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Original Research Article

Prophylactic mirtazapine and ondansetron for the prevention of post spinal anesthesia shivering in lower abdominal surgeries: a randomized clinical study

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ABSTRACT

Background: Spinal anesthesia is a frequently employed method for administering anesthesia during lower abdominal surgeries and is considered a safe anesthetic approach utilized for both elective and emergency operations. However, potential complications can arise, including hypotension, post-dural puncture headache (PDPH), and shivering. Objective was to evaluate the efficacy of prophylactic mirtazapine and ondansetron in the prevention of post spinal anaesthesia shivering (PSAS) among the patients who underwent lower abdominal surgeries.
Methods: The study groups were divided into two, named group M and group O. The total sample size was 88 (44 patients in each group). Patients in group M received mirtazapine 30 mg tablet (Mirtakem 30) with sips of water and group O received ondansetron 4 mg tablet (Ondem 4) with sips of water.
Results: The incidence of PSAS among the patients in mirtazapine and ondansetron groups were 45.5% and 81.8%. PSAS was significantly higher among the patients in the ondansetron group when compared to the mirtazapine group ($p<0.001$). The time of onset of shivering was delayed for the patients in the ondansetron group when compared to the patients in the mirtazapine group, but it was not found to be statistically significant.
Conclusions: It could be safely concluded that prophylactic administration of mirtazapine attenuate shivering with minimal hazards in patients scheduled for lower abdominal surgery under spinal anesthesia when compared to ondansetron.

Keywords: Mirtazapine, Ondansetron, Shivering, Spinal anesthesia

INTRODUCTION

Spinal anesthesia is a frequently employed method for administering anesthesia during lower abdominal surgeries and is considered a safe anaesthetic approach utilized for both elective and emergency operations. Spinal anesthesia offers numerous benefits, such as reduced intraoperative bleeding, lowered risk of venous thromboembolism, and enhanced pain management. However, potential complications can arise, including hypotension, post-dural puncture headache (PDPH), and shivering.[1]

One of the common complications associated with spinal anesthesia is shivering, which occurs due to the loss of thermoregulation. Shivering is defined as the fasciculation of the face, jaw, or head or muscle hyperactivity lasting longer than 15 seconds.[2] Post spinal anesthesia shivering (PSAS) is known to be a frequent complication particularly during lower abdominal surgeries with a reported incidence of 40-70%.[3] It is an involuntary, repetitive contraction of skeletal muscles that occurs in response to core hypothermia as a natural mechanism to increase metabolic heat production.[4] Despite being a transient and self-limiting condition, it can lead to discomfort, increased oxygen consumption, and

potentially adverse outcomes such as surgical site bleeding and wound dehiscence. Apart from the obvious discomfort PSAS is associated with several potentially deleterious effects. These include increased oxygen consumption, CO_2 production, catecholamine release, lactic acidosis, intra ocular pressure, intra cranial tension and may interfere with monitoring of electrocardiogram, blood pressure, pulse rate and oxygen saturation thus predisposing a patient with a low cardiopulmonary reserve to potential harm.[5]

The exact mechanism of post-spinal anesthesia shivering is multifactorial and is not yet clear. It is usually triggered due to hypothermia, and it involves central thermoregulatory dysfunction, sympathetic nervous system activation, and redistribution of body heat. Some suggestive mechanisms are adrenal suppression, decreased sympathetic activity, vasodilatation which facilitates core to peripheral redistribution of heat and decreased shivering threshold.[6] PSAS leads to metabolic changes and hemodynamic effects, such as elevated oxygen consumption, increased CO_2 production, elevated plasma catecholamine levels, and enhanced cardiac output.[7]

The treatment of shivering includes both pharmacological and non-pharmacological methods. The non-pharmacological methods are the use of forced air warming, warming blankets, warmed fluid infusion etc. These methods work by preserving the body temperature above the shivering threshold or by masking the central shivering reflex via warmed skin sensory input.[8] Nonpharmacological methods provide inadequate control of central hypothermia thereby necessitating the use of newer effective drugs for both treatment and prophylaxis of shivering to improve patients' quality of care. Hence, the mainstay of prophylaxis and treatment of PSAS remain pharmacological due to inadequate control of central hypothermia by techniques based on physical principles (e.g., intravenous infusion (IVI) of warm fluids and forced air warmers).[9]

