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The effect of adding intrathecal magnesium sulphate to bupivacaine–fentanyl spinal anaesthesia

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Background: The addition of intrathecal (IT) magnesium to spinal fentanyl prolongs the duration of spinal analgesia for vaginal delivery. In this prospective, randomized, double-blind, controlled study, we investigated the effect of adding IT magnesium sulphate to bupivacaine–fentanyl spinal anaesthesia.
Methods: One hundred and two ASA I or II adult patients undergoing lower extremity surgery were recruited. They were randomly allocated to receive 1.0 ml of preservative-free 0.9% sodium chloride (group S) or 50 mg of magnesium sulphate 5% (1.0 ml) (group M) following 10 mg of bupivacaine 0.5% plus 25 μg of fentanyl intrathecally. We recorded the following: onset and duration of sensory block, the highest level of sensory block, the time to reach the highest dermatomal level of sensory block and to complete motor block recovery and the duration of spinal anaesthesia.
Results: Magnesium caused a delay in the onset of both sensory and motor blockade. The highest level of sensory block was significantly lower in group M than in group S at 5, 10 and 15 min ($P < 0.001$). The median time to reach the highest dermatomal level of sensory block was 17 min in group M and 13 min in group S ($P < 0.05$). The mean degree of motor block was also lower in group M at 5, 10 and 15 min ($P < 0.001$). The median duration of spinal anaesthesia was longer in group M ($P < 0.001$).
Conclusion: In patients undergoing lower extremity surgery, the addition of IT magnesium sulphate (50 mg) to spinal anaesthesia induced by bupivacaine and fentanyl significantly delayed the onset of both sensory and motor blockade, but also prolonged the period of anaesthesia without additional side-effects.

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Key words: analgesic; bupivacaine; fentanyl; inorganic chemicals; local anaesthetics; magnesium sulphate; opioids; spinal anaesthesia.

Opioids such as fentanyl and sufentanil are commonly added to local anaesthetics to produce spinal anaesthesia. However, significant adverse effects, such as pruritus, urinary retention, respiratory depression, haemodynamic instability and, occasionally, severe nausea and vomiting, may limit their use (1–3). Adding magnesium may also improve the quality and increase the duration of spinal anaesthesia (4). Magnesium blocks the *N*-methyl-D-aspartate (NMDA) channels in a voltage-dependent way, producing a dramatic reduction in NMDA-induced currents (5). In experimental studies, intrathecal (IT) administration of magnesium sulphate ($MgSO_4$) significantly potentiated opioid antinociception in rats during spinal anaesthesia in an acute incisional model (6).

Although systemic $MgSO_4$ decreases post-operative opioid requirements in surgical patients, its IT use has not been extensively evaluated clinically (7). However, it has been used safely intrathecally in humans, and its safety profile has been documented by histopathological analysis in experimental studies (8). Magnesium prolongs the duration of spinal opioid analgesia given during labour (4).

This prospective, randomized, double-blind, controlled study was designed to test the hypothesis that, in patients undergoing lower extremity surgery under bupivacaine–fentanyl spinal anaesthesia, the duration of anaesthesia would be prolonged by IT $MgSO_4$ (50 mg).

Methods

Following Ethics Committee approval and informed patient consent, 102 ASA physical status I or II patients undergoing lower extremity surgery were recruited. Exclusion criteria included significant coexisting disease, including hepatorenal, any contraindication to regional anaesthesia, such as local infection or bleeding disorders, long-term opioid

use or a history of chronic pain. Patients were instructed pre-operatively in the use of the verbal rating scale (VRS) for pain assessment. All patients were fasted for 6 h pre-operatively and premedicated with intravenous diazepam, 0.2 mg/kg, 2 h before operation. Intraoperative monitoring included pulse oximetry, automated blood pressure cuff and lead II electrocardiogram. All patients received an intravenous pre-load of 15 ml/kg lactated Ringer's solution before subarachnoid block.

