

## Prophylaxis of Post Spinal Shivering: A Comparative Study between Intravenous Ondansetron and Meperidine

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### Abstract

**Background:** Shivering is a common complication following anesthesia. Many drugs have been documented as a prophylaxis of postanesthesia shivering. The aim of this study was to find out a better drug as an antishivering agent.

**Materials and methods:** This comparative study was carried out in the Department of Anesthesiology in Chittagong Medical College Hospital over a period of 6 months starting from November 2015 to April 2016. A total 90 obstetric patients with American Society of Anesthesiology (ASA) physical status I & II underwent cesarean section received placebo (Group-C, n-30), Inj-Ondansetron 8mg (Group-O, n-30) and Inj-Meperidine 0.4mg/kg (Group-M, n-30). These drugs were administered during intraoperative period just after cord clamp. Incidence of shivering, hemodynamic parameters were observed immediately after spinal anesthesia & then 5 min interval for 30 min throughout the intraoperative period.

**Results:** Shivering was observed in 16 patients (53.33%) of group-C, 4 patients (13.33%) of group O and 8 patients (26.66%) of group M. The number of patient with a shivering grade 3 & 4 were very highly significant ( $p < 0.001$ ) in group C compared with other groups at 15 min & 20 min after block & significant ( $p < 0.05$ ) at 25 min & 30 min after block.

**Conclusion:** Ondansetron was found to be more effective and haemodynamically stable drug than Meperidine in prophylaxis of post spinal shivering

**Key words :** Anesthesia; Meperidine; Ondansetron; Post spinal shivering; Subarachnoid block.

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### Introduction

Shivering is an involuntary, spontaneous, oscillatory mechanical activity of skeletal muscle associated with increased oxygen consumption. The incidence of shivering is between 40-60% and 56.7% following general and neuraxial anesthesia respectively.<sup>1</sup> Post Anesthesia Shivering (PAS) is associated with significant patient discomfort including increase in postoperative pain, sympathetic stimulation, metabolic oxygen demand, lactic acidosis and carbon dioxide production. As a result it imposes increased stress on the cardiopulmonary system, via increases in cardiac output and minute ventilation, which can be detrimental in patients with limited reserves.<sup>2, 3, 4</sup>

Cesarean section is most commonly done under neuraxial anesthesia, which is associated with shivering.<sup>5</sup> Neuraxial anesthesia causes initial decrease in core body temperature due to internal heat redistribution as a result of vasodilatation. Failure of vasoconstriction below the level of the blockade promotes ongoing heat loss and the decrease in the shivering threshold is attributed to the altered perception of temperature in the blocked dermatomes by the hypothalamus<sup>6</sup>. Shivering was graded according to a scale validated by Tsai and Chu.<sup>7</sup>

Many drugs of various classes have been documented in the prevention and treatment of PAS, with different mechanisms of action, varying doses, efficacy and side effect profiles. Hence the choice of pharmacological agent based on patient profile, drug characteristics as well as route of administration.<sup>8</sup>

Meperidine is the most widely used drug in the treatment of PAS. Meperidine (25mg) has been found to be an effective antishivering agent when administered intravenously. It decreases the shivering threshold twice as much as the vasoconstriction threshold. Various studies suggested, the antishivering action of Meperidine was due to combination of effects like stimulation of alpha 2 adrenoreceptors, k opioid receptors, NMDA antagonism

and monoamine reuptake inhibition.<sup>6</sup> Meperidine has the longest standing history as a medical treatment for PAS and there is substantial amount of evidence supporting its use as an anti-shivering agent.<sup>9</sup> However, Meperidine has undesirable side effects like nausea, vomiting, pruritus, respiratory depression etc.<sup>9</sup>