The neurotransmitter pathways involved in PSAS are complex and involves opioids, alpha adrenergic, serotonergic, and anticholinergic systems. Recently it has been found that one of the pathways involved in PSAS is $5HT_3$ receptors, so the drugs acting on these receptors must have a role in prevention of PSAS.[10]

Ondansetron is a $5HT_3$ antagonist usually recommended for post operative nausea and vomiting. The mechanism of $5HT_3$ antagonist in the regulation of body temperature may be related to the inhibition of serotonin uptake on the preoptic anterior hypothalamus region which controls heat production and loss.[11] Serotonin antagonism has been found to lower hypothalamic temperature set threshold and therefore reducing metabolic cold defence and having a role in post operative shivering control.[12]

Mirtazapine, classified as a noradrenergic and serotonergic antidepressant, works by blocking central α_2-autoreceptors and hetero-adrenergic receptors, leading to increased release of both noradrenergic and 5-HT_{1A}-mediated serotonergic neurotransmission. Additionally, mirtazapine exhibits anxiolytic, antiemetic, and antinausea effects by blocking 5-HT_2 and 5-HT_3 receptors. It also possesses antinociceptive properties and has been shown to reduce the incidence of post-dural puncture headache after spinal anesthesia. Mirtazapine is rapidly absorbed, with peak plasma concentration achieved within 1 to 2.1 hours.[13]

Despite the availability of pharmacological agents for preventing post-spinal anesthesia shivering, there remains a lack of consensus regarding the optimal choice of medication, particularly in the context of lower abdominal surgeries. Existing literature predominantly focuses on comparing single interventions such as ondansetron or mirtazapine against placebo or other active agents. Added to it, to the best of our knowledge, none of the studies have been published on the comparison of prophylactic mirtazapine and ondansetron for the prevention of post spinal anesthesia shivering. Moreover, there is also a need for further research to explore the safety profile, optimal dosing regimens, and potential adverse effects associated with the prophylactic use of mirtazapine and ondansetron for preventing post-spinal anesthesia shivering in lower abdominal surgeries. Hanse it became imperative to conduct a randomized clinical study comparing the prophylactic use of mirtazapine and ondansetron for the prevention of post-spinal anesthesia shivering in lower abdominal surgeries in a tertiary care centre to address the existing gaps in knowledge.

METHODS

A randomized control trial was conducted in the department of anesthesiology, Regional Institute of Medical Sciences (RIMS), Imphal, Manipur from May 2022 to April 2024 consisting of 88 patients totally. The permission of the research ethics board, RIMS, Imphal, Manipur was obtained before initiating the study. Informed written consent were taken from all patients.

Inclusion criteria include age between 18 to 60 years, ASA (American Society of Anesthesiology) category 1 and 2. Exclusion criteria include history of allergic to the study drugs, diabetes mellitus, thyroid disorder, cardiopulmonary disease, psychological disorder, neurological deficit, liver disease, treatment with sedative hypnotics, body temperature <36.5°C or >38°C, local site infection, spinal deformity and bleeding tendencies like platelet count <50000/micro litre, PT>14 seconds, INR>1.5.

All the patients were assessed preoperatively for the vitals and a good peripheral line was secured and preloading of Ringer Lactate @10 ml/kg was done along with the standard monitoring setup like ECG, non-invasive blood pressure (NIBP) and pulse oximeter was connected. Baseline parameters such as body temperature, heart rate, systolic blood pressure, diastolic blood pressure, mean

arterial pressure and oxygen saturation were recorded. No premedication was given before commencing spinal anesthesia. The operating room temperature was maintained at an ambient temperature of around 23°C to 25°C.

