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RESEARCH PAPER

# Intravenous Palonosetron and Pethidine as Prophylaxis of Post Spinal Shivering: A Comparive Study

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## Abstract:

***Background:*** Post anaesthesia shivering is a frequent complication and associated with significant patient discomforts including metabolic changes.

***Objectives:*** The study was designed to investigate the safety and efficacy of intravenous Palonosetron in prophylaxis of post spinal shivering in comparison to Pethidine in obstetric patients undergoing cesarean section under subarachnoid block.

***Methods:*** In a prospective, randomised, double-blinded, controlled study, a total of ninety obstetric patients of ASA physical status I & II, aged 20-40 yrs, undergoing cesarean section received placebo (Group-C, n=30), Inj-Palonosetron 0.075mg (Group-O, n=30) and Inj. Pethidine (Group-P, n=30). These drugs were administered during intraoperative period just after cord clamp.

***Result:*** Incidence of shivering, haemodynamic parameters were observed immediate after spinal anesthesia and then 5 min interval for 30 min throughout the intraoperative period. Responses of administered drugs were observed. Shivering was observed in 16 patients (53.3%) in group-C, 4 patients (13.3%) in group O, 8 patients (26.7%) in group P. The number of patients with a shivering grade 3 and 4 were very highly significant ($p$<0.001) in group C compared with other groups at 15 min and 20 min after block and highly significant ($p$<0.05) at 25 min and 30 min after block.

***Conclusion:*** Palonosetron was found to be more effective than Pethidine in prophylaxis of post spinal shivering and also more haemodynamically stable.

**Keywords:** Palonosetron, Pethidine, postspinal shivering, subarachnoid block.

## Introduction

Shivering is defined as an involuntary, spontaneous, oscillatory mechanical activity of skeletal muscle associated with increased oxygen consumption, this can be as much as 600%.[1] Shivering is a frequent complication following anaesthesia, with an incidence of between 40-60% and 56.7% following general and neuraxial anaesthesia respectively. Post anaesthesia 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 cardio-pulmonary system, via increases in cardiac output and minute ventilation, which can be detrimental in patients with limited reserves.[2-4]

Cesarean sectionis most commonly done under neuraxialanesthesia,which is commonly associated with shivering.[5] Neuraxial anaesthesia causes initial decrease in core body temperature due to internal heat redistribution as a result of vasodilatation (Phase 1). Failure of vasoconstriction below the level of the blockade promotes ongoing heat loss (Phase 2) and the decrease in the shivering threshold is attributed to the altered perception of temperature in the blocked dermatomes by the hypothalamus.[6]

Shivering was graded according to a scale validated by Tsai and Chu[7]

Grade 0-no shivering,
Grade 1-piloerection, no visible shivering,
Grade 2-muscular activity in only one muscle group,

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Grade 3-muscular activity in more than one muscle group but not generalised and

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.

Simple physical measures had been described including increasing the ambient temperature of the operative room, preventing convective heat loss by insulation with surgical drapes, space blankets, warm cotton blankets, ensuring warm skin disinfectant being used prior to draping, and the use of warm intravenous fluids and warm local anaesthetics for neuraxial blockade.[8]

Many drugs of various classes have been documented in the prevention and treatment of post anaesthesia shivering, with different mechanisms of action, varying doses, efficacy and side effect profiles. Hence, the choice of pharmacological agent for the treatment of post anaesthesia shivering should be based on patient profile, drug characteristics as well as route of administration.[8]

Pethidine is the most widely used drug in the treatment of post anaesthesia shivering. 25mg of Pethidine has been found to be an effective anti-shivering agent when administered intravenously. It decreases the shivering threshold twice as much as the vasoconstriction threshold. Various studies suggested, the anti-shivering action of PETHIDINE was due to combination of effects like stimulation of alpha 2 adrenoreceptors, k opioid receptors, NMDA antagonism and monoamine reuptake inhibition.[6] Pethidine 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.[9] However, Pethidine has undesirable side effects like nausea, vomiting, pruritus, respiratory depression etc.[9] Recently Palonosetron has been tried to prevent PAS.

