PREVENTION OF POST-ANAESTHETIC SHIVERING UNDER SUB-ARACHNOID BLOCK FOR CAESAREAN SECTION: A RANDOMISED, CONTROLLED STUDY COMPARING TRAMADOL VERSUS ONDANSETRON.

BY

DR NNACHETA, TIMOTHY EKENE
[M.B.,B.S (NAU); DA(WACS)]

A DISSERTATION SUBMITTED TO THE NATIONAL POSTGRADUATE MEDICAL COLLEGE OF NIGERIA IN PART FULFILLMENT OF THE REQUIREMENTS FOR THE FELLOWSHIP OF THE FACULTY OF ANAESTHESIA

MAY, 2017
ATTESTATION BY THE SUPERVISORS

THE STUDY REPORTED IN THIS DISSERTATION WAS DONE BY THE CANDIDATE UNDER OUR SUPERVISION. WE HAVE ALSO SUPERVISED THE WRITING OF THE DISSERTATION.

[Signature] 09/05/2017
DR AJUZIEOGU OBINNA V.
CONSULTANT ANAESTHETIST / SENIOR LECTURER,
UNIVERSITY OF NIGERIA TEACHING HOSPITAL / COLLEGE OF MEDICINE, UNIVERSITY OF NIGERIA, ENUGU CAMPUS,
ENUGU NIGERIA.

FMCA (NOV. 2007)
DATE: 09/05/2017

[Signature] 9/5/17
DR EKWUEME OSAELOKA C.
CONSULTANT PHYSICIAN / SENIOR LECTURER
UNIVERSITY OF NIGERIA TEACHING HOSPITAL / COLLEGE OF MEDICINE, UNIVERSITY OF NIGERIA, ENUGU CAMPUS,
ENUGU NIGERIA.

FMCPH (NOV. 2004)
DATE: 9/5/17
CERTIFICATION BY HEAD OF DEPARTMENT

I affirm that this dissertation titled "prevention of post-anaesthetic shivering under sub-arachnoid block for caesarean section: a randomised, controlled study comparing tramadol versus ondansetron" was carried out by Dr Nnacheta Timothy Ekene and supervised by consultants in the department of Anaesthesia, University of Nigeria Teaching Hospital Enugu. This is in part fulfillment of the requirement for the award of the fellowship of the National Postgraduate Medical College of Nigeria.

Dr Ajuzieogu Obinna
Head of Department,
Department of Anaesthesia,
University of Nigeria Teaching Hospital,
Ituku-Ozalla Enugu.
DECLARATION BY THE CANDIDATE

I hereby declare that this work is original, unless otherwise acknowledged. The work has not been presented to any other college for a fellowship, nor has it been submitted elsewhere for publication.

[Signature]

9/05/2017

Dr T. E. Nnacheta.

May, 2017
DEDICATION

This work is dedicated to all women who undergo caesarean section and all the medical staff who toil relentlessly to ensure safe delivery.
ACKNOWLEDGEMENT

I express appreciation to all my trainers in the residency program. I will always be indebted to Dr H.A Ezike, Dr V.O Ajuzieogu, Dr C.O Ekwueme, Dr T. Onyeka, Dr A. Amucheazi, Dr O.M Nwoke, Dr E. Onyia, Dr E.E Arum, Dr A. Onyekwulu, Dr P. Ufoegbunam, and Dr C. Onuora. My special gratitude to Drs H.A Ezike and V.O Ajuzieogu who particularly helped me to decide on this topic. Drs V.O Ajuzieogu and O.C Ekwueme have always been my tutors and supervisors every bit of the way throughout this work. They are wonderful mentors.

Let me also recognize my colleagues in the department of Anaesthesia for their immense contribution to the success of this work; the theatre pharmacy staff for making the consumables promptly available, and the nursing staff for their tenderly care of the patients.

