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Effects of adding magnesium to bupivacaine and fentanyl for spinal anesthesia in knee arthroscopy

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Abstract
Purpose. The aim of the study was to investigate the effects of adding intrathecal magnesium sulfate 50 mg to low-dose bupivacaine-fentanyl on the spread, duration, regression of spinal block, and postoperative analgesia in patients undergoing knee arthroscopy.
Methods. This study was designed in a prospective, randomized, and double-blinded manner. Sixty American Society of Anesthesiologists (ASA) physical status I or II patients were randomly allocated to receive 50 mg magnesium sulfate (3 ml) or 3 ml of preservative-free 0.9% NaCl following 6 mg bupivacaine 0.5% plus 10 μg fentanyl intrathecally. Date were collected regarding the highest level of dermatomal sensory blockade, the time to reach this level from the time of injection of the spinal anesthetic, Bromage scale of motor blockade at the time of reaching maximum sensory level, time for regression of two segments in the maximum block height, time to L_2 regression, time to ambulation, and postoperative analgesic consumption.
Results. The addition of intrathecal magnesium (50 mg) to spinal anesthesia prolonged the time for regression of two segments in the maximum block height and time to L_2 regression, but did not affect maximum sensory level or the time to reach the highest level of sensory block. Even though the mean times to complete recovery of motor function were similar in the two groups, time to ambulation was significantly longer in the magnesium group than in the saline group. Total analgesic consumption in the first 24 h was not decreased significantly with the addition of magnesium to spinal anesthesia, but the time to first analgesic requirement was prolonged significantly.
Conclusion. Even though the time to first analgesic requirement was prolonged significantly by magnesium, the addition of intrathecal magnesium sulfate to spinal anesthesia is not desirable in patients undergoing knee arthroscopy due to the prolonged time to ambulation and the lack of effect of magnesium on postoperative analgesic consumption.

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Introduction

Outpatient knee arthroscopy may be performed under local, regional, or general anesthesia [1–6]. In recent years spinal anesthesia using a low dose of local anesthetic in combination with an opioid has gained popularity for knee arthroscopy due to the much faster recovery than that with traditional methods of spinal anesthesia, the high success rate and patient satisfaction, and the decreased resource utilization compared with general anesthesia [7–10]. Adequate pain management is essential to facilitate rehabilitation and to accelerate functional recovery after knee arthroscopy, thus enabling patients to return to their normal activity more quickly. Even though regional techniques including spinal anesthesia and psoas compartment block provided superior analgesia in the early postoperative period when compared with general anesthesia, there were no significant differences in opioid use between regional technique and general anesthesia groups [4]. A multimodal analgesic approach, including short-acting opioids, local anesthetics, and nonsteroidal anti-inflammatory drugs, has been suggested to maintain visual analogue scale (VAS) pain scores of 3 or less regardless of intraoperative anesthetic technique [3,6].

Central sensitization is an activity-dependent increase in the excitability of spinal neurons and is considered to be one of the mechanisms implicated in the persistence of postoperative pain [11]. Central sensitization has been shown to depend on the activation of dorsal horn *N*-methyl-D aspartate (NMDA) receptors by excitatory amino acid transmitters such as aspartate and glutamate [11,12]. In a previous study, adding a low dose of ketamine (0.15 $mg \cdot kg^{-1}$, i.v.), a noncompetitive antagonist

of NMDA receptors, to a multimodal analgesic regimen improved postoperative analgesia and functional outcome after outpatient knee arthroscopy [13]. Because magnesium (Mg) is also a noncompetitive antagonist to NMDA receptors, it has the potential to prevent central sensitization from peripheral nociceptive stimulation. However, intravenous (i.v.) application of Mg, even at high doses, is associated with limited passage across the blood-brain barrier [14].

In previous studies, it was demonstrated that intrathecally (i.t.) administered Mg prolonged spinal opioid analgesia both in rats and humans [15,16]. The addition of i.t. Mg to spinal anesthesia improved postoperative analgesia in an orthopedic setting [17,18]. The addition of i.t. magnesium sulfate ($MgSO_4$) to 10 mg bupivacaine plus 25 μg fentanyl prolonged spinal anesthesia in patients undergoing lower-extremity surgery [18]. However, according to our knowledge, no previous study has investigated the effect of adding i.t. $MgSO_4$ to low-dose spinal anesthesia in outpatients undergoing knee arthroscopy.

