

Clinical Comparative Study Comparing Efficacy of Intrathecal Fentanyl and Magnesium as an Adjuvant to Hyperbaric Bupivacaine in Mild Pre-Eclamptic Patients Undergoing Caesarean Section

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Abstract—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. The aim of this study was to evaluate the onset and duration of sensory and motor block, hemodynamic effect, postoperative analgesia, and adverse effects of magnesium or fentanyl given intrathecally with hyperbaric 0.5% bupivacaine in patients with mild preeclampsia undergoing caesarean section. Sixty women with mild preeclampsia undergoing elective caesarean section were included in a prospective, double blind, controlled trial. Patients were randomly assigned to receive spinal anaesthesia with 2 mL 0.5% hyperbaric bupivacaine with 12.5 µg fentanyl (group F) or 0.1 ml of 50% magnesium sulphate (50 mg) (group M) with 0.15ml preservative free distilled water. Onset, duration and recovery of sensory and motor block, time to maximum sensory block, duration of spinal anaesthesia and postoperative analgesic requirements were studied. Statistical comparison was carried out using the Chi-square or Fisher's exact tests and Independent Student's t-test where appropriate. The onset of both sensory and motor block was slower in the magnesium group. The duration of spinal anaesthesia (246 vs. 284) and motor block (186.3 vs. 210) were significantly longer in the magnesium group. Total analgesic top up requirement was less in group M. Hemodynamic parameters were similar in both the groups. Intrathecal magnesium caused minimal side effects. Since Fentanyl and other opioid congeners are not available throughout the country easily, magnesium with its easy availability and less side effect profile can be a cost effective alternative to fentanyl in managing pregnancy induced hypertension (PIH) patients given along with Bupivacaine intrathecally in caesarean section.

Keywords—Analgesia, magnesium, preeclampsia, spinal anaesthesia.

I. INTRODUCTION

THE safety and efficacy of regional anaesthesia for pre-eclamptic patients undergoing caesarean section is established [1]-[3]. However, postoperative analgesia remains an important issue in such cases as spinal anaesthesia alone, provides short duration analgesia [2], [3]. Postoperative pain is

associated with neuroendocrine responses, catecholamine release and increased morbidity [4]. This may be detrimental in pre-eclamptic patients [5]. In addition, effective pain relief facilitates early ambulation, initiation of breast feeding and care of the newborn.

Various adjuvants like fentanyl, clonidine, and magnesium have been well studied for their postoperative analgesia when combined with local anaesthetic agent for spinal anaesthesia. Fentanyl is the most common adjuvant but is limited by its shorter duration and risk of respiratory depression. Magnesium has also been reported for its analgesic action when administered as adjuvant for spinal anaesthesia. The intrathecal magnesium produces anti-nociception 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 as an adjuvant to bupivacaine for spinal anaesthesia in women with mild preeclampsia undergoing caesarean section and compared the findings with bupivacaine-fentanyl spinal anaesthesia.

II. MATERIALS AND METHODS

After approval of the Institutional Ethical Committee and written informed consent, 60 pregnant women with singleton pregnancy diagnosed with mild pre-eclampsia [13], [14] (systolic pressure 140-160 mmHg, diastolic pressure 90-110 mmHg) were enrolled in a prospective, randomized study. Exclusion criteria were American Society of Anaesthesiologists (ASA) physical status >II, renal or hepatic impairment, thrombo-cytopenia, HELLP syndrome, prior magnesium therapy, fetal distress, contraindications to spinal anaesthesia and unwillingness to undergo regional anaesthesia.

Patients were randomized to two groups using computer-generated random numbers and the assignment was sealed in opaque envelopes for concealment. *Group F* received a premixed solution of 0.5% hyperbaric bupivacaine 2 ml, and fentanyl 12.5µg (0.25 ml; 50 µg /ml). *Group M* received a premixed solution of 0.5% hyperbaric bupivacaine 2 ml, and

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preservative-free 50% magnesium sulphate 0.1 ml and preservative free saline 0.15 mL. An insulin syringe was used to measure volumes less than 1 ml. The total volume of injectate was 2.25 ml in both the groups.

