# Comparison of weight-adjusted dose versus fixed dose ondansetron in preventing shivering following spinal anaesthesia for caesarean deliveries

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## Abstract

**Background:** Spinal anaesthesia is an effective regional anaesthesia technique, which is preferred in almost 86% of caesarean sections in the United States and United Kingdom. Eighty percent of caesarean sections done at the Aga Khan University hospital are under spinal anaesthesia. Shivering is a common complication of spinal anaesthesia, it occurs in 40%-64% of patients after neuraxial anaesthesia. Shivering may cause maternal and fetal hypoxemia, maternal discomfort and a problem to the anaesthesiologists when it comes to monitoring the patient during caesarean sections. Ondansetron a 5-HT3 receptor antagonist is effective in treatment and prevention of post-spinal anesthesia shivering. In published studies, use of a fixed dose in patients with different weights, masked the dose effect ondansetron in preventing shivering, such that not adjusting the dose according to the weight of patients' resulted in a higher occurrence of shivering. No study has compared different doses of ondansetron in preventing shivering in parturient women who have had spinal anaesthesia for caesarean section.

**Objectives:** To determine if a weight-adjusted dose is better than a fixed dose of ondansetron in preventing shivering following spinal anesthesia for caesarean delivery.

**Method:** This was a randomized, double-blinded controlled trial of 124 women scheduled for elective caesarean surgery. The women were randomized into two equal groups. The intervention group received intravenous ondansetron weight adjusted dosing at 0.1mg/kg and the control group received a fixed dose of 4mg before spinal anesthesia. The occurrence and severity of shivering and other outcomes, such as headache, pruritus were assessed and recorded during the surgery and post-operative period.

**Results:** A total of 124 patients were included in the study. Social demographic data and baseline vital signs did not differ significantly between the groups. Shivering was observed in 14 patients (22.6%) in the control group that received 4mg ondansetron and 7 patients (11.3%) in the intervention group that had 0.1mg/kg of ondansetron, but there was no statistical difference between the groups (p- value 0.090). The severity of shivering was greater in the control group compared to intervention group where patients who developed grade two shivering were 8.1% to 0% respectively. (P value 0.047).There was no difference in the occurrence of pruritus between the two groups. No patient required treatment for very severe shivering.

**Conclusion:** This study, found that ondansetron weight adjusted dose at 0.1mg/kg, reduced the severity of shivering when compared to a fixed dose ondansetron at 4mg.

**Keywords:** Weight-adjusted dose,fixed dose ondansetron, shivering, spinal anaesthesia, caesarean deliveries.

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## Introduction

Spinal anaesthesia has found to be an effective regional technique that is preferred in almost 86% of caesarean sections[1]. Shivering is an involuntary oscillatory skeletal muscle activity, involving one or several muscle groups. It is a reflex response to increase the production of body heat through muscle contraction[1–3]. A published review

of 21 articles showed an incidence of shivering ranging from 40%-64% with median range of 55% after neuraxial anaesthesia[4].

Shivering is a common cause of discomfort to pregnant women during caesarean sections and it has been shown to aggravates wound pain and interfere with wound healing by stretching incisions. Shivering also causes an increase in oxygen consumption and metabolic rate by 40%-120%.It promotes catecholamine release, which leads to tachycardia, increases cardiac output and hypertension.[5,6]

Shivering has been correlated with an increase in maternal and fetal hypoxemia, as well as increase in the occurrence of maternal myocardial ischemia. Shivering also increases intraocular and intracranial pressures and it's a troublesome side effect to the anesthesiologist because it interferes with blood pressure monitoring and causes artifacts in ECG and pulse oximetry.[1,6,7]

Vasodilatation caused by the regional technique contributes to cutaneus heat loss by causing the re-distribution of heat from the core thermal compartment to the peripheral thermal compartment, where most of it is lost to the enviroment. Core temperatures drops by a range of 0.5°C to 1°C after induction of neuraxial anesthesia. This triggers vasoconstriction and shivering above the level of block[8,9].

Several drugs have been shown to be effective in preventing post anaesthesia shivering in general anaesthesia. But few studies have been done on parturient women undergiong cesarean sections.Tramadol,pethidine,nalbuphine and clonidine have been used in prevention of post anesthesia shivering, but the various side effects of these drugs limit the anesthesiologist from administering these drugs due to harm to the fetus and mother before delivery[10,11-17].

