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## Comparison of Weight-Adjusted Dose versus Fixed Dose Ondansetron in Prevention of Shivering Following Spinal Anaesthesia for Caesarean Deliveries

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### ABSTRACT

**Background:** Spinal anaesthesia is a reasonable alternative of regional anaesthetic that is indicated for around 86 % of caesarean sections performed in the United States and the United Kingdom. Neuroaxial block is used in approximately 80% of caesarean sections performed at Al-Azhar University hospitals. Shivering is a common symptom of spinal anaesthesia, affecting 40 to 64 % of individuals. Shivering could be uncomfortable for the mother and impair anesthesiologists' monitoring of the patient during caesarean procedures. Where ondansetron is a 5-HT<sub>3</sub> receptor antagonist that can be used to treat and prevent shivering after spinal anaesthesia. According to the studies, administering a fixed dose in individuals of varying weight obscured ondansetron's dose effect on avoiding shivering, resulting in a higher frequency of shivering when the dose was not weight-balanced.

**Aim of the work:** To compare weight-adjusted ondansetron to a fixed dose of ondansetron and pethidine as a control treatment for shivering regression during spinal anaesthesia for caesarean deliveries.

**Patients and Methods:** A prospective, randomised, double-blind, controlled clinical trial with 129 patients scheduled for elective caesarean surgery was carried out. Three similar groups of women were assigned at random. Following spinal anaesthesia, the first group (FDO) received a fixed dosage of ondansetron (4mg), the second group (WAO) received a weight-adjusted dose of 0.1mg/kg ondansetron, and the control group (PC) received 0.5 mg/kg pethidine. During surgery and the post-operative period, the frequency and severity of shivering were noted, as well as the occurrence of headache, pruritus, nausea, and vomiting.

**Results:** Shivering was seen in 13 patients (30.2 % ) in the first group (FDO), 11 patients (25.6 % ) in the second group (WAO), and 11 patients (25.6 % ) in the third group (PC), but there was no significant difference between groups ,The first group (FDO) 5 patients (11.6 % ) shivered severely more than the second group (WAO) 3patients ( 7.0 % ).

**Conclusion:** A weight-adjusted dose of 0.1 mg/kg significantly reduced the frequency and intensity of post-spinal shivering while also lowering adverse effects and enhancing hemodynamic stability.

**Keywords:** Ondansetron, avoidance of post-spinal anaesthetic shivering, and caesarean deliveries are the keywords.

### INTRODUCTION

Shivering is an inadvertent muscle tissue activity influencing muscle or more muscle groups. It is a natural reflex that causes muscle contractions to increase body heat production. Spinal anaesthesia had been demonstrated to be an excellent regional technique recommended in almost 86% of caesarean sections.<sup>1</sup>

The incidence of shivering ranging from 40%-64% % after neuraxial anaesthesia.<sup>2</sup>

During caesarean sections, shivering is an obvious topic of concern for pregnant women which has been shown to exacerbate wound pain and anguish and disrupt with wound healing by straining the incisions. Shivering also raises energy expenditure and metabolic processes by 40–120%. It causes tachycardia and hypertension, as well as an increase

in cardiac output, by stimulating catecholamine outflow.<sup>3</sup>

Shivering has been linked to an increase the incidence of maternal and subsequently fetal hypoxemia and maternal myocardial activity with limited oxygen supply causing myocardial ischemia. Shivering occasionally raises intra-ocular and intracranial tension, which is a concern for an anesthesiologist because it interferes with blood pressure monitoring and causes artifacts in ECG and pulse oximetry.<sup>4</sup>

By transferring heat from the core to the peripheral thermal compartment, where the majority of it is lost to the environment, spinal anaesthesia-induced vasodilation contributes to dermal heat loss. Core temperatures drop by 0.5°C to 1°C above the level of the spinal block after neuroaxial anaesthesia is achieved, causing vasoconstriction and shivering.<sup>5</sup>

