

# Role of Magnesium Sulfate in Prolonging the Analgesic Effect of Spinal Bupivacaine for Cesarean Section in Severe Preeclampsics

Sumanta Ghosh Maulik, Arunima Chaudhuri<sup>1</sup>, Suchismita Mallick, Arun Kumar Ghosh, Debashis Saha<sup>2</sup>, Bikash Bisui<sup>3</sup>

Departments of Anesthesiology and <sup>1</sup>Physiology, Burdwan Medical College and Hospital, Burdwan, <sup>2</sup>Department of Anesthesiology, Murshidabad Medical College, Murshidabad, <sup>3</sup>Department of Anesthesiology, Bankura Sammilani Medical College, Bankura, West Bengal, India

## ABSTRACT

**Background:** Magnesium sulfate, N-methyl-d-aspartate receptor antagonist, has both analgesic and sedative properties. **Aim:** The aim was to evaluate the analgesic efficacy of perioperative intravenous (i.v) magnesium sulfate in severe preeclamptic patients scheduled for cesarean section under spinal anesthesia. **Subjects and Methods:** A double blind prospective randomized controlled study was designed conducted on 80 patients randomly allocated into two equal groups (n = 40) to receive either bupivacaine heavy intrathecal – Group B (control group) or bupivacaine heavy intrathecal along with i.v magnesium sulfate – Group BM (study group). Magnesium sulfate 40 mg/kg diluted in 100 ml of normal saline was administered over 15 min about 30 min prior to surgery followed by continuous infusion at the rate of 10 mg/kg/h for the next 24 h while the other group received similar volume of normal saline in the same manner. Intraoperatively, patients were monitored for hemodynamic perturbations, respiratory rate, urine output, Apgar score, uterine tonicity, and any other adverse effects. Postoperatively, duration of analgesia, number of rescue analgesics, signs of any magnesium toxicity, and incidence of postpartum eclampsia in the first 24 h were recorded. Data were analyzed using SPSS version 16. **Results:** At different time intervals, patients in Group BM had less pain than Group B when compared on visual analog scale. Patients in Group BM were significantly more sedated as compared to Group B patients. None of the patients demonstrated bradycardia, hypotensive episodes, hypoxia, or hypoventilation in the postoperative period in the recovery room. There was no significant respiratory depression, Apgar score was comparable, and uterine tonicity was adequate in both the groups. Postoperatively, time required for first analgesic dose was significantly more in Group BM 270 (35.1) min than Group B 223 (31.4) min. There was a significant decrease in total rescue analgesic requirement in Group BM 2.5 (0.4) compared to Group B 3.6 (0.4). Incidence of postpartum eclampsia in study group (one patient) was less than the control group (four patients). **Conclusion:** Preoperative i.v magnesium sulfate, in severe preeclampsia not only reduces the probability of developing peripartum eclampsia, but also significantly prolongs the duration of analgesia and reduces postoperative analgesic consumption without any significant side effects.

**KEY WORDS:** Intravenous magnesium sulphate, preeclampsia, spinal anaesthesia

## INTRODUCTION

Magnesium sulfate being an N-methyl-d-aspartate receptor antagonist has both analgesic and sedative properties and has been extensively used in anesthesia in the recent past.<sup>[1-4]</sup> Role of magnesium sulfate as prophylaxis in severe preeclampsia is well-established.<sup>[1-4]</sup> Intravenous (i.v) loading dose followed by continuous infusion is another well-established technique. Local anesthetic adjuvants have been studied in an attempt to prolong the duration of analgesia after peripheral

nerve blockade. Magnesium has been shown to have an antinociceptive effect in animal and human pain models. i.v magnesium sulfate has been shown to significantly prolong the duration of analgesia when used as an adjuvant in spinal anesthesia for orthopedic cases.<sup>[5-9]</sup> Different regimens of the loading dose (4 g, 6 g and 2 g) followed by infusion at the rate of 1 g/h, 2 g/h, have been tried in the past for prophylaxis of severe preeclampsia.<sup>[4-9]</sup> Considering the toxicity of magnesium sulfate such as renal, central nervous system (CNS), and respiratory compromise, low dose magnesium sulfate (2 g followed by 1 g/h) is advocated in obstetrics practice.<sup>[4-9]</sup>

Severe preeclampsia is defined as sustained elevations in systolic blood pressure (BP) to at least 160 mmHg

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### Address for correspondence

