



## Original Research Article

# Comparison of intrathecal tramadol and Magnesium sulphate for the prevention of post-spinal shivering in infra umbilical surgeries: A randomized, double blinded and controlled study

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## ABSTRACT

**Background:** Post anesthesia shivering is a common complication after spinal anesthesia. Intrathecal Magnesium sulphate (MgSO<sub>4</sub>) and tramadol are the most effective and safe adjuvants with minimal side effects. The aim of this study was to compare the effect of intrathecal tramadol versus intrathecal MgSO<sub>4</sub> with bupivacaine for the prevention of post-spinal anesthesia shivering.

**Materials and Methods:** In this prospective randomized, double-blinded controlled study, 105 patients scheduled for infraumbilical surgeries were randomly allocated into three groups. Group C(35) received 3.0ml of hyperbaric bupivacaine 0.5% (15mg)+0.5ml of normal saline, Group T (35) received 3.0ml of hyperbaric bupivacaine 0.5% (15mg)+25mg of tramadol in 0.5ml saline, and Group M (35) received 3.0ml of hyperbaric bupivacaine 0.5% (15mg)+100mg of magnesium sulphate in 0.5ml saline. The primary outcomes were to find the incidence and intensity of shivering. The secondary outcome was to find out the incidence of complications.

**Results:** All the 3 groups were comparable with respect to demographic characteristics. Shivering was observed in 68.6% of the patients in Group C, 48.6% patients in Group T and 40% patients in Group M. The incidence of shivering were statistically significant between Groups C and T (P= 0.003) and Groups C and M (P=0.001) but not between Groups T and M (P=0.480). The incidence of complications such as hypotension, bradycardia, nausea, vomiting, itching and respiratory depression were not statistically significant in between the groups.

**Conclusion:** This study concluded that both intrathecal MgSO<sub>4</sub> 100mg and tramadol 25mg with hyperbaric bupivacaine reduces the incidence and intensity of shivering compared to control group after spinal anesthesia.

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## 1. Introduction

Post spinal shivering is defined as spontaneous, involuntary and oscillatory fasciculation of the face, jaw, head or muscle hyperactivity lasting longer than 15 seconds or tremor like hyperactivity of skeletal muscles.<sup>1</sup> The shivering incidence ranges between 5 and 65% and varies with age, male gender, induction agents and maintenance of anesthesia, duration

of surgery and modes of ventilator support. It is 40%-60% in regional anesthesia and up to 60% in general anesthesia patients.<sup>2</sup>

Shivering is divided into two types.<sup>3</sup> The most common type is thermoregulatory shivering, which correlates with cutaneous vasoconstriction in response to hypothermia.<sup>4</sup> Only 15% of shivering responses is from non-thermoregulatory shivering, which is associated with cutaneous vasodilatation and possibly with pain and stress.<sup>5</sup> Shivering exhibit two different patterns of muscular

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activity likes tonic pattern with 4-8 cycles/min resembling thermo regulatory shivering and clonic pattern with 5-7 Hz due to uninhibited spinal reflex.

Perioperative hypothermia is defined as a core temperature below 36°C, while the shivering threshold in non anaesthetized patients is 35.5°C. Anesthetic agents increase the threshold for heat and decrease the threshold for cold, thus the normal interthreshold range (hypothalamic set point) is increased.<sup>6</sup> Intraoperatively shivering is known to increase the oxygen consumption, carbon dioxide production, lactic acidosis, intraocular and intracranial pressure, so it may further compromise patients with high metabolism and low cardiopulmonary reserve. Shivering decrease mixed venous oxygen saturation and intra operatively interferes with vital monitoring. Post operatively shivering may contribute to increased surgical site pain, delayed wound healing and extends the hospital stay.

Various non pharmacological and pharmacological therapies like preoperative warming, forced air warming, use of intravenous opioids, ketanserin, propofol, granisetron, doxaparem, physostigmine, clonidine and nefopam has been commonly used for the prevention of perioperative hypothermia and post anesthesia shivering which are the two sides of the same coin.