Some medications have been shown to be effective in preventing shivering after general anaesthesia. However, few studies have been conducted on parturient women who had caesarean procedures. Tramadol, pethidine, nalbuphine, and clonidine were once used to treat perioperative shivering, however the significant adverse effects of these drugs prevent anesthesiologists from administering them before birth, potentially endangering the foetus and mothers.<sup>6, 7</sup>

Ondansetron, a 5-HT<sub>3</sub> receptor antagonist, could be used safely during pregnancy for anti-nausea and anti-emetic action. There was no evidence of a danger or an increase in unfavourable foetal development outcomes in pregnant women who were taken ondansetron during gestation. Ondansetron has also been used to prevent and control nausea and vomiting during surgery, as well as to decrease opioid-caused itching during regional anaesthesia. Ondansetron has a good therapeutic index, which means it has relatively minimal side effects even at large doses, including the elimination and treatment of chemotherapy-related nausea and vomiting. Constipation, headaches, and malaise/fatigue are all common complaints. Hypertension and tachycardia are caused by rapid administration.<sup>8,9,10</sup>

The dose-dependent antishivering effect of ondansetron is weight-dependent, with low-dose ondansetron (4mg) being found to be equally effective as high-dose ondansetron (8mg) in 50kg patients.<sup>10</sup>

Shivering would be treated with ondansetron during general and regional anaesthesia. Shivering drugs act by adjusting central core temperature, whereas 5-HT antagonists, such as ondansetron, can aid with operative shivering. The precise mechanism could be that serotonin reuptake in the anterior hypothalamic preoptic area is inhibited. Heat generation and heat loss pathways may be influenced by 5-HT<sub>3</sub> receptors.<sup>11</sup>

Ondansetron has been used to treat shivering during caesarean delivery while under spinal anaesthetic in a few studies. There has never been a study that looked at different doses of ondansetron to prevent shivering after spinal anaesthesia.<sup>11</sup>

The study compared the efficacy of a prophylactic weight-adjusted and fixed dose of ondansetron against that of a synthetic opioid in pursuit of a safer and more reliable prescription (Pethidine, which is the gold standard drug for shivering control). The purpose of this study was to compare the efficacy, potency, haemodynamic effects, and complications or side effects of a fixed dose of ondansetron (4 mg) versus a weight-adjusted dose of ondansetron (0.1 mg/kg) in suppressing pethidine-related shivering as a control, as well as the degree of shivering between groups after caesarean sections under spinal anaesthesia. A secondary goal is to reduce adverse effects such as headaches and haemodynamic fluctuations.

## PATIENTS AND METHODS

A double-blind, prospective, randomised control trial was used as the study design.

It was studied at Al-Azhar University's Medicine Faculty in Cairo, Egypt, from May 2020 to February 2021, after being approved by the Ethics and Scientific Committee. The study included 129 healthy pregnant women between the ages of 21 and 35 who were scheduled for elective caesarean delivery under spinal anaesthetic at Al-Azhar University Hospitals (Al- Hussein and Bab al-Shaaria) in Cairo, Egypt.

Participants were recruited after signing a written informed consent form indicating their willingness to engage in a research project and the confidentiality of their personal information. They would get the same quality of care as all other patients in the operating room and would not be denied medicines in order to deny participation in the trial. The patient was informed about the study protocol both orally and in writing. Despite the fact that the patient receives no direct benefit from participating in the study, the findings may be used to influence future local practise. They could also leave the study at any time and continue to receive standard care.