The patients were randomly allocated to one of two groups of 50 each. Group S, the saline group, received 10 mg of isobaric bupivacaine 0.5% (2 ml), 25 μg of fentanyl (0.5 ml) and 1.0 ml of preservative-free 0.9% sodium chloride intrathecally. Group M received 10 mg of isobaric bupivacaine 0.5% (2 ml), 25 μg of fentanyl (0.5 ml) and 50 mg of $MgSO_4$ 5% (1.0 ml) intrathecally. Subjects were allocated to the study groups by computer-generated random number assignment, kept in sealed envelopes, before the start of the study. The envelopes were opened just before entry into the study. Both patients and anaesthetists were blind to the treatment.

Lumbar puncture was performed in the sitting position. A 25-gauge Quincke spinal needle was introduced into the subarachnoid space at the L_{2-3} or L_{3-4} vertebral level via a midline approach. With the needle orifice cephalad, cerebrospinal fluid was aspirated, and the pre-mixed solution, 10 mg of isobaric bupivacaine 0.5% (2 ml) and 25 μg of fentanyl (0.5 ml), was injected through the spinal needle over a period of 10 s with no barbotage. The study solution described above, prepared by another researcher not involved in patient care, was then injected intrathecally immediately afterwards. The spinal needle was withdrawn and patients were repositioned supine with slight elevation of the head (15–20°) for comfort. No additional analgesic was administered unless requested by the patient.

Surgery was permitted 20 min after IT injection. Sensory and motor block, systolic and diastolic blood pressures (SBP, DBP), heart rate (HR) and peripheral oxygen saturation (S_pO_2) were recorded by an anaesthetist blind to the patient group, 5 min before IT injection, 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 complete.

The onset and duration of sensory block, highest level of sensory block, time to reach the highest dermatomal level of sensory block, time to complete motor block recovery and duration of spinal anaesthesia were also recorded. The onset of sensory block was defined as the time between injection of the IT anaesthetic and the absence of pain at the T_{10} dermatome, assessed by pinprick; the duration was defined as the time for regression of two segments in the maximum block height, evaluated by pinprick. The highest level of sensory block was evaluated by pinprick every 5 min for 25 min after injection. 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 anaesthesia was defined as the period from spinal injection to the first occasion when the patient complained of pain in the post-operative period.

Pain was assessed using a VRS from 0 to 10 (0, no pain at all; 10, maximum imaginable pain) by an anaesthetist blind to the treatment group. If the VRS exceeded 3, tramadol HCl, 1 mg/kg, was given intravenously for pain relief.

An intravenous bolus of 500 ml lactated Ringer's solution was given to maintain the blood pressure. If SBP was >20% below baseline or <90 mmHg, intravenous (i.v.) ephedrine, 10 mg, was given repeatedly. If HR was less than 50 beats/min, 0.5 mg of atropine sulphate was administered intravenously. The incidence of hypotension (mean arterial pressure, <20% of baseline), bradycardia (HR, <50 beats/min), hypoxaemia and excessive sedation, 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.

Using data from a previous investigation in a similar clinical setting (4), the primary endpoint was defined as a 15-min difference in the median duration of anaesthesia between groups. Power analysis showed that, with a power of 0.8 and significance level of 0.05, 50 subjects per study group were required. Statistical analyses were performed using the statistical package SPSS version 10.0. Normality was checked for each continuous variable, and normally distributed values were expressed as the mean (standard deviation, SD) and others as the

median (range). Demographic (sex, age, weight, height) and clinical (onset time and duration of sensory and motor blockade, and time to first analgesic requirement) data were analysed using two-sample *t*-tests. Sedation scores and the incidence of intra- and post-operative adverse events were analysed using chi-squared tests with Yates' correction and Fisher's exact tests where appropriate. Haemodynamic parameters and respiratory rate were compared by Student's *t*-test. The effect of time in haemodynamic parameters was evaluated by repeated measurement analysis. The highest level of sensory block, time to reach the highest dermatomal level of sensory block, complete motor block recovery and VRS scores were compared between groups with the Mann–Whitney *U*-test. Values of $P < 0.05$ were considered to be statistically significant.