The study groups were divided into two, named group M and group O. The total sample size was 88 (44 patients in each group). Patients were allocated by using computer generated randomization chart. The study drug was prepared in a sealed opaque envelope by an anaesthesiologist not directly involved in the study to keep the study blinded and was given to the patient 2 hour before surgery. Patients in group M received mirtazapine 30 mg tablet (Mirtakem 30) with sips of water and group O received ondansetron 4 mg tablet (Ondem 4) with sips of water. Spinal anesthesia was given by using 25 G Quincke's spinal needle keeping the patient in lateral position with the drug injection bupivacaine 0.5% (Anawin heavy) 2.5-3.0 ml (12.5-15 mg) to reach the desired surgical level taking into consideration the patient's height and weight. Monitoring of the vital parameters such as heart rate, blood pressure, SpO_2 and body temperature was done at intervals of every 5 minutes for the first 30 minutes and then every 10 minutes for the rest of the observation period. Patients were closely monitored for any appearance of shivering and the grading of the shivering was done using the four-point scale as per Wrench. In case of failure to control shivering with the study drugs 0.5 mg/kg injection tramadol was used as rescue therapy. Side effects of the study drug were noted, if any.

Data was collected in predesigned proforma. Baseline information like age, weight, ASA grading, HR, BP, SpO_2, temperature was recorded preoperatively. Intraoperatively, time of onset and disappearance of shivering and the side effects were recorded in due time. Data was entered and analysed in IBM SPSS statistics version 26.0 for windows (Armonk, NY: IBM Corp; 2020). Quantitative data like age, weight, temperature (both body and operating room), time of onset of shivering and hemodynamic parameters (BP, HR, SpO_2) are summarized as mean and standard deviation or median and interquartile range, depending on the type of distribution. Students t test/Mann Whitney U test was used to compare quantitative data like time of onset of shivering. Repeated measures ANOVA was used to compare the change in hemodynamic parameters (BP, HR, SpO_2) between the groups. To compare qualitative data like grades of shivering, ASA grading and any side effects between the two groups Chi square test was applied. A p value of <0.05 was considered as statistically significant.

RESULTS

A total of 88 patients who underwent lower abdominal surgery were included in the study and the flow of the study is shown in Figure 1.

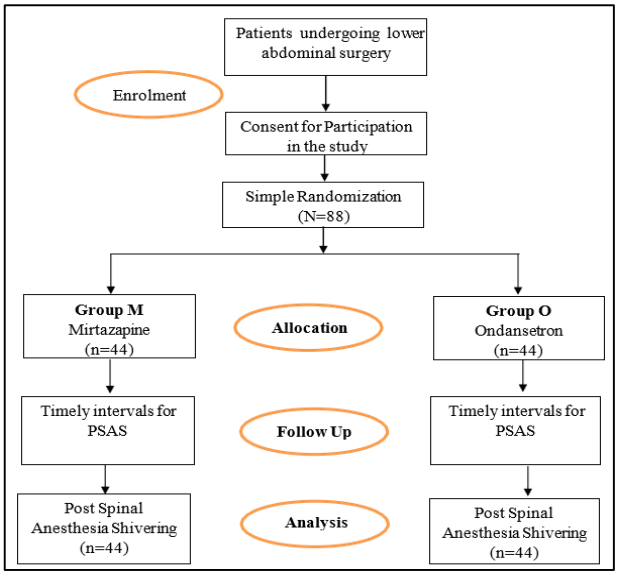

Figure 1: CONSORT diagram showing the flow of study participants.

The mean age of the study participants was 43.8 (10.9) years. The median age of the study participants was 44.5 (36.2-52.7) years with a minimum of 18 years and a maximum of 60 years. The females were the majority in both the groups and both the groups were comparable with respect to gender (p=0.488). The participants were comparable between the groups with respect to their body weight (p=0.941).

Table 1: Comparison of OT temperature between the groups (n=88).

Type of intervention	Temperature in celsius		P value
	Mean	SD	
Group M	24.5	0.5	
Group O	24.4	0.5	0.833

Table 1 shows that the patients were comparable between the groups with respect to OT temperature (p=0.833).

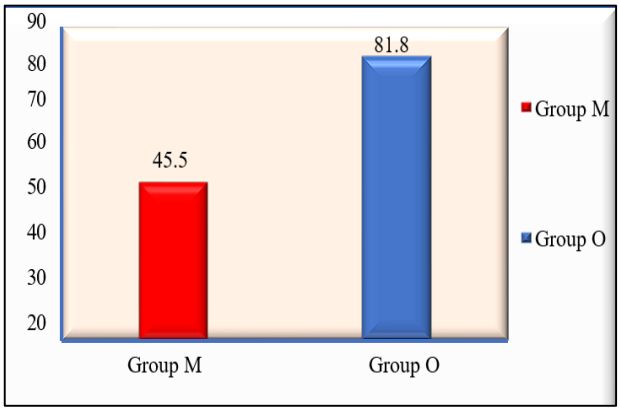

Figure 2: Distribution of the study participants by the incidence of shivering between the groups (n=88).