Dr. Arunima Chaudhuri,  
Krishnasayar South, Borehat,  
Burdwan - 713 102, West Bengal, India.  
E-mail: arunimachaudhuri4u@gmail.com

and/or in diastolic BP to at least 110 mmHg for at least 6 h in association with abnormal proteinuria or if there is hypertension in association with severe proteinuria (at least 5 g/24 h period).<sup>[2]</sup> Preeclampsia is also considered severe in the presence of multi-organ involvement such as pulmonary edema, oliguria (<500 ml/24 h period), thrombocytopenia (platelet count <100,000/mm<sup>3</sup>), abnormal liver enzymes in association with persistent epigastric or right upper quadrant pain, or persistent severe CNS symptoms (altered mental status, headaches, blurred vision, or blindness) even if all criteria of definitions are not fulfilled.<sup>[2,10,11]</sup> Eclampsia is the occurrence of seizures in a preeclamptic that cannot be attributed to other causes. The seizures are grand mal type and may appear before, during, or after labor.<sup>[2,10,11]</sup>

Intravenously administered magnesium sulfate is effective in reducing the incidence of eclampsia in women with severe preeclampsia.<sup>[2-7]</sup> Magnesium sulfate should be considered for women with preeclampsia for whom there is concern about the risk of eclampsia, such as hyperreflexia, frontal headache, blurred vision, and epigastric tenderness.<sup>[2-7]</sup> Duration of treatment should not normally exceed 24 h, and if the i.v route is used for maintenance therapy, the dose should not exceed 1 g/h.<sup>[11-6]</sup> Clinical monitoring of respiration, tendon reflexes, and urine output are enough for monitoring of magnesium toxicity. Progression from mild to severe disease and development of serious maternal complications during antepartum, intrapartum, and postpartum cannot be predicted without close maternal surveillance.<sup>[2-9]</sup>

Considering the safety profile of this regimen particularly in low resource set ups, our study was planned to observe the effect of this low dose regimen on prolongation of spinal anesthesia and improvement in the analgesic quality for cesarean section in these patients.

## SUBJECTS AND METHODS

This prospective cross-sectional double blinded randomized controlled trial was conducted in a time period of 1-year in a tertiary care hospital in West Bengal after taking Institutional Ethical Clearance and informed consent of patients.

### Inclusion criteria

Eighty severe preeclamptic mothers scheduled for caesarean section under spinal anesthesia were chosen for the study. Randomization and sample population were derived using computer-generated Microsoft Excel program. Windows Vista, Microsoft Office 2007, Group B and BM. Group BM ( $n = 40$ ) received magnesium sulfate 40 mg/kg diluted in 100 ml of normal saline administered over 15 min about 30 min prior to surgery followed by

continuous infusion at the rate of 10 mg/kg/h for the next 24 h, while the other group, Group B ( $n = 40$ ) received similar volume of normal saline in the same manner. All patients received loading dose of magnesium sulfate 4 g i.v slowly, 5 g i.m in each buttock and labetalol injection i.v 20 mg on admission, and patients were monitored every 10 min and treated accordingly.

### Exclusion criteria

The American Society of Anesthesiologists  $\geq$  III, eclamptic patients, body mass index (BMI)  $\geq 35$  kg m<sup>2</sup> and <18.5, reported adverse reactions to any of the drugs included in the study, patients with history of ischemic heart disease, renal, hepatic and pulmonary diseases, those on antipsychotics, anticoagulants, epileptics, diabetics, or on any other drug affecting the metabolism of anesthetics used, any chronic pain syndrome, thrombocytopenia, history of seizures, medication use that affects cytochrome P450-3A4 or P450-1A2 metabolism (including smokers and tobacco addicts).

### Preoperative assessment

A thorough clinical history was obtained. They were physically examined, laboratory investigations were reviewed. The patients were also explained about the procedures of anesthesia. The patients were counseled about the anesthetic management and potential complications of both surgery and anesthesia. The purpose, protocol of the study, and use of visual analog scale (VAS) was explained to patients. All patients eligible for the trial had the following information documented preoperatively: Medication list, age, sex, height, weight, BMI, serum urea, fasting sugar, creatinine, calculated creatinine clearance (Cockcroft–Gault), liver function tests (aminotransferase, alkaline phosphatase, total bilirubin), serum electrolytes, coagulation profile, electrocardiogram, chest X-ray, primary diagnosis, and scheduled procedure.

### Airway assessment

Malampatti classification, mouth opening, neck movement, altered anatomy of the mouth, thyromental distance, Wilson scoring system was noted to find out any possibility of difficult intubation. If there is a chance of significant difficult intubation, they were excluded from the study. Instructions for preoperative fasting were given as per Nil per Oral guidelines.