My special thanks go to members of my family who have always loved and supported me in all my endeavours.
# ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANOVA</td>
<td>Analysis of Variance</td>
</tr>
<tr>
<td>APGAR</td>
<td>Appearance, Pulse, Grimace, Activity and Respiration.</td>
</tr>
<tr>
<td>ASA</td>
<td>American Society of Anesthesiologists</td>
</tr>
<tr>
<td>BJR</td>
<td>Bezold-Jarisch Reflex</td>
</tr>
<tr>
<td>ECG</td>
<td>Electrocardiography</td>
</tr>
<tr>
<td>Fig.</td>
<td>Figure</td>
</tr>
<tr>
<td>G</td>
<td>Gauge</td>
</tr>
<tr>
<td>Group O</td>
<td>Ondansetron group</td>
</tr>
<tr>
<td>Group S</td>
<td>Saine (placebo) group</td>
</tr>
<tr>
<td>Group T</td>
<td>Tramadol group</td>
</tr>
<tr>
<td>iu</td>
<td>international units</td>
</tr>
<tr>
<td>I.V</td>
<td>Intravenous</td>
</tr>
<tr>
<td>JUTH</td>
<td>Jos University Teaching Hospital</td>
</tr>
<tr>
<td>Kg</td>
<td>Kilograms</td>
</tr>
<tr>
<td>MAP</td>
<td>Mean Arterial Blood Pressure</td>
</tr>
<tr>
<td>Mg</td>
<td>Milligrams</td>
</tr>
<tr>
<td>ML</td>
<td>Millilitres</td>
</tr>
<tr>
<td>N</td>
<td>Number</td>
</tr>
<tr>
<td>NIBP</td>
<td>Non-invasive Blood Pressure</td>
</tr>
<tr>
<td>ORT</td>
<td>Operating Room Temperature</td>
</tr>
<tr>
<td>SAB</td>
<td>Subarachnoid Block</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
</tr>
<tr>
<td>--------------</td>
<td>---------------------------------</td>
</tr>
<tr>
<td>SD</td>
<td>Standard Deviation</td>
</tr>
<tr>
<td>SPSS</td>
<td>Statistical Package for Social Sciences</td>
</tr>
<tr>
<td>TMT</td>
<td>Tympanic Membrane Temperature</td>
</tr>
<tr>
<td>UNTTH</td>
<td>University of Nigeria Teaching Hospital</td>
</tr>
<tr>
<td>5HT&lt;sub&gt;3&lt;/sub&gt;</td>
<td>5-Hydroxytryptamine</td>
</tr>
<tr>
<td>%</td>
<td>Percentage</td>
</tr>
</tbody>
</table>
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Title Page</td>
<td>i</td>
</tr>
<tr>
<td>Attestation by the Supervisors</td>
<td>ii</td>
</tr>
<tr>
<td>Certification by head of department</td>
<td>iii</td>
</tr>
<tr>
<td>Declaration by the Candidate</td>
<td>iv</td>
</tr>
<tr>
<td>Dedication</td>
<td>v</td>
</tr>
<tr>
<td>Acknowledgement</td>
<td>vi</td>
</tr>
<tr>
<td>Abbreviations</td>
<td>vii</td>
</tr>
<tr>
<td>Table of Contents</td>
<td>ix</td>
</tr>
<tr>
<td>List of Tables</td>
<td>xi</td>
</tr>
<tr>
<td>List of Figures</td>
<td>xii</td>
</tr>
<tr>
<td>Summary</td>
<td>1</td>
</tr>
</tbody>
</table>

## CHAPTER 1

Introduction  2
Objectives  5

## CHAPTER 2

Literature Review  6
Justification for the Study  24

## CHAPTER 3

Methodology  25

## CHAPTER 4

Results  32
**LIST OF TABLES**

Table I: Demographic Variables, Total Operating Times and Volumes of intravenous fluid 35

Table II: Baseline Vital Signs and Baseline Operating Room Temperatures 36

Table III: Peak Sensory Levels in the study groups 37

Table IV: APGAR scores of the Newborn in the study groups 38

Table V: Number of Patients with Shivering in the Study Groups 39

Table VI: Grades of Shivering in the Study Groups 40

Table VII: Intra-operative Bradycardia, Hypotension and Cumulative Ephedrine Consumption in the study groups 41

Table VIII: Prevalence of Sedation, Headache, Nausea and Vomiting in the groups 42

Table IX: Within-group Changes in the Mean Operating Room Temperatures 43
LIST OF FIGURES

Figure 1: Mean Tympanic Membrane Temperatures at Intervals 44
Figure 2: Prevalence of Intra-operative Hypothermia 45
SUMMARY

Shivering is a frequent, undesirable peri-operative event in patients undergoing caesarean delivery under spinal anaesthesia. Many drugs have been tried, with varying success rates, in preventing post-spinal shivering.

This was a prospective, randomized, placebo-controlled study comparing the effectiveness of single dose intravenous tramadol versus ondansetron in preventing shivering among women undergoing caesarean section under spinal anaesthesia. One hundred American Society of Anesthesiologists’ (ASA) class I-II patients undergoing elective or emergency caesarean section under spinal anaesthesia were randomly allocated into three groups: control group (group S, n=33), tramadol group (group T, n=33) or ondansetron group (group O, n=34).

Immediately after establishing spinal anaesthesia, patients in group S were given 4ml of 0.9% saline intravenously, patients in group T were given 50mg of tramadol (diluted to a volume of 4ml with sterile water for injection) intravenously while patients in group O were given 4mg of ondansetron (diluted to a volume of 4ml with sterile water for injection) intravenously. The patients were monitored and records of shivering, vital signs and adverse effects of the drugs were taken. Neonatal APGAR scores were also recorded.

Shivering occurred in a significantly less number of patients in group O than group T (5.9% versus 39.4%, p=0.001). There was no statistical difference in the incidence of shivering between groups T and S (39.4% versus 48.5%, p=0.460). Core body temperature was better preserved in group T than groups S and O. Cumulative ephedrine consumption was lowest in group O (42mg) compared to group T (54mg) or group S (102mg). There was no record of nausea and vomiting in group O as against 18.2% and 6.1% in groups T and S respectively. Less number of patients had sedation in group O (6, 12.6%) than group T (11, 33.3%). The newborn APGAR scores were similar across the three groups.