In the present study, the effects of adding i.t. $MgSO_4$ to low-dose bupivacaine-fentanyl on spread, duration, regression of spinal block, and postoperative pain were investigated in patients undergoing knee arthroscopy. We used 50 mg i.t. $MgSO_4$, a dose and route which had been previously shown to prolong fentanyl analgesia without producing motor block in patients [16], and we tested the hypothesis that this dose of magnesium improves postoperative analgesia without prolonging ambulation time.

Methods

The institutional ethics committee approved the protocol of this study and informed consent was obtained from each patient. We studied 60 American Society of Anesthesiologists (ASA) physical status I or II patients who were scheduled to receive spinal anesthesia for elective knee arthroscopy. Patients with any contraindication to the spinal anesthesia or a history of allergy to opioids, and patients who had peripheral or central neuropathies were excluded from the study. After arrival in the operating theater, patients were given 0.05 $mg \cdot kg^{-1}$ i.v. midazolam as premedication, then an infusion of 15–20 $mg \cdot kg^{-1}$ normal saline. Standard monitors included electrocardiography (ECG), noninvasive arterial blood pressure (BP), and pulse oximetry. The patients were randomly assigned, using sealed envelopes, to two groups of 30 patients (groups S and M). Both the patients and the anesthetists were blind to the treatment. Patients in both groups received 6 mg of 5 $mg \cdot ml^{-1}$ hyperbaric bupivacaine and 10 μg of fentanyl in 0.2 ml, after free flow of cerebrospinal fluid. Then, patients in group S received 3 ml of preservative-free 0.9% NaCl; patients in group M received 50 mg $MgSO_4$ in 3 ml of 0.9% NaCl. The 50 mg $MgSO_4$ was prepared by withdrawing 3 ml from a mixture of 1 ml of preservative-free 15% $MgSO_4$ with 8 ml of preservative-free 0.9% NaCl.

Lumbar puncture was performed in a standard fashion at the L_{2-3} or L_{3-4} interspace with the operative knee in the dependent position. Using a median approach, a 25-G pencil-point needle was introduced with the needle aperture directed laterally towards the dependent side. The lateral decubitus position was maintained for 10 min from the beginning of the injection to provide selective spinal anesthesia.

An independent observer who was blinded to the study recorded the evolution of sensory and motor blocks on both sides 5, 10, 15, 20, 25, and 30 min after i.t. injection, and subsequently every 15 min until the time of complete regression of spinal block. Sensory block was assessed as complete loss of sensation to pinprick test. When complete loss of sensation to pinprick test was achieved at T12 on the operative limb, patients were considered ready for surgery.

Motor block was assessed using a modified Bromage scale (0, no motor block; 1, hip blocked; 2, hip and knee blocked; 3, hip, knee, and ankle blocked). Full motor recovery was defined as 0 on the Bromage scale. After comple resolution of the sensory and motor blocks, patients were assessed every 15 min for the ability to walk without support. Time to ambulation was defined as the time elapsed between i.t. injection and ability to walk without assistance.

Data were collected regarding the highest dermatomal level of sensory blockade, the time to reach this level from the time of injection of the spinal anesthetic, Bromage scale of motor blockade at the time of reaching maximum sensory level, time for regression of two segments in the maximum block height, time to L_2 regression, and time to discharge readiness. All times were recorded from the time of injection of the spinal anesthetic.

Systolic blood pressure 20% below baseline or less than 90 mmHg was treated with an i.v. bolus of lactated Ringer's solution followed by i.v. ephedrine, if required. If the heart rate was less than 45 $beats \cdot min^{-1}$, 0.5 mg atropine sulfate was administered intravenously. Side effects, including pruritus, nausea, and vomiting, as well as hypotension, bradycardia, and hypoxemia (peripheral oxygen saturation; $S_{P_{O_2}} < 90$) were recorded.