On the day of surgery baseline parameters such as heart rate, systolic BP, distolic BP, mean arterial pressure, and oxygen saturation were measured (SpO<sub>2</sub>). An i.v line was started.

Both groups received heavy bupivacaine intrathecally. Magnesium sulfate 40 mg/kg diluted in 100 ml of normal saline was administered over 15 min about 30 min prior

to surgery followed by continuous infusion at the rate of 10 mg/kg/h for the next 24 h while the other group received similar volume of normal saline in the same manner. The drugs were prepared by anesthesiologists totally ignorant about the study, and observations were made by another group of anesthesiologists and obstetricians who were unaware of the type of drug received by each patient.

Spinal anesthesia was performed through the L3-L4 or L4-L5 interspace in the lateral decubitus position. After dural puncture with a 27 G spinocan needle (Braun, India), hyperbaric bupivacaine 0.5% solution was injected intrathecally. Intraoperatively, patients were monitored for hemodynamic perturbations, respiratory rate, urine output, Apgar score, uterine tonicity, and any other adverse effects. Postoperatively, duration of analgesia, number of rescue analgesics, signs of any magnesium toxicity, and incidence of postpartum eclampsia in the first 24 h were recorded.

Pain at rest (i.e. with patient not carrying any activity) was evaluated using the 0-10 cm VAS (0 – No pain at all to 10 – Worst pain imaginable) at emergence from anesthesia and 2, 4, 6, 12, and 24 h after surgery. During first 4 h, the patients were in the recovery room, and rescue analgesia was provided at VAS > 3 in the form of diclofenac sodium 75 mg i.m. Sedation was monitored using a four-point rating scale (1 – patient fully awake, 2 – patient somnolent, but responds to verbal commands, 3 – patient somnolent, but responds to tactile stimulation, 4 – patient asleep, but responds to pain). Thereafter, the patients were sent to ward and diclofenac sodium 75 mg intramuscularly was given on demand. The timing and dosage of rescue analgesic and total consumption of diclofenac sodium during first 24 h after operation was noted. Postoperative nausea and vomiting were reported by obstetricians and nursing personnel. Data were analyzed using SPSS version 16. (SPSS Inc. Released 2007. SPSS for Windows, Version 16.0. Chicago, SPSS Inc.)  $P < 0.01^{**}$  was considered as highly significant and  $< 0.05^{***}$  as significant. Unpaired *t*-test was used to analyze numerical data [Tables 1-4] and Chi-square test to analyze categorical data (vomiting and shivering).

## RESULTS

The demographic profiles, baseline hemodynamic parameters, duration of surgery of patients in two groups were comparable. Postoperatively, time required for first analgesic dose was significantly more in Group BM 270 (35.1) min than Group B 223 (31.4) min [Table 1 and Figure 1]. There was a significant decrease in total rescue analgesic requirement in Group BM 2.5 (0.4) compared to Group B 3.6 (0.4) [Table 1

**Table 1: Time interval of first analgesic requirement and total rescue analgesic requirement**

Parameter	Mean (SD)		P
	Group BM	Group B	
Postoperative first requested analgesic dose required (min)	270 (35.1)	223.6 (31.40)	<0.001**
Total analgesic requirement postoperatively (g)	2.5 (0.4)	3.6 (0.4)	<0.001**

\*\* $P < 0.01$  (highly significant). SD – Standard deviation

**Table 2: Sedation scores of patients in the recovery room**

Parameter	Mean±SD		P
	Group BM	Group B	
Sedation score in the recovery room immediately after transferring the patient	2.7 (0.9)	1.4 (0.5)	<0.001**
Sedation score in recovery room 2 h after shifting the patient	2.6 (0.98)	1.3 (0.5)	<0.001**
Sedation score in the recovery room 4 h after shifting the patient	1.1 (0.6)	1.2 (0.4)	<0.001**

\*\* $P < 0.01$  (highly significant). SD – Standard deviation

**Table 3: Assessment of pain in postoperative period (VAS)**

Parameter	Mean (SD)		P
	Group BM	Group B	
2 h after surgery	1.2 (0.7)	1.7 (0.9)	<0.001**
4 h after surgery	1.3 (0.8)	1.9 (0.4)	<0.001**
8 h after surgery	2.7 (1.3)	3.5 (1.3)	<0.001**
16 h after surgery	1.4 (0.7)	2 (0.7)	<0.001**
24 h after surgery	0.7 (0.6)	1.3 (0.4)	<0.001**

\*\* $P < 0.01$  (highly significant). SD – Standard deviation; VAS – Visual analog scale