In conclusion, this study has demonstrated the superiority of ondansetron over tramadol in preventing post-anaesthetic shivering in women undergoing caesarean section under spinal anaesthesia.
CHAPTER 1

INTRODUCTION

Spinal anaesthesia is a widely-used and safe anaesthetic technique for caesarean section in both elective and emergency situations.\(^1\) This method of anaesthesia is however often associated with shivering: an undesirable, involuntary, oscillatory muscular activity.

Varying incidences of shivering following spinal anaesthesia have been reported in the literature. A low incidence (8.15\%) of shivering was reported by Luggya and colleagues\(^2\) among women undergoing caesarean section under spinal anaesthesia in Uganda. On the other hand, Giovani de Figueiredo\(^3\) recorded a relatively high incidence of 62.5\% shivering among women undergoing caesarean deliveries under spinal anaesthesia in Brazil. However, a median incidence of 55\% shivering following neuraxial anaesthesia was reported by Crowley and Buggy\(^4\) from a meta-analysis of 21 studies.

The precise aetiology of post-anaesthetic shivering is uncertain.\(^5\) It is thought that spinal anaesthesia-induced alteration of autonomic thermoregulation, with associated drop in core body temperature, together with the cold environment of the operating rooms are the major causal factors.\(^5,6\) However, shivering has been noted in normothermic patients and in patients whose core body temperatures have not dropped significantly.\(^7,8\) Shivering has also been reported following transfusion reactions, drug reactions, high grade fever, or infusion of contaminated intravenous fluids.\(^9\) Shivering, therefore, may not be purely a thermogenic reaction. Its relationship with body temperature remains inconsistent.\(^10,11\)

Irrespective of its aetiology, peri-operative shivering has a multitude of deleterious effects. Shivering makes patients uncomfortable.\(^12\) It also causes a marked increase (up to 500\%) in oxygen consumption.\(^13\) There is a tendency to have arterial hypoxaemia, increased cardiac output and increased risk of myocardial ischaemia during shivering.\(^14\) Shivering also increases intraocular and intracranial
pressures.\textsuperscript{15} Artifactual interference with intra-operative patient monitoring, increased wound pain, delayed wound healing, and delayed discharge from post-anaesthetic care are all complications of shivering.\textsuperscript{16,17}

Physical and pharmacological measures have been applied in the prevention and treatment of post-spinal shivering. The physical measures are essentially aimed at attenuating perioperative core hypothermia. They include: application of radiant heat, use of warm ambient air, use of heated blankets and use of warm intravenous fluids. These physical methods are however cumbersome, expensive and yield limited success in preventing shivering.\textsuperscript{5}

Pharmacological agents that have been used in the prevention or control of shivering include opioids such as pethidine, tramadol and butorphanol\textsuperscript{18}. Others are 5HT\textsubscript{3} receptor antagonists such as ondansetron, N-methyl-D-aspartate (NMDA) antagonist such as ketamine, magnesium sulphate and alpha\textsubscript{2} receptor agonists such as clonidine.\textsuperscript{5,19}

Majority of these pharmacological agents have undesirable effects which make them unsuitable for use as anti-shivering agents in the parturient. Clonidine induces bradycardia, hypotension, respiratory depression and dry mouth.\textsuperscript{18} Magnesium sulphate has tocolytic effect and may worsen perioperative uterine bleeding.\textsuperscript{20} Ketamine causes glandular hypersecretion, maternal sedation and in high doses it may induce general anaesthesia leading to loss of airway protection and emergence delirium.\textsuperscript{21}

Pethidine, an opioid drug, has good anti-shivering properties.\textsuperscript{22} However, it is associated with high incidence of nausea and vomiting, dose-related depression of maternal ventilation, orthostatic hypotension, and has the potential for neonatal depression.\textsuperscript{12} In doses of 0.25-0.5mg/kg (single bolus intravenous injection), tramadol has been shown to be effective in controlling post-anaesthetic shivering under regional anaesthesia without significant adverse effects.\textsuperscript{23}
Ondansetron, a 5HT₃ receptor antagonist, primarily used for the treatment and prevention of nausea and vomiting, is essentially devoid of serious side effects even in amounts several times the recommended dose.²² However, studies on the use of ondansetron as anti-shivering agent have yielded conflicting results. While Shakya and colleagues²¹ showed that ondansetron was effective in preventing shivering among patients undergoing non-obstetric lower abdominal surgeries under spinal anaesthesia, Browning and co-workers²⁴ failed to demonstrate any difference in anti-shivering activity between ondansetron and placebo among women undergoing caesarean section under spinal anaesthesia.

Ondansetron has generated much interest because of its excellent pharmacological profile. It is a drug with a wide therapeutic index and so is devoid of toxicity even in moderately supra-clinical doses.²² Ondansetron has an excellent activity against nausea and vomiting. It has been demonstrated to be useful in attenuating hypotensive and bradycardic response to spinal anaesthesia.²⁵,²⁶ It also appears to have a substantial anti-shivering activity.⁹,²⁷ In low-income countries like Nigeria, a single drug that has activity against these anaesthesia-induced complications (namely nausea and vomiting, hypotension and bradycardia, and post-anaesthetic shivering) will be most useful. But the anti-shivering potency of ondansetron has not been fully studied in our obstetric population undergoing sub-arachnoid block for caesarean section.

