ORIGINAL ARTICLE



A randomised study of magnesium sulphate as an adjuvant to intrathecal bupivacaine in patients with mild preeclampsia undergoing caesarean section

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ABSTRACT

Background: Adequate analgesia following caesarean section decreases morbidity, hastens ambulation, improves patient outcome and facilitates care of the newborn. Intrathecal magnesium, an NMDA antagonist, has been shown to prolong analgesia without significant side effects in healthy parturients. We therefore studied the effect of adding intrathecal magnesium sulphate to bupivacaine-fentanyl spinal anaesthesia in patients with mild preeclampsia undergoing caesarean section.

Methods: Sixty women with mild preeclampsia undergoing caesarean section were included in a prospective, double blind, placebo-controlled trial. Patients were randomly assigned to receive spinal anaesthesia with 2 mL 0.5% hyperbaric bupivacaine and 25 μg fentanyl with either 0.1 mL of 0.9% sodium chloride (control group) or 0.1 mL of 50% magnesium sulphate (50 mg) (magnesium group). Onset, duration and recovery of sensory and motor block, time to maximum sensory block, duration of spinal anaesthesia and postoperative analgesia requirements were studied.

Results: The onset of both sensory and motor block was slower in the magnesium group. The duration of spinal anaesthesia (229.3 vs. 187.7 min) and motor block (200 vs. 175.3 min) were significantly longer in the magnesium group. Diclofenac requirement for 24 h following surgery was significantly lower in the magnesium group (147.5 vs.182.5 mg, P=0.02). Haemodynamic parameters and side effect profile were similar in the two groups.

Conclusions: In parturients with mild preeclampsia undergoing caesarean delivery, the addition of magnesium sulphate 50 mg to the intrathecal combination of bupivacaine and fentanyl prolongs the duration of analgesia and reduces postoperative analgesic requirements without additional side effects.

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Keywords: Caesarean delivery; Spinal anaesthesia; NMDA antagonists; Magnesium sulphate; Postoperative analgesia

Introduction

The safety and efficacy of regional anaesthesia for preeclamptic patients undergoing caesarean section is established, ^{1–3} but one limitation of spinal anaesthesia is the relatively short duration of postoperative analgesia. Postoperative pain is associated with neuroendocrine responses, catecholamine release and increased morbidity.⁴ This may be detrimental especially in preeclamptic patients.⁵ In addition, effective pain relief facilitates early ambulation and care of the newborn.

Animal studies have shown that intrathecal magnesium produces antinociception and potentiation of opioid activity, presumably by its action as a voltage-gated NMDA-receptor antagonist.⁶ Clinical trials in obstetric^{7,8} and non-obstetric^{9–12} populations have shown that intrathecal magnesium increases the duration of analgesia without increasing side effects. Intrathecal magnesium has been found to be safe and effective as an adjuvant to bupivacaine in normal parturients for labour analgesia.⁷ We therefore investigated the effect of adding intrathecal magnesium sulphate to bupivacaine-fentanyl spinal anaesthesia in women with mild preeclampsia undergoing caesarean section.

Methods

After approval of the Institutional Ethical Committee and written informed consent, 60 pregnant women with singleton pregnancies diagnosed with mild preeclampsia (systolic pressure 140-160 mmHg, diastolic pressure 90-110 mmHg) were enrolled in a prospective, randomised controlled double-blind study. Exclusion criteria were

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ASA grade >II, renal or hepatic impairment, thrombocytopenia, HELLP syndrome, magnesium therapy, fetal distress, contraindications to spinal anaesthesia and unwillingness to undergo regional anaesthesia.

Patients were randomly assigned to one of two groups using computer-generated random numbers; the assignment was sealed in opaque envelopes. The control group received a premixed solution of 0.5% hyperbaric bupivacaine 2 mL, fentanyl 25 µg and preservative free saline 0.1 mL. The magnesium group received a premixed solution of 0.5% hyperbaric bupivacaine 2 mL, fentanyl 25 µg and preservative-free 50% magnesium sulphate 0.1 mL. An insulin syringe was used to measure volumes less than 1 mL. The total volume of injectate was 2.6 mL in both groups, and was prepared by an anaesthesiologist not involved in outcome measurement. Patients and the anaesthesiologist collecting data were all blinded to group allocation.