Recently Ondansetron has been tried to prevent PAS. Ondansetron, a 5-HT<sub>3</sub> antagonist, is widely used to prevent postoperative & pregnancy induced nausea and vomiting.<sup>8</sup> The antishivering effect of Ondansetron may be related to central mechanism by inhibiting 5HT (Serotonin) reuptake in the preoptic anterior hypothalamic region.<sup>9</sup> Several studies have demonstrated that Ondansetron can prevent PAS which made it a promising drug for prevention of postoperative complications like shivering, nausea, vomiting, post dural puncture headache.<sup>10-13</sup> when compared to other drugs, Ondansetron is devoid of hemodynamic side effects.<sup>9,19</sup> It is a serotonin receptor antagonist, has been effectively used for prevention of postspinal hypotension.<sup>10-13</sup> The effect has been attributed to blocking Bezold-Jarisch reflex (BJR) by the inhibitory effects of ondansetron on serotonin receptors.<sup>14</sup>

Hence, we planned to do a comparative study between Meperidine and Ondansetron to see the efficacy, safety and adverse effects of those drugs.

#### Materials and methods

All obstetric patients, aged 20-40 yrs, ASA I & II physical status who were scheduled for elective & emergency cesarean section were enrolled in this study. This comparative study was carried out in the Department of Anesthesiology in Chittagong Medical College Hospital over a period of 6 months starting from November 2015 to April 2016. Proper permission was taken for this study from the ethical committee of Chittagong Medical College.

Patients were excluded if they had known hypersensitivity, history of cardiac, pulmonary, renal & liver diseases, severe PET, eclampsia, placenta previa and who were unwilling to participate. Written informed consent was taken. 90 cards were prepared & 30 cards in each group (O, M and C). Those were kept in a box in the preoperative room. Patients were asked to pick up 1 card from the box & then they were randomly allocated into 3 groups according to the card they had

chosen & it was written on the record book. Group O received inj. Ondansetron 8 mg, Group M received inj. Meperidine 0.4mg/kg, Group C received normal saline (Placebo). The volume of each drug was 4ml & the drugs were prepared by a co-worker. The investigator & patients blinded about the drugs.

On arrival to the operation theatre, a standard monitoring including pulse oximeter and noninvasive BP was applied. Baseline data were noted. Patients were preloaded with 15ml/kg lactated ringer solution. The operation theatre temperature was maintained at 24±0.6°C for all cases. All preloading fluids & drugs were injected at room temperature. Sub-arachnoid block was performed with 10mg 0.5% hyperbaric bupivacaine. The study drugs were administered by the co-worker just after cord clamp of the baby. Shivering, MBP, HR, SpO<sub>2</sub> of the patient were recorded by the investigator every 5 min interval throughout the intraoperative period for 30 min. Shivering was graded using a scale which was validated by Tsai and Chu.<sup>11</sup>

Grade 0-No shivering.

Grade 1-Piloerection, 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.

Grade 4-Shivering involving the whole body.

Grade 1 & 2 assumed to have no shivering and grade 3 & 4 were considered as shivering in this study. In cases, when SBP dropped < 80mm Hg or decreases >30% of the baseline, inj. Ephedrine 10mg was injected intravenously. If the patients shiver (Grade 3) after 15 min administration of prophylactic drug, then it was considered significant and prophylaxis was ineffective. Then Inj. Diazepam 0.1mg/kg was used as rescue drug. Side effects such as hypotension, nausea, vomiting and sedation were recorded. If the parturient developed shivering before delivery of the baby, it was managed by covering the body with blanket and was excluded from the study.

The sociodemographic variables studied were age, weight and ASA grading. The preoperative variables were pulse, blood pressure, SpO<sub>2</sub>, respiratory rate. The outcome variables were the Occurrence of shivering as well as per-operative hemodynamic stability by recording pulse, NIBP, SPO<sub>2</sub> and

RR. A structured case record form was developed containing all the variables of interest.

Collected data was compiled, checked and edited. Data processing and analysis was done with the help of computer using statistical software SPSS (Statistical Package for Social Sciences) version 20 (Chicago, IL, USA). Cross tabulation was prepared  $\chi^2$  test, analysis of variance (ANOVA) and correlation were done to see the association. The results were presented in tables and figures. The statistical terms was included in this study are mean, standard deviation, percentage. Statistical significance was set at  $p < 0.05$  and confidence interval set at 95% level.