Postoperative analgesia consisted of i.v. tramadol HCl (1 $mg \cdot kg^{-1}$). 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 at which 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. The home discharge criteria consisted of absence of nausea, vomiting, or bleeding, minimal or no pain, and ability to walk without support. Voiding was not included among the criteria for discharge. A follow-up telephone call was made 24 h after surgery and again 1 month later, during which patients were asked about total analgesic consumption, side effects, and dysesthesia of the lower limbs or buttocks.

On the basis of our clinical experience resulting from our previous pilot study and from a previous study analyzing the discharge characteristics of patients receiving low-dose bupivacaine plus fentanyl for outpatient knee arthroscopy performed at our institution [19], we determined that a sample size of 27 patients per group would have 80% power to detect a difference of at least 20% at $\alpha = 0.05$ in both time to ambulation and time to first analgesic requirement. Because of possible dropouts, we decided to randomize 30 patients to each group. Statistical analyses were performed using the statistical package SPSS version 13 (SPSS, Chicago, IL, USA). Values are presented as means ± SD or as medians (ranges). Data were analyzed using the Mann-Whitney *U*-test, Fisher's exact test, and Student's *t*-test when appropriate. For all determinations, a *P* value of less than 0.05 was considered significant.

Results

There were no significant differences between groups with regard to patient characteristics (Table 1). Readiness for surgery, as defined above, was achieved in all study patients and none of the patients experienced pain during the intraoperative period. Time to reach the highest dermatomal level of sensory block was not different between the two groups (Fig. 1; Table 2). No difference in the highest level of sensory block was observed between the two groups on either the operated or nonoperated sides (Fig. 1, Table 2). Time for regression of two segments in the maximum block height, and time to L_2 regression were significantly longer in group M than in group S (Table 2, $P < 0.05$).

The mean degree of motor block was not different between the two groups on both the operative and nonoperated sides. A strictly unilateral motor block (Bromage score 0 on the nonoperated side) was observed in 30 patients (100%) in group S and 25 (83%) patients in group M ($P > 0.05$). Even though the mean times to complete recovery of motor function were

Table 1. Demographic data for the two groups

	Group M ($n = 30$)	Group S ($n = 30$)
Age (years)	41.2 ± 15.3	38.7 ± 14.4
Sex (F/M)	11/19	12/18
Weight (kg)	74.2 ± 12.1	75.5 ± 8.1
Height (cm)	171.6 ± 10.3	172.6 ± 7
Duration of surgery (min)	56.3 ± 20.8	52.9 ± 18.2

Values are manes ± SD or numbers of patients

Table 2. Characteristics of spinal anesthesia

	Group M	Group S
Sensory block		
Time to reach maximum sensory level (min)	21.5 ± 4.5	22.9 ± 5
Maximum sensory level on the operated side	T7 (T4–T10)	T7 (T4–T10)
Time to two-segment regression (min)	58.9 ± 22.8	44.7 ± 18.9*
Time to L_2 regression (min)	161.9 ± 37.6	135.7 ± 52.7*
Maximum sensory level on the nonoperated side	T11 (T4–L2)	T11 (T4–∅)
Motor block		
Motor block on the operated side (Bromage scale: 0-1-2-3)	2-0-3-25	2-0-7-21
Motor block on the nonoperated side (Bromage scale: 0-1-2-3)	25-0-1-4	30-0-0-0
Time to full motor recovery (min)	86.3 ± 23.7	82 ± 36
Time to ambulation (min)	359.8 ± 90.7	263.8 ± 110.7*
Time to first analgesic requirement (min)	469.1 ± 186.8	36.5.5 ± 121*
Tramadol consumption (number of 50-mg tablets)	2 ± 1	2.6 ± 1.4

* $P < 0.05$ compared with group M
Values are means ± SD, or medians and ranges, or numbers of patients
∅, no sensory block