All patients received a 500-mL i.v. preload of normal saline before spinal anaesthesia. Lumbar puncture was performed in the left lateral position using a 26gauge Quincke needle at L2-3 or L3-4 using a midline approach. After free flow of cerebrospinal fluid (CSF), the premixed solution was injected over 10 s with the needle orifice directed cephalad. The patient was immediately turned supine with left uterine displacement using a wedge under the right hip. Sensory block was assessed every minute by pinprick in the midclavicular line until a stable level of block was achieved. Surgery was permitted after T4 sensory block to pain was achieved. The duration of sensory block was defined as the time from intrathecal injection to regression of the sensory block to T12. Motor block was assessed using a modified Bromage score [0 = no motor loss;1 = inability to flex hip; 2 = inability to flex hip and knee; 3 = inability to flex hip, knee and ankle, with motor recovery assumed when the score was zero. The duration of spinal anaesthesia was defined as the period from spinal injection to the time of administration of first rescue analgesic for pain in the postoperative period.

Heart rate, systolic and diastolic pressure and mean arterial pressure (MAP) were noted at baseline, immediately after block insertion and then every 3 min for the first 20 min, and every 10 min until the end of the surgery. Hypotension was defined as a fall in systolic pressure >20% below baseline and was treated by increasing the normal saline infusion rate and by 5-mg boluses of ephedrine. Bradycardia (heart rate <50/min) was treated with intravenous atropine sulphate 0.3 mg. The incidence of side effects such as sedation, pruritus, nausea and vomiting were noted every 15 min during surgery and 2, 4, 8, 12 and 24 h postoperatively. Pruritus was graded as 0=none; 1=mild; and 2=severe. Sedation was measured using the Observer's Assessment of Alert-

ness/Sedation Score. Nausea and vomiting were graded as 0=no nausea or vomiting; 1=nausea no vomiting; 2=both nausea and vomiting present; and 3=more than 2 episodes of vomiting in 30 min. Intravenous ondansetron 4 mg was given as rescue medication for vomiting and severe pruritus. Neonatal outcome was assessed by Apgar score at 1 and 5 min, umbilical artery pH and the need for neonatal mask ventilation and tracheal intubation by a paediatrician who was unaware of the study medication.

Pain was assessed using a verbal numeric scale (VNS) from 0 to 10 (0=no pain; 10=maximum imaginable pain) every 15 min after the block until the end of the surgery and 2, 4, 8, 12, 24 h postoperatively. Intraoperative pain with VNS >3 was treated with i.v. fentanyl 1 μg/kg. Postoperatively, intramuscular diclofenac 75 mg was given for rescue analgesia whenever the pain score was >3. Overall patient satisfaction with anaesthesia and analgesia was scored at 24 h as 1=excellent; 2=good and 3=bad.

Statistical analysis

To detect a difference of 20 min in the mean pain-free duration with an α error of 0.05 and β error of 0.05, at least 26 patients needed to be included in each group. We included 30 patients in each group to allow for dropouts and protocol violations. Data were analysed using SPSS (SPSS 15.0, SPSS Inc, Chicago, II, USA). Parametric data were expressed as mean and standard deviation (SD) and analysed using the independent t test. Non-parametric data were expressed as median and interquartile range (IQR) and analysed using the Mann Whitney U test. The Kaplan Meier survival graph was used to analyze the postoperative pain-free interval. The sum of all pain scores (Cumulative VNS score) measured after surgery was calculated for each patient and differences between the two groups were analysed using the Mann Whitney U test. The effect of time on hemodynamic parameters was analyzed using repeated measurement analysis of variance. The χ^2 test was used to analyze the incidence of adverse events. A P value < 0.05 was considered statistically significant.