The incidence of PSAS among the patients in mirtazapine and ondansetron groups were 45.5% (95% CI: 30.7-61.0%) and 81.8% (95% CI: 66.8-91.3%). PSAS was significantly higher among the patients in the ondansetron group when compared to the mirtazapine group (p<0.001).

Table 2: Time of onset of shivering between the groups (n=56).

Type of intervention	Time of onset (minutes)		P value*
	Median	IQR	
Group M	10.0	10.0-15.0	
Group O	14.6	10.0-18.7	0.106

Table 2 box plot showing the time of onset of shivering between the groups (N=56), shows that the time of onset of shivering was delayed for the patients in the ondansetron group when compared to the patients in the mirtazapine group, but it was not found to be statistically significant (p=0.106).

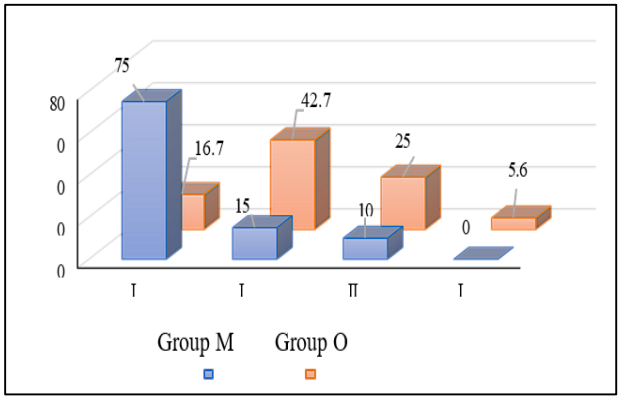

Figure 3: Comparison of severity of shivering between the groups (n=56).

Figure 3 shows that the lesser grade of severity (grade I) was higher among the patients in the mirtazapine group when compared to the ondansetron group and it was found to be statistically significant (p<0.001).

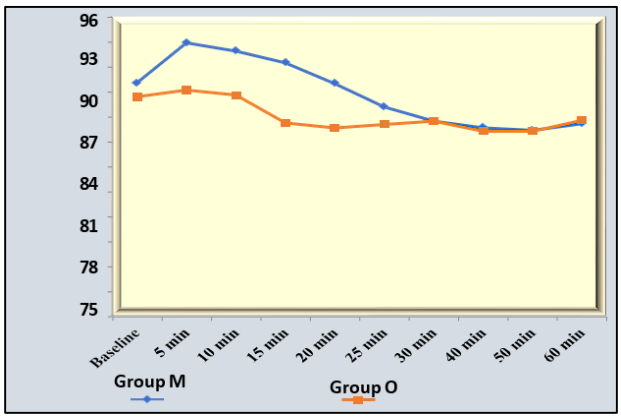

Figure 4: Mean heart rate at various time between the two groups (n=88).

Figure 4 shows that the effect size of change in mean heart rate over time between the two groups was 0.019 and it was not found to be statistically significant (p=0.200). However, the test for a difference in mean heart rate over time was highly statistically significant (effect size =0.145; p<0.001), which thus shows that there was a significant fall in heart rate over time but there was no significant difference between the groups.

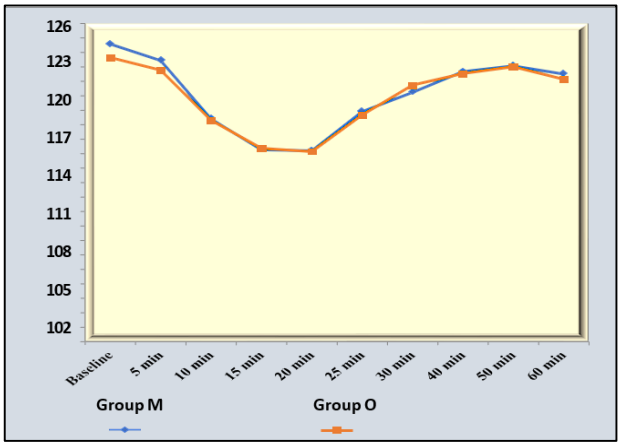

Figure 5: Mean systolic blood pressure at various time between the two groups (n=88).

