Comparison of Prophylactic Intravenous Magnesium Sulfate with Tramadol for Postspinal Shivering in Elective Cesarean Section: A Placebo Controlled Randomized Double-blind Pilot Study

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Abstract

Background and Aims: Cesarean sections are performed mostly under spinal anesthesia. Shivering is one of the distressing complications. The aim of the study was to compare the efficacy of intravenous (i.v) magnesium sulfate and tramadol with placebo (normal saline) on postspinal shivering in elective cesarean section when used as prophylaxis. Methods: One hundred and thirty-five pregnant women between 18 and 35 years age, belonging to the American Society of Anesthesiologists’ physical Status II, undergoing elective cesarean section under spinal anesthesia were enrolled into the study. Patients belonging to Group C (control group, n = 45) received isotonic saline 100 mL i.v, Group T (tramadol group, n = 45) received tramadol 0.5 mg/kg in 100 mL isotonic saline i.v, whereas those in Group M (magnesium sulfate group, n = 45) received magnesium sulfate 30 mg/kg in 100 mL isotonic saline i.v after administering spinal anesthesia. Incidence and grades of shivering were noted. Data were analyzed using one-way ANOVA test and Chi-square test. Results: The incidence of shivering in Group C, Group T, and Group M were 67.5%, 43.9%, and 39%, respectively. The incidence of shivering in Group M and Group T was significantly low when compared to Group C (P = 0.008; P = 0.026), whereas there was no statistically significant difference between Groups T and M (P = 0.654). Conclusion: Magnesium sulfate and tramadol significantly reduce the incidence of shivering compared to placebo when used as prophylaxis in pregnant women undergoing cesarean section under spinal anesthesia. Magnesium sulfate reduces the severity of the shivering.

Keywords: Cesarean section, magnesium sulfate, shivering, tramadol

INTRODUCTION

Lower segment cesarean section is one of the most frequently performed surgeries in obstetrics. Most cesarean sections are performed under spinal anesthesia.1-3 Shivering is one of the distressing complications of the surgeries performed under regional anesthesia. The reported incidence of shivering ranges from 40% to 70%, in patients undergoing surgery under regional anesthesia.4-6 Shivering is known to increase oxygen consumption and carbon dioxide production. Besides being distressing to the patients, shivering also contributes to adverse postoperative events such as wound infection and bleeding. The resultant adrenergic activation can result in morbid cardiac events, arterial hypoxemia, lactic acidosis, and increase in the intracranial and intracranial pressures. Intraoperative shivering interferes with the monitoring of heart rate (HR), blood pressure (BP), electrocardiogram (ECG) etc.4-5 Various pharmacological and nonpharmacological methods have been tried to reduce the postspinal shivering. Although pethidine is the gold standard drug it has its own limitations in pregnant women.

Magnesium sulfate has drawn attention in the field of anesthesia and pain medicine since 1996.6-8 It has been widely used in

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pre-eclampsia and eclampsia.\cite{7} Magnesium being a calcium competitor and N-methyl D-Aspartate receptor antagonist has been reported to reduce shivering threshold.\cite{8} It is also a mild muscle relaxant.\cite{9} To the best of our knowledge, very few studies have reported the use of magnesium as a prophylactic anti-shivering agent in pregnant women. Because its role as antishivering agent is still not established – this study was undertaken to see if this could provide at least comparable results to that of the commonly used drug to prevent/treat shivering (tramadol) to evaluate if magnesium sulfate could really bring about significant reduction in shivering compared to control group.

Aim of this study was to compare the efficacy of intravenous (i.v) magnesium sulfate and tramadol to placebo (normal saline) on incidence and severity of postspinal shivering in elective cesarean section, when used as prophylaxis.

**Methods**

The study was conducted in a tertiary hospital. After obtaining institutional ethical committee approval, 135 pregnant women between 18 and 35 years age, belonging to the American Society of Anesthesiologists’ physical Status II, undergoing elective cesarean section under spinal anesthesia were enrolled in the study. Informed written consent was obtained from all the patients involved in the study.

Patients with the severe cardiopulmonary, renal or liver disease, pre-eclampsia, eclampsia, hypo or hyperthyroidism, those with psychiatric disorder, morbidly obese, with height <145 cm or >160 cm, basal body temperature >38°C or <36°C or those who received blood transfusion or >2000 mL fluid intra-operatively were excluded from the study. Patients allergic to study drug were also excluded from the study.