Results

One hundred and two patients were enrolled and 100 patients completed the study protocol, $n = 50$ in each group. Two patients were excluded from the study due to inadequate spinal analgesia. The demographic variables of the patients are shown in Table 1. There were no differences between groups with regard to the patient characteristics (sex, age and weight) or duration of surgery.

The median onset of sensory blockade to the maximum level of spread was slower in the magnesium group (17 min vs. 12 min, $P < 0.05$; Fig. 1), and the mean degree of sensory blockade was less in group M at 5, 10 and 15 min ($P < 0.05$). However, the duration of sensory block was similar for the two groups (Table 2). The highest dermatomal level of sensory block was lower in group M at 5, 10 and 15 min: T_{12} vs. T_{11} at 5 min ($P < 0.05$), T_{10} vs. T_7 at 10 min ($P < 0.001$) and T_7 vs. T_6 at 15 min ($P < 0.005$). However, at 20 min, sensory block levels were similar in the two groups (Table 2).

Table 1

Demographic characteristics.

	Group S	Group M	*P*
Age (years)	38.4 ± 7.6	38.3 ± 15.7	0.8
Height (cm)	169.4 ± 7.9	169.5 ± 6.5	0.6
Weight (kg)	73.2 ± 10.2	74.0 ± 8.6	0.9
Sex (female/male)	17/31	17/32	0.9
Duration of surgery (min)	93.7 ± 34.0	89.3 ± 31.2	0.5

Data are means ± standard deviation.

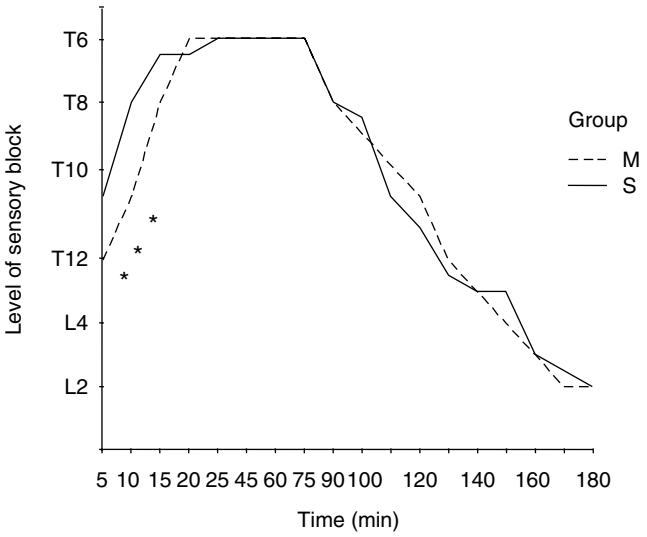

*Fig. 1. Relationship between time and level of sensory block in the groups given magnesium (group M) and saline (group S). *P < 0.05 between groups S and M by Mann–Whitney U-test.*

The median time to reach the highest level of sensory block (T_6) was 17 min in group M vs. 13 min in group S ($P < 0.05$).

Motor blockade, as assessed by Bromage scores, was also delayed in the magnesium group (Fig. 2; $P < 0.001$). As with sensory block, the mean degree of motor block was lower in group M at 5, 10 and 15 min (1.3 ± 0.4 vs. 1.7 ± 0.5 at 5 min, 1.7 ± 0.5 vs. 2.4 ± 0.7 at 10 min, 1.7 ± 0.5 vs. 2.9 ± 0.4 at 15 min;

Table 2

Characteristics of spinal block.