**Results**

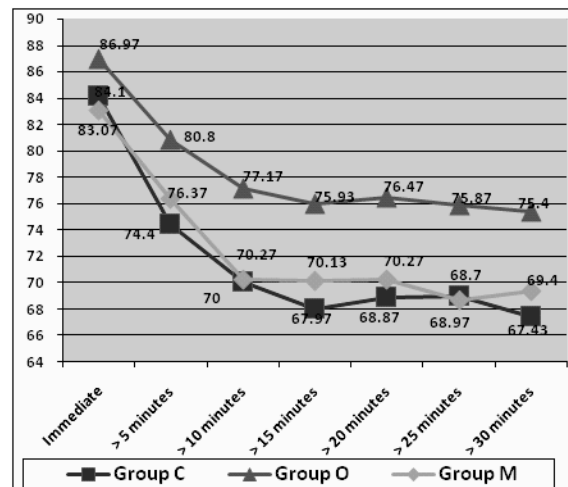
**Table I :** Demographic data among the study subjects (n = 90)

Age(Yrs)	n	Mean	±SD	Median	Range	p value
Group C	30	24.80	3.94	24.50	20-33	$p > 0.05$
Group O	30	25.87	4.76	25.00	20-40	Not
Group M	30	24.53	4.01	24.50	20-35	Significant
Total	90	25.07	4.25	25.00	20-40	
Weight (Kg)	n	Mean	±SD	Median	Range	p value
Group C	30	64.50	5.90	64.00	55-78	$p > 0.05$
Group O	30	64.60	5.14	64.50	55-80	Not
Group M	30	64.93	5.96	65.00	55-77	Signifiant
Total	90	64.68	5.62	65.00	55-80	

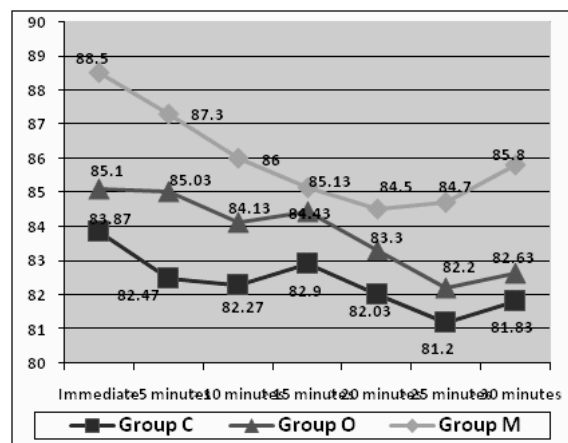
**Table II :** Occurrence of shivering at different time among the study patients (n=90)

Occurrence of Shivering		Group C (n=30)	Group O (n=30)	Group M (n=30)	p Value
5min after block	Yes	00	00	00	...
	No	30	30	30	
10 min after block	Yes	00	00	00	...
	No	30	30	30	
15 min after block	Yes	11	00	00	$p < 0.001$
	No	19	30	30	HS
20 min after block	Yes	16	01	01	$p < 0.001$
	No	14	29	29	HS
25 min after block	Yes	16	03	08	$p < 0.01$
	No	14	27	22	S
30 min after block	Yes	16	04	08	$p < 0.03$
	No	14	26	22	S
Total		30	30	30	

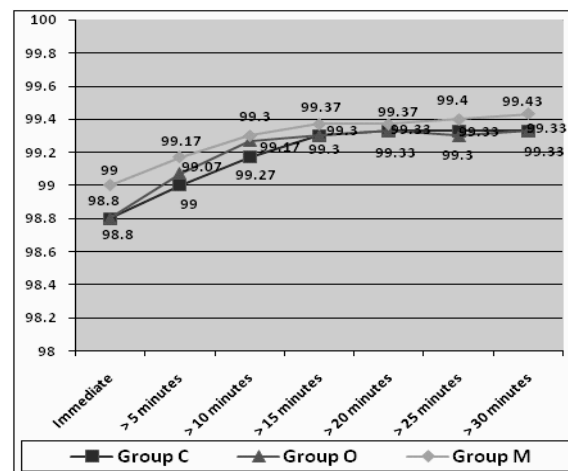
HS = Highly Significant; S = Significant.



