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Research Article

Intrathecal vs intravenous magnesium as an adjuvant to bupivacaine spinal anesthesia for total hip arthroplasty

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KEYWORDS

Intrathecal magnesium;
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Abstract *Background:* The aim of this study was to investigate the effect of intravenous infusion vs intrathecal magnesium sulfate during spinal anesthesia on postoperative pain, analgesic consumption, and intraoperative blood loss on patients undergoing total hip arthroplasty surgery.
Methods: In this prospective randomized controlled study, 75 adult patients, ASA physical status I and II scheduled for total hip arthroplasty, were included and randomized into three groups. Patients in Group I (control) received spinal anesthesia with hyperbaric bupivacaine and fentanyl. In Group II (IT Mg), 50 mg of magnesium sulfate was added to bupivacaine and fentanyl. In Group III (IV Mg), after induction of spinal anesthesia as in group I, a bolus dose of i.v. magnesium sulfate 40 mg kg^{-1} was injected over 10 min, followed by continuous infusion of 15 mg kg^{-1} h^{-1} till the end of surgery. Arterial blood pressure, heart rate, electrocardiography, and O_2 saturation were continuously monitored. Onset, duration of sensory and motor block, and postoperative pain scores were assessed. Serum magnesium concentrations were checked before induction of anesthesia, immediately after surgery, at 6 h and 24 h after surgery. Total analgesic consumption and intraoperative blood loss were calculated.
Results: There were no significant differences between the study groups in terms of onset time and maximum sensory level achieved, as well as onset and duration of motor block. Postoperative pain scores and 24 h analgesic consumption were lower in group II and III with insignificant differences between them. Intraoperative blood loss was significantly lower in group III. Postoperative Mg levels were higher in group III, without significant side effects.
Conclusions: Both i.v. infusion and intrathecal injection of Mg sulfate improved postoperative analgesia after total hip replacement. In addition, i.v. infusion of Mg sulfate reduced intraoperative blood loss.

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1. Introduction

Postoperative pain following total hip replacement arthroplasty is usually moderate to severe in nature. Adequate postoperative pain management is essential for early rehabilitation [1,2].

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Magnesium (Mg) is an inorganic ion that has a non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist property with antinociceptive effects in animals and human models [3,4]. Magnesium has been used as an anticonvulsant for the treatment of preterm labor, preeclampsia and eclampsia, myocardial protection after ischemia, hemodynamic stability during endotracheal intubation, and severe attacks of bronchial asthma [5,6].

Magnesium acts as a stabilizer for the cell membrane and intracytoplasmic organelles through intervention in the activation of membrane Ca ATPase and Na-K ATPase involved in the transmembrane exchange of ions during depolarization and repolarization phases. Mg also inhibits the outflow of Ca from the sarcoplasmic reticulum through its effect on L-type calcium channels in the membranes and sarcoplasmic reticulum. In addition, Mg has a vasodilator effect by increasing the synthesis of prostacyclin and inhibiting the activity of angiotensin-converting enzyme. A dose dependent myocardial depressant effect of Mg has been reported [7,8].

Previous studies have demonstrated that Mg sulfate infusion during general anesthesia shorten the induction time by propofol, reduced anesthetic requirement as well as the postoperative analgesic consumption [9,10]. Other studies, however, suggested that perioperative administration of Mg had little effect on postoperative pain [11,12]. The effect of Mg sulfate during spinal anesthesia either as an adjuvant to intrathecal bupivacaine or as intravenous infusion started immediately after the induction of spinal anesthesia has not been fully established.

Accordingly, the aim of this prospective randomized study was to evaluate the effect of supplementary i.v. infusion of magnesium sulfate vs intrathecal magnesium during spinal anesthesia on postoperative pain, analgesic consumption, and intraoperative blood loss in patients undergoing total hip replacement surgery.

2. Methods

Following Institutional Ethical Committee approval and informed written consent from each patient, 75 adult patients American Society of Anesthesiologists (ASA) physical status I and II undergoing unilateral total hip arthroplasty were enrolled in this prospective randomized controlled study. Exclusion criteria included bleeding disorders, cardiac, renal or hepatic dysfunction, neuromuscular diseases, opioid abuse, known allergy to the medications used, and treatment with calcium channel blockers. The study was conducted at Kasr El Aini hospitals, and patients were recruited in the period between January 2011 and May 2012.

Patients were randomly assigned to one of three groups (25 patients each) using closed envelopes. On arrival to the operating theater, each patient received 500 mL of Ringer's solution over 10–15 min. Standard monitoring including electrocardiography (ECG), pulse oximetry, and noninvasive blood pressure was applied.