Figure 5 shows that the effect size of change in mean systolic blood pressure over time between the two groups was 0.003 and it was not found to be statistically significant (p=0.635). However, the test for a difference in systolic blood pressure over time was highly statistically significant (Effect size =0.476; p<0.001), which thus shows that there was a significant fall in systolic blood pressure followed by rise in it over time but there was no significant difference between the groups.

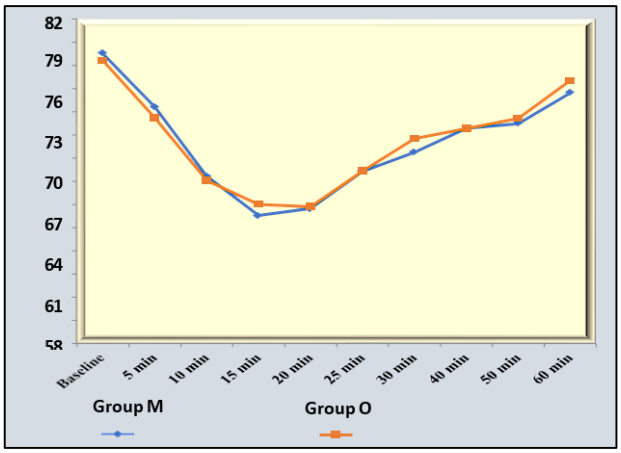

Figure 6: Mean diastolic blood pressure at various time between the two groups (n=88)

Figure 6 shows that the effect size of change in mean diastolic blood pressure over time between the two groups was 0.001 and it was not found to be statistically significant (p=0.792). However, the test for a difference in

systolic diastolic pressure over time was highly statistically significant (Effect size =0.429; p<0.001), which thus shows that there was a significant fall in diastolic blood pressure followed by rise in it over time but there was no significant difference between the groups.

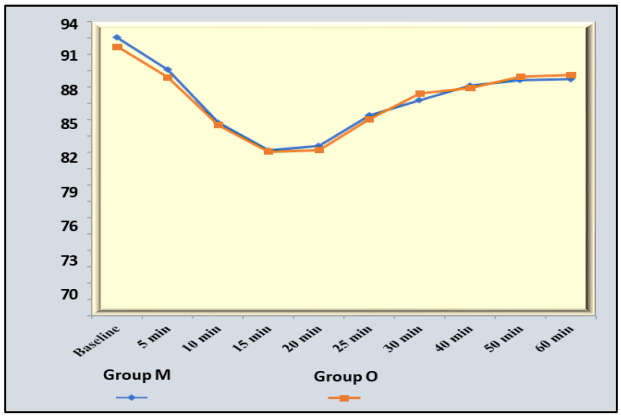

Figure 7: Mean of mean arterial pressure at various time between the two groups (n=88).

Figure 7 shows that the effect size of change in mean of mean arterial pressure over time between the two groups was 0.001 and it was not found to be statistically significant (p=0.791). However, the test for a difference in systolic diastolic pressure over time was highly statistically significant (Effect size =0.427; p<0.001), which thus shows that there was a significant fall in mean arterial pressure followed by rise in it over time but there was no significant difference between the groups.

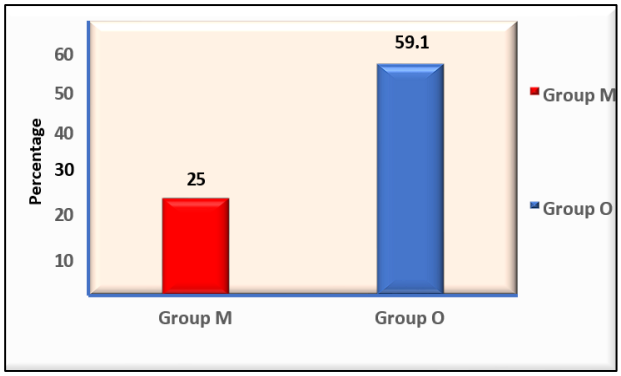

Figure 8: Comparison of side effects between the groups (n=88).