Magnesium sulphate (MgSO<sub>4</sub>), which is a NMDA receptor antagonist used in postoperative shivering, indicating that the agent reduces the shivering threshold.<sup>7</sup> It has a good safety profile, with no side effects related to the intrathecal use of the drug and no significant changes in haemodynamic parameters.<sup>8</sup> Intravenous (IV) MgSO<sub>4</sub> has been effectively examined in many trials but only few trials involving intrathecal MgSO<sub>4</sub><sup>9-11</sup> to control shivering have been conducted.

Tramadol is a weak opioid agonist which inhibits reuptake of norepinephrine, dopamine and serotonin. It is widely used intravenously and intrathecally because of its low cost, easy availability and ability to prolong the duration of sensory block, motor block and postoperative analgesia.<sup>12-14</sup> A few studies have shown intrathecal tramadol has anti shivering efficacy but the exact dose is yet to be proved.

All the drugs studied to prevent post anesthesia shivering were commonly used in intravenous route, but intrathecal use of these drugs may reduce their dosage as well as side effects associated with it. So, we hypothesized that intrathecal tramadol or MgSO<sub>4</sub> given along with hyperbaric bupivacaine could reduce the post spinal shivering in infra umbilical surgeries.

The aim of this study was to evaluate the efficacy and to compare the effects of intrathecal tramadol 25mg and MgSO<sub>4</sub> 100mg with hyperbaric bupivacaine on the prevention of post spinal shivering in infra umbilical surgeries. The primary outcomes were to find the incidence

and intensity of shivering. The secondary outcome was to find out the incidence of complications such as hypotension, bradycardia, nausea, vomiting, pruritus and respiratory depression.

## 2. Materials and Methods

This prospective randomized double-blind and controlled study was done after getting approval from the institutional ethical committee and written informed consent from all the patients. The ethical principles of Declaration of Helsinki were strictly followed while doing this trial in Annapoorana medical college and Hospital in the Department of Anesthesiology.

A total of 120 patients scheduled for various infra umbilical surgeries were enrolled. The inclusion criteria were patients aged between 20 and 50 years and patients with American Society of Anesthesiologists (ASA) class I & II physical status. The exclusion criteria were patients who refused sub arachnoid block, patients with coagulopathy, patients with known history of allergic reactions to local anesthetics or patients with diseases of cardio respiratory, neuromuscular and middle ear pathology, surgeries which might require administration of blood or blood products were excluded. Obesity, hyper or hypothermia, and those with a history of convulsions, thyroid diseases, Parkinson's disease, and Reynaud's disease were excluded.

In the operating room, all the patients were secured with a 18 gauge intra venous cannula and premedication and preloading were not given for all the groups. Ringers lactate as maintenance fluid at 2 ml/kg/h was given intra operatively and adjusted according to hemodynamic response. All the intravenous fluids were kept at room temperature.

The baseline mean arterial pressure (MAP), heart rate (HR) and oxygen saturation (SPO<sub>2</sub>) were recorded for all patients using a multi parameter monitor. Core temperature was measured in tympanic membrane using digital infrared ear thermometer. The operating room temperature was maintained between 22 and 24°C. An anesthetic machine with oxygen supply, airway devices, laryngoscope and resuscitation drugs were made readily available in the operating room. Under strict aseptic precaution spinal block was performed at the L3-L4 or L4-L5 inter space using a 25 gauge quincke spinal needle with the patient in sitting position and the study drug was given. All the patients were lied down immediately after the spinal block to supine position and oxygen was supplemented by a simple face mask.

All the patients were randomly selected into three groups using computer-generated randomization tables.