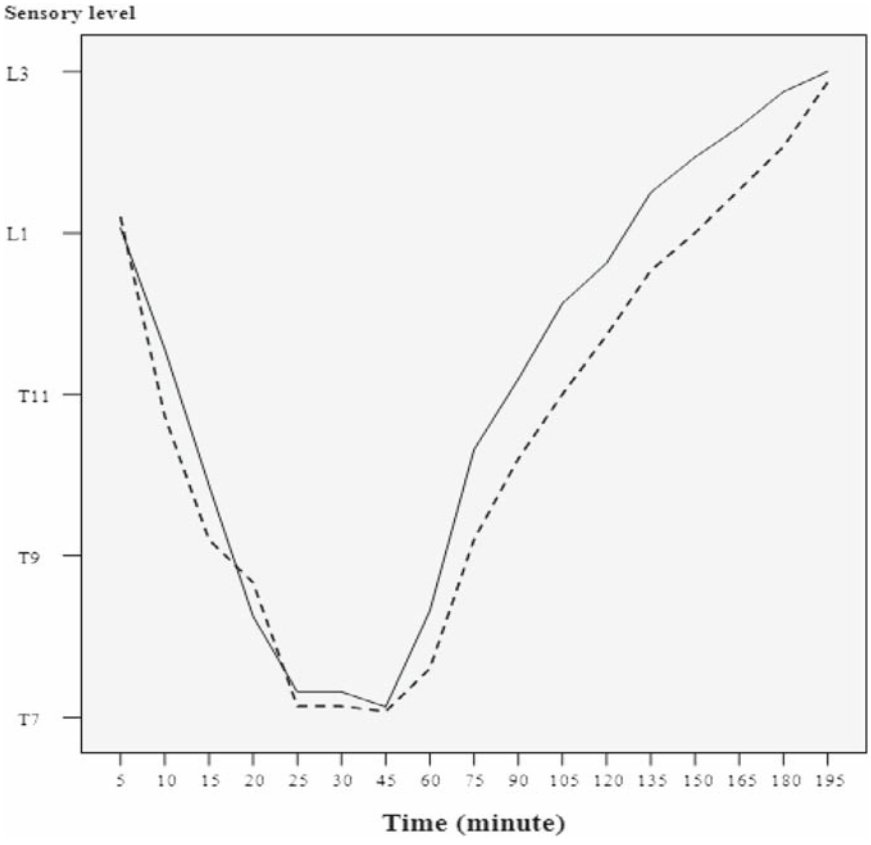

Fig. 1. Evolution of sensory block on operated side. *Continuous line*, Group S (saline); *dotted line*, group M ($MgSO_4$)

similar in the two groups, time to ambulation was significantly longer in group M than in group S (Table 2; $P < 0.05$). Time to discharge readiness was not prolonged in any patient due to unmanaged pain, nausea, vomiting, or bleeding. Voiding was not included among the criteria for discharge. Thus, time to discharge readiness was not different from the time to ambulation in any patient. Time to first analgesic requirement was significantly longer in group M than in group S, but total analgesic consumption did not differ significantly between the two groups (Table 2).

As shown in Table 3, the two groups were not different significantly in terms of intraoperative and postoperative side effects. None of the patients in either group had a hypotensive episode, bradycardia, or hypoxemia requiring treatment (Table 3). In group S, one male patient aged 42 years needed a urethral catheter due to urinary retention after hospital discharge. Another two patients (one patient from each group) had mild difficulty initiating micturition. In group M, one male patient aged 37 years experienced very severe postspinal headache which required readmission to the hospital. The postspinal headache persisted for 4 days, despite adequate hydration and i.v. analgesic treatment, and then it resolved. No patient in either group had any sensory or motor complications identified in the first month after surgery.