Ondansetron a 5-HT3 receptor antagonist is used safely in pregnancy for its anti-nausea and anti-emetic effects. No evidence of harm or an increase in adverse fetal outcomes has been reported in pregnant women exposed to ondansetron throughout the course of pregnancy[18,19]. Other/span> uses of ondansetron include prevention and treatment of post-operative nausea and vomiting and treatment of opioid induced pruritus during regional anesthesia. Ondansetron has a high therapeutic index meaning that it has minimal toxic effects when given at high doses as in the case of preventing and treatment of nausea and vomiting during chemotherapy. Common adverse effects include headache, constipation, malaise/fatigue. Rapid administration can cause hypotension and tachycardia[20]. Ondansetron has been used to prevent shivering in general and regional anaesthesia. Drugs that lower shivering, can exert their effect by disturbing the central body temperature, so 5-HT antagonist receptors such as ondansetron can be effective in reducing shivering after surgery. The mechanism of action could be related to the inhibition of serotonin reuptake on the pre-optic anterior hypothalamic region. 5-HT3 receptors may also influence both heat production and heat loss pathways[21,24].

Weight seems to affect the dose dependent effect of ondansetron in preventing shivering. Low dose ondansetron 4mg, was shown to be as effective as 8mg in patients who weighed 50kg[10]

There is a paucity of studies done where ondansetron was used to prevent shivering after spinal anaesthesia for cesarean sections. No study has compared different doses of ondansetron in the prevention of shivering post spinal anaesthesia. This study sought out to investigate whether a weight adjusted dosing of ondansetron, was more effective than a fixed dose in preventing shivering after spinal anesthesia during caesarean sections.

The study was designed to compare the effectiveness of prophylactic ondansetron weight adjusted and fixed dose in the prevention of post anaesthesia shivering following spinal anaesthesia for caesarean delivery. Our study question was: is weight adjusted ondansetron dosing more effective than fixed dosing in preventing post spinal anesthesia shivering in patients undergoing caesarean delivery?

We hypothesized that there is no difference in the occurrence of post-anaesthesia shivering between patients who receive a prophylactic weight-adjusted or fixed dose ondansetron, before spinal anesthesia for caesarean section. Our primary objective was to compare the effectiveness of a weight adjusted dose and a fixed dose ondansetron in preventing shivering, post-spinal anaesthesia for caesarean sections. Our secondary objectives were to compare the grade of shivering between the groups and occurrence of pruritus.

**Methods**

The study was performed following approval from the department of anaesthesia and the Ethical and scientif-

ic review Committee at the Aga Khan University, East Africa. Patients were recruited after having signed an informed consent, which clearly stated that it is a research study being conducted and that their information will be kept confidential. They would receive health care as all other patients who come to theatre, they would not be denied care if they declined to participate in the study. For those who did not understand English, the above information was explained in Swahili. An explanation of the study procedure was given to the patient both verbally and in written form. It was made clear that, there was no direct benefit and no added expenses to the patient arising from participation in the study, but that the results could be used to change local practice in the future.

The patients voluntarily signed the consent form and were recruited in the pre-anesthesia clinic or maternity ward before coming to the operating theatres. The operation did not commence until adequate sensory block was established prior to incision. The patients were free to withdraw from the study at any stage and were to be accorded standard care. This was a prospective double-blinded randomized control trial, where the patient and the anaesthesiologist were blinded as to what dose of ondansetron was administered. The study population included patients admitted for cesarean deliveries at Aga Khan University Hospital, under spinal anaesthesia. The sample population included American Society of Anesthesiologists (ASA) 1 and 2 gravid patients going to theatre for cesarean deliveries under spinal anaesthesia.

All healthy patients over 18 years scheduled for caesarean deliveries under spinal anaesthesia were included in the study. Reasons for exclusion from the study were:

1. Pre-operative use of ondansetron, tramadol, pethidine or clonidine.
2. Allergy or intolerance to ondansetron.
3. Presence of shivering prior to administration of spinal anaesthesia

We based our sample size and power computations on non-inferiority/superiority testing for two sample parallel proportions. For the current study, we assumed a 55% incidence in proportion of post-anesthesia shivering from the average incidence from studies done in the United States and United Kingdom[4]. Furthermore, for the weight-adjusted dose, we are willing to accept incidence proportion of post-anesthesia shivering that is 18% lower than for the fixed dose. This translates to a superiority margin of 18%. Based on these conservative parameters, at an alpha of 0.05, power of 0.80 and sample allocation ratio of 1, we determined that we required 62 patients in each treatment arm, to make a total of 124 patients. Study participants were recruited from the pre-operative anaesthesia clinic (during the pre-anaesthetic review) and the in-patient maternity ward. Flow diagram of patent participation is shown in figure 1.

