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ORIGINAL ARTICLE

Effects of adjunct intrathecal magnesium sulfate to bupivacaine for spinal anesthesia: a randomized, double-blind trial in patients undergoing lower extremity surgery

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Abstract
Purpose The aim of this study was to evaluate the effect of additional magnesium sulfate ($MgSO_4$) 100 mg to intrathecal (IT) isobaric 0.5% bupivacaine 3 ml on spinal anesthesia in patients undergoing lower extremity orthopedic surgery.
Methods In a double-blind randomized clinical trial, 79 American Association of Anesthesiologists (ASA) I or II adult patients undergoing lower extremity orthopedic surgery were recruited. The patients were randomly allocated to receive 100 mg $MgSO_4$ 5% (0.2 ml) plus 15 mg of bupivacaine 0.5% ($MgSO_4$ group) or 15 mg bupivacaine 0.5% combined with 0.2 ml normal saline (control group) intrathecally. Response to treatment was assessed as onset and duration of sensory block, the highest level of sensory block, time to complete motor block recovery, duration of spinal anesthesia, and postoperative analgesic requirement.
Results The onset of the sensory block was slower in the $MgSO_4$ group than in the control group (13.3 vs. 11.6 min, $P = 0.04$), and the duration of the sensory blockade was significantly longer in the $MgSO_4$ group than the control group (106.5 vs. 85.5 min, $P = 0.001$). Total analgesic requirements for 24 h following surgery were lower in the $MgSO_4$ group than in the control group (96.8 vs. 138.5 mg, $P = 0.001$). Mean duration of spinal anesthesia was not significantly different between two groups (178.0 vs. 167.4 min, $P = 0.23$).
Conclusion In patients undergoing lower extremity surgery with spinal anesthesia, the addition of 100 mg IT $MgSO_4$ to 15 mg bupivacaine without opioid supplement, prolonged the duration of the sensory block, decreased postoperative analgesic consumption, and significantly prolonged the onset of spinal anesthesia.

Keywords Bupivacaine · Drugs · Efficacy · Intrathecal · Magnesium sulfate · Spinal anesthesia

Introduction

The limitations of spinal anesthesia are the relatively short duration of the anesthesia and a possible increase in the postoperative analgesic requirement in patients undergoing lower extremity surgery. Both animal and human studies have shown that the addition of intrathecal (IT) magnesium sulfate ($MgSO_4$) prolongs spinal anesthesia and reduces the incidence of side effects observed when local anesthesia are used in high doses or combined with opioid analgesia [1, 2]. $MgSO_4$ produces anti-nociception and potentiation of opioid activity, presumably by its action as a voltage-gated *N*-methyl-D-asparate (NMDA) receptor agonist [3].

The mechanism of action of $MgSO_4$ in reducing postoperative pain and prolonging the duration of sensory blockade in these patients fits well with current knowledge on the pharmacological mechanisms underlying the anti-nociceptive action of the Mg^{2+} ion. The Mg^{2+} ion blocks NMDA receptor-associated channels, which are ligand-gated ion channels that generate slow excitatory post-synaptic currents at glutamatergic synapses, in a voltage-dependent manner [4, 5].

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Only a few clinical trials have examined the effect of adding $MgSO_4$ to IT bupivacaine plus opioids in patients undergoing orthopedic surgery [6–8], and the results of these studies have been conflicting. In some of these clinical trials in orthopedic [7, 9] and nonorthopedic [10–13] populations, the adjunction of 50 mg IT $MgSO_4$ to bupivacaine plus opioids to spinal anesthesia increases the duration of analgesia without increasing side effects; however, other trials did not demonstrate any direct benefit [4, 8, 14]. It would appear that to increase the effect of adding $MgSO_4$ to bupivacaine, higher doses of $MgSO_4$ are required. Although the results of adding $MgSO_4$ 50 mg to IT bupivacaine are conflicting, the effect of increasing the dose of additional $MgSO_4$ has not been fully investigated.

