

*Review Article*

## Safety and Efficacy of Two Drugs, Ondansetron and Meperidine, in Preventing Shivering after Anesthesia in Orthopedic Surgery Candidates: A Systematic Review Study

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### ABSTRACT

**Introduction:** Due to the fact that orthopedic surgeries have increased a lot in recent years and some of these patients undergo surgery under G/anesthesia, the shivering possibility after surgery has increased in them. Therefore, it is necessary to take preventive measures; this study was conducted as a systematic review to investigate the safety and effectiveness of two drugs, ondansetron and meperidine, in preventing shivering after anesthesia in patients who are candidates for orthopedic surgeries.

**Methodology:** This research is a systematic review based on the PRIZMA guidelines in 2022 by searching the keywords ondansetron, meperidine, prevention, chills, orthopedics, and general anesthesia in all databases that publish medical articles without restrictions.

**Results:** The average number of minutes of zero shivering score in all patients who were fully treated before the 10<sup>th</sup> minute in the two groups was in the 7<sup>th</sup> minute and earlier in the meperidine group than in the ondansetron group and was significantly different. 29% in the ondansetron group and 31% in the meperidine group did not reach zero score at the 10<sup>th</sup> minute, and there was a need to re-inject the drug to control shivering.

**Conclusion:** Although ondansetron is effective in the shivering treatment after general anesthesia, its strength and speed are weaker compared to meperidine. Therefore, the results of this study could not prove that ondansetron has different efficacy and safety compared to ondansetron or vice versa.

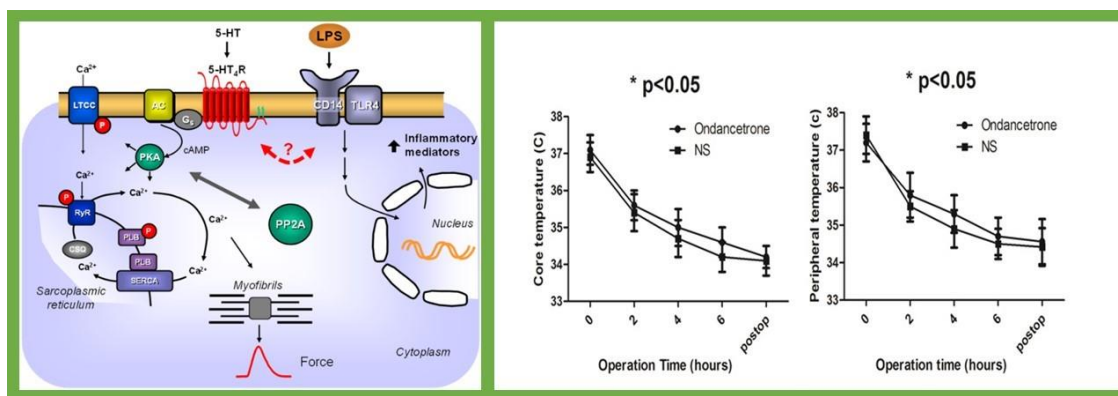
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## GRAPHICAL ABSTRACT



### Introduction

Post-operative shivering (Figure 1) is one of the side-effects after surgery and can cause many problems for patients [1-3]. The shivering incidence after anesthesia is about 10-65%, which has now decreased due to the opioids use during anesthesia and keeping patients normothermic. This complication is mainly due to the remaining effects of anesthetic drugs or due to a decrease in the patient's body temperature for various reasons, which in any case leads to an increase in oxygen consumption by 100-600% [4-6]. Shivering after the operation, apart from causing an unpleasant feeling for the patient, increases the body's metabolism, and therefore the heart rate, cardiac output, and ventilatory volume will increase [7-9]. In addition, the eyeball pressure, intracranial pressure, and tension on the surgical site increases, which can expose susceptible people to angina pectoris, arrhythmia, heart attack, and even death [10-13]. Furthermore, shivering after surgery may cause vasoconstriction, hypoperfusion, and metabolic acidosis, and it can also disrupt the special function of platelets and delay the metabolism of most drugs [14]. Post-operative shivering in most cases as a result of disturbances in body temperature regulation and following hypothermia [15-17].