**Fig 1:** MBP at different times among the study patients (n=90)



**Fig 2:** Mean HR at different times among the study patients (n=90)



**Fig 3:** Mean SpO<sub>2</sub> at different times among the study patients (n=90)

Demographic data concerning the patient age and weight were comparable among three groups. No statistically significant difference was found ( $p>0.05$ ). [Table-I].

The number of patients with a shivering grade 3 & 4 were very highly significant ( $p<0.001$ ) in group-C compared with other groups at 15 min & 20 min after block and significant ( $p<0.01$ ) at 25 min & 30 min after block. [Table-II].

In group-C, MBP decreased from  $84.10\pm 8.35$  to  $67.43\pm 8.22$

In group-M, MBP decreased from  $83.07\pm 9.25$  to  $69.40\pm 8.01$  In group-O, MBP decreased from  $86.97\pm 9.68$  to  $75.40\pm 10.50$

The result was statistically significant in all three groups [Figure 1].

HR and SpO<sub>2</sub> were stable throughout the intraoperative period in all three groups. ( $p>0.05$ ) [Figure 2, 3].

### Discussion

The present study was carried out with the objectives evaluation of comparative efficacy of prophylactic Ondansetron & Meperidine in preventing post spinal shivering in obstetric patients.

Regarding the occurrence of shivering after administration of block, the number of patients with a shivering grade 3 & 4 were very highly significant ( $p<0.001$ ) in group-C compared with other groups at 15 min & 20 min after block and significant ( $p<0.01$ ) at 25 min & 30 min after block. Shivering was observed in 16 patients (53.33%) in group-C, 8 patients (26.66%) in group-M and 4 patients (13.33%) in group-O.

Similar study was done by Kelsaka et al where 75 patients undergoing elective orthopedic surgery under spinal anesthesia were randomly divided into 3 groups.<sup>14</sup> Group O, M, C received intravenous inj. Ondansetron 8mg, inj. Meperidine 0.4mg/kg & saline respectively immediately before spinal anesthesia. Tab. Diazepam 10mg was used as premedication 45 minutes before surgery which also has antishivering property. 10ml/kg/h lactated Ringer's solution warmed to 37°C was infused over 30 min before spinal anesthesia. Core temperature was preserved in both groups. The ambient temperature was maintained at 21°C-22°C with constant humidity. The incidence of shivering was 36% in Control group & 8% in group O & M. They concluded that Ondansetron

possessed similar effects like Meperidine in reducing post spinal shivering.

In our study, shivering was graded using a scale that was validated by Tsai and Chu.<sup>12</sup> We used the same dose of drugs as Kelsaka study but only in obstetric patients and the study drugs were administered just after cord clamp to avoid the adverse effects of Meperidine on fetal outcome. We found that the incidence of shivering was 53.33% in control group, 26.66% in group M & 13.33% in group O. The difference was statistically highly significant ( $p<0.001$ ) between the study groups. The control group had more shivering (53.33% Vs 36%) than the above Kelsaka study. In our obstetrics patients, no premedication was used and also preloading was done at room temperature, so the core temperature could not be maintained. These might explain the higher incidence of shivering in our study than Kelsaka study.

Another study was done by Ferianto Pandit who compared 8mg IV ondansetron with 0.4mg/kg Meperidine in prevention of shivering in pregnant patients undergoing cesarean section with SAB. The study drugs were administered 10 minutes before SAB.<sup>15</sup> They found the incidence of shivering in Ondansetron group was 4.2% & Meperidine group was 12.5%. But the difference was not statistically significant ( $p>0.05$ ). In our study, we included control group and the study drugs was administered just after cord clamp. The incidence of shivering in study groups was more (26.66%, 13.33%) than Ferianto Pandit study and that might be due to difference in timing of administration of drugs.