The objective of this study, therefore, was to compare the effects of adding 100 mg IT $MgSO_4$ to 15 mg bupivacaine with a 15 mg bupivacaine in combination with normal saline to investigate their tolerability and relative efficacy.

Patients and methods

The study was approved by the institutional ethical committee. The patient cohort comprised 100 consecutive American Society of Anesthesiologists (ASA) PS 1–2 adult patients who were scheduled for orthopedic lower extremity surgery (fracture of tibia and/or fibula) under spinal anesthesia from July 2008 to February 2009. Patients were excluded from the study if they had any contraindication to the spinal anesthesia, a history of long-term opioid use, chronic pain, peripheral or central neuropathies, or pre-existing severe cardiac, endocrinological, hematological, hepatic, renal, metabolic, neurological, or psychiatric disorders.

After obtaining informed consent, patients were instructed preoperatively in the use of the verbal rating scale (VRS) for pain assessment (0, no pain at all; 10, maximum pain imaginable). Patients were randomized to one of the two treatment groups using a list of computer-generated numbers. The group assignments were concealed in opaque, sealed envelope until just before the spinal anesthesia was given.

All patients fasted for the 8 h immediately preceding the operation and received intravenous diazepam 0.2 mg/kg 2 h before the operation. All patients received an intravenous pre-load of 15 ml/kg lactated Ringer's solution before the spinal anesthesia. Intra-operative monitoring included pulse oximetry, automated blood pressure measurement, and lead II electrocardiogram. Patients in the control group received a premixed solution of 15 mg isobaric bupivacaine 0.5% (3 ml) and 0.2 ml of preservative-free 0.9% sodium chloride intrathecally, and those in $MgSO_4$ group received a premixed solution of 15 mg isobaric bupivacaine 0.5% (3 ml) and 100 mg of $MgSO_4$ 5% (0.2 ml) (Pasteur Institute Co, Tehran, Iran) intrathecally. Both patients and anesthesiologists were blind to the treatment. Spinal anesthesia was given with the patient in the sitting position. A 25-gauge Quincke spinal needle was introduced into the subarachnoid space at the L_{3-4} vertebral level via a midline approach. With the needle orifice in a cephalad orientation, cerebrospinal fluid was aspirated, and the premixed solution was injected through the spinal needle over a period of 10 s with no barbotage. The spinal needle was withdrawn, and patients were repositioned supine with slight elevation of the head for comfort. No additional analgesic was administered unless requested by the patient.

Masking of the both treatments was preserved by creating treatments that looked identical. Participants were evaluated by a qualified anesthesiologist (GA) at baseline and after the start of the therapy to evaluate the efficacy parameters and the development of side effects of the medications.

Surgery was commenced at least 20 min after the IT injection. Sensory and motor block, systolic and diastolic blood pressures, heart rate, respiratory rate, and peripheral oxygen saturation (SpO_2) were recorded 5 min before IT injection, the first 5, 10, 15, 20, and 25 min after IT injection, and subsequently every 15 min until the patient complained of pain. Pain scores were recorded 5 min before IT injection, after the start of surgery, and subsequently every 15 min until surgery was completed.

The onset and duration of the sensory block, highest level of the sensory block, time to reach the highest dermatomal level of sensory block, time to complete motor block recovery, duration of spinal anesthesia, and total dose of analgesic consumption were also recorded. The onset of the sensory block was defined as the time between IT injection and the absence of pain at the T10 dermatome, as assessed by pinprick; the duration of sensory block was defined as the time for regression of two segments in the maximum block height, as evaluated by pinprick. The highest level of the sensory block was evaluated by pinprick every 5 min for 25 min after injection. The motor block was assessed by modified Bromage score (0, no motor loss; 1, inability to flex the hip; 2, inability to flex the knee; 3, inability to flex the ankle); complete motor block recovery was assumed when the modified Bromage score was zero. The duration of spinal anesthesia was defined as the period from spinal injection to the first occasion when the patient complained of pain in the postoperative period.