During the preoperative visit, detailed history and examination of the patients were done. Investigations such as hemoglobin estimation, complete blood count, urine routine and microscopy, random blood sugar, blood urea, and serum creatinine were performed as an institutional protocol. All patients received tablet ranitidine 150 mg and tablet metoclopramide 10 mg the night before surgery and i.v ranitidine 50 mg and metoclopramide 10 mg before the surgery as per the institutional protocol.

Once in the operating room, all patients were monitored with noninvasive blood pressure, ECG, pulse oxymeter (SpO\(_2\)), and digital thermometer. The temperature of the operating room was maintained in the range of 24–25°C. The baseline values of all vital parameters were noted. All patients were co-loaded with 10 mg/kg Ringer lactate solution at room temperature.

The patients were randomly allocated to Groups C, T, or M on the basis of computer generated random numbers. Patients belonging to Group C (control group, \(n = 45\)) received 100 mL isotonic saline, Group T (tramadol group, \(n = 45\)) received tramadol 0.5 mg/kg in 100 mL isotonic saline while those belonging to Group M (magnesium sulfate group, \(n = 45\)) received magnesium sulfate 30 mg/kg in 100 mL isotonic saline after administering spinal anesthesia.

Randomization and allocation concealment were ensured by having a computer generated group of numbers that enclosed in sealed envelopes by a neutral observer not involved in the study. Once the patient was recruited for the study, the sealed envelope was opened and the study drug prepared by the same observer. The study drug was administered as infusion in 100 mL isotonic saline over 20 min, using a separate infusion set, piggy backed to the primary infusion. The patient and anesthesiologist administering the spinal anesthesia was unaware of the study drug and this person collected the study data till the end of the study for all patients. All patients received fentanyl 1 \(\mu\)g/kg i.v after the delivery of baby.

The subarachnoid block was performed using 25/26 G Quincke type spinal needle in sitting position at L\(_{1-2}\) or L\(_{4-5}\) interspace. Spinal anesthesia was established using 2.0–2.2 mL of 0.5% hyperbaric bupivacaine. The volume of bupivacaine administered was based on the height of the patients (145–150 cm received 2 mL; 150–160 cm received 2.2 mL).

The vital parameters were recorded every 5 min from the time spinal anesthesia was performed to 2 h from the time of block. Axillary temperature and grades of shivering were noted every 10 min by the same anesthesiologist who performed the spinal anesthesia using Crossley and Mahajan scale,\cite{10} which is 0 = No shivering, 1 = Cyanosis and piloerecton, 2 = Visible tremors only in one muscle group, 3 = Visible tremors in more than one muscle group and 4 = Intense shivering, tremors of the head, arm.

Arterial hypotension was defined as systolic BP <90 mm Hg or <25% of the basal mean arterial blood pressure (MAP) reading and injection ephedrine 6–12 mg i.v was administered. Injection atropine 0.5 mg i.v was administered if HR <50 bpm. Pethidine 0.5 mg/kg i.v was administered as a rescue drug if grade III shivering persisted for >10 min. Sedation score was assessed using a four point scale as per Filos\cite{11} 1 = Alert and awake; 2 = Drowsy responsive to verbal stimuli; 3 = Drowsy, arousable to physical stimuli; 4 = Unarousable. Side effects such as nausea, vomiting, bradycardia, arrhythmia, and hypotension were noted. All patients were monitored in the post anesthesia care unit for the side effects of the study drug.

Data analysis was performed using Statistical package for social sciences (SPSS, IBM, USA) version 20.0. Results were reported as mean ± standard deviation for quantitative variables. Comparison with respect to demographic data and duration of surgery was done using one-way ANOVA test. Comparison of three groups with mean HR, MAP and mean temperature was done using one-way ANOVA test. Pair-wise comparison of three groups with MAP and HR at different points of time was done by Tukeys multiple post hoc testing. Categorical data were compared using Chi-square test. The value of \(P < 0.05\) was considered statistically significant.
RESULTS

The study included 135 patients. Four patients from Group M, four from Group T, and five from Group C were excluded from the study either because they had to be administered general anesthesia or received blood or fluids in excess of 2000 mL intraoperatively. Therefore, the final analysis included 122 patients.