Table 3. Side effects

	Group M	Group S
Pruritus	—	—
Respiratory depression	—	—
Hypotension	—	—
Bradycardia	—	—
Nausea	3 (10%)	1 (3.3%)
Vomiting	—	—
Difficulty voiding	1 (3.3%)	2 (6.7%)
Headache	5 (16.7%)	3 (10%)

Values are numbers of patients (%)

Discussion

In the present study, the addition of $MgSO_4$ to spinal anesthesia prolonged the time to first analgesic requirement, but did not reduce total analgesic consumption in the first 24 h. These results are consistent with a previous study conducted in patients undergoing lower-extremity surgery during spinal anesthesia [18]. In that study, the addition of i.t. $MgSO_4$ (50 mg) to 10 mg bupivacaine plus 50 µg fentanyl prolonged the period of spinal anesthesia, defined as the period from spinal injection to the first occasion when the patient complained of pain in the postoperative period, but there

were no significant differences in mean pain scores at any time [18].

We think there are a few possible causes of the finding that Mg did not decrease total analgesic consumption. First of all, it has been claimed that the effects of $MgSO_4$ on the NMDA receptor complex are weaker than those of some other NMDA receptor antagonists [20]. Combined administration of NMDA receptor antagonists such as Mg and ketamine may allow more profound analgesic effects. The second possible cause is the weak effect of NMDA receptor antagonists on postoperative pain. Recently, some studies done in an animal model of postoperative pain showed that NMDA antagonists did not modify nociception and suggested that NMDA receptors do not play an important role in the maintenance of postoperative pain [21]. According to the results of these studies, the investigators claimed that the receptor mechanism involved in postoperative hyperalgesia related more to non-NMDA (α-amino-3-hydroxy-5-methyl-4-isoxazole-proprionic acid [AMPA]/kainate) receptors than to NMDA receptors [21–23]. Thirdly, in the present study, analgesic consumption was used as a measure of postoperative central sensitization mediated by the NMDA receptor. Analgesic consumption and pain score at rest have been shown to be correlated with primary hyperalgesia caused by the increased responsiveness of primary afferent nociceptors rather than by central sensitization [22]. Finally, the dose of Mg used in the present study was based on data from Buvanendran et al. [16], where 50 mg i.t. $MgSO_4$ potentiated fentanyl antinociception without producing motor block in patients during labor. However, it is well known that the endogenous opioid analgesic system is activated during labor and the pain threshold can be changed [24]. In a recent placebo-controlled trial [17], patients undergoing major orthopedic surgery (total hip or knee replacement) during spinal anesthesia (levobupivacaine and sufentanil) were randomly assigned to receive i.t. $MgSO_4$ (94.5 mg; 6.3%), epidural $MgSO_4$ (2%; 100 $mg \cdot h^{-1}$), i.t. and epidural $MgSO_4$ combined or spinal anesthesia alone (controls). Postoperative morphine consumption was assessed in all groups by patient-controlled analgesia (PCA). Morphine consumption at 36 h after surgery was 38% lower in patients receiving spinal anesthesia plus epidural $MgSO_4$, 49% lower in those receiving spinal anesthesia plus i.t. $MgSO_4$, and 69% lower in the i.t.-epidural $MgSO_4$ combined group relative to control patients receiving spinal anesthesia alone [17]. It seems that, to decrease total analgesic consumption, higher doses of $MgSO_4$ are required than that used in the present study (50 mg).

In the present study, the addition of i.t. $MgSO_4$ (50 mg) to spinal anaesthesia did not affect the time to complete recovery of motor function, but caused a significant delay in ambulation time. In the present study, time to ambulation was defined as the time elapsed between i.t. injection and ability to walk without assistance. Safe ambulation requires normal dorsal column function (proprioception and vibration sense) and maintaining of accurate balance, as well as normal lower-limb motor function [25]. Dorsal column somatosensory function is impaired by spinal anesthesia, as assessed clinically by distal joint proprioception, vibration sense, and Romberg's sign. Maintaining balance requires sensory input from the somatosensory (skin sensation, joint and muscle proprioception), visual, and vestibular systems. Thus, there is a disparity between the time to return of gross motor and sensory function and the time to recovery of functional balance after spinal anesthesia [25]. Even though both motor and proprioceptive fibers are similar in diameter (12–20 μm), proprioceptive fibers are rapidly conducting A and A alpha fibers, which have a greater baseline rate of discharge. The frequency of the discharge rate has been shown to be a major determinant of sensitivity to local anesthetics [26]. Thus, proprioceptive fiber conduction can be impeded by local anesthetics while motor fiber conduction is normal [26]. The addition of 50 mg i.t. $MgSO_4$ to spinal anesthesia might have prolonged dorsal column somatosensory dysfunction (especially proprioception), which could have contributed to the delayed unassisted walking in our magnesium group. In some instances, orthostatic hypotension may also hinder stable walking following spinal anesthesia. However, we do not think that orthostatic hypotension contributed to the delayed unassisted walking in our magnesium group. As recommended previously [27], orthostatic blood pressure testing is obtained in all patients before assessing their ability to walk without support following spinal anesthesia at our clinic. Postural hypotension was not observed in any patients when the patients assumed the upright position. We also did not observe any symptoms of hypotension such as dizziness, light headedness, headache, feeling faint, or blurred vision during walking in any patient in either group.