Safavi et al compared intrathecal Meperidine 0.2mg/kg with intravenous Ondansetron 8mg for prophylaxis against shivering in orthopedic surgery in elderly patients >50 y of age.<sup>16</sup> Warmed IV fluid was used 30 min before SAB. In this study, incidence of shivering was 37% in control group, 15% in group O, 2.5% in group M. Intrathecal Meperidine more effectively reduced shivering than intravenous Ondansetron. We used both the study drugs intravenously. Moreover, we included only obstetric patients & preload was done by lactated ringer's solution at room temperature that might explain higher incidence of shivering in C and M group. But the incidence of shivering in group O was 15% which was close to our study.

In our study, MAP, HR & SpO<sub>2</sub> were measured immediately after block & then at 5 min interval for 30 min throughout the intraoperative period. MAP decreased more in group C & M at 10, 15 min after SAB than group O which was statistically highly significant ( $p < 0.01$ ). HR, SpO<sub>2</sub> was stable throughout the intraoperative period.

But in Kelsaka study there was no difference among the groups regarding hemodynamic parameters that might be due to their non-obstetric patient samples. As our study population was only obstetric and ondansetron could attenuate post spinal hypotension by blocking the Bezold-Jarish Reflex (BJR). That might explain the higher incidence of hypotension in C & M group.

Marashi et al compared two different doses of ondansetron with placebo on attenuation of spinal induced hypotension & shivering.<sup>17</sup> MAP & HR decreased more in placebo group which was statistically significant. Similarly in our study, MAP decreased more in control & meperidine groups than ondansetron group and that was statistically highly significant ( $p < 0.01$ ).

In a study done by Owczuk R et al where 71 patients under spinal anesthesia were allocated into two groups.<sup>18</sup> The study group received 8mg IV ondansetron compare to saline group, prior to anesthesia. They concluded that ondansetron attenuated decrease in HR & MBP effectively. Similar result was also observed in our study.

Another study was done by Walid Trabelsi et al who showed prophylactic effect of ondansetron on the attenuation of hypotension in healthy parturients undergoing spinal anesthesia.<sup>19</sup> Sahoo et al worked on 52 parturients to see effect of ondansetron on spinal induced hypotension.<sup>20</sup> In both the studies, they concluded that decrease in mean arterial pressure was significantly lower in ondansetron group.

### Limitations

There are certain limitations of our study:

Firstly, the current study assessed the incidence of post spinal shivering within short duration of observation (Only 30 minutes) so we could not exclude the possibility of occurrence of shivering after transfer to the ward.

Secondly, we could not measure core temperature because of unavailability of temperature probe.

Thirdly, the study drugs could not be administered before SAB as we included only obstetric patients and Meperidine might develop fetal respiratory depression.

Fourthly, our relatively small sample size might limit the interpretation of our results.

Lastly, humidity could not be maintained and intravenous fluid was administered without pre-warming.

### Conclusion

In conclusion, the findings of our study suggest that the prophylactic administration of intravenous Ondansetron was more effective and haemodynamically stable antishivering agent than Meperidine. Moreover, Ondansetron can be administered before delivery of fetus as it does not cause neonatal respiratory depression.

So, on the basis of  $\chi^2$  test and ANOVA, we can conclude that Ondansetron is better as antishivering agent than Meperidine.

### Recommendation

Multicentre large scale study is recommended.

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### Contribution of authors

SAB-Conception, design, acquisition of data drafting & final approval.

SH-Acquisition of data, data analysis, critical revision & final approval.

CKB - Acquisition of data, interpretation of data, drafting & final approval.

YAB-Data analysis, critical revision & final approval.

MRS-Acquisition of data, data analysis, critical revision & final approval.

GAC-Design, critical revision & final approval.

### Discloser

All the authors declared no competing interest.

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