Patients who met either of the following criteria were excluded from the study:

1. Ondansetron or pethidine can be given before surgery.
  2. Ondansetron or pethidine allergy
  3. Shivering occurs before spinal anaesthesia.
  4. Premature labour, antepartum haemorrhage, a history of hyperemesis gravidarum, pregnancy-induced toxemia, and other complications of pregnancy
- Sample-size calculation;

The MedCalc® version 12.3.0.0 programme "Ostend, Belgium" was used for sample size measurements, as was a statistical calculator based on a 95 % confidence interval and a 5 % error 80 % analysis power. A previous research (Gicheru et al., 2019)<sup>12</sup> found shivering was higher in the intervention group (11.3%) than in the control group (22.6 %). Thus, it could be used in this research; based on these values, a sample size of 108 cases was calculated; however, to identify such a variation, the sample size was determined in the entire study group to 135 cases. However, six patients met the exclusion criteria, leaving 129 patients who participated in the study and were assigned equally using a computer programme. Subdivided into three;

- Group I (43 cases); ondansetron 4mg (FDO).  
 Group II (43 cases); 0.1mg/kg dose-adjusted (WAO).  
 Group III (43 cases); 1 mg/kg pethidine (PC).

The test drugs were prepared in identical 10 ml syringes by an anesthesiologist who did not participate in any other aspect of the study, syringes labelled with the active drug of the study were again packed in an opaque envelope to the same code as the randomly selected patient.

Upon admission to the operating theatres, cardiovascular baseline parameters were assessed via automated non-invasive blood pressure measurement, electrocardiography, and pulse oximetry. Core temperature had been measured also by the monitor as part of the baseline parameters (GE Healthcare Finland model B40i).

All patients received 15ml/kg solution at ambient temperatur

by spinal midline approach administered at the L3/L4 interspace with a 25 French gauge Quincke Type point (B/BRAUN, Spinocan) needle following a 2ml 2% local Lidocaine solution. 2mls of bupivacaine and 20ug fentanyl were administered after free fluid flow (CSF). Till repositioning the patient supine having 15 degrees left lateral slope, that one was administered immediately after spinal anaesthesia. (The first group (FDO) received a fixed dose of 4 mg of ondansetron, the second group (WAO) a weight-adjusted dose of 0.1 mg/kg, and the third group (control group) received 0.5 mg/kg of pethidine, each prepared in 10 ml syringes.

Surgery began when the sensory block reached the reported target level.

Preoperative hemodynamic data (mean blood pressure and heart rate) were gathered 15, 30, 45, 60, 90, and 120 minutes after spinal anaesthesia.

Temporal thermometer fluctuations were recorded at intervals of 15, 30, 45, 60, 90, and 120 minutes.

A four-point Bedside Shivering Assessment Scale for measuring shivering (BSAS) was established and validated for two hours following spinal anaesthesia whenever shivering occurred; cases of shivering above grade 3 or causing discomfort were treated with i.v. pethidine 40 mg;

- 0= indicates there's no shivering.
- 1= Slight face/neck fasciculation.
- 2= Tremor in many muscle groups.
- 3=Extensive all-body shivering.

**RESULTS**

The following tables and figures illustrate the findings of this research.

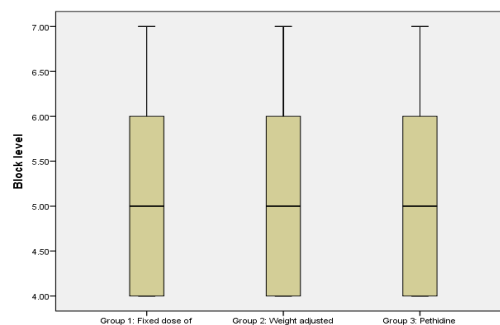
There were no statistically significant differences between groups in terms of demographic data, as seen in table (1).

Demographic data	Group A: FDO (n=43)	Group B: WAO (n=43)	Group C: P (n=43)	P-value
Age (years)	28.88±3.53	28.74±3.32	29.16±3.68	0.854
Weight (kg)	83.84±4.67	83.51±4.49	84.37±4.73	0.686

**Table 1:** Demographic data

*P-value>0.05 NS, the mentioned data expressed as Mean±SD.*

There was no statistically significant difference in spinal block level between classes, as illustrated in figure 1 and table 2.