Although it is possible that in patients who were normothermic during anesthesia, shivering may occur after the operation with a mechanism unrelated to the body's thermal regulation system (Non-Therm Oregulat Ory Shivering) due to some anesthetic drugs or due to pain, but it has been proven that reduction of the central body temperature of half a degree can cause shivering after the operation [18-20]. Regulating the threshold of shivering and vasoconstriction is through mechanisms that are exerted by mediators such as norepinephrine, dopamine, acetylcholine, prostaglandin E1, and 5-hydroxytryptamine (Figure 2). Therefore, it seems that drugs that act on these mediators can also be effective in controlling tremors [21-23]. The most important effect of ondansetron as a serotonin receptor antagonist drug is the antiemetic effect, which is applied by acting on the vagus nerve endings and its central receptors, thus preventing nausea and vomiting by inhibiting the vomiting reflex [24-26]. Its most important uses are in the treatment and prophylaxis of nausea after surgery and in patients with advanced cancer undergoing chemotherapy [27-29]. The ondansetron effect in preventing shivering has also been investigated in different studies [30].

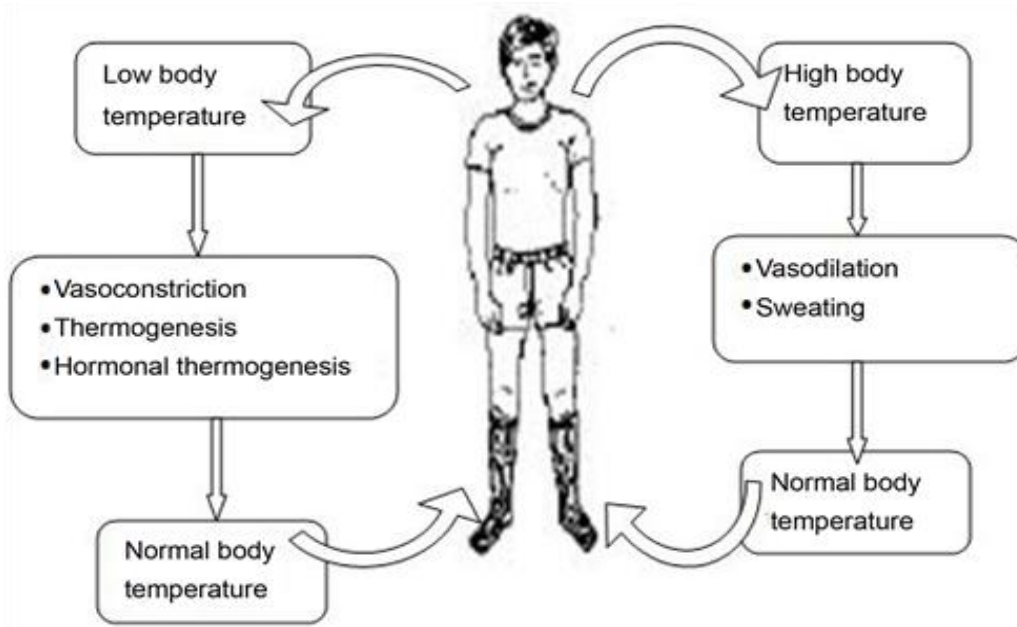


Fig. 1. Post-operative shivering mechanism.