In the operating room, standard monitors including 5 lead electrocardiogram, noninvasive blood pressure and pulse oximeter were attached and baseline readings were recorded. After securing an intravenous access, 500 mL normal saline was administered intravenously. Lumbar puncture was performed in the left lateral position using a 25-gauge Quincke needle at L2-3 or L3-4 space using a midline approach. After free flow of cerebrospinal fluid (CSF), the premixed solution was injected over 10 seconds with the needle orifice directed cephalad. The drugs were prepared by an independent anaesthesiologist who was not involved in administration of spinal anaesthesia or monitoring of the patient. The person who administered spinal anaesthesia was unaware of the drugs in the premixed syringe and thus was blinded. The patient was also kept blinded regarding the group allocation. 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 mid-clavicular line until a stable level of block (i.e. same sensory level on three consecutive checkups) was achieved. Surgery was allowed after T6 sensory block to pain was achieved. In case of inadequate sensory block at T6, the case was labelled as failure, managed as per conventional and excluded from analysis. 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). The complete motor block assessed as a score of 3 and complete motor recovery was assessed as a score of 0. The duration of analgesia 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 blood pressure and mean arterial pressure (MAP) were noted at baseline, immediately after block administration and then, every 3 min for the first 20 min and every 10 min until the end of surgery. Hypotension was defined as a fall in systolic blood pressure >20% below baseline and was treated by bolus of 250 mL of normal saline and/or 6-mg bolus of intravenous mephentermine. 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 hours (h) postoperatively. Pruritus was graded as 0=none; 1=mild and 2=severe. Sedation was measured using the Modified Ramsey Sedation Score: 1 = Cooperative, oriented, tranquil. 2 = Responds to commands only. 3 = Brisk response to light glabellar tap or loud noise. 4 = Sluggish response to light glabellar tap or loud noise. 5 = No response.

Nausea and vomiting were graded as: 0=no nausea or vomiting; 1=nausea no vomiting; 2=both nausea and vomiting; 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, and the need for neonatal mask ventilation and tracheal intubation by a pediatrician who was unaware of the study medication.

Pain was assessed using a Visual Analogue Scale (VAS) 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 hrs postoperatively. Intramuscular Ketorolac 30 mg was given postoperatively, for rescue analgesia whenever the pain score was >3.

Overall patient satisfaction with anaesthesia and analgesia was scored at 24 hrs as 1=excellent; 2=good and 3=bad.

III. STATISTICAL ANALYSIS

Sample size analysis determined that $n=30$ per group was required to detect a 25 min difference in the duration of analgesia (primary outcome variable) between groups, with a power of 90% and a significance level of 5%. Statistical analysis was performed with SPSS for windows version 15.0. Statistical comparison was carried out using the Chi-square or Fisher's exact tests and Independent Student's t-test where appropriate. A value of $P<0.05$ was considered statistically significant. The results were expressed as mean (SD).

IV. RESULTS AND OBSERVATIONS

Out of 72 patients, sixty patients which met the inclusion criteria were randomized to two groups (30 in each). No patients were excluded after the randomization and all were included for analysis. The two groups were comparable with respect to age, weight, height, gestational age and preoperative drug intake. The duration of surgery was also comparable (Table I).

TABLE I
 PATIENT CHARACTERISTICS

	Group F (n=30)	Group M(n=30)	P value
Age (years)	27 ± 3	26 ± 4	0.38
Weight (kg)	62 ± 5	61 ± 5	0.87
Height (cm)	155 ± 5	154 ± 5	0.87
Gestational age (weeks)	36 ± 1	36 ± 1	0.52
Duration of surgery (min)	64 ± 13	66 ± 11	0.10

Characteristics of spinal anaesthesia are presented in Table II. The highest sensory level achieved was similar in both the groups (T6). The time to reach maximum block height and the onset of motor block were significantly slower in group M than in the group F. Sensory block regressed to T12 more slowly in the magnesium than in the fentanyl group ($P<0.001$).

The percentage of patients with effective analgesia 3 h after spinal anaesthesia was higher in the group M (100%) than in group F (60%). No patient in any group complained of pain during surgery. In the postoperative period, pain scores [median] were significantly lower at 4 h in the magnesium group as compared to fentanyl 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 VAS scores in the first 24 h were

significantly lower in group M[9 (8- 10); P=0.035] than in group F [10 (8 – 11)]. The total pain free period and duration of motor block were significantly longer in the magnesium group (P<0.001).

Preoperative hemodynamic variables (heart rate, systolic blood pressure, diastolic blood pressure and MAP) were comparable in the two groups and all decreased 5 to 15 min after spinal anaesthesia, with no difference between them. The incidences of hypotension seen with group F were similar to group M. There were no episodes of bradycardia. Mean systolic pressure were comparable throughout the surgery with no patient recording it less than 110mm of Hg. (Fig. 1).

TABLE II
CHARACTERISTICS OF SPINAL ANESTHESIA

	Group F (n=30)	Group M (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)	5.3 ± 0.5	8.7 ± 0.5	< 0.001
Time to T12 (min)	200± 12.0	244 ± 12	< 0.001
Duration of analgesia (min)	246 ± 11.0	284 ± 15	< 0.001
Time to onset of motor block (min)	5 ± 1.0	6 ± 1	0.005
Time to complete motor block (min)	8.9 ± 1.0	9.2 ± 2	0.214
Time to complete motor recovery (min)	186.3 ± 12	210 ± 10	< 0.001

(Data are mean ± SD)

The incidences of side effects in group M were less as compared to group F throughout the study period (Table III). Intra-operatively 19 patients (32%) had mild sedation with lethargic response to name spoken in normal tone; the incidence being more in group F. No patient was sedated in the postoperative period. Fifteen patients (25%) complained of nausea intra-operatively, with no difference between groups.