After obtaining baseline values of hemodynamic variables, spinal anesthesia was performed in the lateral decubitus position using Quincke spinal needle 25 G inserted via a midline approach through the L3–4 or L4–5 interspace under proper aseptic conditions with the surgical side down. 12–15 mg Hyperbaric bupivacaine (Astra Zeneca, Sweden) and solution with 0.5 mL (25 mcg) fentanyl were injected intrathecally in all patients of Group I (control) ($n = 25$). The dose of Bupivacaine was based on patients' height (< 155 cm = 12 mg, 155–170 cm = 13 mg, 170–180 cm = 14 mg, 180 cm = 15 mg) [13].

In Group II (IT Mg) ($n = 25$), 0.5 mL (50 mg) of magnesium sulfate was added to the previous mixture before intrathecal injection in all patients of this group. In Group III (IV Mg) ($n = 25$), the same dose of bupivacaine and fentanyl were injected intrathecally as in group I, a bolus dose of magnesium sulfate 40 mg kg^{-1} in 100 mL of isotonic saline was infused i.v. to all patients of this group over 10 min after a stable block level and hemodynamic status, and before the start of the surgery, followed by continuous infusion of 15 mg kg^{-1} h^{-1} till the end of surgery.

Immediately after intrathecal injection of the local anesthetic, patients were turned into the supine position. Oxygen 3 L/min was applied to all patients via nasal prongs. Mean arterial pressure was monitored every 5 min intraoperatively and every 10 min in the postanesthesia care unit (PACU) and recorded at the following times: before induction (base line T0), immediately after spinal anesthesia (T1), and at 5, 10, 15, 30, 60, 90, 120 min thereafter, and at 30 min, 1, 4, 12, and 24 h after surgery (T2–T13). Hypotension (systolic blood pressure < 90 mmHg or mean arterial pressure decreased by > 20% from baseline) was treated with a bolus dose of ephedrine 5 mg and fluid as indicated. Atropine 0.5 mg was given to treat bradycardia (HR < 50 b/min).

Bilateral sensory block to pinprick was tested in a cephalad to caudal direction in the midclavicular line bilaterally, measurements included the onset (time from intrathecal injection of drugs to reach T10 sensory level), highest dermatome level achieved, and the duration of sensory block (time from peak of sensory block till regression to S1).

Motor blockade of the lower extremity muscles was assessed using Bromage Score: (0 = no motor block, ability to raise hips, knees, and ankles. 1 = unable to raise extended legs, able to move knees and feet. 2 = unable to raise extended leg or move knee; able to move feet. 3 = unable to move any part of the lower limbs) [14] measurements included the onset (time from induction of spinal anesthesia till Bromage = 3) and duration (time from complete block till Bromage = 0).

At the end of surgery, patients were transferred to the PACU. The level of pain based on visual analog scale (VAS) (where 0 = no pain and 10 = worst pain) was assessed immediately after surgery, 1 h, 2 h, 6 h, 12 h, and 24 h after surgery.

Patients were also assessed for side effects as nausea, vomiting, bradycardia, and hypotension.

Intraoperative blood loss was estimated based on the amount of blood in the suction container and the difference in weights between the dry and blood soaked towels.

Preoperative serum Mg level was checked in each patient, and then, blood samples for measuring serum Mg were obtained immediately postoperative, at 6 and 24 h after surgery.

A standard postoperative analgesia was performed using i.v. ketorolac 30 mg/6 h and i.v. paracetamol 1 gm/6 h. Meperidine 50 mg i.m was given whenever VAS > 3. Meperidine was also given whenever needed by the patient in between the assessment visits, provided that 4 h at least should be passed since the last dose.

The time to first analgesic requirement was estimated as well as the total meperidine consumption in the first 24 h postoperative.

2.1. Statistical analysis

Statistical analysis was done using Prism 5.0a (GraphPad Software, Inc.). Data were expressed as mean (SD), median, and range or ratio as indicated. One-way analysis of variance (ANOVA) was used for comparisons between groups. Categorical variables were compared using the Chi-square test. A p value of < 0.05 was considered statistically significant.

3. Results

There were no significant differences as regard age, height, body weight, and operative time between the three study groups (Table 1).

Baseline MAP and HR were insignificantly different in the three groups. However, MAP values were significantly lower in group III compared to the other 2 groups at 30 min after spinal anesthesia and up to 1 h postoperative (Fig. 1). Three patients in group III developed intraoperative hypotension which was treated with ephedrine 5 mg and fluid (250 mL of Ringer's solution) boluses. HR variables were insignificantly different between the three study groups throughout the study (Fig. 2). Two patients in group III compared to one patient in group I and another one in group II had bradycardia, and the HR dropped below 50/min and returned to normal value after atropine 0.5 mg. The SpO_2 was higher than 95% in all patients of the three groups, either during surgery or in the PACU.