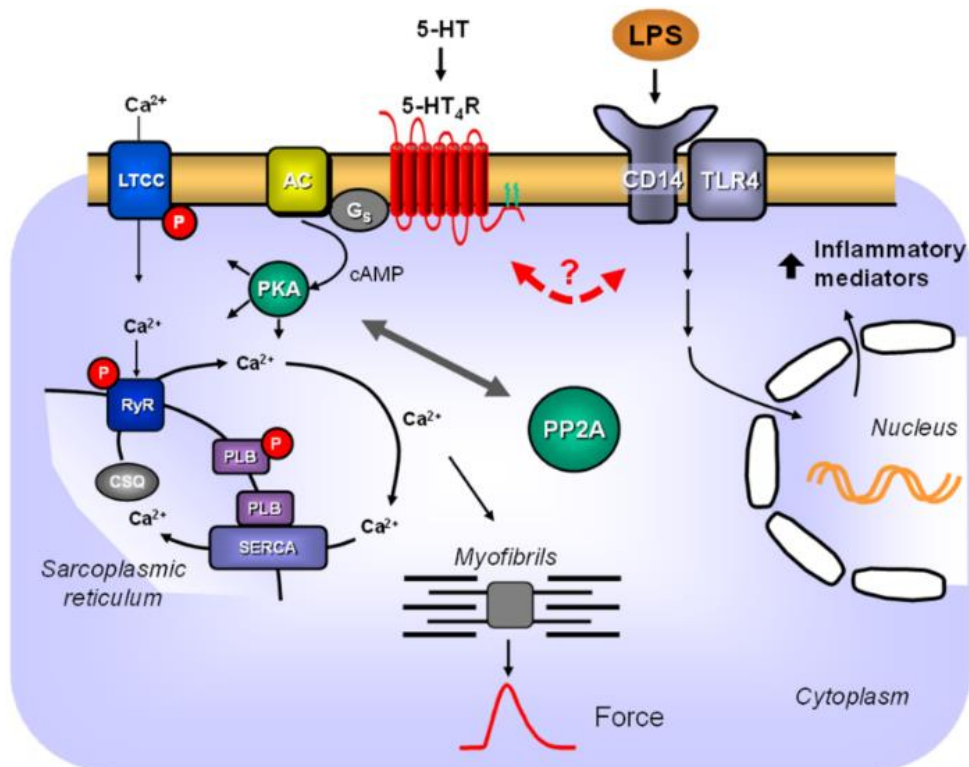
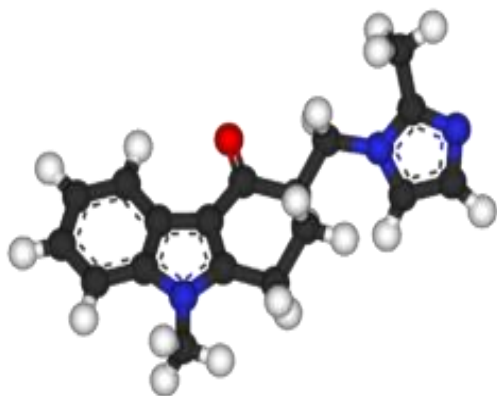


Figure 2. 5-hydroxytryptamine.



**Figure 3.** Ondansetron molecule.

The administration of ondansetron and saline as a placebo before anesthesia induction in patients undergoing orthopedic, urological, and general surgeries has shown a reduction in the shivering incidence after anesthesia in the ondansetron group. Also, no difference between 8 mg of ondansetron (Figure 3) and pethidine has been reported in the shivering prevention after anesthesia in patients who received spinal anesthesia [31-33]. Ondansetron did not play a role in changing the threshold of shivering, sweating, and vasoconstriction in awake volunteer patients and did not cause hypothermia [34-36].

Due to the fact that orthopedic surgeries have increased a lot in recent years and some of these patients undergo surgery under G/anesthesia, the shivering possibility after surgery has increased in them. Therefore, it is necessary to take preventive measures [37-39]. This study was conducted as a systematic review to investigate the safety and effectiveness of two drugs, ondansetron and meperidine, in preventing shivering after anesthesia in patients who are candidates for orthopedic surgeries [40-42].

### Methodology

This research is a systematic review conducted according to PRISMA guidelines in 2022 by searching the keywords ondansetron,

meperidine, prevention, shivering, orthopedics, and general anesthesia in all databases that publish medical articles without time limit. In the course of this research, patients with shivering after G/anesthesia for laparotomy under the condition of ASA I and II, the age range of 20-60 years old, surgery duration between 2-3 hours, no history of liver disease, heart disease, drug allergy, no prohibition of pethidine use (history of disease Pulmonary, convulsions, and drug allergy). In all cases, the temperature of the surgical rooms was kept in the range of 22 to 24, and in case of discrepancy, the intervention was not performed.

The measured scale for shivering was based on the following scoring: zero score: no shivering, 1: peripheral cyanosis or peripheral vasoconstriction, 2: shivering and clear movement in a muscle group, 3: tremors and clear tremors in more than one muscle group, 4: full and intense shaking in the whole body.