TABLE III
SIDE EFFECT PROFILE

	Group F (n=30)	Group M (n=30)	P value	
Hypotension	7 (23.3)	4 (13.3)	0.32	
Sedation				
	Awake and responds readily to name spoken in normal tone	13 (43.3)	28 (93.3)	0.79
	Awake but lethargic response to name spoken in normal tone	17 (56.7)	2 (6.6)	
Nausea	7 (23.3)	8 (26.6)	0.10	
Pruritus				
	Mild	0	0	
	Severe	0	0	
Patient satisfaction score				
	Good	25 (83.3%)	24 (80)	0.001
	Excellent	5 (16.7%)	6 (20)	
Bradycardia	0	0		
Shivering	3(10%)	0		
PDPH or Neurological complications	0	0		
Response(Nausea)to Adnexal or Peritoneal Handling	6(20%)	1(3.4%)	< 0.05	

(Data are Numbers (%))

Our findings reinforce the role of magnesium sulphate, an NMDA antagonist, as an effective adjuvant for spinal anesthesia. 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 signaling

No patient vomited intraoperatively. There was no nausea or vomiting in the postoperative period in either group. None of the patients complained of intraoperative or postoperative pruritis, may be because the dose of fentanyl used was very less. 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.

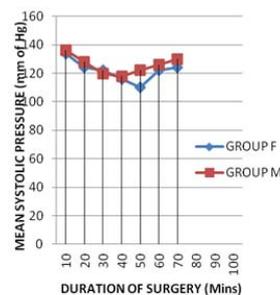


Fig. 1 Haemodynamic Parameters

V. DISCUSSION

Our study demonstrates that the addition of magnesium as adjuvant to hyperbaric bupivacaine improves the duration of post-operative analgesia and reduces the postoperative analgesic consumption as compared to fentanyl- Bupivacaine for spinal anaesthesia in patients with mild preeclampsia undergoing caesarean section. Our findings are comparable to Marzouk et al. for reductions in analgesic requirements with addition of magnesium as intrathecal adjuvant [12]. The cumulative VAS score and 24-h postoperative analgesic consumption were significantly less in the magnesium-bupivacaine group as compared to fentanyl-bupivacaine group.

that culminates in long-term synaptic plasticity, wind-up phenomenon and central sensitization [15], [16]. These events appear to be relevant as they determine, in part, duration and intensity of postoperative pain [17]. NMDA receptor antagonists are thought to prevent the induction of central sensitization attributed to peripheral nociceptive stimulation.

Even large systemic doses of magnesium sulphate may fail to achieve effective CSF concentrations because of insufficient blood-brain barrier penetration. Ko et al. demonstrated an inverse relationship between CSF magnesium concentration and postoperative analgesic requirement [18]. Hence intrathecal magnesium can potentiate spinal analgesia without risking the side effects of the large (IV) 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-bupivacaine group as compared to fentanyl-bupivacaine group. Ozalevli et al. observed a similar delay in onset of spinal anaesthesia when adding intrathecal magnesium to isobaric bupivacaine [9]. The 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. Malleeswaran observed that addition of intrathecal magnesium sulphate to bupivacaine-fentanyl anaesthesia prolonged the duration of analgesia which was found to be significant [19]. Arcioni et al. also observed that intrathecal and epidural magnesium sulphate potentiated and prolonged motor block [11].

Though IV magnesium is known to cause hypotension when used to treat eclampsia [20], we found no significant haemodynamic effect following the addition of 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 IV magnesium [21], we did not find an increase in sedation following intrathecal magnesium. An increased risk of respiratory depression in laboring parturients has also been reported with IV magnesium [21]. 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 comparable in the two groups. The incidence of pruritus in our study was nil with both the groups.

The safety of intrathecal magnesium has been extensively evaluated in animals [22], [23]. 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 [7]; 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 [7]–[10].

Our study may be limited by the fact that the urinary retention effect of opioids could not be evaluated as all patients undergoing caesarean section required foley's catheterization.

VI. CONCLUSION

The addition of intrathecal magnesium sulphate 50 mg as an adjuvant to bupivacaine in patients with mild pre-eclampsia undergoing caesarean section prolongs the duration of analgesia and reduces postoperative analgesic requirements without additional side effects.