Insignificant differences were recorded between the three study groups as regard onset of sensory blockade and, the maximal dermatome height achieved. Time to two segment regression and the duration of sensory blockade were significantly shorter among patients of group I compared to group II and III with insignificant differences between them (Table 2).

The mean onset time and the time to complete recovery of motor blockade were insignificantly different between the 3 study groups (Table 2).

The pain scores (VAS) were significantly lower in group II and III compared to group I at 2 h, 6 h, and 12 h postoperative. Insignificant differences between group II and III were recorded throughout the study (Table 3).

The time to first analgesic request was prolonged significantly in group II and III compared to group I. In addition, the total postoperative 24 h meperidine requirement was significantly higher in group I compared to the other 2 groups (Table 4).

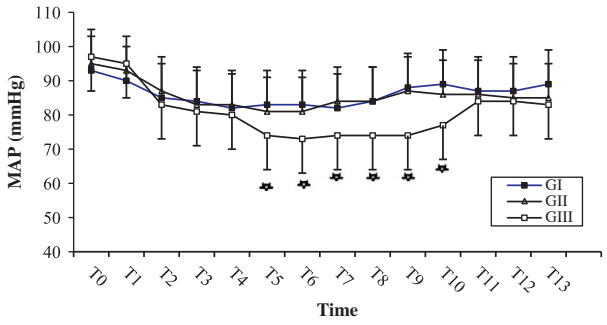

Figure 1 Perioperative mean arterial pressure (mmHg). GI (control); GII (IT Mg); Group III (IV Mg). T0 (before induction); T1 (postinduction); T2 (5 min); T3 (10 min); T4 (15 min); T5 (30 min); T6 (60 min); T7 (90 min); T8(120 min); T9 (30 min postoperative); T10(1 h postoperative); T11(4 h postoperative); T12(12 h postoperative); T13 (24 h postoperative); *statistically significant compared to group I and II.

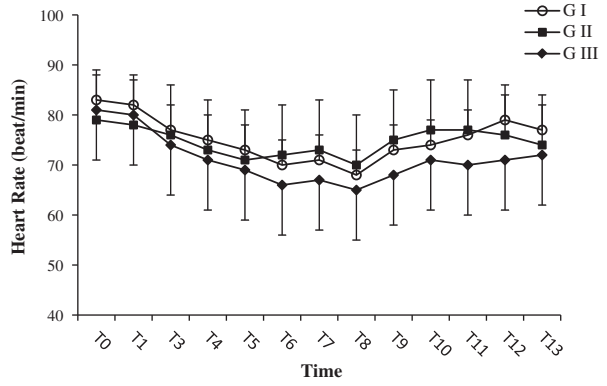

Figure 2 Perioperative heart rate (Beat/min). GI (control); GII (IT Mg); Group III (IV Mg). T0 (pre induction); T1 (postinduction); T2 (5 min); T3 (10 min); T4 (15 min); T5 (30 min); T6 (60 min); T7 (90 min); T8(120 min); T9 (30 min postoperative); T10(1 h postoperative); T11(4 h postoperative); T12(12 h postoperative); T13 (24 h postoperative).

Table 1 Demographic and operative data {mean (SD) and ratio}.

	Group I (control) (n = 25)	Group II (IT Mg) (n = 25)	Group III (IV Mg) (n = 25)
Age (years)	63.04(4.49)	64.8(2.29)	62.72(2.57)
Weight (kg)	76.1(4.3)	78.6(6.02)	79.2(4.7)
Height (cm)	167(9.4)	165(8.7	164(11.7)
Sex (male/female)	12/13	14/11	12/13
Duration of surgery (min)	118(16.3)	126(10.02)	122(11.7)
Intraoperative blood loss (mL)	790(66.14)	778(75.11)	428(57.88)*

IT = intrathecal, IV = intravenous.
* Statistically significant compared to group I and II.

Table 2 Onset and duration of sensory and motor block in the study groups {mean (SD) and median and range}.