**Fig. 1:** Spinal block level.

Spinal block level	Group A: FDO (n=43)	Group B: WAO (n=43)	Group C: P (n=43)	P-value	F/x2#
Median (IQR)	T5 (T2)	T5 (T2)	T5 (T2)	0.649	H=0.434
Range	T4-T7	T4-T7	T4-T7		

**Table 2:** Spinal block level

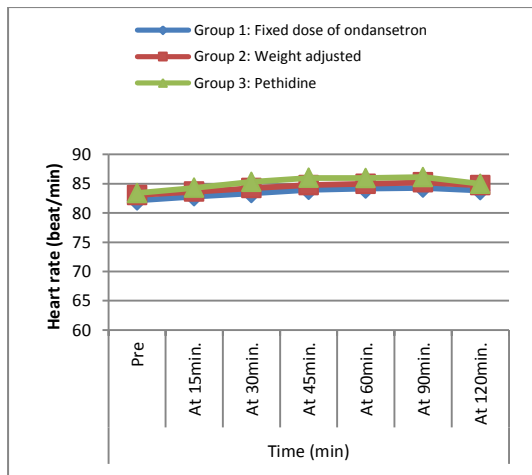
The mentioned data expressed as median and range H=Kruskal Wallis, P-value>0.05 NS

Regarding heart rate, although there was a small rise in pulse rate in the pethidine group as compared to the other groups, but the difference was not statistically important, as seen in Table (3) and figure (2).

Heart rate (beat/min)	Group A: FDO (n=43)	Group B: WAO (n=43)	Group C: P(n=43)	p-value
<b>Pre-operative</b>	82.14±7.88	83.07±7.90	83.40±7.81	0.745
<b>At 15min.</b>	82.81±6.89	83.65±6.76	84.30±6.64	0.594
<b>At 30min.</b>	83.35±7.22	84.23±7.14	85.30±6.74	0.438
<b>At 45min.</b>	83.93±7.10	84.77±7.03	85.98±6.73	0.393
<b>At 60min.</b>	84.16±7.83	84.98±7.57	85.95±6.75	0.533
<b>At 90min.</b>	84.30±7.63	85.23±7.47	86.12±7.09	0.526
<b>At 120min.</b>	83.86±8.12	84.72±7.51	84.98±6.89	0.772

**Table 3:** Heart rate (beat/min)

The mentioned data expressed in Mean±SD.

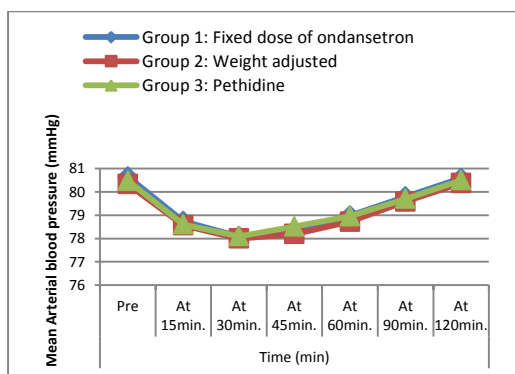


**Fig. 2:** Heart rate (beat/min). The mentioned data expressed in Mean±SD.

As regard to blood pressure, in all groups, there was a slight decline in mean arterial blood pressure (mmHg) values at 30 minutes to 60 minutes interval, but it was not statistically important, as seen in table(4) and figure (3).