Palonosetron, a 5 HT3 antagonist, is widely used to prevent postoperative & pregnancy induced nausea and vomiting.[8] Theantishivering effect of Palonosetron may be related to central mechanism by inhibiting 5HT (serotonin) reuptake in the preoptic anterior hypothalamic region.[9]

Several studies have demonstrated that Palonosetron can prevent PAS which made it a promising drug for prevention of postoperative complications like PAS, nausea, vomiting. It also decreases the incidence of post dural puncture headache.[10]

When compared to other drugs, Palonosetron is devoid of haemodynamic side effects.[9] It is a serotonin receptor antagonist, has been effectively used for prevention of postspinal hypotension.[10] The effect has been attributed to blocking Bezold-Jarisch reflex (BJR) by the inhibitory effects of Palonosetron on serotonin receptors.

It was planned to do a comparative study between Pethidine and Palonosetron to see the efficacy, safety and adverse effects of those drugs.

## Materials and Methods

The present study was a double-blinded randomised controlled trial (RCT) to compare effectiveness of intravenous Palonosetron compared to intravenous Pethidine in reducing postspinal shivering.

This study was conducted in the department of anesthesiology of Rajshahi Medical College & Hospital. Patients admitted for elective and emergency cesarean section in the department of Gynaecology & Obstetrics in Rajshahi Medical College & Hospital during the study period.

Patients of 20-40 years age with ASA physical status I & II scheduled for elective and emergency cesarean section were enrolled in this study, who fulfilled the inclusion criteria were included in the study.

Patients were randomly allocated equally, 30 in each group.

Group O: Inj. Palonosetron 0.075mg, Group P: Inj. Pethidine 0.4mg/kg,Group C: 4ml normal saline.

This study was conducted after approval of the ethical committee. 90 obstetric patients aged between 20-40yrs with ASA I and II physical status who were scheduled for elective and emergency cesarean section at Rajshahi Medical College & Hospital enrolled in this study. Written informed consent was taken. 90 cards were prepared and 30 cards in each group (O,P, and C). Those were kept in a box in the preoperative room. Patients were asked to pick up 1 card from the box and then they were randomly allocated into 3 groups according to the card they

had chosen in the preoperative room, and it was written on the record book. Group O received inj. Palonosetron 0.075mg, group M received inj. Pethidine 0.4mg/kg and 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, noninvasive BP were applied. Baseline data were noted. Patients were preloaded with 15ml/kg lactated ringer solution. The operation theatre temperature was maintained at 24±0.6ºC for all cases. All preloading fluids & drugs were injected at room temperature. Sub- arachnoid block was performed with 10- 15mg 0.5% hyperbaric bupivacaine.

The study drugs were administered by the co-worker just after cord clamp. Shivering, MBP, HR & $SpO_2$ 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.[7]

In cases, when SBP dropped < 80mm Hg or decreases >30% of the baseline, inj. Ephedrine 10mg was injected intravenously.

If the patients shiver to at least grade 3, 15 min after administration of prophylactic drug, then it was considered significant and prophylaxis was ineffective. Then Inj. Diazepam 0.5mg/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 were excluded from the study.

## Results

Ninety women were successfully recruited. The patient characteristics were also recorded (table I). Demographic data concerning the patient age, weight and ASA class were comparable among the 3 groups (group C, O, P). Patient's age and weight (table II), 03 and ASA class (figure 1) were collected. No statistically significant difference was found ($p$>0.05).

Shivering was observed in 16 patients (53.33%) in group-C, 8 patients (26.66%) in group-P and 4 patients (13.33%) in group-O. 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 highly significant ($p$<0.01) at 25 min & 30 min after block.

**Table I:** Statistics of demographic data(age in years) among the study subjects (with ANOVA test significance) (n = 90)

| Age (Years) | N | Mean | ± SD | Median | *p value* |
|---|---|---|---|---|---|
| Group C | 30 | 24.80 | 3.94 | 24.50 | $p > 0.05$ |
| Group O | 30 | 25.87 | 4.76 | 25.00 | *Not Significant** |
| Group P | 30 | 24.53 | 4.01 | 24.50 | |
| TOTAL | 90 | 25.07 | 4.25 | 25.00 | *ANOVA |

**Table II:** Statistics of demographic data(weight in Kg) among the study subjects (with ANOVA test significance) (n = 90)

| Weight (Kg) | n | Mean | ± SD | Median | *p value* |
|---|---|---|---|---|---|
| Group C | 30 | 64.50 | 5.90 | 64.00 | $p > 0.05$ |
| Group O | 30 | 64.60 | 5.14 | 64.50 | *Not Significant** |
| Group P | 30 | 64.93 | 5.96 | 65.00 | |
| TOTAL | 90 | 64.68 | 5.62 | 65.00 | *ANOVA |