	Group I (control) (n = 25)	Group II (IT Mg) (n = 25)	Group III (IV Mg) (n = 25)	P value
Sensory blockade				
Onset (Time to reach T10) (min)	4.78(0.78)	4.97(0.74)	5.0(0.69)	0.5492
Maximum sensory level	T5 (T4–T6)	T6 (T5–T7)	T5 (T4–T6)	0.0925
Time to Two segment regression (min)	77.84(8.65)*	127.2(10.32)	131.6(11.46)	0.0001
Duration (min)	227.1(16.26)*	299.7(18.31)	303.7(21.77)	0.0001
Motor blockade				
Onset (Time to Bromage = 3) (min)	7.68(0.70)	6.72(2.97)	7.34(0.80)	0.1288
Duration (Time to Bromage = 0) (min)	193.8(21.42)	200.4(11.81)	198.1(24.03)	0.6695

IT = intrathecal, IV = intravenous.
* Statistically significant compared to group II and III.

Table 3 Postoperative VAS at different times of the study {median (rang)}.

	Group I (control) (n = 25)	Group II (ITMg) (n = 25)	Group III (IV Mg) (n = 25)
Immediate postoperative	0 (0–2)	0 (0–1)	0 (0–1)
1 h Postoperative	0 (0–3)	0 (0–2)	0 (0–2)
2 h Postoperative	4 (3–5)*	2 (0–3)	2 (0–2)
6 h Postoperative	5 (4–6)*	3 (2–4)	3 (1–4)
12 h Postoperative	4 (3–5)*	1 (0–3)	1 (0–2)
24 h Postoperative	2 (2–3)	2 (1–3)	2 (1–3)

VAS = Visual Analog Score, IT = intrathecal, IV = intravenous.
* Statistically significant compared to group II and III ($p < 0.05$).

Table 4 Time for first analgesic request and total postoperative 24 h meperidine consumption [mean (SD)].

	Group I (Control) (n = 25)	Group II (IT Mg) (n = 25)	Group III (IV Mg) (n = 25)
Time for 1st. analgesic request (min)	185 (6.44)*	242 (9.78)	238 (9.5)
Total postoperative 24 h meperidine consumption	164 (22.9)*	120 (25)	118 (24.49)

IT = intrathecal, IV = intravenous.
* Statistically significant compared to group II and III ($p < 0.05$).

Table 5 Perioperative serum magnesium concentrations (mmol/L) at different times of the study {mean (SD)}.

Serum Mg (mmol/L)	Group I (control) (n = 25)	Group II (IT Mg) (n = 25)	Group III (IV Mg) (n = 25)	P value
Preoperative	1.17(0.25)	1.16(0.24)	1.04(0.20)	0.0912
Immediately postoperative	1.024(0.18)	1.29(0.24)	2.16(0.19)*	0.0001
Postoperative 6 h	1.04(0.18)	1.10(0.13)	1.66(0.40)*	0.0001
Postoperative 24 h	0.98(0.13)	1.08(0.14)	1.05(0.21)	0.1167

IT = intrathecal, IV = intravenous.
* Statistically significant compared to group I and II.

Intraoperative blood loss was reduced significantly among patients of group III compared to the other 2 groups ($P < 0.0001$) (Table 1).

The incidence of nausea and vomiting was insignificantly different between the three groups during the study.

Postoperative serum Mg in group III was significantly higher than the other 2 groups immediately postoperative and, at 6 h postoperative. Serum Mg levels returned to the normal values at 24 h postoperative (Table 5).

4. Discussion

This study demonstrated that both i.v infusion of Mg sulfate and intrathecal Mg during THA surgery under spinal anesthe-

sia reduced postoperative pain and analgesic consumption. Intraoperative infusion of Mg sulfate was associated with significant reduction in intraoperative MAP and blood loss as well.

Total hip arthroplasty (THA) has been a major advance for treatment of chronic arthritis of the hip, providing patients with pain relief and mobility. Blood loss (related to intraoperative tissue trauma), cardiovascular instability, and postoperative analgesia are major concerns during hip surgery [15].

Seyhan et al. [16] studied the effect of three different doses of Mg on postoperative consumption of morphine, and a single dose of 40 mg kg^{-1} was found to decrease postoperative morphine consumption, when this dose was followed by a continuous infusion of 10 mg kg^{-1} h^{-1}, the effect was enhanced. However, increasing the infusion dose to 20 mg kg^{-1} h^{-1} led to hemodynamic instability without additional analgesic effect. Perioperative administration of Mg sulfate (50 mg kg^{-1}) and continuous infusion of (15 mg kg^{-1} $h^{-1)}$ in gynecology patients receiving total i.v anesthesia decreased rocuronium requirements and improved postoperative analgesia without significant side effects [17,18]. Several studies have investigated the effect of intrathecal and i.v. Mg as adjuvant to bupivacaine and fentanyl spinal anesthesia on postoperative pain and analgesic consumption and have shown that both intrathecal and i.v Mg are safe and prolong the time to first analgesic requirement [13,19]. Based on the previous studies, we used a bolus dose of magnesium sulfate (40 mg kg^{-1}) and continuous infusion of (15 mg kg^{-1} $h^{-1)}$ in group III and a dose of (50 mg) magnesium sulfate as intrathecal adjuvant to bupivacaine in group II.