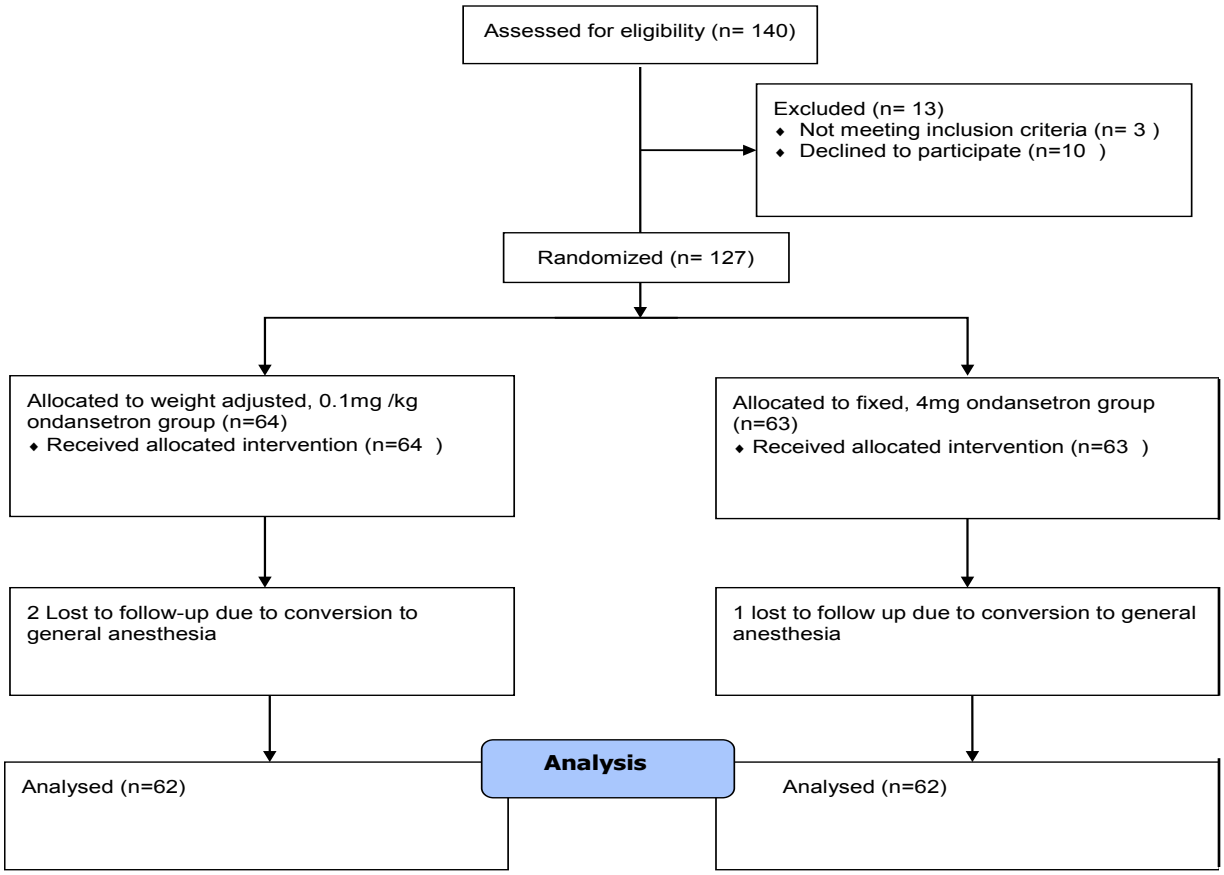


**Figure 1:** Flow of patient distribution

Simple randomization was done using a computer program; the principal investigator generated a random sequence of numbers. Each of the random numbers were sequentially assigned to either;