**Table 4: MAP 30 min and 60 min following administration of spinal anesthesia**

Parameter	Mean (SD)		P
	Group BM	Group B	
MAP (30 min after spinal)	80.7 (8)	95.3 (4.3)	<0.001**
MAP (60 min after spinal)	98.1 (2.20)	98.8 (1.8)	0.04

\*\* $P < 0.01$  (highly significant). MAP – Mean arterial pressure; SD – Standard deviations

and Figure 2]. Patients in Group BM were significantly more sedated as compared to Group B patients [Table 2 and Figure 3]. At different time intervals, patients in Group BM had significant less pain than Group B when compared on VAS [Table 3]. None of the patients demonstrated bradycardia, hypotensive episodes, hypoxia, or hypoventilation in the postoperative period in the recovery room. Intraoperatively, Group BM had significant hypotension as compared to Group B [Table 4]; but readily correctable with vasopressors. There was no significant respiratory depression, Apgar score was comparable, and uterine tonicity as reported by obstetricians, who were blind to the study drug used, was adequate in both the groups. Incidence of postpartum eclampsia in study group (one patient) was less than the control group (four patients). In group BM, three patients had shivering, 4 had postoperative nausea and vomiting, and in Group B, eight patients had shivering and 9 had postoperative nausea vomiting and the difference between the groups was not significant.

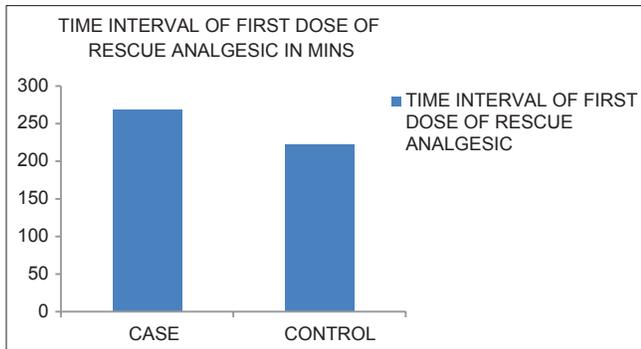


Figure 1: Time interval of first analgesic requirement

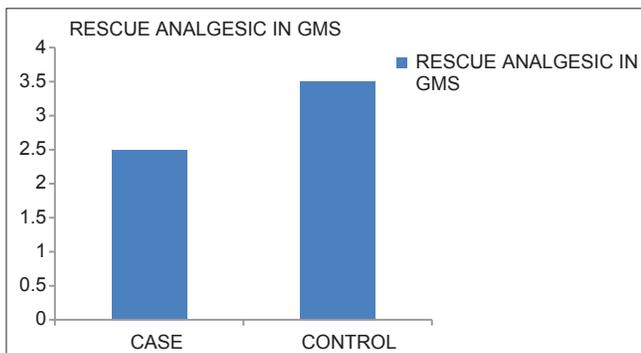


Figure 2: Total rescue analgesic requirement

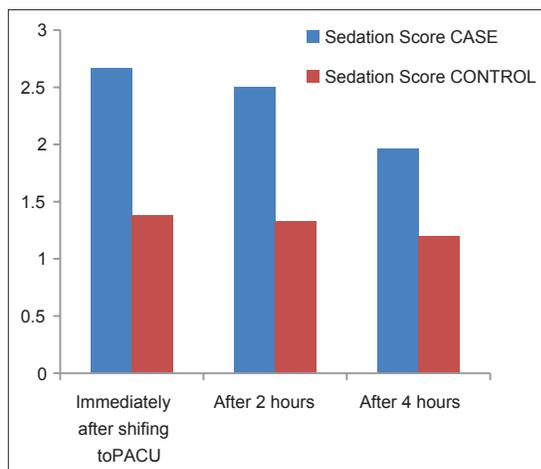


Figure 3: Sedation score

## DISCUSSION

Our study has shown that infusion of magnesium sulfate given before induction of anesthesia followed by low dose infusion per-operatively is associated with less postoperative pain in severe preeclamptic patients undergoing cesarean section under spinal anesthesia. Patients in Group BM were significantly more sedated as compared to Group B patients. At different time, intervals patients in Group BM had significant less pain than Group B when compared on VAS. None of the patients demonstrated bradycardia, hypotensive episodes, hypoxia, or hypoventilation in the

postoperative period in the recovery room. Intraoperatively, Group BM had significant hypotension as compared to Group B.