**Table-III:** Occurrence of shivering at different times after administration block

| Occurrence of Shivering | | Group C (n = 30) | Group O (n = 30) | Group (n = 30) | *p* value |
|---|---|---|---|---|---|
| 5 minutes after Block | Yes | 00 | 00 | 00 | – |
| | No | 30 | 30 | 30 | |
| 10 minutes after Block | Yes | 00 | 00 | 00 | – |
| | No | 30 | 30 | 30 | |
| 15 minutes after Block | Yes | 11 | 00 | 00 | $p < 0.001$ |
| | No | 19 | 30 | 30 | |
| 20 minutes after Block | Yes | 16 | 01 | 01 | $p < 0.001$ |
| | No | 14 | 29 | 29 | |
| 25 minutes after Block | Yes | 16 | 03 | 08 | $p < 0.01$ |
| | No | 14 | 27 | 22 | |
| 30 minutes after Block | Yes | 16 | 04 | 08 | $p < 0.03$ |
| | No | 14 | 26 | 22 | |
| Total | | 30 | 30 | 30 | |

HS = Highly Significant; S = Significant

Occurrence of shivering at different times after administration of block among the study subjects.Baseline haemodynamic variables in preoperative area showed no significant difference ($p>0.05$) among the study subjects.

**Table IV:** Distribution of baseline hemodynamic variables (Mean ± SD) among the study subjects (with ANOVA test significance) (n = 90)

| | Group C (n = 30) | Group O (n = 30) | Group P (n = 30) | *p* value |
|---|---|---|---|---|
| Heart Rate (per Minute) | 86.07±11.69 | 85.73±10.25 | 87.20±9.48 | $p > 0.05$ Not Significant |
| Systolic BP (mmHg) | 122.07±9.75 | 124.20±11.01 | 124.87±9.74 | $p > 0.05$ Not Significant |
| Diastolic BP (mmHg) | 73.50±9.17 | 75.30±8.73 | 72.93±8.78 | $p > 0.05$ Not Significant |
| Mean BP (mmHg) | 87.73±8.57 | 91.00±10.20 | 90.07±11.44 | $p > 0.05$ Not Significant |
| $SpO_2$ (%) | 98.83±0.38 | 98.87±0.35 | 98.77±0.43 | $p > 0.05$ Not Significant |

## Discussion

This study compared the efficacy of prophylactic Palonosetron and Pethidine in preventing post spinal shivering in obstetric patients. Haemodynamic parameters like HR, MBP, $SpO_2$ were also monitored every 5 minutes interval throughout surgery.Similar study was done by Kelsaka et al where 75 patients undergoing elective orthopaedic surgery under spinal anaesthesia were randomly divided into 3 groups.[4] Group O, P, C received intravenous inj. Palonosetron 0.075mg, inj. Pethidine 0.4mg/kg & saline respectively immediately before spinal anaesthesia. There was no significant difference in demographic data among three groups. 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 37ºC was infused over 30min before spinal anaesthesia. Core temperature was preserved in both groups.

The incidence of shivering was 36% in Control group and 8% in group O & P. They concluded that Palonosetron possessed similar effects like Pethidine

in reducing post spinal shivering. In our study, shivering was graded using a scale that was validated by Tsai and Chu.[7]

The same dose of drugs was used in Kelsaka study but only in obstetric patients and the study drugs were administered just after cord clamp to avoid the adverse effects of Pethidine on fetal outcome. We found the incidence of shivering was 53.3% in control group, 26.7% in group P & 13.3% in group O. The difference was statistically highly significant (p<0.001) between the study groups. The control group had more shivering (53.3% vs 36.0%) 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 FeriantoPandit who compared 0.075mg IV Palonosetron with 0.4mg/kg Pethidine in prevention of shivering in pregnant patients undergoing cesarean section with SAB.[8] The study drugs were administered 10 minutes before SAB. They found the incidence of shivering in Palonosetron group was 4.2% and Pethidine 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 (26.7%, 13.3%) than Ferianto Pandit study and that might be due to difference in timing of administration of drugs.