Patients who met the conditions for entering the study were covered with a blanket for 3 minutes after determining the initial score of shivering in recovery, and their body temperature was increased by heating the skin surface with a warm touch device. In the case of failure to control shivering and score more than 2 after warming up, using the method of random forms and with the approval of the project's anesthesiologist, the patients were injected with 25 mg of pethidine and 8 mg of ondansetron, and the assistant anesthetist of the project did not know the type of drug injected, he/ or she recorded shivering score every minute to 10 minutes. After 10 minutes, if there was no improvement in group 1, 25 mg of pethidine was used, and in group 2, an additional dose of pethidine was used in the amount of 15 mg. Finally, the time to zero shivering score and the average shivering score in each group were compared in different minutes.

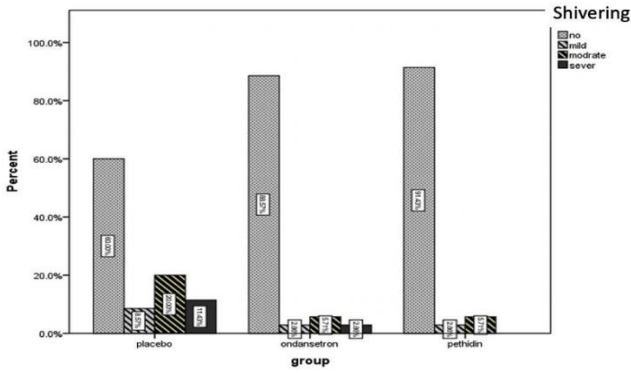


Figure 4. Shivering results in different times.

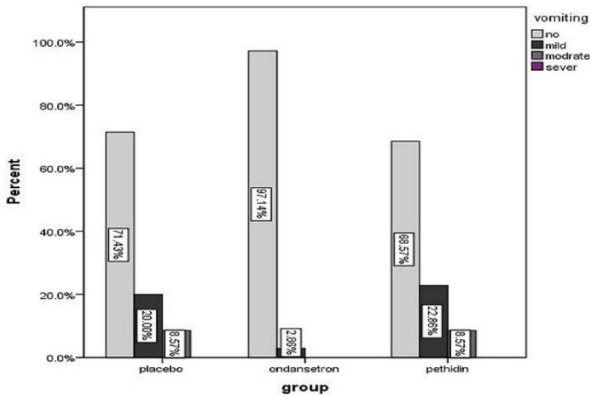


Figure 5. Shivering results in different times.

### Results

The average number of minutes of zero shivering score in all patients who were fully treated before the 10<sup>th</sup> minute in both groups was in the 7<sup>th</sup> minute and earlier in the meperidine group than

in the ondansetron group and was significantly different (Figures 4 and 5). 29% in the ondansetron group and 31% in the meperidine group did not reach zero score at the 10<sup>th</sup> minute, and there was a need to re-inject the drug to control shivering (Figure 6).

### Discussion

The results of this study determined that although ondansetron is effective in treating shivering after anesthesia, the speed and power of treating shivering is much better with meperidine [43-45]. The use of 5-hydroxytryptamine receptor antagonists has been confirmed for the prevention and treatment of nausea and vomiting and has been used in various studies in the last two decades to prevent shivering after anesthesia and surgery [46-48]. Its possible mechanism is the central regulation of the shivering threshold and the effect on vasoconstriction and expansion through the other catecholamines [49-51].

Most studies in this field have used drugs of this category to prevent the shivering occurrence after anesthesia and compared them with other commonly used drugs and have obtained completely different results [52-54].

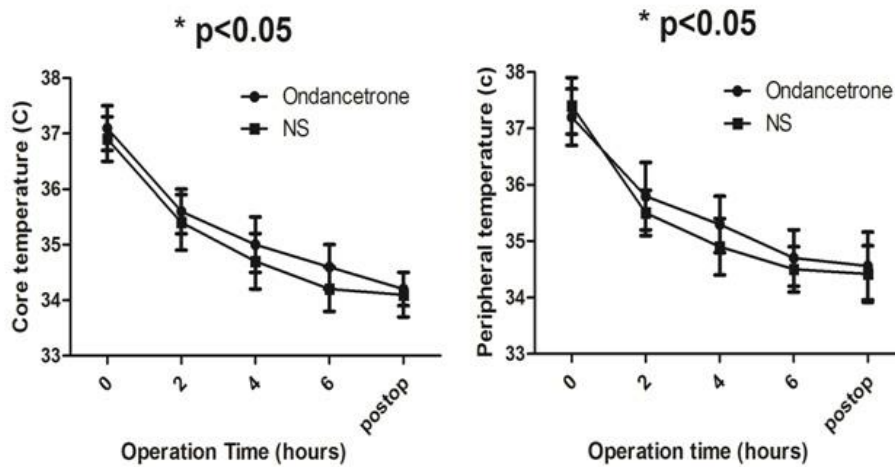


Figure 6. Shivering results in different times.