The three groups were similar with regard to demographic characteristics and duration of surgery [Table 1]. The incidence of shivering was much higher in Group C compared to Groups T and M (67.5%, 43.9% and 39%, respectively) [Table 2] which was statistically significant (Group C vs. Group M, \( P = 0.008 \); Group C vs. Group T, \( P = 0.026 \)). There was no statistically significant difference between Group T and Group M (\( P = 0.654 \)).

The number of patients with mild shivering (grade 1 or 2) or severe shivering (grade 3 or 4) among the patients who had shivering is shown in the Table 2. Significantly less number of patients had grade 3 or 4 shivering in Group M (6/16) compared to Group C (21/27) (\( P = 0.008 \)). There was no statistically significant difference with respect to grade of shivering when Group M was compared to Group T (\( P = 0.464 \)).

Mean temperature changes was comparable among the groups at all study points. The mean basal temperature in Group C, Group T, and Group M was 36.36 ± 50, 36.39 ± 52, and 36.61 ± 43, respectively. The mean temperature at the end of 120 min in Group C, Group T, and Group M was 35.19°C ± 45°C, 35.25°C ± 55°C, and 35.27°C ± 54°C, respectively.

There was significant change with respect to HR at 15 min in Group M (\( P = 0.005 \)), however the changes over 120 min remained insignificant [Figure 1]. There was significant fall in the MAP in Group M when compared with the Group C [Figure 2]. Hypotension occurred in 65.85% of patients in the Group M and 36.59% of patients in Group T. Five patients in Group M and one patient in Group T had bradycardia which was treated with i.v atropine (\( P < 0.023 \)).

There was no significant difference with respect to nausea and vomiting among the groups [Table 3]. The sedation score was significantly higher in the Group M when compared with the Group T and Group C (\( P < 0.002 \)) [Figure 3].

DISCUSSION

In the present study, the incidence of shivering was significantly reduced when magnesium was used as prophylactic drug for shivering compared to the control group. The mechanism by which magnesium reduces shivering remains unclear. It could be central or peripheral. Magnesium also reduces the gain of shivering.[12]

In a study by Ibrahim et al. magnesium sulfate 50 mg/kg i.v administered as a bolus dose following intrathecal injection along with 2 mg/kg/h infusion in the intraoperative period resulted 15% incidence of grade 3 or 4 shivering. The authors concluded that prophylactic magnesium sulfate infusion lowers the incidence of shivering. However, they also observed frequent hypotension in these patients. The incidence of grade 3 or 4 shivering in saline group was 50%.[13]

Magnesium sulfate 30 mg/kg i.v bolus and pethidine 0.5 mg/kg bolus were studied for postanesthesia shivering following general anesthesia. The study concluded that magnesium

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**Table 1: Demographic data of patients and duration of surgery**

| Variables               | Group C (n=40) | Group T (n=41) | Group M (n=41) | \( P \) |
|-------------------------|----------------|----------------|----------------|-------|
| Age (years)             | 24.53±2.25     | 25.66±3.10     | 25.63±3.17     | 0.134 |
| Height (cm)             | 153.50±4.57    | 152.39±3.93    | 154.32±3.82    | 0.109 |
| Weight (kg)             | 59.03±6.52     | 55.05±7.02     | 57.24±8.24     | 0.053 |
| Duration of surgery (min)| 32.25±4.80   | 32.93±6.71     | 35.73±10.87    | 0.113 |

Mean±SD. Group C=Group control, Group T=Group tramadol, Group M=Group magnesium sulfate, SD=Standard deviation

**Table 2: Incidence and severity of shivering**

| Shivering                                      | Group C (n=40) | Group T (n=41) | Group M (n=41) | \( P \) |
|------------------------------------------------|----------------|----------------|----------------|-------|
| Number of patients with shivering/total number of patients (incidence of shivering) | 27/40 (67.5)   | 18/41 (43.9)   | 16/41 (39.02)  | C versus T 0.026* |
| Number of patients with mild shivering (Grade 1 or 2)/number of patients with severe shivering (Grade 3 or 4) | 6/21           | 9/9            | 10/6          | C versus M 0.008* T versus M 0.654 |