Mean Arterial blood pressure (mmHg)	Group A: FDO (n=43)	Group B: WAO (n=43)	Group C: P (n=43)	p-value
Pre-operative	80.65±4.26	80.33±4.14	80.47±4.13	0.936
At 15min.	78.74±4.77	78.56±4.69	78.60±4.88	0.983
At 30min.	78.09±4.76	78.00±4.64	78.09±4.70	0.994
At 45min.	78.35±4.39	78.19±4.47	78.51±4.52	0.944
At 60min.	78.98±4.11	78.72±4.08	78.95±3.95	0.949
At 90min.	79.79±4.10	79.58±3.95	79.70±3.92	0.971
At 120min.	80.58±4.28	80.37±4.17	80.49±4.23	0.974

**Table 4:** Mean arterial blood pressure (mmHg) changes; Data expressed as Mean±SD.



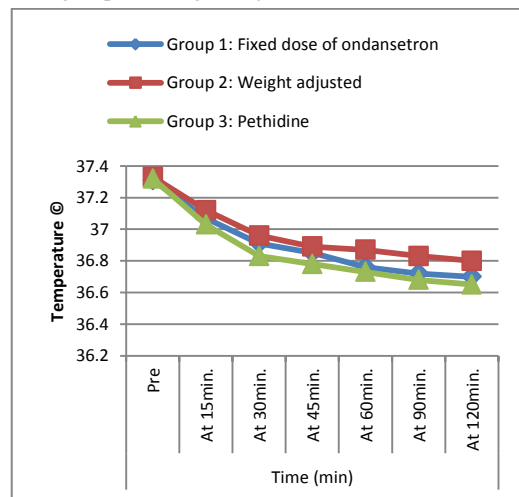
**Fig. 3:** Mean arterial blood pressure (mmHg) changes.

AS regard to body temperature, the three groups had equal temperatures prior to spinal anesthesia. The three groups experienced a steady decline in temperature that began at 30 minutes and peaked at 120 minutes. The control group (PC) had seen a

greater decrease in core temperatures. This is shown in the following table 5 and figure 4.

Temperature °C	Group A: FDO (n=43)	Group B: WAO (n=43)	Group C: CP (n=43)	P-value
Pre-operative	37.31±0.49	37.33±0.45	37.32±0.41	0.167
At 15min.	37.07±0.48	37.12±0.45	37.03±0.41	0.250
At 30min.	36.91±0.48	36.96±0.44	36.83±0.41ab*	0.016*
At 45min.	36.85±0.48	36.89±0.44	36.78±0.40ab*	0.004*
At 60min.	36.76±0.48	36.87±0.44a*	36.73±0.40b*	0.011*
At 90min.	36.72±0.48	36.83±0.44a*	36.68±0.40b*	0.013*
At 120min.	36.7±0.48	36.8±0.44a*	36.65±0.40b*	0.022*

**Table 5:** Temperature changes; P-value>0.05 NS; \*p-value <0.05, a: significant difference with group I (Fixed dose of ondansetron), b: significant difference with group II (Weight Adjusted ondansetron).



**Fig. 4:** Temperature changes (°C).

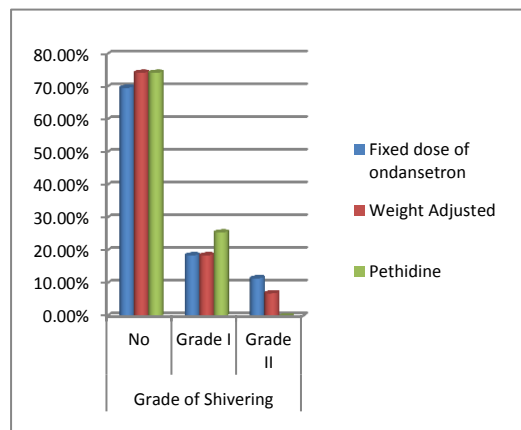
There were no statistically important differences in the duration of surgery between the groups. As seen in Table 6, shivering was found in 13 patients (30.2 %) in the first group (FDO), 11 patients (25.6 %) in the second group (WAO), and 11 patients (25.6 %) in the third group (PC), all of whom complained of grade I shivering, but there was no statistically significant difference between the groups. In contrast to the second group (WAO), the magnitude of shivering (grade II) was greater in the first group (FDO) (11.6 %) 5 patients (7.0 %) 3 patients, as regard to the start of shivering This table illustrates a statistically significant difference between groups. Shivering was maximally delayed in the control group (after 39.27±3.35 minutes), earlier in the first group FDO (after 29.92±7.68 minutes), and began later in the WAO group (after 33.55±4.76 minutes). Shivering duration was significantly longer in the (FDO) group than in the (WAO) group, with the shortest time in the (PC) group. As shown in Table 6 and Figures 5 and 6, respectively.