Likewise, these drugs have been evaluated before regional anesthesia to control post-operative shivering and have given relatively good results. In the Kolsaka study, ondansetron was compared with meperidine and saline, and also it was found that both drugs reduced shivering after spinal anesthesia and further maintained the central body temperature. Compared to ketamine, granistrone has not been successful in controlling shivering after spinal anesthesia in urology patients, and ondansetron has not reduced the shivering severity and prevalence after spinal epidural anesthesia in women candidates for caesarean section.

Among the other cases of success and useful application of this drug class in preventing shivering is the ondansetron administration before general anesthesia in gynecological surgeries by Etziri Assal *et al.* In their study, despite the same body temperature drop in all groups, ondansetron and meperidine were significantly more successful in preventing shivering after general anesthesia compared to the normal saline. Other studies that have used ondansetron to prevent shivering and achieved positive effects include the study by Lin *et al.* on the shivering prevalence after caudal anesthesia in children, the study by Nalam (2017) on shivering after spinal anesthesia in cesarean section and the research of Shakia *et al.* (2010) compared to ketamine indicated that all of them have resulted in recording a successful effect in preventing tremors. The other drug of this category (5-hydroxytryptamine antagonist), granisterone, compared to meperidine, did not show any difference in the shivering prevention after general anesthesia in laparoscopic surgeries and was equally effective.

In our search of the sources, only two studies were found on the ondansetron use in the treatment of post-anesthesia shivering, one of which was a study by Mahori *et al.* in 2014, which proved that ondansetron at a dose of 8 mg and not 4 mg was as effective as meperidine in

controlling shivering. In that study, the measurement of the patient's central and peripheral temperature during surgery was omitted, and the measurement of peripheral body temperature during recovery also showed no difference between the two groups, but the prescribed dose of ondansetron was considered the key point for effectiveness.

The shivering of 100% of patients treated with butorphanol and 92.3% of patients treated with tramadol was controlled after 5 minutes, while in the ondansetron group only 23.5% in the first 10 minutes and less than 30% within the period 20 minutes after the drug injection, the shivering had reached zero score, and the obtained results were significantly different from the effect time of ondansetron in the control of shivering in our study. The lack of ability to control shivering as well as prevent shivering was more in the studies on patients who were subjected to spinal anesthesia, and maybe the reason for their difference with the results of the present study is the same difference in the type of anesthesia and severe changes in systemic vascular resistance and a significant drop in central temperature. Due to limitations in most studies, they have not been measured and reported.

### Conclusion

The important and positive point of most of the previous studies in the field of prevention of chills is the use of central temperature monitoring and its recording during surgery, which was absolutely necessary according to the type of study and the time of drug injection. The injection of pre-anesthesia drug and its effect on post-operative shivering requires the provision of completely identical conditions in patients in terms of factors affecting body temperature, including ambient temperature, temperature of injected fluids, and (2) central temperature control to increase the prevalence and severity of post-operative shivering. Action does not create unusual interference. In our study, the shivering

severity was investigated regardless of the temperature of environment and liquids, the type of operation, and the operation duration, and also only according to the shivering severity, the initial recorded score, and the possibility of the ondansetron effectiveness in shivering treatment, as well as the treatment speed by recording the shivering score every minute. Therefore, the necessity of temperature monitoring in advance during surgery is removed. Besides, monitoring the surface temperature of the patient's body is not helpful and does not determine the shivering possibility after the operation. The higher speed of meperidine in the shivering treatment and the faster reduction of shivering score to zero proved that ondansetron is a weaker drug than meperidine in the shivering treatment after anesthesia and most patients need additional treatment.

Although ondansetron is effective in the shivering treatment after general anesthesia, its strength and speed are weaker compared to meperidin, the results of this study could not prove that ondansetron has different efficacy and safety compared to ondansetron or vice versa.

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