Figure 8 shows that the incidence of side effects was significantly lower among the patients in the mirtazapine group when compared to the patients in the ondansetron group (25.0% versus 59.1%; p=0.002).

DISCUSSION

Post-spinal anesthesia shivering (PSAS) is a common phenomenon encountered in patients undergoing lower abdominal surgeries under spinal anesthesia. It is an involuntary response to core hypothermia resulting from vasodilation and inhibition of thermoregulatory mechanisms. PSAS not only causes discomfort but also leads to increased oxygen consumption, carbon dioxide production, and catecholamine release, potentially predisposing patients to adverse outcomes such as myocardial ischemia and wound complications. Therefore, effective prevention strategies are crucial to enhance patient comfort and safety during the perioperative period. Both mirtazapine and ondansetron have shown promising results as prophylactic agents for preventing PSAS. And despite the potential efficacy of mirtazapine and ondansetron in preventing PSAS, there is a paucity of randomized clinical studies directly comparing their prophylactic effects in patients undergoing lower abdominal surgeries under spinal anesthesia. The peak impact of the mechanism of spinal anesthesia inducing core hypothermia typically occurs within the initial 30 to 60 minutes following the block. So, it is essential to closely monitor patients during this period, actively employ warming techniques, and administer anti-shivering interventions. Therefore, in this study the first 90 minutes after spinal anesthesia has been opted as the timeframe.[7] And hence, a randomized controlled trial was conducted among the patients who underwent lower abdominal surgeries to compare the effectiveness of prophylactic mirtazapine and ondansetron for preventing PSAS, which would provide valuable insights into the optimal pharmacological approach to PSAS prevention, potentially improving patient outcomes and enhancing perioperative care protocols.

The study participants were comparable between the groups with respect to age, gender, body weight, ASA status and OT temperature. Ondansetron is a specific antagonist of the 5-HT_3 receptor, commonly used to prevent and manage nausea and vomiting during or after surgical procedures. Previous research has shown that serotonin (5-HT), a neurotransmitter found in the brain and spinal cord, plays a crucial role in neurotransmission. Studies have also indicated the involvement of the serotonergic system in the regulation of post-anesthesia shivering.[14] Ondansetron may influence perioperative thermoregulation and help to prevent PAS. The exact mechanism through which 5-HT_3 antagonists modulate body temperature regulation and prevent PAS remains unclear, one proposed mechanism suggests that it could involve enhancing the inhibitory effect of serotonin reuptake in the preoptic anterior hypothalamus region.[15] Mirtazapine on the other hand also acts by mirtazapine-induced serotonin uptake inhibition in the preoptic anterior hypothalamic part which controls heat production and loss.[16] Our study showed that the incidence of PSAS among the patients in mirtazapine and ondansetron groups were 45.5% (95% CI: 30.7-61.0%) and 81.8% (95% CI: 66.8-91.3%). Contrary to our study finding, the available literatures by Esmat et al and Majeed et al, had concluded that the incidence of PSAS was 16.0% in both their studies, which is considerably lower than that of our study.[17,20] With regards to ondansetron, the available literatures show

a lower incidence of PSAS. A study by Shakya et al had concluded that only 10% patients experienced PSAS in their study, which is much lower than our study.[18] Similarly, a study by Lakhe et al, showed an incidence of shivering as 16.7%.[19] Similar lower incidence of shivering had been reported in various other studies conducted elsewhere.[14] The observed higher incidence of PSAS in our study could be attributable to difference in the study population, sample size or may be simply a chance variation, which necessities further larger studies.