Group 1; fixed dose of ondansetron 4mg

Group 2; weight adjusted dose at 0.1mg/kg

The study drug was prepared by a pharmacist not involved in any other aspect of the study in identical 10 mls syringes labelled study drug. The pharmacist held the code for randomization and group allocation. The drug was then presented to the anaesthesiologist and administered before spinal anaesthesia. The presentation was similar; the only difference was the concentration of the drug in the syringe. Patients scheduled for caesarean section were randomized into two equal groups. The control group received a prophylactic fixed dose 4mg ondansetron and the intervention group received a prophylactic weight adjusted dose of 0.1mg/kg before placement of spinal anesthesia. The anaesthesiologist conducting the procedure received together with the data entry form the study drugs that was prepared in pharmacy. On arrival to the operating theatres, monitoring was carried out with an automated non-invasive blood pressure measurement, electrocardiography and pulse-oximetry for baseline cardiovascular parameters. Core temperature was also taken in the base line parameters and then every 5min until end of surgery, using a Temporal Thermometer (TAT-2000c T)

After a local infiltration of 2ml 2% Lidocaine solution, a midline puncture with a 25 French gauge pencil point

needle was performed at L3/L4 interspace, with the patient in the sitting position. After obtaining free flow of cerebrospinal fluid (CSF), 1.8mls of bupivacaine and 15ug fentanyl was administered. The patient was then turned supine with a 15 degree left lateral tilt. All patients received crystalloids at room temperature at 20mls/kg. The sensory block level to both light touch and temperature was checked and modified Bromage motor score recorded. Surgery commenced as soon as the sensory block reached the desired level. Exposed skin was covered with a blanket during preparation and after establishing spinal anaesthesia.

Shivering was graded by the 4-point Bedside Shivering Assessment Scale developed and validated by Badjatia and colleagues[28]:
0= None,
1= Mild fasciculation in face or neck,
2= Visible tremor in more than one muscle group,
3 =Shivering involving whole body.
This was checked every 5 minutes during surgery shivering above grade 3 or causing distress was to be managed with i.v pethidine 25mg and any intervention recorded. Intra-operative data was collected by the anesthesiologist administering anesthesia or research assistant (both blinded to patients' group allocation) using the data collection form. Upon collection, data was entered into the statistical software (SPSS. Inc. Chicago, Illinois, USA) on the same day in a coded form and saved, awaiting analysis. The data was verified and In the case of missing data, a follow up to collect the missing data from the patient's medical records was done. In case of conversion to general anesthesia, the patient data was not be analyzed. Standard precautions were taken to respect the privacy of the patients whose data was collected and analyzed in this study. A unique identifier number was used to identify the patient's data. However, in the course of monitoring data quality and adherence to the study protocol only the study supervisors were allowed to refer to the recruited patient's medical records. After analysis, the data was stored in soft copy with the research support unit. Hard copies were also stored in the supervisors' office.

Data analysis was conducted using SPSS (SPSS. Inc. Chicago, Illinois, USA). Descriptive statistics were used to compare patient's characteristics in terms of age, weight, temperature, heart rate and blood pressure. Paired sample T test was used to compare if the two groups were statistically different. Bivariate analysis was used to test for correlation between elective and urgent cesarean sections between intervention and control groups. The data was summarized as means and presented in table form. Two-way ANOVA analysis was used to test associations for shivering, shivering grading, pruritus and sensory level between intervention and control groups. Data was presented as mean +/- standard deviation unless otherwise specified. P≤ 0.05 was considered statistically significant.

**Results**

A total of 124 patients were included in the study, 62 patients in each arm. Social demographic data and baseline vital signs did not differ significantly between the groups as shown in table 1.

**Table 1:** Demographic data

| Parameter | Intervention n=62 | Control n=62 | P value |
|---|---|---|---|
| **Age** | 30.1 ± 4.6 | 31.5 ± 5.2 | 0.110 |
| **Weight** | 80.7 ± 9.1 | 81.1 ± 10.1 | 0.819 |
| **Elective** | 41.3% | 52.4% | 0.761 |
| **Urgent** | 57.1% | 46.0% | 0.512 |

We used paired sample T test to test for association between mean age, weight for both intervention and control. In both cases, there was no association. P values > 0.05. Bivariate analysis used to test for correlation between elective and urgent caesarean sections between intervention and control group. There was no correlation. P values >0.05.The pre-operative baseline parameters and block heights were similar in both groups. This is shown in table 2 and 3 respectively. The temperature before spinal anesthesia was comparable between the two groups. There was gradual reduction in temperature in the two groups that was maximum at 30 min .The intervention group had a higher drop in core temperatures. This is illustrated in figure 2 below.