Sedation was assessed using a 5-point scale (0, hyper alert; 1, fully awake and alert; 2, drowsy; 3, light sleep; 4, deep sleep, not arousable by verbal contact). If the VRS exceeded 3, tramadol HCl, 1 mg/kg, was given intravenously for pain relief. The first dose of tramadol was given

when the patient requested analgesia. Time to first analgesic requirement was measured from the time of spinal injection to the first time that the patient complained of pain in the postoperative period. Patients were allowed to take tramadol tablets, 50 mg every 6 h, following surgery, when they requested analgesics for subsequent pain relief. An intravenous bolus of 500 ml lactated Ringer's solution was given to maintain the blood pressure. If the systolic blood pressure was >20% below baseline or <90 mmHg, intravenous ephedrine 10 mg was given repeatedly. If the heart rate was <60 beats/min, 0.5 mg of atropine sulfate was administered intravenously. The incidence of hypotension (mean arterial pressure <20% of baseline), bradycardia (heart rate <60 beats/min), hypoxemia (SpO_2 <90), and excessive sedation (sedation score ≥3), pruritus, dizziness, nausea, and vomiting was recorded. Patients were discharged from the recovery room when the motor block was completely resolved. The discharge criteria for the ward were stable vital signs, no nausea or vomiting. and no severe pain or bleeding. Patients were also assessed for the presence of motor or sensory complications on the day after surgery by an observer blind to the treatment group.

We calculated that 40 patients per treatment group would be required to provide the study with 80% power to detect (with a two-sided alpha of 0.05) a mean difference of 15 min in the duration of spinal anesthesia between groups. The results for the groups that received $MgSO_4$ or normal saline were compared with Student's t test for independent samples. We used the chi-square or Fisher's exact test to compare proportions. The results are expressed as the mean (standard deviation, SD), and $P < 0.05$ was considered to be statistically significant. All statistical tests were two-sided. Analysis was performed using the SPSS package for Windows (SPSS, Chicago, IL).

Results

A total of 100 patients were recruited in the study. Six patients refused to participate, and 15 patients did not meet our study criteria. Thus, 79 patients were randomized and assigned to both groups, as described in Table 1. The two treatment groups were generally matched at baseline in terms of age, gender, height, weight, body mass index and duration of surgery. No differences were found in cardiorespiratory variables (systolic and diastolic blood pressure, heart rate, respiratory rate, or SpO_2) between the groups during surgery.

Although the $MgSO_4$ group had a longer duration of spinal anesthesia, there was no significant differences in the duration of spinal anesthesia [mean difference 10.6 min; 95% confidence interval (CI) −6.8 to 28.0; $P = 0.23$] and time to complete motor recovery (mean difference −2.0 min; 95% CI −44.8 to 4.0; $P = 0.93$) between the $MgSO_4$ and control groups. Total intravenous tramadol consumption during first 24 postoperative hours was higher in the normal saline group than in the $MgSO_4$ group (138 vs. 96.8 mg; $P = 0.001$).

There was a non-significant increase in average time to maximum sensory block for the $MgSO_4$ group (mean difference 2.0 min; 95% CI −0.3 to 4.3; $P = 0.09$). The mean time to the onset of the sensory block was significantly increased by 1.7 min (95% CI 0.01–3.4; $P = 0.04$) in the $MgSO_4$ group compared to control group. The average duration of sensory block was significantly increased by 21 min (95% CI 12.5–29.5; $P = 0.001$) in the $MgSO_4$ group compared to control group (Table 2).

$MgSO_4$ treatment was tolerated well, and most of the adverse events reported were mild in severity. The most common side effects of $MgSO_4$ were nausea ($n = 6$), pruritus ($n = 6$), and vomiting ($n = 4$). The most common side effects of normal saline were also nausea ($n = 4$), pruritus ($n = 5$), and vomiting ($n = 2$). There were no significant differences in the incidences of these side effects, and none of the patients in either group had hypotension, bradycardia, or hypoxemia requiring treatment.