\( P<0.05 \) - *Significant. Group C=Group control, Group T=Group tramadol, Group M=Group magnesium sulfate
sulfate is as effective as pethidine in the treatment of postanesthesia shivering.\cite{14}

We presume the incidence of shivering and the severity of shivering in our study could have been reduced further with an additional infusion of magnesium sulfate. Higher dose of magnesium is associated with peripheral vasodilatation with consequent hypotension, bradycardia, and hypothermia.\cite{8,13,15,16}

Therefore, we limited the dose of magnesium sulfate in our study to 30 mg/kg. There was no significant change in the mean temperature among the three groups in our study. As in some previous studies, we did not find any correlation between incidence of shivering and temperature change.\cite{17}

Various mechanisms other than hypothermia which include uninhibited spinal reflexes, decreased sympathetic activity, pyrogen release, and adrenal suppression have been implicated for postoperative shivering.\cite{18}

Magnesium sulfate 80 mg/kg i.v administered as bolus over 30 min followed by infusion of 2 g/h significantly reduced shivering in patients receiving spinal anesthesia for transurethral resection of prostate though it increased the risk of hypothermia. Shivering occurred in 6.7% of patients who received magnesium and 66.7% of patients who received saline.\cite{19}

Magnesium sulfate as an antishivering agent was found to be as effective as pethidine, in middle-aged patients who underwent spinal anesthesia. Magnesium probably could replace pethidine as the incidence in magnesium group was 28% as against 68% in pethidine group.\cite{20}

Intrathecal magnesium lowered the shivering grades in patients who underwent elective cesarean section.\cite{21}

Tramadol is µ receptor agonist with minimal effect on kappa and delta receptors. It inhibits the neuronal uptake of norepinephrine and 5-hydroxytryptamine and facilitates the release of 5-hydroxytryptamine release. All these mechanisms are responsible for the thermoregulatory control.\cite{22-24} The number of patients with grade 3 or 4 shivering were 9 in Group T compared to Group M which was 6. The study found both tramadol and magnesium sulfate to be equally effective in control of postoperative shivering and superior to the control group.

In a study by Javaherforoosh et al. tramadol 1 mg/kg i.v was effective in reducing the incidence of shivering to 8.8% when compared to placebo (86.6%) in cesarean section. Mild and moderate shivering was observed in 4.4% of parturients who received tramadol. Mild and moderate shivering was observed in 13.3% and 73.3% of parturients who received saline, respectively.\cite{25}

We observed hypotension (65.85%) and bradycardia (12.20%) which was managed with i.v ephedrine and atropine in our study. There were no adverse events, which required discontinuation of the study drug. Hypotension was noticed in patients receiving magnesium which was easily managed with i.v ephedrine. Since the study drugs were administered soon after intrathecal administration of the local anesthetic, it is difficult to ascertain how much hypotension was contributed by the study drug. However, overall incidence of hypotension was higher in Group M than the other groups which would mean that when using prophylactic magnesium sulfate for preventing postoperative shivering, one should aggressively monitor for hypotension.

However, hypotension was not statistically significant in the study by Ibrahim et al. the incidence being 15%.\cite{13}

Hypotension was observed in two patients who received pethidine and one patient who received magnesium.\cite{29}

Tramadol 1 mg/kg i.v did not have any hemodynamic implications.\cite{25}
Future studies with higher sample strength may be able to establish the effectiveness of magnesium sulfate in controlling shivering with conviction. Further, we assume that perioperative infusion of magnesium rather than a single bolus infusion may result in better control of postspinal shivering.

Preoperative magnesium sulfate infusion reduces the postoperative pain and requirement of analgesia in cesarean section. The analgesic efficacy of magnesium was not evaluated in our patients. However, sedation scores were significantly higher in the Group M in our study.

Magnesium was used as bolus infusion in our study. Further studies are required to see whether the incidence of shivering could be reduced further, by administering magnesium infusion following with the bolus in the postoperative period.

Studies could also evaluate the onset and duration of the shivering in the postoperative period with the administration of magnesium. Our evaluation was limited to a period of 120 min.

CONCLUSION

Prophylactic administration of magnesium sulfate or tramadol significantly reduces the incidence and grades of shivering in pregnant women undergoing cesarean section under spinal anesthesia. Magnesium reduces the severity of the grade more than tramadol.

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Conflicts of interest

There are no conflicts of interest.

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