**Table 2:** Pre-operative baseline signs

| Parameter | Intervention n =62 | Control n=62 | P value |
|---|---|---|---|
| **Pulse** | 91 ± 13.0 | 91.61 ± 12.2 | 0.811 |
| **Systolic** | 118.6 ± 12.6 | 118.7 ± 14.0 | 0.980 |
| **Diastolic** | 73.2 ± 10.6 | 74.0± 12.3 | 0.749 |
| **MAP** | 82.8± 18.2 | 87.7 ± 14.6 | 0.093 |
| **Baseline Temperature** | 37.8 ± .54 | 37.0+ 0.58 | 0.070 |

**Table 3**: Block height

| Block level | Intervention n=62 | Control n=62 | P value |
|---|---|---|---|
| **T4** | **46.8 %( 29)** | **62.9 %( 39)** | **0.301** |
| **T5** | **33.9 %( 21)** | **19.4 %( 12)** | |
| **T6** | **19.4 %( 12)** | **16.1 %( 10)** | |
| **T7** | **0 %( 0)** | **1.6(1)** | |

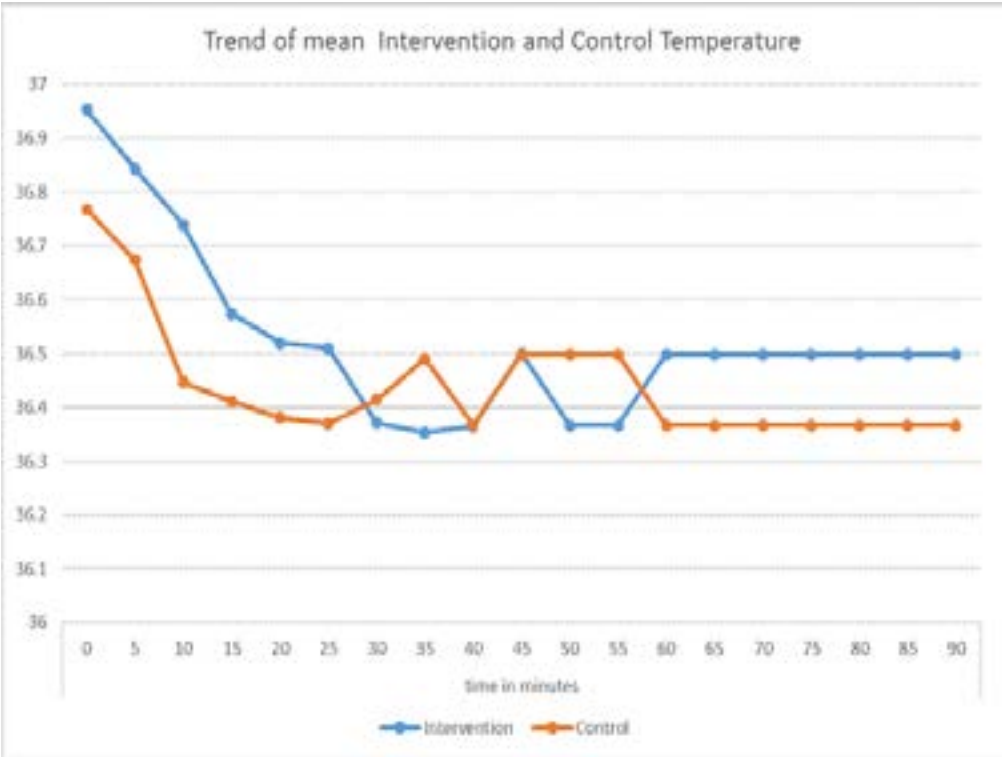


**Figure 2:** Temperature Trend

Shivering was observed in 14 patients (22.6%) in the control group that received 4mg ondansetron and 7 patients (11.3%) in the intervention group that had 0.1mg/kg of ondansetron, but there was no statistical difference between the groups (p- value 0.090). This is shown in table 4 and illustrated in figure 3.