	Group S ($n = 50$)	Group M ($n = 50$)
Sensory block		
Onset time (min)	12.5 ± 3.8	16.5 ± 2.4*
	12 (8–25)	17 (10–20)
Duration of block (min)	85.9 ± 8.4	84.1 ± 8.4
	85 (60–110)	85 (70–115)
Time to reach highest dermatomal level of sensory block (min)	13 ± 5.4	16.7 ± 3.2*
	13 (9–26)	17 (11–22)
Time to complete recovery of motor block (min)	140.6 ± 17.1	142.5 ± 21
	140 (90–230)	140 (115–220)
Duration of spinal anaesthesia (min)	160.7 ± 19.5	173.6 ± 19.7*
	155 (130–220)	173 (130–240)

Data are shown as the mean ± standard deviation and median (minimum–maximum).
Duration of spinal anaesthesia was defined as the period from spinal injection to the first occasion when the patient complained of pain in the post-operative period.
*$P < 0.05$ between groups S and M by Mann–Whitney *U*-test.

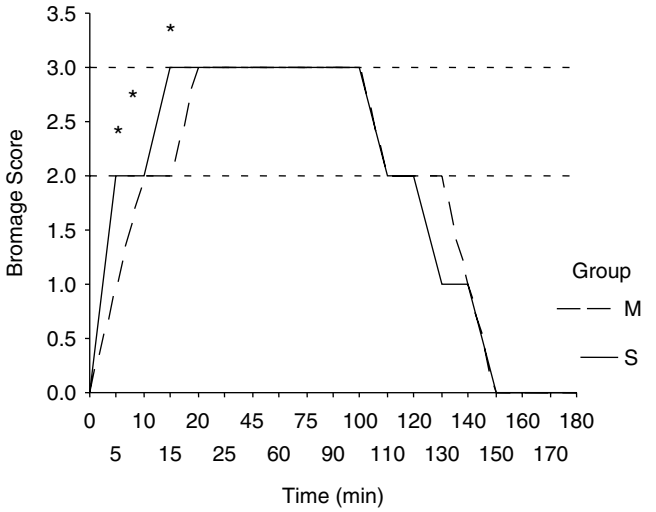

*Fig. 2. Relationship between time and Bromage scores in the groups given magnesium (group M) and saline (group S). *P < 0.05 between groups S and M by Mann–Whitney U-test.*

$P < 0.001$). Thereafter, there were no significant differences between the groups (Table 2). The mean times to complete recovery of motor function were similar (143 ± 21 min in group M vs. 142 ± 17 min in group S; Table 2).

The duration of spinal anaesthesia was longer in group M (median 173 min vs. 155 min; $P < 0.001$), but there were no significant differences in mean pain scores at any time. SBP and DBP were significantly lower 5 min after spinal injection in both groups compared with 5 min before ($P < 0.001$). However, thereafter, no significant difference was found at any study period between the two groups (data not presented). In 13 patients, a decrease in blood pressure required 10 mg boluses of i.v. ephedrine to maintain SBP within 20% of baseline values or >90 mmHg. Seven of these were in group M and six in group S.

The side-effects and complications seen during the peri-operative period are shown in Table 3. No neurological deficit or other major complication was observed in any patient receiving magnesium or saline in the first post-operative week after surgery. The most common complication reported was pruritus (25–30%).

Table 3

Side-effects and complications of spinal block.

	Group S ($n = 50$)	Group M ($n = 50$)
Absent	26	27
Present	24 (48%)	23 (46%)
Shivering	1	0
Pruritus	8	11
Nausea	4	6
Vomiting	2	0
Respiratory depression	0	0
Hypotension	5	7
Bradycardia	0	1

Discussion

The main finding of this study was that, in patients undergoing lower extremity surgery under bupivacaine–fentanyl spinal anaesthesia, the addition of 50 mg IT $MgSO_4$ led to a significant delay in the onset of both sensory and motor blockade, and prolonged the duration of spinal anaesthesia, without increasing side-effects.

In normal rats, Kroin et al. (6) demonstrated that acute bolus dosing of IT $MgSO_4$ produced a dose-dependent potentiation of the antinociceptive effect of morphine to noxious thermal stimulation and mechanical stimulation at an incisional pain site. The delay observed in this study with IT magnesium during IT bupivacaine and fentanyl has not been reported previously. It is possible that the solution to which $MgSO_4$ was added had a different pH, which might explain our findings. However, we cannot offer a satisfactory explanation for this delay and further studies are needed.