Discussion

In this trial, the addition of 100 mg IT $MgSO_4$ to 15 mg bupivacaine without opioids reduced total analgesic consumption in the first 24 h and prolonged the onset and duration of the sensory blockade, without side effects. To the best of our knowledge, this is the first study to compare the effect of adding 100 mg $MgSO_4$ to IT 15 mg bupivacaine without opioids with adding normal saline to IT 15 mg bupivacaine without opioids in patients undergoing lower extremity surgery. No unusual or unexpected safety risks were found with $MgSO_4$ therapy in our study population. The spectrum of most frequent adverse events is similar to that reported in previous studies of $MgSO_4$ treatment, which have also shown that the use of $MgSO_4$ is fairly safe [7, 8, 11].

Compared with the saline group, the $MgSO_4$ group had a reduced total dose consumption of tramadol of approximately 42 mg. Similar reductions in analgesic requirements have been reported in other orthopedic and non-orthopedic populations [7, 9, 12, 15, 16]. This effect is in contrast to that reported in a number of other studies [3, 8]. Taken together, these results seem to indicate that in order for total analgesic consumption to be reduced, higher doses of $MgSO_4$ are required, similar to the dose used in our study (100 mg) and that of Arcioni et al. [9].

In our study, the addition of 100 mg $MgSO_4$ to spinal anesthesia did not affect the time to complete motor

Table 1 Characteristics of patients undergoing lower extremity orthopedic surgery who received adjunct magnesium sulfate ($MgSO_4$, 100 mg) to bupivocaine or bupivocaine and normal saline

Patient characteristics	$MgSO_4$ group[a] ($n = 40$)	Control group[a] ($n = 39$)	Differences (95% CI)	*P* value
Age (years)	36.4 (14.6)	41.3 (16.2)	−4.9 (−11.8 to 2.0)	0.16
Height (cm)	167.4 (8.1)	166.0 (7.7)	1.4 (−2.1 to 4.9)	0.43
Weight (kg)	68.7 (8.4)	69.1 (9.9)	−0.4 (−4.5 to 3.7)	0.85
Body mass index (kg/m^2)	24.5 (1.8)	24.8 (2.6)	−0.3 (−1.3 to 0.7)	0.55
Duration of surgery (min)	78.9 (23.1)	70.8 (12.6)	8.1 (−0.3 to 16.5)	0.07
Gender				
Men	30 (75.0)	30 (76.9)	−1.9 (−20.8 to 16.9)	0.42
Women	10 (25.0)	9 (23.1)	–	

CI confidence interval

[a] Data are presented as the mean, with the standard deviation (SD) in parentheses, except for Gender, for which data are presented as the number (*n*), with the percentage in parentheses

Table 2 Comparison of characteristics of spinal block in 79 patients undergoing lower extremity surgery treated with $MgSO_4$ and bupivocaine and normal saline and bupivocaine

Characteristics of spinal block	Treatment group[a]		Difference (95% CI)	*P* value
	$MgSO_4$ group ($n = 40$)	Control group ($n = 39$)		
Time to maximum sensory block (min)	21.5 (3.6)	19.5 (6.4)	2.0 (−0.3 to 4.3)	0.09
Time to onset of sensory block (min	13.3 (4.0)	11.6 (3.5)	1.7 (0.01 to 3.4)	0.04
Duration of sensory block (min)	106.5 (22.0)	85.5 (15.3)	21.0 (12.5 to 29.5)	0.001
Duration of spinal anesthesia[b] (min)	178.0 (44.4)	167.4 (32.0)	10.6 (−6.8 to 28.0)	0.23
Time to complete motor recovery (min)	120.0 (133.1)	122.0 (18.2)	−2.0 (−44.8 to 40.8)	0.93
Total dose of analgesic consumption (mg)	96.8 (33.4)	138.5 (51.2)	−41.7 (−61.0 to −22.4)	0.001

CI confidence interval

[a] Data are presented as the mean, with the SD in parentheses

[b] Duration of spinal anesthesia was defined as the period from spinal injection to the first occasion when the patients complained of pain in the post-operative period

recovery, but it did cause a significant increase in the duration of the sensory block. Previous data are inconsistent regarding the effects of prolongation of the sensory block by $MgSO_4$ [7, 8, 17], with some studies reporting increases in the duration of the sensory block [7] and others reported decreases [8, 17]. The mechanisms whereby $MgSO_4$ exerts a positive or negative effect on the duration of sensory block are not clear. We are currently unable to explain this increase in duration of the sensory block in spinal anesthesia with adjunct IT $MgSO_4$ to bupivacaine, and this topic should be addressed in further studies.