Parameters	Fixed dose of ondansetron (n=43)	Weight Adjusted (n=43)	Pethidine (n=43)	Test	p-value
<b>Duration of surgery (min)</b>					
Mean±SD	62.44±4.11	61.72±4.43	63.30±3.68	F=1.615	0.203
<b>Grade of Shivering</b>					
No	30 (69.8%)	32 (74.4%)	32 (74.4%)	x <sup>2</sup> =5.502	0.240
Grade I	8 (18.6%)	8 (18.6%)	11 (25.6%)		
Grade II	5 (11.6%)	3 (7.0%)	0 (0.0%)		
<b>Time of onset (min)</b>					
Mean±SD	29.92±7.68	33.55±4.76	39.27±3.35ab*	F=8.019	0.002*
<b>Duration (min)</b>					
Mean±SD	21.85±6.38	17.64±2.98a*	16.45±2.07a*	F=5.067	0.012*

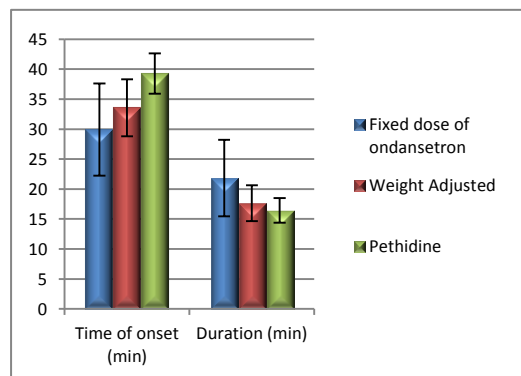
**Table 6:** Using: F-One Way Analysis of Variance; x<sup>2</sup>: Chi-square test

Post HOC test: LSD: a: significant difference with group I (Fixed dose of ondansetron); b: significant difference with groupII (Weight Adjusted ondansetron)

P-value >0.05 NS; \*p-value <0.05 S.



**Fig. 5:** Grade of shivering.



**Fig. 6:** Time of onset and duration of shivering.

## DISCUSSION

Shivering during caesarean sections is a major source of concern for pregnant women, and extending incisions has been found to aggravate wound soreness and slow tissue repair. Shivering raises oxygen consumption and metabolism by 40 to 120%. It also induces catecholamine release,

tachycardia, increased heart activity, and hypertension.<sup>3</sup>

The key finding of the study was that ondansetron at 0.1 mg/kg reduced shivering following spinal anaesthesia compared to a fixed 4 mg ondansetron dose, however this difference was not statistically meaningful. Shivering was significantly less common when 0.1mg/kg ondansetron was delivered versus 4mg. The intervention group averaged 8.1mg, according to the study. Previously, ondansetron was used in different doses up to 8mg to minimize shivers under anaesthesia.

Weight-based dosage was justified on the grounds that physiological changes in pregnant women, such as increased total body water and fat composition, contribute to better drug metabolic rates. If albumin concentration falls, medication binding falls and total free concentrate rises. Increased renal tubular flow of blood and glomerular filtration may result in more rapid medication clearance. Those variances may result in an incorrect adjustment of the drug's dosage (underdosing or overdosing).<sup>12</sup>

A weight-adjusted dose of 0.1 mg/kg ondansetron was found to be more effective in combating postoperative shivering than pethidine (the ideal anti-shivering medication), with less postoperative patient anxiety (due to nausea, vomiting, and pethidine-aggravated pruritis) and a concurrently shorter hospital stay. While headache occurred more frequently in the Ondansetron groups than in the pethidine groups, it was not common (statistically insignificant) and did not cause annoyance or prolong hospitalisation.