We found that the median duration of spinal anaesthesia was significantly prolonged by magnesium to 173 min, compared with 155 min in group S, which is consistent with the findings of Buvanendran et al. (4). This prolongation of anaesthesia is consistent with the experimental synergistic interaction between spinal local anaesthetics and NMDA antagonists, such as magnesium, which exert antinociceptive effects via different mechanisms; hence the rationale for combining the two. The NMDA receptor channel complex contains binding sites for non-competitive antagonists such as magnesium and ketamine. Activation of C-fibres leads to neuronal excitation, which is diminished by NMDA receptor antagonists; hence the use of magnesium as an adjuvant for IT block (9). It acts as an antagonist at the NMDA receptor; NMDA receptor antagonists can prevent central sensitization due to peripheral nociceptive stimulation, and can abolish such hypersensitivity once it is established (5).

Ketamine, a better known NMDA receptor antagonist, has also been demonstrated to prolong the duration of spinal anaesthesia (10, 11). However, it has been reported that magnesium and ketamine inhibit the NMDA system differently (12). The differences between ketamine and magnesium may stem from differing effects on non-NMDA systems.

Evidence suggests that both hyperalgesia after tissue injury and the development of opiate tolerance involve activation of the NMDA receptor and subsequent biochemical processes resulting in central sensitization (13). Sharing of NMDA receptor activation by both processes suggests that ketamine may substantially enhance opiate-induced antinociception (13).

In rats in which unilateral experimental peripheral mononeuropathy had been induced, IT boluses of magnesium blocked ipsilateral hyperaesthesia, without affecting thermal sensitivity on the sham-operated side (14, 15). Furthermore, an inverse relationship between cerebrospinal fluid magnesium concentration and analgesic consumption was demonstrated when magnesium was given intravenously (16).

The safety of IT magnesium administration has been evaluated in animal and human studies. In rats, boluses of magnesium produced transient motor and sensory block with no adverse clinical or histological consequences. In a randomized, controlled canine study, no neurological deficit or change in cord histopathology was reported following IT magnesium administration (45–60 mg) (8). A recent human study found no deleterious effects of IT magnesium on spinal opioid analgesia in labouring parturients (4). Thus, IT $MgSO_4$ seems to have a good safety profile.

The dose of magnesium used in this study was based on data from Buvanendran et al. (4) where 50 mg of IT $MgSO_4$ potentiated fentanyl antinociception. Larger doses have also been used. In 1985, Lejuste (17) described the inadvertent IT injection of 1000 mg of $MgSO_4$, producing a dense motor block followed by complete resolution within 90 min, with no neurological deficit at long-term follow-up. Further investigation is required to determine whether larger doses of magnesium produce greater potentiation of spinal analgesia without causing any neurological deficit when administered intrathecally.

The use of IT opioids is associated with the risk of respiratory depression (18). However, fentanyl, a lipid-soluble opioid, binds fairly rapidly with the opioid receptors in the dorsal horn of the spinal cord leaving only small amounts of substance for cephalad migration to the fourth ventricle, in contrast with the less lipid-soluble morphine. Varassi et al. (19) reported that the subarachnoid administration of 25 μg of fentanyl during spinal anaesthesia in non-pre-medicated men did not cause early respiratory depression in elderly patients. An increased risk of respiratory depression in labouring parturients has been reported with $MgSO_4$ therapy (20), and an increased incidence of respiratory depression may be expected when these two drugs are combined; however, we did not observe this.

In conclusion; in patients undergoing lower extremity surgery, IT $MgSO_4$ (50 mg), when added to spinal anaesthesia induced by bupivacaine and fentanyl, delayed the onset of both sensory and motor blockade and prolonged the duration of anaesthesia, without increasing the incidence of side-effects.

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