Group C (N=35) received 3.0ml of bupivacaine (H) 0.5% (15mg) +0.5ml of normal saline, Group M (N=35) received 3.0ml of bupivacaine (H) 0.5% (15mg) +100mg MgSO<sub>4</sub> in 0.5ml saline (2 ml of 50% MgSO<sub>4</sub> diluted with normal

saline up to 5 ml, so 1 ml = 200 mg and from that 0.5ml (100mg) was taken), Group T (N=35) received 3.0ml of bupivacaine (H) 0.5% (15 mg) +25 mg of preservative free tramadol in 0.5ml saline.

The anesthesiologist involved in data collection was blinded to the treatment group, as were the patients. The specific drug was prepared aseptically in identical 5 ml unlabeled syringes in the operating room by an independent anesthesiologist not involved in the study. All the intrathecally administered drugs were preservative free and kept at room temperature. Intravenous fluids stored in room temperature were used. All the patients were covered with a single layer of surgical drapes over the chest, arms, and abdomen intra operatively and blanket post operatively. No external warming device was used. The incidence shivering was noted and the intensity of shivering was graded using the Crossley and Mahajan scale.<sup>15</sup>

Grade 0= no shivering,

Grade 1= piloerection or peripheral vasoconstriction but no visible shivering,

Grade 2= muscular activity in only one muscle group,

Grade 3= muscular activity in more than one muscle group but not generalized shivering,

Grade 4= shivering involving the whole body.

The core temperature was monitored using a digital infrared thermometer in the ear before the block, immediately after the block and every 10 min for 2 hours. The patient's HR, MAP and SPO2 was recorded every 5min for the first 15min and then every 10min for 2 hours. The patients with shivering grade 3 and 4 were considered as significant and intravenous tramadol 1mg/kg was given.

The patients were monitored for complications like Hypotension (MAP below 60 mmHg or 20% decrease from baseline) was treated with incremental administration of 6mg of ephedrine and 200ml of lactated Ringer's solution. Bradycardia (HR<60 or 20%decrease from baseline)was treated with intravenous bolus of 0.2 mg of glycopyrrolate. Nausea and vomiting was treated with 4 mg of ondansetron intravenously. All patients were shifted and monitored in the post anesthesia care unit.

### 2.1. Statistical analysis

The sample size was calculated using sample size calculator (PS version 3.0.0.34) with  $\alpha$  error 0.05 and power of 80%. The data were tabulated in MS Excel 2010 and statistical analysis performed using SPSS 25.0 for Windows (Statistical Package for the Social Sciences, Chicago, IL, USA).The quantitative variables were presented as range and mean plus standard deviation, and the qualitative variables were presented as frequencies and percentage. Sex and ASA grade were presented as numbers and percentage. Age, weight, and surgery duration were presented as means and standard deviation. Shivering incidence, intensity, and complications were presented as numbers and percentage.

One way Analysis of variance (ANOVA) followed by post-hoc test were used for comparison of parametric data between 3 groups. The Kruskal Wallis test was used to compare nonparametric data while the Mann-Whitney U test was used to compare differences between 3 groups. The chi-square test was used for comparison between percentage and frequencies. The P-value of less than 0.05 was considered to be significant.

### 3. Result

One hundred and twenty patients were enrolled for this study. Five patients were excluded from the study because of bleeding during surgery and need of blood transfusion. Five patients were excluded due to inadequate spinal block, who needed general anesthesia. Five patients had unexpected shivering before spinal anesthesia and were also excluded from this study.

A total of 105 patients completed the study, who were divided into three groups each consisting of 35 patients. The three groups were comparable with respect to age, sex, weight, ASA 1 & 2 and duration of surgery (Table 1)

Three groups were comparable in terms of the baseline vital signs (pulse rate, mean arterial blood pressure, tympanic membrane temperature, and peripheral oxygen saturation) and baseline operating room temperature (Table 2).

