesium sulphate (50 mg kg\(^{-1}\) bolus and maintenance 15 mg kg\(^{-1}\) h\(^{-1}\) of magnesium sulphate) in gynaecology patients receiving total i.v. anaesthesia reduced rocuronium requirement and improved the quality of postoperative analgesia without any significant side-effects.5-8 Accordingly, in the present study, we administered a 50 mg kg\(^{-1}\) bolus and a maintenance dose of 15 mg kg\(^{-1}\) h\(^{-1}\).

Postoperative VAS scores and cumulative PCA consumption were both markedly lower in Group M at 4, 24, and 48 h. There was no significant difference of postoperative pain and analgesic use immediately and 30 min after surgery, which we attribute to the residual effect of spinal anaesthesia. Theoretically, two groups of patients using PCA in the present study should have titrated to much the same pain scores irrespective of an adjuvant drug. However, previous studies of the effect of Mg on postoperative analgesia also showed different VAS scores between the control and the Mg groups, even though the patients used PCA in the postoperative period.4,5,9,11 Possible explanations include: PCA use can reduce postoperative pain but cannot make it zero, and PCAs use opioids with or without ketorolac, which have dose-related side-effects, such as nausea and vomiting, and these side-effects stop unlimited use of the PCA. In addition, PCA settings include a lockout time to prevent overdose and patients may not, at times, get as much analgesic as they want. Adjuvant drugs such as magnesium sulphate can further reduce pain and analgesic consumptions in postoperative patients using PCA.

After surgery, patients in Group M had higher serum Mg concentrations than those in Group S, but there was no side-effect associated with hypermagnesemia. Theoretically, minor side-effects of parenteral Mg such as flushing, nausea, and headache are expected at the serum Mg level above 2 mmol litre\(^{-1}\), and potentially life-threatening complications, primarily involved in the cardiovascular and neuromuscular systems, occur when serum Mg concentrations exceed 5 mmol litre\(^{-1}\).12 In the present study, the average serum Mg concentration after surgery in Group M was 1.31 (0.13) mmol litre\(^{-1}\), which is below the level of minor side-effects. Serum Mg concentrations decreased to 1.10 (0.13) mmol litre\(^{-1}\) at 1 h after surgery and normalized at 24 h after surgery [0.93 (0.07) mmol litre\(^{-1}\)]. Conversely, hypomagnesemia frequently occurs during the perioperative period and Group S in our study showed low normal serum Mg concentrations in the postoperative period.10,13

Magnesium causes a dose-dependent negative inotropic effect, and in humans, haemodynamic studies have shown that it has a peripheral (predominantly arteriolar) vasodilatory effect.14-16 After rapid infusion of 3 or 4 g of magnesium sulphate, systolic arterial pressure decreased in relation to decreased systemic vascular resistance.10 In the present study, considering the negative inotropic effect of Mg, prehydration with 500 ml of lactated Ringer’s solution was performed and the Mg bolus dose was infused over 15 min, which is probably why no significant hypotension
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was encountered after administering the Mg bolus dose and no significant inter-group haemodynamic differences were observed during the surgery.

In the present study, time to first pain sensation and spinal block height were similar in the two groups, which is in accord with the findings of a previous study. There was no significant difference between the Mg and the control groups in terms of spinal block height or the duration of motor block. It should be noted that we did not assess the duration of motor block during the present study, because the protocol at our institute after total hip replacement arthroplasty is that patients should not move their legs during the early postoperative period.

Magnesium sulphate administration may have another benefit, namely, as it has been suggested that it potentiates neuromuscular block during general anaesthesia. It has been shown that the basic mechanisms involve a reduction of acetylcholine released from motor nerve terminals and a decrease in the depolarizing action of acetylcholine at the endplate, or a depression of muscle fibre membrane excitability. Accordingly, i.v. Mg administration during spinal anaesthesia may facilitate muscle relaxation and surgical procedures that require extensive joint rotation, such as total hip replacement arthroplasty. However, further study is required to validate this hypothesis.

In summary, we found that magnesium sulphate given i.v. during spinal anaesthesia reduced postoperative pain and analgesic consumption without complications.

References
2 Fischer HB, Simanski CJ. A procedure-specific systematic review and consensus recommendations for analgesia after total hip replacement. Anaesthesia 2005; 60: 1189–202
7 Ko SH, Lim HR, Kim DC, Han YJ, Choe H, Song HS. Magnesium sulfate does not reduce postoperative analgesic requirements. Anesthesiology 2001; 95: 640–6