Consistent with published results [3, 7], we found that the mean duration of spinal anesthesia was prolonged with the addition of IT $MgSO_4$, but this difference was not statistically significant. The absence of a statistically significant difference may simply indicate that IT $MgSO_4$ actually does not prolong the duration of spinal anesthesia, or it may be due to the limited statistical power of the study. The finding of a non-significant increase in the mean duration of spinal anesthesia warrants further investigation with a larger sample size.

Our findings are consistent with those of Ozalevli et al. [7] who observed a similar delay in the onset of spinal anesthesia when IT $MgSO_4$ was added to fentanyl and isobaric bupivacaine. These authors suggested that differences in the pH and baricity of the solution containing $MgSO_4$ contributed to the delayed onset. In another trial, parturients undergoing cesarean section during spinal anesthesia were randomly assigned to receive 50 mg $MgSO_4$, normal saline, or 25 μg of fentanyl following 10 mg IT bupivacaine 0.5%. In that study, $MgSO_4$ did not shorten the onset time of the sensory and motor blockade or prolong the duration of spinal anesthesia, as seen with fentanyl [17].

As the ideal dose or concentration of IT $MgSO_4$ that provides satisfactory analgesia and patient comfort during orthopedic surgeries has yet to be found, the choice of dose or concentration to achieve the desired clinical effect may

be important. The dose of $MgSO_4$ that we used was two-fold that of previous studies [3, 7]. Compared to previously published data and from the clinical point of standpoint, the 100 mg $MgSO_4$ used in our study does not seem to have had any more desirable effects than 50 mg $MgSO_4$. Although 100 mg $MgSO_4$ reduced the postoperative analgesic requirement, there were no substantial differences between the $MgSO_4$ and normal saline groups in the frequency or pattern of side effects. This study also explored the possibility that the addition of high-dose $MgSO_4$ could replace fentanyl, thereby avoiding opioid side effects, such as sedation, pruritus, and respiratory depression. The IT dose of 100 mg $MgSO_4$ that we used was based on data from the study of Arcioni et al. [9], who found that a larger $MgSO_4$ dose than that used in previous studies [7] decreased the postoperative analgesic requirement without inducing adverse reactions. The safety of IT $MgSO_4$ administration has been evaluated in animal and human studies [3, 7, 9]. Although only a limited number of studies have been performed in humans to determine the risk of neurotoxicity with IT $MgSO_4$, the clinical trials performed to date have not reported any evidence of neurological squeal or other deleterious effects [3, 7]. However, in animal studies, one study [18] demonstrated that IT $MgSO_4$ 1 mg/kg was neurotoxic in rabbits, whereas other studies demonstrated no neurotoxicity after repeated IT administration of $MgSO_4$ in rats [19] or a single injection in canines [20]. Further studies are needed to determine whether larger doses of $MgSO_4$ produce a greater potentiation of spinal anesthesia without causing any neurological deficit when administered IT.

There are several limitations to this study. We did not assess the incidence and severity of chronic pain after lower extremity orthopedic surgery, which also might have revealed the action of $MgSO_4$ in modulating wind-up and synaptic plasticity. This trial could draw criticism because of the use of a relatively small sample of patients. The efficacy should therefore be tested in a larger sample. The results presented here clearly need to be replicated and extended across multiple centers and investigators.

In conclusion, in patients undergoing lower extremity orthopedic surgery with spinal anesthesia, the addition of 100 mg IT $MgSO_4$ to 15 mg of isobaric 0.5% bupivacaine and without opioid supplement caused small, but significant changes in the properties of the isobaric bupivacaine spinal anesthesia, including the prolonged duration of the sensory blockade and decreased postoperative analgesic consumption, without additional side effects.

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Conflict of interest The authors report no conflict of interest.

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