Results

Sixty patients were enrolled, 30 in each group. No patients were excluded. The two groups were comparable with respect to age, weight, height, gestational age and preoperative drug intake. The duration of surgery was also similar (Table 1).

Characteristics of spinal anaesthesia are presented in Table 2. The highest sensory level achieved was similar in the two groups. The time to reach maximum block height and the onset of motor block were significantly slower in the magnesium than in the control group, but the time to complete motor block was similar in

S. Malleeswaran et al.

Table 1 Patient characteristics

	Control group (n=30)	Magnesium group (n=30)	P
Age (years)	27 ± 3	26 ± 4	0.38
Weight (kg)	$62\pm\ 5$	62 ± 5	0.87
Height (cm)	155 ± 5	154 ± 5	0.87
Gestational age (weeks)	36 ± 1	36 ± 1	0.52
Duration of surgery (min)	79 ± 13	84 ± 11	0.10

Data are mean \pm SD.

the two groups. Sensory block regressed to T12 more slowly in the magnesium than in the control group (P<0.001). The total pain free period and duration of motor block were significantly longer in the magnesium group (P<0.001).

Preoperative haemodynamic variables (heart rate, systolic pressure, diastolic pressure and MAP) were similar in the two groups and all decreased significantly 5 to 15 min after spinal anaesthesia in both the groups, with no difference between them (Fig. 1). The incidence of hypotension requiring treatment was similar in the two groups. There were no episodes of bradycardia.

The proportion of patients in either group with continuing postoperative analgesia as a function of time is shown in the Kaplan-Meier analysis (Fig. 2). The percentage of patients with effective analgesia 3 h after spinal anaesthesia was higher in the magnesium group (100%) than in the control (60%). A log-rank test between pairs of curves was significant between the groups $(\chi^2 = 63.71; P < 0.001)$. No patient in either group complained of pain during surgery. In the postoperative period, pain scores [median (IQR)] were significantly lower at 4 h in the magnesium group [1 (1-2) vs. 2 (2-2); P < 0.001], though the pain scores at 2, 8, 12 and 24 h were similar. Cumulative VNS scores in the first 24 h were significantly lower in the magnesium group [9 (8 -10); P=0.035] than in the controls [10 (8 - 11)] (Fig. 3). The cumulative requirement of diclofenac over 24 h was significantly less in the magnesium than in the control group (147.5±53.9 mg vs. 182.5±58.0 mg; P=0.02).

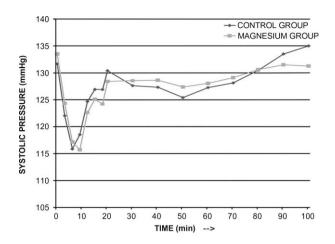


Fig. 1 Intraoperative systolic blood pressure. Significant fall in systolic pressure from 5–15 min after spinal injection compared to baseline in both groups. No significant differences between groups.

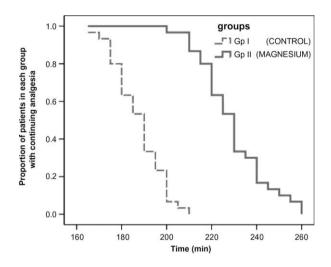


Fig. 2 Kaplan-Meier analysis showing the proportion of patients in each group with continuing pain relief as a function of time. A log-rank test showed a significant difference between curves (P < 0.001).

Table 2 Characteristics of spinal anaesthesia

	Control group (n=30)	Magnesium group (n=30)	P
Highest sensory level [n (%)] T4	21/30 (70%)	14/30 (46.7%)	0.067
T6	9/30 (30%)	16/30 (53.3%)	
Time to maximum sensory block (min)	7.7 ± 0.8	8.7 ± 0.9	< 0.001
Time to T12 (min)	165.7 ± 12.0	197.8 ± 13.8	< 0.001
Duration of spinal anaesthesia (min)	187.7 ± 11.0	229.3 ± 15.1	< 0.001
Time to onset of motor block (min)	5.1 ± 1.0	5.7 ± 0.7	0.005
Time to complete motor block (min)	8.9 ± 1.0	9.2 ± 0.8	0.214
Time to complete motor recovery (min)	175.3 ± 18.3	200 ± 17.8	< 0.001

Data are mean \pm SD unless otherwise specified.