In our study, overall incidence of Shivering was noted in 55 patients (52.4%). Out of this, in Group C the incidence of shivering was higher with 24 patients (68.6%), in Group T 17 patients (48.6%) and in Group M shivering was noted only in 14 patients (40%). (Table 3) The differences in the incidence of shivering were statistically significant between the Groups C and T (P<0.003) and Groups C and M (P<0.001) but not between Groups T and M (p=0.5) (Table 2).

Regarding the intensity of shivering, in Group C out the 24 patients (5, 9, 9, 1) had Grade (1, 2, 3, 4) shivering respectively. In Group T, out of the 17 patients (10, 7, 0, 0) had shivering Grade (1, 2, 3, 4) respectively. In Group M, out of the 14 Patients (9,5, 0, 0) had Grade (1, 2, 3, 4) shivering respectively. None of our patients in group T and M had Grade 3 and 4 shivering (Figure 2).

In Group C, 8 patients (22.8%) had nausea and vomiting, 3 patients (8.5%) and 1 patient (2.5%) in Group T and Group M respectively. Post operative nausea and vomiting was maximum in Group C and minimum in Group M. Hypotension was most in Group C and least in Group M. In Group C 5 patients (14.2%) had hypotension, 4 patients (11.4%) in Group T and 3 patients (8.5%) in Group M had hypotension. Intra operative bradycardia was noted in four patients (11%) in Group C, three patients (8.5%) in Group T and one patient (5.7%) in Group M (Table 4)

Intra operatively, all the Groups had drop in the mean tympanic membrane temperature compared to the baseline,

which was not statistically significant in between the groups. (Figure 1)

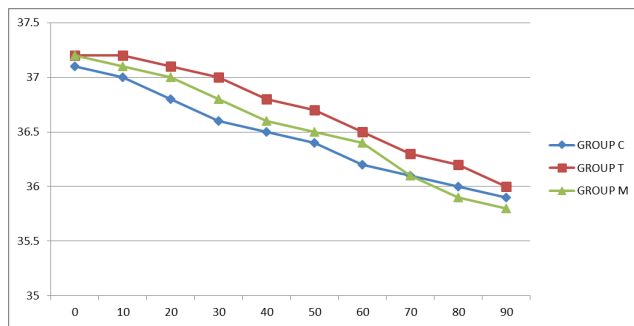


Fig. 1: Mean temperature at time interval among all groups

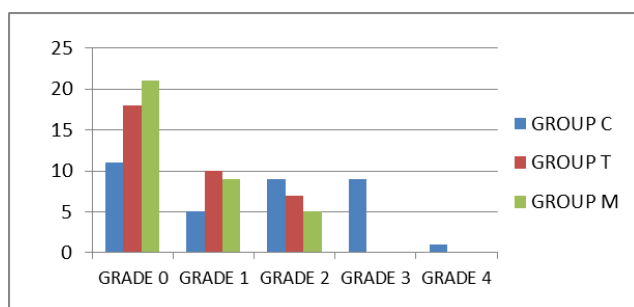


Fig. 2: Intensity of shivering among the groups

#### 4. Discussion

Our double blinded controlled study compared the efficacy of intrathecal MgSO<sub>4</sub> and tramadol in preventing the incidence and reducing the severity of post spinal shivering in infra umbilical surgeries. We found that intrathecal MgSO<sub>4</sub> 100 mg and 25 mg tramadol given along with hyperbaric 0.5% bupivacaine effectively reduced the incidence and severity of post spinal shivering compared to control group in infra umbilical surgeries.

Post anesthesia shivering and hypothermia are common complications of regional anesthesia. The median incidence of shivering following regional anesthesia in various studies was 55%, which was comparable to our study 52.4%. The etiology of shivering was multifactorial and mechanism is yet to be proved.

Post anesthesia shivering is mostly a combination of thermoregulatory and non thermoregulatory. Thermoregulatory shivering occurs in response to hypothermia which is due to redistribution of heat from core to periphery during spinal anesthesia. The resultant vasoconstriction and shivering is restricted to upper body due to the blockade of somatic and sympathetic neural fibers below the level of spinal block. Shivering may also occur in normothermic patients due to inhibited spinal

reflexes, reduced sympathetic activity, antigen release, steroid suppression and respiratory alkalosis.