In the present study, intraoperative hemodynamics were stable in all patients of group I and II. Patients in groups III had lower intraoperative MAP and blood loss. These results are in agreement with the previous studies which used Mg sulfate infusion as a hypotensive agent during clipping of cerebral aneurysm, major maxillofacial surgery, and in functional endoscopic sinus surgery [8,20,21]. Magnesium has been used in hypertensive patients undergoing cataract surgery under local anesthesia, and it was effective in controlling blood pressure during surgery. It has been proved in a previous study that Magnesium increased cerebral blood flow velocity which has a beneficial effect during hypotensive anesthesia technique [22,23].

In the current study, insignificant differences were recorded between the three study groups as regard the onset, the maximum sensory level achieved, as well as the onset and duration of motor blockade. These results are in accordance with the results of a previous study which reported that concomitant intrathecal administration of MgSO4 with bupivacaine in patients undergoing cesarean section did not reduce the onset time of sensory and motor blockade or prolong the duration of spinal anesthesia [24]. Hwang et al. [13] reported similar results with i.v. infusion of Mg sulfate as regard the height of spinal block.

VAS scores and total meperidine consumption in the first 24 h postoperative reported in our study were significantly lower in group II and III compared to group I.

Clinical trials have shown conflicting results while investigating analgesic efficacy of magnesium. Tramer and colleagues [25] reported that magnesium supplementation to patients undergoing lower abdominal surgery has led to 30% reduction in postoperative consumption of morphine. Other clinical studies [7,26,27] also demonstrated significant reduction in postoperative morphine, fentanyl, and piritramide consumption following uterus, knee, and lumbar surgeries. These results, however, are in agreement with our results.

The current study results are still in agreement with the work done by Tauzin et al. [28] who demonstrated that skin infiltration of MgSO4 and ropivacaine for postoperative analgesia after radical retropubic prostatectomy lead to significant reduction in tramadol requirements.

Our results are in line with another study which suggested that supplementation of spinal anesthesia with intrathecal and epidural MgSo4 significantly reduced postoperative analgesic consumption in patients undergoing orthopedic surgery [29]. In addition, other investigators have found that i.v. Mg sulfate administration during lower limb surgery under spinal anesthesia reduced postoperative pain and total morphine consumption [30].

Our results are partly in accordance with the previous results [31] where 5 mg kg^{-1} Mg sulfate boluses were given to patients after spinal anesthesia and followed by a 500 mg h^{-1} infusion or saline for 24 h. Postoperative analgesic consumption was lower in Mg group, while VAS scores were indifferent in both groups during the first 24 h postoperative period. This could be explained by that Mg dose was insufficient for postoperative analgesia.

On the other hand, previous reports have suggested that both i.v. and intrathecal magnesium failed to reduce the severity of postoperative pain and the cumulative analgesic consumption [11,12,19]. In the first study [11], however, fentanyl was not given for intraoperative analgesia. In the second study [12], different doses of magnesium have been used. Whereas in the third study [19], magnesium sulfate 50 mg was added to low-dose (6 mg) bupivacaine 0.5% plus 10 mcg fentanyl intrathecally. Although the exact mechanism of interaction between the NMDA receptors and opioid antinociception has not been fully elucidated, magnesium supplementation proved to potentiate the analgesic effect of opioids and delay the development of tolerance [12].

In the present study, serum Mg concentrations in group III were significantly higher than the other 2 groups, immediately after surgery and at 6 h postoperative. These high levels, however, were safely less than the toxic levels (Mg toxicity begins at serum concentration of 2.5–5 mmol/L, cardiac arrest occurs at 12.5 mmol/L) [32].

An inverse relationship has been found between the severity of postoperative pain and serum magnesium level. Accordingly, prevention of perioperative hypomagnesaemia is an important factor for antinociceptive mechanism [32].

5. Conclusion

This study suggested that co-administration of intravenous Mg sulfate or intrathecal Mg given to patients undergoing spinal anesthesia for total hip arthroplasty could improve pain control for the first 24 h after surgery. While there was no significant difference between the two modalities as regard pain scores, however, i.v. magnesium led to relative hypotension and decreased blood loss. Further studies are still needed to verify these results.

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