PSAS was significantly higher among the patients in the ondansetron group when compared to the mirtazapine group ($p<0.001$). The time of onset of shivering was delayed for the patients in the ondansetron group when compared to the patients in the mirtazapine group, but it was not found to be statistically significant. Severity (grade I) was significantly higher among the patients in the mirtazapine group when compared to the ondansetron group ($p<0.001$). There are no previous literatures directly comparing both the drugs. However, the observed difference could be attributable to the following reasons. Firstly, mirtazapine, as a noradrenergic and serotonergic antidepressant, exerts its effects by antagonizing central α_2-auto- and hetero-adrenoceptors, thereby enhancing the release of both noradrenergic and serotonergic neurotransmitters. Its action on multiple receptor systems, including serotonin (5-HT) and noradrenaline, may provide more comprehensive modulation of thermoregulatory pathways compared to ondansetron, which primarily acts as a 5-HT_3 receptor antagonist. Mirtazapine has broader pharmacological profile which may contribute to more effective prevention of PSAS. Also, its antagonism of 5-HT_2 and 5-HT_3 receptors, along with its enhancement of serotonergic neurotransmission, may play a role in attenuating the serotonergic-mediated response involved in PSAS. By modulating serotonin signalling pathways more extensively than ondansetron, mirtazapine may exert stronger inhibitory effects on shivering mechanisms. Secondly, while both mirtazapine and ondansetron have antiemetic properties, mirtazapine's additional anxiolytic effects may contribute to overall patient comfort and reduced sympathetic activation, thereby mitigating the risk of PSAS. Reduced perioperative anxiety and stress levels associated with mirtazapine use could indirectly influence thermoregulatory responses and shivering propensity. Like the current study, Shen et al and a plethora of studies documented that prophylactic 5-HT_3 receptor antagonists were efficient for decreasing the occurrence of perioperative shivering (POS) in patients after SA.[11,20]

Additionally, both the drugs were hemodynamically stable and there was no significant difference in the hemodynamic parameters between the groups. When ondansetron is used for the prevention of PSAS, the hemodynamic profile of the patient does not change, which is beneficial for safety in anesthesia. Furthermore, ondansetron is also associated with a lower risk of hypotension and bradycardia. Also, mirtazapine's hemodynamic stability stems from its central α_2-adrenergic receptor antagonism, serotonergic modulation, mild anticholinergic activity, and lack of significant QT prolongation. These properties, along with its anxiolytic effects, contribute to maintaining blood pressure and heart rate stability during the perioperative period.

Nevertheless, the study also showed that the incidence of side effects was significantly lower among the patients in the mirtazapine group when compared to the patients in the ondansetron group (25.0% versus 59.1%; $p=0.002$). The results of Abdel-Ghaffar et al and Chen et al were in concordance with our recent findings concerning the lower percentage of side effects in mirtazapine group which can be well attributed to the antipruritic and antiemetic efficacy due to 5-HT_3 receptor blockers properties of mirtazapine.[11,21] It is also noteworthy to mention that the adverse effects are lesser in ondansetron group too, though it is relatively higher in our study.[19] Even in a study by He et al, ondansetron exhibited a lower risk of hypotension compared to placebo, with no significant difference in hypotension when compared to pethidine.[22]

CONCLUSION

Of 88 patients enrolled in the study, the mean age of the study participants was 43.8 years.

The study participants were comparable between the groups with respect to age, gender, body weight, ASA status and OT temperature. The incidence of PSAS among the patients in Mirtazapine and Ondansetron groups were 45.5% (95% CI: 30.7-61.0%) and 81.8% (95% CI: 66.8-91.3%). PSAS was significantly higher among the patients in the ondansetron group when compared to the mirtazapine group ($p<0.001$). The time of onset of shivering was delayed for the patients in the ondansetron group when compared to the patients in the mirtazapine group, but it was not found to be statistically significant.

Severity (grade I) was significantly higher among the patients in the mirtazapine group when compared to the ondansetron group ($p<0.001$). There was a significant fall in heart rate over time but there was no significant difference between the groups. There was a significant fall in systolic blood pressure, diastolic blood pressure and mean arterial pressure followed by its rise over time but there was no significant difference between the groups. The incidence of complications was significantly lower among the patients in the Mirtazapine group when compared to the patients in the Ondansetron group (25.0% versus 59.1%; $p=0.002$).

It could be safely concluded that prophylactic administration of mirtazapine attenuated shivering with minimal hazards in patients scheduled for lower abdominal surgery under spinal anesthesia when compared to ondansetron. However, further larger multicentric trials could add robustness to our study findings.

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