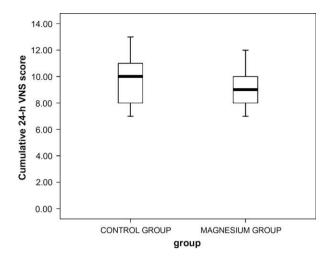


Fig. 3 Box plots of cumulative pain scores. Median presented as solid line; box represents 25th and 75th percentiles; whiskers represent 10th and 90th percentiles. Scores are significantly lower in the magnesium group (P = 0.035).

The incidence of side effects was similar in the two groups throughout the study period (Table 3). Intraoperatively 33 patients (55%) had mild sedation with lethargic response to name spoken in normal tone; the incidence was comparable in the two groups. No patient was sedated in the postoperative period. Twenty patients (33.3%) complained of nausea intra-operatively. with no difference between groups. No patient vomited intraoperatively. There was no nausea or vomiting in the postoperative period in either group. Thirty-one patients (51.6%) developed pruritus intraoperatively, five of whom had severe pruritus requiring treatment with ondansetron. The incidence of pruritus was similar in the two groups. No patient had pruritus in the postoperative period. Overall patient satisfaction was better in the magnesium group (P=0.001).

Neonatal outcome was also similar in the two groups and no baby required mask ventilation or tracheal intubation.

Discussion

The current study demonstrates that the addition of magnesium to bupivacaine and fentanyl for spinal anaesthesia significantly improves the duration of postoperative analgesia and reduces the postoperative analgesic consumption in patients with mild preeclampsia undergoing caesarean section. Earlier clinical investigations reported an increase in duration of analgesia with intrathecal magnesium of 18-48 min in various obstetric and non-obstetric populations.^{8,9} We found that the addition of intrathecal magnesium increased the duration of spinal anaesthesia by 42 min. Although the decrease in pain scores at various times during the first 24 h after surgery was not statistically significant, cumulative VNS score and 24-h postoperative analgesic consumption were significantly less in the magnesium group. Similar reductions in analgesic requirements have been reported by Marzouk et al. who studied the effect of three different doses of intrathecal magnesium. 12 Since pain may lead to either high VNS scores or high analgesic consumption, the comparable pain scores in our study may be explained by an efficient regimen of rescue analgesia.

Our findings reinforce the role of magnesium sulphate, an NMDA antagonist, as an effective spinal adjuvant. NMDA receptor channels are ligand-gated ion channels that generate slow excitatory post-synaptic currents at glutamatergic synapses. Evidence suggests that sustained NMDA receptor activation promotes intracellular signalling that culminates in long-term synaptic plasticity, wind-up phenomenon and central sensitization. 14,15 These events appear to be relevant as they determine, in part, duration and intensity of postoperative pain. 16 NMDA receptor antagonists are thought to prevent the induction of central sensitization attributed to peripheral nociceptive stimulation. ¹⁷ They also potentiate opioid antinociception by blocking the spinally mediated facilitatory component evoked by repetitive C-fibre stimulation.⁶ Even large systemic doses of

Table 3 Side effects

		Control group (n=30)	Magnesium group (n=30)	P
Hypotension		7 (23.3)	4 (13.3)	0.32
Sedation	Awake and responds readily to name spoken in normal tone	13 (43.3)	14 (46.7)	0.79
	Awake but lethargic response to name spoken in normal tone	17 (56.7)	16 (53.3)	
Nausea	•	7 (23.3)	13 (43.3)	0.10
Pruritus	Mild	15 (50)	11 (36.7)	0.13
	Severe	4 (13.3)	1 (3.3)	
Patient satisfaction score	Good	25 (83.3%)	13 (43.3%)	0.001
	Excellent	5 (16.7%)	17 (56.7%)	
Umbilical artery pH (mean =	± SD)	$7.32 \pm .057$	$7.31 \pm .063$	0.521