This study was designed to compare the efficacy of ondansetron (a seemingly triple-action agent) to that of tramadol (a drug with known anti-shivering activity) in preventing post-anaesthetic shivering in a population of Nigerian women undergoing elective or emergency caesarean section under sub-arachnoid block.
OBJECTIVES

General objective:
To compare the efficacy of intravenous tramadol versus ondansetron for preventing post-anaesthetic shivering among women undergoing caesarean section under spinal anaesthesia.

Specific objectives:
1) To determine the efficacies of tramadol and ondansetron in preventing post-anaesthetic shivering among women undergoing caesarean section.
2) To compare the effects of tramadol versus ondansetron on body temperature during spinal anaesthesia among women undergoing caesarean section.
3) To compare the side effect profiles of tramadol versus ondansetron among women undergoing caesarean section.
CHAPTER 2

LITERATURE REVIEW

Incidence of post-anaesthetic shivering

Post-anaesthetic shivering is one of the most frequent problems encountered during regional anaesthesia for caesarean deliveries. Onyekwulu and co-workers identified shivering as the second commonest (hypotension being the commonest) complication of spinal anaesthesia in South- Eastern Nigeria. However, wide variations of incidences of shivering under spinal anaesthesia have been reported in the literature by different researchers.

Giovani de Figueiredo studied the incidence of shivering after spinal anaesthesia, with or without intrathecal sufentanil, among Brazillian women undergoing elective caesarean section. The study was a prospective, randomized clinical trial. Giovani de Figueiredo recruited 80 women for the study. The women were randomized into two groups of equal numbers. Patients in group I were given intrathecal 10mg of 0.5% heavy bupivacaine without sufentanil while patients in group II were given intrathecal 10mg of 0.5% heavy bupivacaine plus 2.5micrograms of sufentanil. The author recorded a 62.5% incidence of shivering in group I compared to 32.5% in group II. The incidence rate of 62.5% shivering as reported in this study was quite significant. The researcher however did not state the ambient operating room temperature range under which the study was done. Ambient temperature affects the prevalence of shivering.

Chan and colleagues reported a 39% incidence of shivering in patients who had caesarean section under regional anaesthesia in Hong Kong. This was a relatively lower incidence of shivering compared to that reported by Giovani de Figueiredo. However, Chan and co-workers added morphine to the bupivacaine given neuraxially for anaesthesia. Morphine has been reported to possess some anti-
shivering activity.\textsuperscript{30} They also included both elective and emergency cases in the study. It is not certain if there is any correlation between the exigency of surgery and post-anaesthetic shivering.

Onyekwulu and co-workers\textsuperscript{29} recorded a 21% incidence of post-anaesthetic shivering among patients undergoing various forms of surgeries under spinal anaesthesia in two tertiary hospitals in South-Eastern Nigeria. The objective of their study was to evaluate the intra-operative complications associated with the practice of spinal anaesthesia. The authors recruited 100 patients of age range 18-75 years undergoing gynaecologic, obstetric, general, urologic or lower limb orthopaedic surgeries under spinal anaesthesia. Spinal anaesthesia was induced in all patients with 0.5\% heavy bupivacaine. The researchers recorded that the commonest complication of spinal anaesthesia was hypotension (which occurred in 28\% of the patients). This was followed by shivering, which occurred in 21\% of the patients. This incidence rate of 21\% was lower than the values recorded in the study by Giovani de Figueiredo\textsuperscript{3} as well as the one noted by Chan and co-workers.\textsuperscript{23} The reasons for this low incidence of shivering may be because 9\% of the patients in their study required additional analgesics during surgery and this was provided with intravenous fentanyl. Fentanyl has been noted to have an anti-shivering effect when given intravenously.\textsuperscript{30} Secondly, 9\% of their patients were elderly (65-75 years). Shivering has been noted to be rare in the elderly because age per se impairs normal thermoregulatory control.\textsuperscript{31} Also, the operating room temperature, under which the surgeries were done, was not reported. Ambient temperature is a major factor to consider when studying shivering.\textsuperscript{12}

Kolawole and Bolaji\textsuperscript{32}, in their study at Ilorin Nigeria, found the incidence of neuraxial anaesthesia-induced shivering among non-obstetric surgical patients to be as low as 8.18\%. Two factors might have accounted for this very low incidence. First, 11\% of the patients had incomplete spinal block which was supplemented with ketamine and pentazocine. Both ketamine and pentazocine have been
found to reduce the incidence and severity of shivering.\textsuperscript{21,33} Secondly, 9\% of the patients received midazolam sedation and midazolam has also been found to prevent shivering to a significant degree\textsuperscript{19}.