Safavi et al compared intrathecal Pethidine 0.2mg/kg with intravenous Palonosetron 0.075mg for prophylaxis against shivering in orthopedic surgery in elderly patients >50 y of age.[9] 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 P. Intrathecal Pethidine more effectively reduced shivering than intravenous Palonosetron. We used both the study drugs intravenously. Moreover, this study included only obstetric patients and preload was done by lactated ringer's solution at room temperature that might explain higher incidence of shivering in C and P group. But the incidence of shivering in group O was 15% which was close to our study.

In our study, MAP, HR & $SpO_2$ were measured immediately after block and then at 5 min interval for 30 min throughout the intraoperative period. MAP decreased more in group C & P at 10, 15 min after SAB than group O which was statistically highly significant ($p$<0.01). HR, $SpO_2$ 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. The incidence of hypotension in non-obstetric patients has been reported to be 33.0% whereas in obstetric patients it had been estimated to be as high as 50-60%.[26] As our study population was only obstetric and Palonosetron 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 Palonosetron with placebo on attenuation of spinal induced hypotension and shivering. MAP & HR decreased more in placebo group which was statistically significant.[10] Similarly in our study, MAP decreased more in control & Pethidine groups than Palonosetron 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.[10] The study group received 8 mg IV Palonosetron compare to saline group, prior to anesthesia. They concluded that Palonosetron attenuated decrease in HR & MB P effectively. Similar result was also observed in our study. Another study was done by Walid Trabelsi et al who showed prophylactic effect of Palonosetron on the attenuation of hypotension in healthy parturientsundergoing spinal anesthesia.[19] Sahoo et al worked on 52 parturients to see effect of Palonosetron on spinal induced hypotension. In both the studies, they concluded that decrease in mean arterial pressure was significantly lower in Palonosetron group.

## Conclusion

In conclusion, the findings of our study suggest that the prophylactic administration of intravenous Palonosetron 0.075mg was more effective antishivering agent than Pethidine (0.4mg/kg) and Palonosetron was more haemodynamically stable drug than Pethidine. Moreover,Palonosetron can be administered before delivery of foetus as it does not cause neonatal respiratory depression. So it is recommended that Palonosetron is better as antishivering agent than Pethidine.

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## References

1. Honarmand A. And Safavi MR, Comparison of prophylactic use of midazolam, ketamine and ketamine plus midazolam for prevention of shivering during regional anaesthesia. British Journal of Anaesthesia. 2008; 101: 557-62.
2. Raj S,Verma S, Pandey H P,Yadap P, Patel A. Role of butorphanol and ondasetron premedication in reducing postoperative shivering after general and spinal anesthesia:A randomized comparative study from north india. Anesth Essay Res 2016;10:319-23.
3. ManoharPanneer,PrakashMurugaiyan, SufalaViswas Rao. A comparative study of intravenous Dexmedetomidine and clonidine for postspinal shivering in patients undergoing lower limb orthopedic surgeries. Anesth Essays Res. 2017;11:151-154.
4. AlirezaMahoori, HeyderNorooziniz, Maryam Soltanahmadi. Comparison of Palonosetron and PETHIDINE for treatment of postoperative shivering: A randomized controlled clinical trial. Iran Red Cresent Med J 2014;16:e13079
5. Ahmed A. Badewy, Ali M. Mokhtar. The role of ondasetron in prevention of post-spinal shivering in obstetric patient.Egyptian J of Anaesth. 2017;33:29-33.
6. Morgan GE, Mikhail MS, Murray MJ. Clinical Anaesthesiology fourth edition. 2006. 148 – 150.
7. Tsai YC, Chu KS.A comparison of tramadol, amitryptyline and PETHIDINE for postepidural anesthetic shivering in parturients. Anesth Analg. 2001; 93:1288-92.
8. Khalifa OM. A comparative study of prophylactic intravenous granisetron, Palonosetron, and ephedrine in attenuating hypotention and its effect on motor and sensory block in elective cesarean section under spinal anesthesia.Ain-Shams J Anaesthesiol. 2015;8:166-72
9. Sharma M, Kharbuja K, Khadka B. Comparison of Pethidine and Tramadol for the control of shivering in patients under going elective surgery under spinal anesthesia. J of Lumbini Medical College. 2016;4:64-7.
10. QuinmTE. PETHIDINE-what's all the fuss? Pain relief connection. 2003;2:3-6.