A meta-analysis of 905 individuals undergoing surgery from eight randomised controlled studies found that 4mg and 8mg ondansetron significantly reduced the prevalence of shivering.<sup>13</sup>

Ejiro BA et al. already compare low-dose ondansetron (4 mg) against tramadol Vs placebo to reduce shivers under spinal anaesthesia in caesarean deliveries in a related trial. Shivering was recorded in 20% of patients in the ondansetron group, compared to 16.7% of patients in tramadol group and 53%

in placebo group patients. In terms of preventing shivering, ondansetron 4 mg was shown to be comparable to tramadol. The findings supported the findings of the first group in our investigation, which obtained 4mg. Shivering was reported by 30% of our study participants.<sup>8</sup>

Powell RM and Buggy DJ investigated the effects of low ondansetron (4 mg) versus high ondansetron (8 mg) on shivering during general anaesthesia. Shivering was reported by 33% and 15% of subjects, respectively. Shivering differed by 18% between the two groups. This was consistent with the findings of this study, which found that shivering occurred in 23.3 % of people given a weight-adjusted dose of 0.1 mg/kg ondansetron and 30.2 % of people given a fixed dose of 4 mg ondansetron. The difference was 6.9 %. The difference between the two groups was not statistically relevant in either sample.<sup>14</sup>

Furthermore, Browning et al. observed a difference in the degree of shivering between placebo and 8 mg ondansetron. This is in contrast to current study, which found a significant difference between the low fixed 4 mg group and the control group (pethidine group). Browning et al's shivering classifications differed from the current study in that they defined grade one as piloerection and peripheral vasoconstriction but no muscle activation. This is a common physiological reaction that is frequently unrelated to clinically significant shivering. It could explain not just the difference among placebo vs 8mg ondansetron, but also the higher prevalence of severe shivering.<sup>16</sup>

In a systematic investigation, Bonnet et al. discovered that low and high dosages of ondansetron are effective in reducing shivering caused by intrathecal opioids.<sup>17</sup>

In the current study, a modest dose of 4mg ondansetron reduced shivering by 30.2 % in a weight-adjusted dose comparable to 23.6 %. This was, indeed, not statistically significant. This can be transferred into normal hospital care by employing intrathecal fentanyl in the current investigation. Intrathecal fentanyl has also been proven to minimise shivering in parturient women undergoing caesarean section under spinal and epidural anaesthesia. The prevalence of pruritus was statistically equivalent between the modified weight dose and the fixed dose, with only one patient (2.3 p%) developing pruritus compared to three patients (6.9 % ) in the WAO group with a higher prevalence of pruritus, and seven patients (16.3 %) in the control group (pethidine group) who developed patient dissatisfaction.

Ondansetron is a 5-hydroxytyptamine (5-HT) receptor antagonist that is frequently used to prevent and treat PONV. The specific mechanism of ondansetron's antishivering action is unknown. Ondansetron's most commonly reported side effect is headache, but a weak 5-HT1 antagonistic impact might induce headache in susceptible individuals, such as migraine patients and post-operative patients who are sensitive to withdrawal due to fasting general anaesthetic requirements. This could explain

why the WAO group had more headaches than the FDO group.<sup>18</sup>

#### The limitations of the study;

- 1- There is no assessment of the effect of worry on shivering or the symptoms that shivering can induce.
- 2- The study comprised a small number of individuals with similar socioeconomic backgrounds, which may restrict the generalizability of the findings.
- 3- It is applied only on pregnant patients, to be applied on various surgeries.

### CONCLUSION

A weight-adjusted dose of onansterone of 0.1 mg/kg reduced the incidence and severity of spinal anaesthesia shivering after caesarean births, with fewer adverse effects except haedach and a shorter hospital stay for patients.

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