**Table 4:** Incidence of shivering

| Shivering | Intervention n=62 | Control n=62 | P value |
|---|---|---|---|
| Occurrence | 11.3 %( 7) | 22.6% (14) | 0.090 |
| No occurrence | 88.7 (52) | 77.4 (48) | |

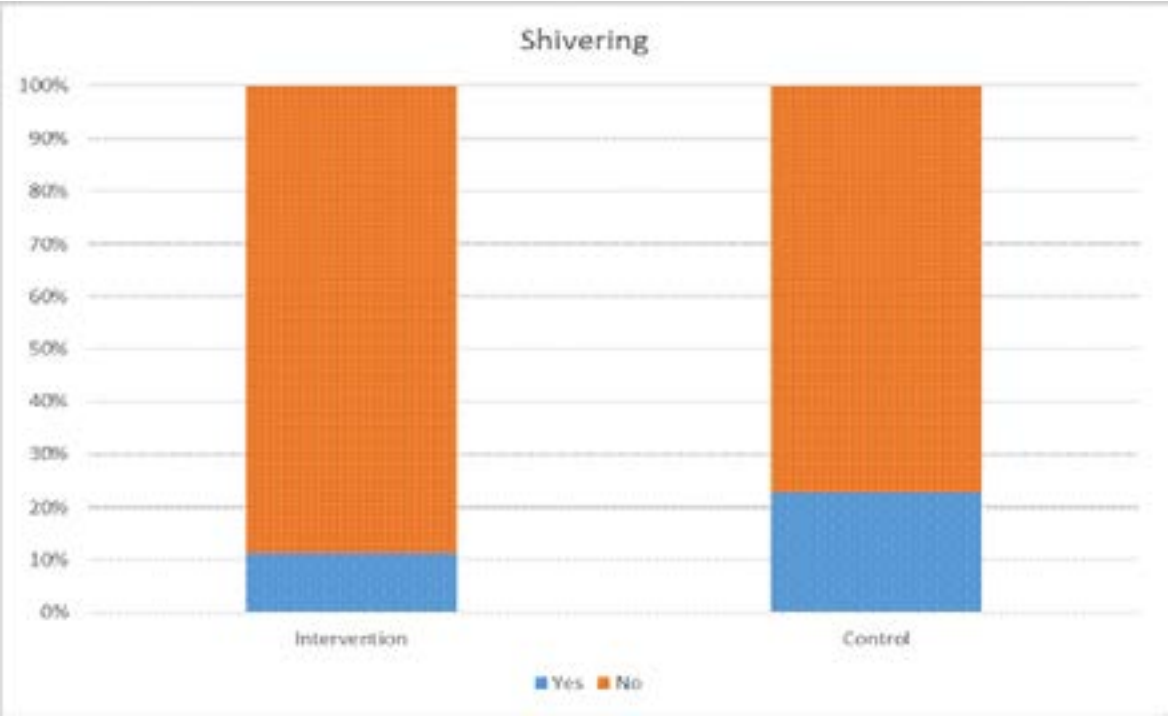


**Figure 3:** Occurrence of shivering

The intervention group had significantly less patients who developed more than grade one shivering compared to control group, 0% to 8.1 % respectively. (P value 0.047) as illustrated in table 5 and figure 4.

**Table 5:** Severity of shivering

| Severity of shivering | intervention | control | P value |
|---|---|---|---|
| Grade 1 | 11.3% (7) | 12.9% (8) | |
| Grade 2 | 0% (0) | 8.1% (5) | 0.047 |