**Adverse effects, mechanism of action and diagnosis of post-anaesthetic shivering**

During shivering, metabolic activity increases and oxygen consumption may increase by as much as 600\%.\textsuperscript{34} There is a tendency for the patient to develop arterial hypoxaemia and lactic acidosis while shivering.\textsuperscript{17} Peri-operative shivering increases the risk of postoperative wound pain, wound dehiscence, wound infection and, subsequently, delay in wound healing.\textsuperscript{17} Both intra-ocular and intra-cranial pressures increase during shivering.\textsuperscript{15} Shivering also induces artifacts in intra-operative monitoring especially with electrocardiogram (ECG), non-invasive blood pressure monitoring and pulse oximetry.\textsuperscript{16} Patients often express marked discomfort during shivering.\textsuperscript{5}

The mechanism of spinal anaesthesia-induced shivering is poorly understood. One proposed mechanism is that during spinal anaesthesia, local anaesthetics deposited in the intra-thecal space block sympathetic flow. This leads to peripheral vasodilatation and increased cutaneous blood flow below the level of sympathetic block.\textsuperscript{21} There is, subsequently, a core-to-periphery heat redistribution with an increased heat loss to the environment and this could be significant given that most operating rooms are cold. With a drop in body core temperature the anterior hypothalamic thermoregulatory thermostat is reset and shivering response is triggered above the level of block with the aim of raising metabolic heat production and core body temperature.\textsuperscript{21}

Electromyographic studies however indicate that post-anaesthetic shivering differs from shivering due to cold and bears similitude to myoclonus.\textsuperscript{14} It has therefore been suggested that anaesthetic agents suppress descending neural pathways which normally inhibit spinal reflexes and, consequently, uninhibited spinal reflexes manifest as shivering.\textsuperscript{35} This may be more likely than response to intra-operative core hypothermia although both factors may contribute to shivering in the same patient.\textsuperscript{14}
Regardless of its mechanism, shivering has multiple undesirable effects ranging from patient’s discomfort to catastrophic physiologic states and interference with patient monitoring. It is therefore clinically worthwhile to prevent it and to promptly diagnose and control it in the event that it occurs. Diagnosis of post-spinal shivering is mainly clinical. The patient’s complaints range from discomfort, body shakes to ‘feeling of cold’. In extreme cases patients complain of premonition of impending doom and there is this hollow look in their eyes.

Crossley and Mahajan\textsuperscript{36} initially described a scale for grading the intensity of post-anaesthetic shivering. This was later validated by Tsai and Chu\textsuperscript{37} as follows: grade 0 = No shivering; grade 1 = piloerection or peripheral vasoconstriction but no visible shivering; grade 2 = muscular activity in only one muscle group; grade 3 = muscular activity in more than one muscle group but not generalized; grade 4 = shivering all over the body. Shivering therefore becomes grossly detectable from grade 2.

**Methods of preventing and controlling post-anaesthetic shivering**

Both non-pharmacological and pharmacological methods have been applied in preventing and controlling post-anaesthetic shivering and these have been found to have varying efficacies and shortcomings. The non-pharmacological methods are mainly based on measures aimed at preventing core hypothermia. These include giving warm intravenous fluids to maintain core temperature at normal, actively warming the skin with radiant warmers (in order to obliterate the core-to-periphery temperature gradient and thereby prevent redistribution hypothermia) or passive insulation with space blankets to prevent heat loss from the skin to the surrounding. The non-pharmacological methods are expensive, cumbersome and have limited success in preventing shivering.\textsuperscript{5}

Parveen and co-workers\textsuperscript{38} studied the effectiveness of warm intravenous fluids in preventing shivering among women undergoing caesarean section under spinal anaesthesia. The study was a randomized, controlled trial. Sixty-four American Society of Anesthesiologists’ (ASA) class I-II patients
were randomly allocated to two groups of equal numbers (group 1 and group 2). Patients in group 1 received intravenous fluid at room temperature (22°C) throughout surgery while patients in group 2 received warm intravenous fluid (at 39°C) via a fluid warmer. All patients had spinal anaesthesia induced with 2.5ml of 0.5% hyperbaric bupivacaine. Core body temperatures were recorded at intervals and patients were monitored for presence or absence of shivering. The results showed a decrease in mean core body temperature in both groups compared to the baseline values. The decrease was statistically worse in group 1 compared to group 2 (p<0.001). However, there was no statistical difference in the incidence of shivering between groups 1 and 2 (31.3% vs 25.0%; p=0.63). The authors concluded that warm intravenous fluids decreased the degree of core hypothermia but was not effective in preventing shivering.

Radiant heat warming of the skin is rarely used in clinical practice because it requires at least one hour of gentle pre-warming to be effective. Aggressive and shortened period of pre-warming cause extreme discomfort and a counter-productive sweating. Radiant heat warmer may also interfere with surgical access.