Lee *et al.* in 2012<sup>[12]</sup> enrolled 66 patients undergoing arthroscopic rotator cuff repair. Interscalene nerve block was performed with 0.5% bupivacaine 20 mL with epinephrine (1:200,000) plus either 10% magnesium sulfate 2 mL (magnesium group) or normal saline 2 mL (saline group). The duration of analgesia was longer in the magnesium group than in the saline group. The onset times and durations of sensory and motor blocks were not significantly different between the two groups. They concluded that the addition of magnesium sulfate to a bupivacaine-epinephrine mixture for interscalene nerve block prolongs the duration of analgesia and reduces postoperative pain.

A study was undertaken by Kiran *et al.* in 2011<sup>[11]</sup> to study efficacy of a single dose of i.v magnesium sulfate to reduce postoperative pain in patients undergoing inguinal surgery. The patients of magnesium sulfate group (Group-I) received magnesium sulfate 50 mg/kg in 250 ml of isotonic sodium chloride solution i.v whereas patients in the control group (Group-II) received same volume of isotonic sodium chloride over 30 min preoperatively. Pain in the postoperative period was significantly lower in magnesium sulfate group in comparison to control group at emergence from anesthesia and 2, 4, 6, 12 and 24 h postoperatively.

The studies by Lee *et al.*<sup>[12]</sup> and Kiran *et al.*<sup>[11]</sup> are not exactly the same scenario as this current study but our study also demonstrated less requirement of analgesics in patients receiving i.v magnesium sulfate as it prolongs the duration of analgesia and reduces postoperative pain.

Hwang *et al.* in 2010<sup>[13]</sup> conducted a study on 40 patients undergoing total hip replacement arthroplasty under spinal anesthesia. After the induction of spinal anesthesia, the magnesium group (Group M) received magnesium sulfate by continuous i.v infusion until the end of surgery. The saline group (Group S) received the same volume of isotonic saline over the same period. After surgery, a patient-controlled analgesia (PCA) device containing morphine and ketorolac was provided for the patients. Postoperative pain scores, PCA consumption, and the incidences of shivering, postoperative nausea, and vomiting were evaluated immediately after surgery and at 30 min, 4, 24, and 48 h after surgery. Serum magnesium concentrations were checked before the induction of anesthesia, immediately after surgery, and at 1 and 24 h after surgery. Postoperative pain scores were significantly lower in Group M at 4, 24, and 48 h after surgery. Cumulative postoperative PCA consumptions were also significantly lower in Group M at 4, 24, and 48 h after surgery. Postoperative

magnesium concentrations were higher in Group M, but no side-effects associated with hypermagnesemia were observed. Hemodynamic variables and the incidences of shivering, nausea, and vomiting were similar in the two groups.

They concluded that i.v magnesium sulfate administration during spinal anesthesia improved postoperative analgesia. The results of these studies are comparable with the present study.

Magnesium may induce hypotension directly by vasodilatation as well as indirectly by sympathetic blockade and inhibition of catecholamine release. We did observe hypotensive episodes in our patients who were readily managed with treated with vasopressors. Zarauza *et al.* in 2000<sup>[10]</sup> and Tramèr and Glynn in 2007<sup>[11]</sup> observed similar hypotensive episodes following use of magnesium sulfate as supplementary analgesic. While Kiran *et al.*<sup>[1]</sup> observed transient fall in BP at induction in both groups which they attributed to use of propofol as an induction agent. They did not observe any hypotensive episode during the operative period. They used magnesium sulfate only as single bolus dose whereas most of the studies and our study used magnesium sulfate as subsequent infusion also in addition to initial single bolus.

A study was conducted by Elgebaly *et al.* in 2011<sup>[14]</sup> on 105 patients randomly allocated to one of the three groups; the control Group B received spinal anesthesia with 10 mg of 0.5% heavy bupivacaine, the test Group FB received spinal anesthesia with 10 mg of 0.5% heavy bupivacaine plus 25 µg of preservative-free fentanyl and the test Group MB received spinal anesthesia with 10 mg of 0.5% heavy bupivacaine along with i.v magnesium sulfate. The time required for the first postoperative analgesic requirement was significantly more in Groups FB and MB, as compared to the control group. Perioperative sedation was significantly higher in Group FB as compared to Group B and Group MB. Nine patients in Group FB had postoperative nausea and vomiting, whereas, none of the patients in the control group and the difference too was statistically significant. We also noticed decreased incidence of postoperative nausea and vomiting in patients receiving magnesium sulfate.

## CONCLUSION

Preoperative i.v magnesium sulfate, in severe preeclampsia not only, reduces the probability of developing peripartum

eclampsia, but also significantly prolongs the duration of analgesia and reduces postoperative analgesic consumption without any significant side effects.

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