In the present study, the pinprick test was used for the assessment of the dermatomal sensory level of spinal anesthesia. Even though a number of methods have been described for the assessment of sensory block, pinprick (pain discrimination) and ethyl chloride spray (temperature discrimination) are used most often [28]. The advantage of pain and cold discrimination is the sharp cutoff point obtained. However, these tests are associated with discomfort and infection (pin prick) and pollution and expense (ethyl chloride). In a previous study, it was shown that warm sensation was a simple, noninvasive and reliable alternative to ethyl chloride spray, without the disadvantages of pollution [29].

The two groups in our study were not different in terms of postoperative side effects. A severe case of postspinal headache was seen in only one patient, in the magnesium group. In previous clinical studies performed with i.t. Mg, the authors also did not observe any difference between the magnesium and placebo groups in terms of postspinal headache [17,18]. Thus, we currently do not have enough data to conclude that i.t. Mg exacerbated postspinal headache.

The safety of i.t. $MgSO_4$ administration has been evaluated both in animals and humans. A 1.26-mg i.t. bolus of $MgSO_4$ given to rats on alternate days over a 30-day period produced transient sensory and motor block with no adverse clinical or histological consequences [30]. In a canine study, i.t. $MgSO_4$ (3 $mg \cdot kg^{-1}$) was administered before aortic cross-clamping; no change in cord histopathology was reported in postoperative histological examination [31]. Haubald and Meltzer [32] reported that i.t. $MgSO_4$ (1000–2000 mg) in humans produced spinal anesthesia, including profound motor and sensory block-associated transient sedation, without neurological deficit. An inadvertent i.t. injection of 1000 mg $MgSO_4$ produced intense motor block, which resolved within 90 min, with no neurological deficit during long-term follow up [33]. However, in a recent study done by Saeki et al. [34], the neurotoxicity of i.t. 0.3, 1, 2, or 3 $mg \cdot kg^{-1}$ of $MgSO_4$ was examined in rabbits, and significant sensory dysfunction was observed in the 3-$mg \cdot kg^{-1}$ group 7 days after administration. Motor dysfunction was observed in two rabbits, one in the 2-$mg \cdot kg^{-1}$ and one in the 3-$mg \cdot kg^{-1}$ group. An area of destruction in the intermediate area of the gray matter was observed in one, two, and one rabbit in the 1-, 2-, and 3-$mg \cdot kg^{-1}$ groups, respectively [34]; these authors have claimed that the dose of 1 $mg \cdot kg^{-1}$ represents the maximum tolerable dose in rabbits from a neurotoxic standpoint. In the present study, about 0.7 $mg \cdot kg^{1}$ (50 mg) of i.t. $MgSO_4$ was used, and no neurological deficit was observed during the 1-month follow-up period.

In conclusion, the addition of i.t. Mg (50 mg) to spinal anesthesia prolonged the time for regression of two segments in the maximum block height and time to L_2 regression, but did not affect maximum sensory level and the time to reach the highest level of sensory block. Even though the time to first analgesic requirement was prolonged significantly by Mg, the addition of i.t. $MgSO_4$ to spinal anesthesia is not desirable in patients undergoing knee arthroscopy, due to the prolonged time to ambulation and the lack of effect of Mg on postoperative analgesic consumption.

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