Post anesthesia shivering is often preceded by core hypothermia and vasoconstriction but sometimes it is not so. The major risk factor in regional anesthesia for hypothermia is advanced age, level of sensory block, operating room temperature and the temperature of intravenous solution. In our study, the temperature of the operation room was maintained at 24°C and all the intravenous fluids and drugs were kept at room temperature.

Pharmacological means do not raise the body temperature but resets the shivering threshold to lower level. A wide variety of drugs with different mechanism of action such as opioids,  $\alpha$  2 adrenergic, serotonergic and anticholinergic receptors were used to prevent and treat shivering.

MgSO<sub>4</sub> is a physiologically occurring calcium and NMDA antagonist, which exerts neuro, cardio protection and anti shivering effect. It mostly reduces the shivering threshold by vasodilatation and does not affect the gain of shivering. NMDA receptor antagonist modulate thermoregulation at multiple level such as pre optic anterior hypothalamus, locus coeruleus and dorsal horn of spinal cord.<sup>16,17</sup> Most of the studies used MgSO<sub>4</sub> for the prevention of shivering by intravenous route. Some of the studies used 50 mg, 75 mg and 100 mg as an adjuvant for investigating its analgesic effect.<sup>18</sup> So, we have chosen a dose of 100 mg MgSO<sub>4</sub> intrathecally for prevention of shivering.

Tramadol is a synthetic opioid that acts at multiple sites. It is a weak  $\mu$ -opioid receptor agonist and has minimal activity at  $\kappa$ - or  $\sigma$ -receptors. It is also a partial inhibitor of norepinephrine and serotonin. Tramadol also inhibits the NMDA receptor at clinically relevant concentration. Tramadol normally contain preservatives such as sodium metabisulphite, methylparaben or chlorocresol which are neurotoxic agents. In our study, we used only preservative free tramadol. Earlier studies evaluating the anti shivering efficacy of intrathecal tramadol was used in low doses (10 mg & 20 mg), which attenuated but did not eliminate post spinal shivering.<sup>19</sup> So, we have chosen a higher (25mg) dose of intrathecal tramadol which was safe and with minimal adverse effects.

In our study, it was observed that both MgSO<sub>4</sub> and tramadol were effective in reducing the incidence of post anesthesia shivering. Incidence of shivering in Group C was 68.6%, in Group T was 48.6% and in Group M was 40%. The differences in incidence of shivering were statistically significant between Groups C and T (P<0.003), Groups C and M (P<0.001) but not between Groups T and M (p=0.5). Two to Three fold reduction of shivering incidence occurred in Group T and Group M compared to control Group.

In our study, in Group C 22.8% of patients had nausea and vomiting, compared to 8.5% and 2.5% patients in

**Table 1:** Demographic data

	Group C (n=35)	Group T (n=35)	Group Mg (n=35)	P value
Age in Years (Mean (SD)*)	35.9(8)	33.8(9.2)	34.4(8.6)	0.59
Weight in Kg (Mean (SD)*)	50.74(5.2)	49.77(5)	51.46(5.2)	0.36
Sex Male/Female	19/16	20/15	17/18	
ASA 1 Number/percentage	19(54.3%)	20(57.1%)	19(54.3%)	
ASA 2 Number/percentage	16(45.7%)	15(42.9%)	16(45.7%)	