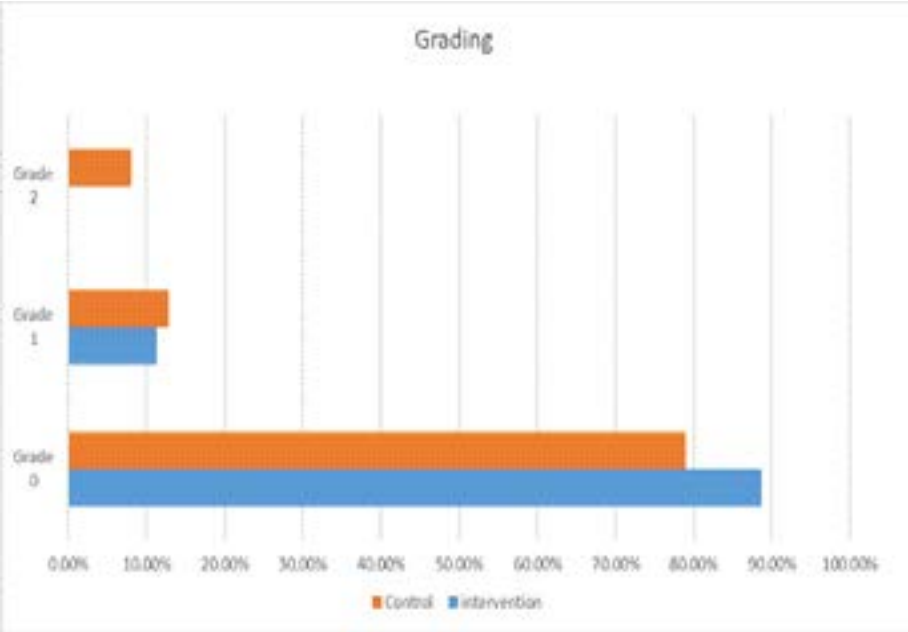


**Figure 4:** Grading of severity of shivering

Occurrence of pruritus was less in the intervention group compared to the control group at 4 patients (6.5 %) to 7 patients (11.3 %) respectively. However, the occurrence was comparable statistically. (P-value 0.398) as illustrated in table 6 and figure 5.

**Table 6:** Incidence of pruritus

| Pruritus | Intervention | Control | P value |
|---|---|---|---|
| **No Pruritus** | **93.5% (58)** | **88.7% (55)** | **0.398** |
| **Presence of pruritus** | **6.5% (4)** | **11.3% (7)** | |

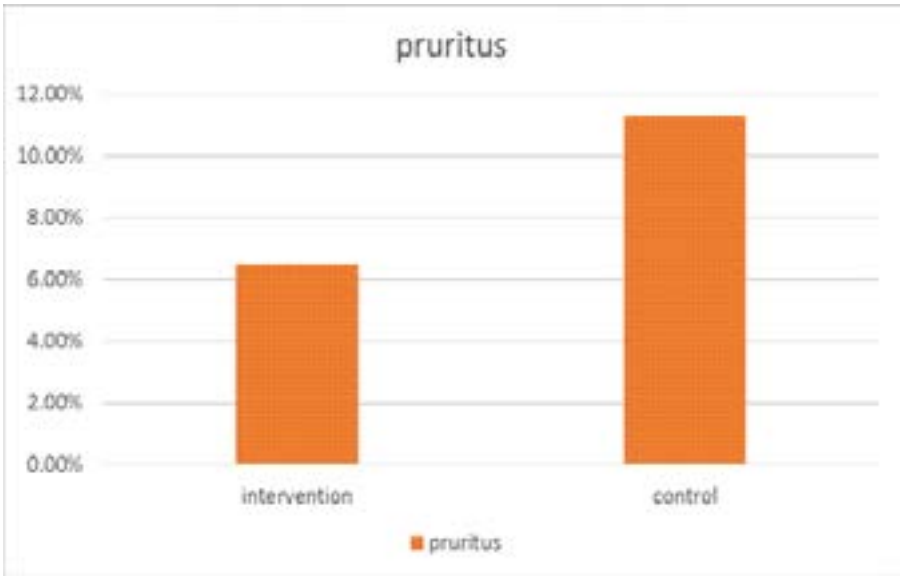


**Figure 5:** Occurrence of pruritus

**Discussion**

The major findings in this study was that ondansetron at 0.1mg/kg, reduced the occurrence of shivering compared to a fixed dose 4mg,after spinal anaesthesia but this was not statistically significant. The severity of shivering when 0.1mg/kg was administered was less compared to 4mg group, and this was statistically significant. Ondansetron has been used in previous studies in doses ranging from 4mg to 8mg, to prevent shivering occurring during regional and general anesthesia, the average dose in our intervention group was 8.1mg[17,21-24]. The rationale for using a weight based dosing was that in pregnant women there are physiological changes that include; increase in total body water and body fat composition that lead to an increase the volume of distribution of the drug. Reduction in albumin concentration may reduce the drug binding and increase total free drug concentration. Increase in renal blood flow and glomerular filtration may lead to a rapid drug excretion. These changes may lead to drug under dosing or over dosing. A weight-adjusted dose at 0.1mg/kg was seen to be effective in treatment of post-operative shivering.