Data are number (%) unless otherwise specified.

magnesium sulphate may fail to achieve effective CSF concentrations because of insufficient blood-brain barrier penetration. Ko et al. gave a magnesium 50-mg/kg i.v. bolus followed by a 15 mg·kg⁻¹h⁻¹ infusion and found that CSF magnesium concentrations were similar between the control and i.v. magnesium groups. ¹⁸ They also demonstrated an inverse relationship between CSF magnesium concentration and postoperative analgesic requirement. Hence intrathecal magnesium can potentiate spinal analgesia without risking the side effects of the large i.v. doses of magnesium required to achieve effective CSF concentrations.

The onset and resolution of motor blockade and the time to attain maximum sensory level were longer in the magnesium group. Though hyperbaric bupivacaine was used in our study. Ozalevli et al. observed a similar delay in onset of spinal anaesthesia when adding intrathecal magnesium to fentanyl and isobaric bupivacaine. These authors suggested that the difference in pH and baricity of the solution containing magnesium contributed to the delayed onset, which may also be the case in our study, although this delay of approximately one minute is probably insignificant. In our study, the time to complete motor recovery was prolonged in the magnesium group; Arcioni et al. also observed that intrathecal and epidural magnesium sulphate potentiated and prolonged motor block. 11 The prolongation of motor block was not clinically relevant in our patients, as during this period they are still restricted to bed.

Though i.v. magnesium is known to cause hypotension when used to treat eclampsia, ¹⁹ we found no significant haemodynamic effect following the addition magnesium to our spinal solution. This may be attributed to the absence of systemic vasodilator effects of spinal magnesium. Although an increased incidence of drowsiness and confusion was reported in eclamptic parturients treated with i.v. magnesium, 20 we did not find an increase in sedation following intrathecal magnesium. An increased risk of respiratory depression in labouring parturients has also been reported with i.v. magnesium.²⁰ Though a significant risk may be anticipated when magnesium is combined with intrathecal fentanyl, we did not encounter this. It is likely that intrathecal magnesium sulphate potentiates spinal anaesthesia by a localised action on spinal nociceptive pathways, which may explain the absence of central side effects seen following systemic administration of large doses of magnesium.

Nausea and vomiting during caesarean delivery performed with regional anaesthesia may be associated with hypotension and visceral pain. In our study the incidence of nausea was 33.3% with no difference between the groups, which can be explained by the groups' similar haemodynamics. The incidence of pruritus in our study was 51.6% with no difference between the groups. Gurkan et al. showed a similar incidence of pruritus (68%) when fentanyl $25~\mu g$ was added to bupivacaine 7-10~mg.

The safety of intrathecal magnesium has been extensively evaluated in animals. ^{22–24} Studies in which intrathecal magnesium was given to various different groups of patients found that none had symptoms suggestive of neurotoxicity, ^{7–12} nor did they exhibit signs of systemic toxicity such as hypotension, arrhythmias, somnolence or weakness, during the study. The dose of magnesium used in this study was based on data from Buvanendran et al. who found that 50 mg of intrathecal magnesium potentiated fentanyl antinociception; ⁹ this represented 10% of a dose shown to be non-toxic in dogs. ²² In various other clinical studies, intrathecal magnesium 50 mg was found to be safe and effective. ^{8–10} Our findings are similar to those of Buvanendran et al. ⁷ and Gita et al., ⁸ reinforcing the safety of maternal intrathecal magnesium.

We did not assess the incidence and severity of chronic pain after caesarean section, which also might have revealed the action of magnesium in modulating wind up and synaptic plasticity. Further studies should also explore whether the addition of magnesium can reduce intrathecal dose requirement of local anaesthetic agents, and possibly even replace fentanyl, thereby avoiding opioid side effects such as sedation, pruritus and respiratory depression.

In conclusion, The addition of intrathecal magnesium sulphate 50 mg to the combination of bupivacaine and fentanyl in patients with mild preeclampsia undergoing caesarean section prolongs the duration of analgesia and reduces postoperative analgesic requirements without additional side effects.

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