**Table 2:** Patient's baseline data

	Group C (n=35)	Group T (n=35)	Group Mg (n=35)	P value
Heart rate in beats/mins (Mean(SD)*)	77.2(9)	76.8(11.8)	80.2(10.18)	0.34
Mean arterial pressure in mmHg (Mean(SD)*)	85.66(14.4)	92.31(11.21)	91.14(10.8)	0.06
Tympanic temperature in oC (Mean(SD)*)	37.47(0.24)	37.47(0.26)	37.47(0.24)	0.99
SPO2 in % (Mean(SD)*)	96.51(2.1)	96.23(1.5)	96.66(1.5)	0.37
Operating room temperature in oC(Mean(SD)*)	24.9(0.67)	24.7(0.69)	24.9 (0.74)	0.46
Duration Surgery in minutes (Mean(SD)*)	81.6(7.6)	80.26(8.4)	80.56(10.3)	
Median level of sensory block dermatome	T6	T6	T6	
<b>Types of operation</b>				
General surgery : n(%)	10(0.28)	13(0.37)	14(0.4)	
Orthopaedic : n (%)	11(0.31)	14(0.4)	14(0.4)	
Obstetric : n (%)	10(0.28)	8(0.22)	7(0.2)	

**Table 3:** Shivering incidence across the study groups

	Number of patients with shivering	Mean rank	Sum of ranks	Mann-Whitney U value	P
Group C vs Group T	24(68.6%)	42.2	1477.54	377	0.003
Group C vs Group M	17(48.6%) 24(68.6%)	28.7 43.3	1000.5 1515.5	3395	0.001
Group T vs Group M	14(40%) 17(48.6%) 14(40%)	27.7 37.19 33.8	969.5 1301.5 1183.5	553.5	0.5

**Table 4:** Shivering incidence among the groups

		Group C (n=35)	Group T (n=35)	Group Mg (n=35)	Total
<b>Shivering</b>	No	N	11	18	21
		%	31.4	51.4	60
	Yes	N	24	17	14
		%	68.6	48.6	40

**Table 5:** Complications

	Group C	Group T	Group M
Nausea and Vomiting	8(22.8)	3(8.5)	1(2.8)
Hypotension	5(14.2)	4(11.4)	3(8.5)
Bradycardia	4(11)	3(8.5)	2(5.7)
Itching	0	0	0
Respiratory Depression	0	0	0

Group T and Group M respectively. Post operative nausea and vomiting (PONV) is highest in Group C and least in Group M. This finding suggests that MgSO<sub>4</sub> probably has inhibitory action on nausea which may be advantageous compared to intrathecal opioids. In contrast to our study, a higher incidence of PONV has been reported with intrathecal tramadol by Frikha et al.<sup>20</sup> This might be due to their studies being done in the obstetric population and surgical procedures with higher incidence of nausea and vomiting.

Hypotension was most in Group C and least in Group M. 14.2% patients in Group C, 11.4% patients in Group T and 8.5% patients in Group M had hypotension which was similar to study of Hemalatha et al.<sup>21</sup> Hypotension responded to 6 mg ephedrine and intravenous bolus of crystalloids. Intra operative bradycardia was noted in four patients in Group C, three patients in group T and one patient in group M, which was similar to Ruche tendon et al<sup>22</sup> and managed with IV glycopyrrolate 0.2mg.

In our study, other than hypotension and bradycardia no other side effects such as pruritus, sedation, and respiratory depression were observed in any of the Groups. Ravishankar et al<sup>23</sup> and Susmita Chakraborty et al<sup>21,23</sup> recorded no itching in the group treated with tramadol in their studies which was proved with our study also.

Limitations of our study were, the exact temperature of crystalloid solution infused was difficult to measure and we were unable to correlate between the core body temperature and the incidence of shivering. Further studies may be done with a different sample size and different doses of both the drugs.

## 5. Conclusion

We concluded that either intrathecal tramadol 25 mg or MgSO<sub>4</sub> 100 mg used with 0.5% bupivacaine were effective in reducing the incidence and intensity of post spinal shivering compared to control in infra umbilical surgeries with minimal side effects.

## 6. Source of Funding

None.

## 7. Conflicts of Interest


There are no conflicts of interest.

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