REFERENCES

- [1] Wallace DH, Leveno KJ, Cunningham FG, et al. Randomized comparison of general and regional anesthesia for cesarean delivery in pregnancies complicated by severe pre-eclampsia. *Obstet Gynecol* 1995; 86:193–9.
- [2] Karinen J, Rasanen J, Alahuhta S, et al. Maternal and uteroplacental haemodynamic state in pre-eclamptic patients during spinal anaesthesia for caesarean section. *Br J Anaesth* 1996; 76:616–20.
- [3] Hood, David D. MD; Curry, Regina RN. Spinal versus epidural anesthesia for cesarean section in severely pre-eclamptic patients: A retrospective study. *Anesthesiology* 1999; 90:1276–1282.
- [4] Roseag OP, Lui ACP, Cicutti NJ, et al. Perioperative multimodal pain therapy for caesarean section: analgesia and fitness for discharge. *Can J Anesth* 1997; 44:803–9.
- [5] Schobel HP, Fischer T, Heuszer K, et al. Preeclampsia: a state of sympathetic overactivity. *N Engl J Med* 1996; 335:1480–5.
- [6] Kroin JS, McCarthy RJ, Von Roenn N, et al. Magnesium sulphate potentiates morphine antinociception at the spinal level. *Anesth Analg* 2000; 90:913–7.
- [7] Buvanendran A, McCarthy RJ, Kroin JS, et al. Intrathecal magnesium prolongs fentanyl analgesia: a prospective, randomized, controlled trial. *Anesth Analg* 2002; 95:661–6.
- [8] Shoebi G, Sadegi M, Firazian A, Tabassomi F. The additional effect of magnesium to lidocaine in spinal anaesthesia for caesarean section. *Int J Pharmacol* 2007; 3:425–7.
- [9] Ozalevli M, Cetin TO, Unlugence H, et al. The effect of adding intrathecal magnesium sulphate to bupivacaine fentanyl spinal anaesthesia. *Acta Anaesthesiol Scand* 2005; 49:1514–9.
- [10] Mageed Nabil A, El-Ghoniemy Yasser F. Intrathecal fentanyl-magnesium for fast-track cardiac anaesthesia. *Eg J Anaesth* 2005; 21:289–93.
- [11] Arcioni R, Palmisoni S, Tigano S et al. Combined intrathecal and epidural magnesium sulfate supplementation of spinal anaesthesia to reduce post-operative analgesic requirements: a prospective, randomized, double-blind, controlled trial in patients undergoing major orthopedic surgery. *Acta Anaesthesiol Scand* 2007; 51:482–9.
- [12] Marzouk S, El-Hady NA, Lotfy M, Darwish HM. The effect of three different doses of intrathecal magnesium sulphate on spinal opioid analgesia. *Eg J Anaesth* 2003; 19:405–9.
- [13] Report of the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy. *Am J Obstet Gynecol*. Jul 2000; 183(1):S1–22.
- [14] American College of Obstetricians and Gynecologists: *Hypertension in pregnancy*. ACOG Technical Bulletin No. 219. Washington DC: 199
- [15] Liu HT, Hollman MW, Liu WH et al. Modulation of NMDA receptor function by ketamine and magnesium. Part 2. *Anesth Analg* 2001; 92:1173–81.
- [16] Woolf CJ, Chong MS. Preemptive analgesia-treating postoperative pain by preventing the establishment of central sensitization. *Anesth Analg* 1993; 77(2):362–79.
- [17] Woolf CJ, Thompson SW. The induction and maintenance of central sensitization is dependent on N-methyl-D-aspartic acid receptor activation; implications for the treatment of post-injury pain hypersensitivity states. *Pain* 1991; 44:293–9.
- [18] Ko SH, Lim HR, Kim DC, et al. Magnesium sulfate does not reduce postoperative analgesic requirements. *Anesthesiology* 2001; 95:640–6.
- [19] S. Malleeswaran, N. Panda, P. Mathew, R. Bagga. A randomized study of magnesium sulphate as an adjuvant to intrathecal bupivacaine in

- patients with mild pre-eclampsia undergoing caesarean section. *International Journal of Obstetric Anesthesia* (2010) 19, 161-166.
- [20] Jeffrey MichaelSmith, Richard F Lowe, Judith Fullerton, et al. An Integrative Review of the Side Effects Related to the Use of Magnesium Sulfate for Pre-eclampsia and Eclampsia Management. *BMC Pregnancy Childbirth*. 2013;13(34)
- [21] Witlin AG, Sibai BM. Magnesium sulfate therapy in preeclampsia and eclampsia. *ObstetGynecol*1998; 92:883-9.
- [22] Simpson JI, Eide TR, Schiff GA et al. Intrathecal magnesium sulphate protects the spinal cord from ischaemic injury during thoracic aorta cross clamping. *Anesthesiology* 1994; 81: 1493-9.
- [23] Takano Y, Sato E, Kaneko T, Sato I. Antihyperalgesic effects of intrathecally administered magnesium sulphate in rats. *Pain* 2000; 84:175-9.