Pharmacological methods of controlling shivering are simple, cost-effective and easy to implement. One of the earliest studies on the use of pharmacological agents to control shivering was conducted by Casey and colleagues. The aim of their study was to determine the effectiveness of intravenous pethidine in controlling maternal shivering during caesarean section under regional anaesthesia. Forty ASA class I parturients who shivered following epidural anaesthesia were randomized into two groups of 20 patients each. The patients in group 1 were given intravenous pethidine 50mg single bolus after delivery of baby while patients in group 2 received 0.9% saline as placebo. The authors noted that administration of pethidine resulted in significant decrease in severity of shivering compared to placebo (p=0.01). The incidence of repeat shivering was also significantly lower.
in the pethidine group compared to the placebo group (p=0.01). A sample size of 40 patients as used by
the researchers for this study is quite low. Also all patients were given 50 micrograms of fentanyl via
epidural catheter 30 minutes after the extraction of baby. Epidural fentanyl has anti-shivering effects. Its
presence confounded the outcome of the study. This notwithstanding, the study by Casey and co-
workers demonstrated that pethidine has a substantial pharmacological action against shivering.
However, the authors noted that maternal sedation was significantly higher in the pethidine group than
the placebo group (p=0.01). In addition to causing maternal sedation, it has been reported that pethidine
causes maternal ventilatory depression, promotes postoperative nausea and vomiting and depresses the
newborn APGAR scores. Thus, despite its record of effectiveness, pethidine cannot be regarded as the
pharmacological agent of choice for prevention of shivering during caesarean delivery under regional
anaesthesia.

Shakya and colleagues compared the efficacy of intravenous ketamine versus ondansetron in
preventing post-spinal shivering. One hundred and twenty patients were randomized into three groups of
equal numbers. The groups received intravenous 0.25 mg/kg ketamine, 4mg ondansetron or placebo
normal saline respectively immediately after induction of spinal anaesthesia with 3ml of 0.5% heavy
bupivacaine. The operating room temperature was maintained at 24-26 °C. The researchers recorded
that shivering occurred in 42.5% of patients in the placebo group, 10% of patients in the ondansetron
group and 2.5% of patients in the ketamine group. The study demonstrated that both ketamine and
ondansetron were statistically superior to placebo in preventing shivering (p=0.001). At this low dose
(0.25mg/kg), intravenous ketamine effectively prevented post-spinal shivering in 94.1% of the patients.
But even at this low dose, unacceptable levels of sedation were recorded in up to 95% of the patients
given ketamine. There were no records of sedation in either of the ondansetron and placebo groups.
Though larger proportion of patients had hypotension in ondansetron group (22.5%) compared to the
ketamine group (10%) and the placebo group (20%), these differences were not statistically significant (p=0.22).

Shakya and co-workers\textsuperscript{21} gave 0.2mg/kg oral diazepam to all the patients in that study 1 hour prior to induction of spinal anaesthesia. The combined sedative effects of residual diazepam plus that of ketamine may have contributed to the high rate of sedation noted in the ketamine group. But then this high rate of sedation still underscores the tendency of ketamine to cause unacceptable degree of sedation even in low doses. In addition to causing sedation, ketamine is also known to cause unpleasant psychotomimetic effects, promote glandular hyper-secretion and worsen postoperative nausea and vomiting.\textsuperscript{41} It is certainly not the ideal agent for preventing shivering in the parturient undergoing caesarean delivery under spinal anaesthesia.

A study to determine the efficacy of intravenous magnesium sulphate for both prophylaxis and treatment of post-spinal shivering was conducted by Ibrahim and co-workers.\textsuperscript{42} The study was a prospective, randomized, placebo-controlled trial. One hundred and twenty patients undergoing lower abdominal and lower limb orthopaedic surgeries under spinal anaesthesia were randomly allocated to three groups of 40 each, namely groups P, T and C. Immediately after induction of spinal anaesthesia with 20mg of hyperbaric bupivacaine, patients in group P (prophylactic group) were given intravenous magnesium sulphate 50mg/kg bolus followed by 2mg/kg/hour continuous infusion. Patients in group T (treatment group) received magnesium sulphate 50mg/kg intravenous bolus if shivering occurred. Patients in group C (control group) received saline placebo. The operating room temperature was maintained at 22-24 °C. Patients were monitored and records of shivering and adverse effects of the drugs taken. The results showed that magnesium sulphate was statistically superior to placebo in both prevention (p<0.01) and treatment (p<0.01) of shivering. There was no correlation between the prevalence of shivering and core body temperature. However, there was an unacceptably high
prevalence of hypotension, hypothermia, and nausea and vomiting among the prophylactic magnesium group compared to the treatment and the placebo groups. The reason for the high rate of these complications in the prophylactic magnesium group may be because after a bolus dose, the patients in that group also received continuous intravenous infusion of magnesium sulphate. The authors did not state the reason for this continuous infusion in that group. Magnesium sulphate is known to cause tocolysis and, when used during caesarean section, may cause uterine atony and post-partum haemorrhage.\textsuperscript{20} It is clearly not the pharmacological agent of choice for prevention of shivering during caesarean section under spinal anaesthesia.

Clonidine has an appreciable degree of anti-shivering activity.\textsuperscript{43} However, it is known to cause hypotension, dry mouth and drowsiness all of which are not favourable in parturients undergoing spinal anaesthesia.\textsuperscript{18}

It is obvious that there are many drugs that possess anti-shivering activities. However, considering the peculiarities of pregnancy and caesarean section under spinal anaesthesia, there is a continued search for anti-shivering agents that offer a combination of optimal anti-shivering effects, maximal safety profile and minimal side effects.