From a meta-analysis by K He et al both 4mg and 8mg ondansetron were found to reduce the occurrence of shivering significantly, they evaluated a total of 905 patients going for surgery from 8 randomized control trials[25]. Ejiro et al carried out a similar study and compared low dose ondansetron at 4mg with tramadol and placebo in preventing shivering post spinal anesthesia for cesarean sections. The incidence of shivering was 20%, in the ondansetron group compared to 16.7% and 53% in the tramadol and placebo group respectively. The conclusion was that at 4mg ondansetron was comparable to tramadol in preventing shivering. The results tallied with what was found in the control group arm of our study where 4mg was administered. The occurrence of shivering was at 22.6% in our study[17].

Powel compared a low dose ondansetron at 4mg and a higher dose of 8mg to reduce the occurrence of shivering during surgery under general anesthesia. Results showed an occurrence of shivering of 33% and 15% respectively. This was an 18% difference in the occurrence of shivering between the groups. This was comparable to our study, where the occurrence of shivering was 11.3% in the weight adjusted dose of 0.1mg/kg compared to 22.6% in the fixed dose 4mg.The difference was 11.3%. In both studies, the difference in the results in the two groups were not statistically significant[21].

Browning et al compared 8mg ondansetron to placebo in preventing shivering after combined spinal epidural anesthesia. They found an occurrence of 47% in placebo group compared to 42% in the ondansetron group. Compared to our study where 0.1mg/kg ondansetron was ad-

ministered the occurrence was less at 11.3%. Browning concluded that ondansetron does not reduce the occurrence of shivering compared to placebo[23]. Browning also did not find a difference in the severity of shivering between placebo and 8mg of ondansetron. This differed from our study where 0.1mg/kg ondansetron reduced the severity of shivering significantly compared to a fixed dose at 4mg. Although there was no statistical difference in the severity of shivering between 8mg ondansetron and placebo, the number of patients who required clonidine for treatment of severe shivering were more on the placebo group compared to 8mg group. Three patients in the placebo group compared to none in the ondansetron group. This study differed from our study in the grading of shivering where grade one was termed as the presence of piloerection and peripheral vasocnstriction without muscle activity. This is a normal physiological response and does not necessarily reflect a clinically important shivering response. This may have led to an increased observation of severe shivering and the lack of difference between placebo and 8mg ondansetron[23].

The current study found a reduction in the incidence of shivering in the weight-adjusted dose compared to the low dose 4mg ondansetron, 22.6% compared to 11.6% respectively. However, this was not statistically significant. The reason for this could be the use of intrathecal fentanyl in our study, as it is the standard of care in the hospital. Intrathecal fentanyl is shown to reduce the occurrence of shivering by up to 50% in parturient women going for cesarean section under spinal and epidural anesthesia[26].The occurrence of pruritus between the higher weight adjusted dose and fixed lower dose was shown to be similar statistically, however the higher dose had fewer patients who developed pruritus. 6.5% compared to 11.5% respectively with a p value of 0.398. From a systematic review by Bonnet et al both low and high dose ondansetron were effective in preventing shivering due to intrathecal opioids[27].

**Strengths of the study**

After a rigorous literature review, it appears that this is the first prospective randomized controlled study that has compared different doses of ondansetron in preventing shivering in parturient women who have had spinal anaesthesia for caesarean section. Therefore, this study will add to the body of literature and knowledge on prevention of shivering following spinal anaesthesia given for caesarean section and probably form a basis for many other studies in the future.

**Limitations of the study**

We did not factor the effects of anxiety on shivering which could have a similar presentation. The study was conducted at a single center and involved a relatively small number of patients; this may affect the generalizability of the results of this study. The calculation of the power of the current study was based on small and not large randomized clinical trials due to paucity of published studies on use of ondansetron in parturient women going for caesarean sections.

**Conclusion**

On the basis of the results of this study, ondansetron weight adjusted dose at 0.1mg/kg, reduced the severity of shivering when compared to a fixed dose ondansetron at 4mg in patients undergoing spinal anaesthesia for caesarean delivery.

**Conflict of interest**

None declared.

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