**Pharmacology of tramadol and its use as anti-shivering agent**

Tramadol does have advantages over other opioid drugs that have been used as anti-shivering agents in that it is not a controlled drug. It is therefore readily available. Compared to pethidine, it causes less respiratory depression and sedation at equipotent doses.\textsuperscript{37}

Tramadol is an atypical opioid analgesic.\textsuperscript{44} Its opioid action is preferentially mediated via the mu-receptor with minimal effects at the delta and kappa receptors.\textsuperscript{44} Tramadol also inhibits noradrenaline and serotonin reuptake as well as activating the monoaminergic receptors of the descending neuraxial inhibitory pathways.\textsuperscript{44}
Tramadol has a half life of about 6 hours.\textsuperscript{45} It is metabolized in the liver through cytochrome p450 enzymes to O-desmethyltramadol which is a more potent mu-opioid receptor agonist.\textsuperscript{45} Tramadol and its metabolites undergo metabolic and renal elimination.\textsuperscript{45} Ninety percent of the metabolites are excreted in the kidney via urine; the remaining 10\% through faeces.\textsuperscript{45}

Possible side effects of tramadol include: nausea, vomiting, dizziness, sweating, confusion and hallucinations, respiratory depression, sedation (the latter two less commonly than morphine).\textsuperscript{45} Convulsions have been reported especially when tramadol is combined with drugs that reduce seizure threshold e.g. tricyclic antidepressants, serotonin re-uptake inhibitors and monoamine oxidase inhibitors.\textsuperscript{45}

Tramadol has been used as analgesic for labour pains without adversely affecting the mother or new born.\textsuperscript{23} With its pharmacodynamic advantage in causing less respiratory depression and sedation and its unique status of not being a controlled drug, it has a potential use as one of the best drugs for prevention and control of shivering in the obstetric patients because it is more convenient and theoretically safer than pethidine.\textsuperscript{23,37}

One of the earliest researches on the usefulness of tramadol in controlling shivering was done by Chan and colleagues.\textsuperscript{23} It was a prospective, randomized, controlled trial. Thirty-six women who shivered during caesarean section under regional (spinal or epidural) anaesthesia were randomized into three groups. Group T0.5 (n=12) patients were given intravenous tramadol 0.5mg/kg; group T0.25 (n=13) patients were given intravenous tramadol 0.25mg/kg while group NS (n=11) patients received 0.05ml/kg normal saline placebo. The ability of the treatments to stop shivering was noted. Side effects of the study drugs (such as sedation, nausea and vomiting) were also noted. The results showed that 80\% of patients who shivered in group T0.5 and 92\% of patients who shivered in group T0.25 had their shivering controlled compared to 27\% in the placebo group (p=0.001). There were no records of
sedation in all the study groups. However there were more cases of nausea and vomiting in the tramadol groups (50% in group T0.5, 23% in group T0.25) than the placebo (18%) though the differences were not statistically significant (p=0.20). The authors concluded that intravenous tramadol (0.25-0.5mg/kg) was effective in the treatment of intra-operative shivering during regional anaesthesia for caesarean section.

This study, by Chan and colleagues, evaluated tramadol as anti-shivering agent in the context of treatment of shivering, not its prevention. Also the sample size of 36 patients for this study was inadequate. The occurrence of nausea and vomiting in 50% of patients given 0.5mg/kg tramadol, 23% of patients given 0.25mg/kg tramadol and only 18% of patients given placebo is a pointer to the tendency of tramadol to cause nausea and vomiting in a dose-dependent fashion. However, a subsequent study by Atashkhoyi and Negargar could not demonstrate a similar pattern of side effects.

Atashkhoyi and Negargar studied the effect of tramadol for prevention of shivering during spinal anaesthesia for caesarean section. Seventy American Society of Anesthesiologists’ (ASA) class I-II women aged 18-40 years who presented for caesarean section under spinal anaesthesia were randomized into two groups of 35 patients each. Spinal anaesthesia was induced with 1ml of 5% lignocaine plus 10 micrograms of fentanyl in all patients. Patients in group 1 were given intravenous tramadol 1mg/kg just immediately after the induction of spinal anaesthesia while patients in group 2 received equivalent volume of placebo normal saline. The operating room temperature was kept at 23-25 °C. Haemodynamic parameters, incidences of shivering and prevalence of adverse drug effects were recorded. The results indicated that 28.6% of patients in the tramadol group had post-spinal shivering compared to 65.7% in the placebo group (p=0.0001). Only one patient (2.85%) complained of nausea in the tramadol group compared to 4 (11.42%) in the placebo group (p=0.35). Larger number of patients had sedation in the tramadol group compared to the placebo (11.42% vs 5.7%). The authors concluded that tramadol was
effective in prevention of shivering during spinal anaesthesia for caesarean section with no statistically or clinically-significant incidence of side effects such as nausea, vomiting, central or respiratory depression on the parturients. The study demonstrated that tramadol has good preventive effect on shivering with minimal side-effect profile. However, introduction of fentanyl intrathecally was a confounding factor in this study since intrathecal fentanyl is known to have anti-shivering property. Combined anti-shivering effects of intrathecal fentanyl and intravenous tramadol may have contributed to the high efficacy of tramadol recorded in the study. The fact that the prevalence of sedation in the tramadol group was double that in the placebo remains an issue to worry about. This actually reveals that tramadol might not be the ideal prophylactic anti-shivering agent.

Tobi and co-workers could not demonstrate any anti-shivering advantage of prophylactic intravenous tramadol over placebo (saline) among patients undergoing lower limb orthopaedic surgeries under spinal anaesthesia in Benin City Nigeria. In the prospective, placebo-controlled trial, Tobi and colleagues randomized 86 ASA class I or II patients aged 16-65 years into two groups of 43 patients each. All the patients received 10mg of diazepam the night before surgery and on the morning of surgery. Immediately after establishing spinal anaesthesia, patients in the tramadol group were given intravenous 0.5mg/kg of tramadol while patients in the placebo group received intravenous 2ml of normal saline. The aim of the study was to evaluate the effect of tramadol on perioperative shivering in lower limb orthopaedic surgeries under spinal anaesthesia. Additional bolus dose of intravenous tramadol (1mg/kg) was given to any patient who shivered during the course of the study irrespective of the study drug. The researchers noted that the incidences of shivering were 13.93% and 16.20% in tramadol and placebo groups respectively. The difference in incidences of shivering between these two groups was not significant (P=1.00). However, severity of shivering was lower in tramadol group than saline group. The researchers also noted that all patients who shivered during the course of the study did
not have a recurrence of shivering after a rescue dose of 1mg/kg tramadol was administered. They concluded that tramadol offers no preventive advantage over placebo against perioperative shivering under spinal anaesthesia but it promptly abolishes shivering when used as a rescue drug against shivering.

The overall incidence of shivering in this study by Tobi and group\textsuperscript{47} was lower than the values reported by Atashkhoyi and Negargar\textsuperscript{44}. Some factors may have been responsible for this. First, the age range for the study (by Tobi and colleagues\textsuperscript{47}) was too wide apart at 16-65 years. It is on record that the older a patient gets, the rarer he/she shivers, this being a result of age-associated thermoregulatory insufficiencies\textsuperscript{31}. Secondly, non-obstetric patients were the participants for the study by Tobi and co-workers\textsuperscript{47} while obstetric patients were the participants in the study by Atashkhoyi and Negargar\textsuperscript{44}. Under spinal anaesthesia, obstetric patients have been noted to have higher incidence of shivering than non-obstetric population\textsuperscript{4, 23}. Thirdly, all patients for Tobi and colleagues’ study were given 10mg of diazepam in the morning of surgery. Benzodiazepines have been known to possess anti-shivering potency\textsuperscript{19}. Fourthly, Tobi and colleagues\textsuperscript{47} used warm intravenous fluids for both pre-loading and maintenance infusion. This might have reduced the degree of anaesthesia-induced core-to-periphery heat re-distribution and core hypothermia thereby reducing the tendency to post-anaesthetic shivering.

The ability of tramadol to abolish shivering and prevent its recurrence, in the study by Tobi and co-workers\textsuperscript{47}, shows that tramadol has a good anti-shivering activity. Its failure to offer a prophylactic effect may be because 0.5mg/kg was sub-optimal for a preventive activity. For example, at a dose of 0.5mg/kg, a 70-kg man would be given only 35mg tramadol; it would take as much as a 100kg body weight to have a dose of 50mg tramadol.
**Pharmacology of ondansetron and its use as anti-shivering**

Ondansetron is a 5HT₃ serotonergic receptor antagonist. It is well established for the treatment of nausea and vomiting associated with cancer chemotherapy, radiotherapy, anaesthesia and surgery. It has both central and peripheral anti-emetic effects and its central anti-emesis has a vagolytic component. However, it does not affect dopamine receptors and unwanted central effects are therefore rare. Ondansetron has frequently been used in intractable nausea and vomiting of pregnancy.

A major advantage of ondansetron is that it has a wide therapeutic index. It is essentially devoid of serious side effects, even in amounts several times the recommended doses. It is not associated with extrapyramidal side effects, excessive sedation or significant prolongation of anaesthesia. The wide distribution of 5HT₃ receptors in the body and the role of these receptors in disease have provided the rationale for investigation of ondansetron in many novel applications including post-anesthetic shivering and treatment of pruritus following intrathecal administration of opioids.

Ondansetron can be given orally, subcutaneously, intramuscularly, rectally or intravenously. It undergoes hepatic metabolism and renal excretion and has only 60% bioavailability when administered orally due to first-pass hepatic metabolism. The most commonly reported side effect of ondansetron is headache. It slightly prolongs Q-T interval on ECG especially in patients taking anti-arrhythmic drugs. Other side effects include constipation and flushing.

A formative study of ondansetron as an anti-shivering agent in anaesthesia was carried out by Powell and Buggy. The study was a prospective trial aimed at determining the effectiveness of ondansetron, given prior to induction of general anaesthesia, in reducing post-anaesthetic shivering. Eighty-two patients (aged 18-60 years) undergoing orthopaedic, general or urologic surgeries were randomized in double-blinded, placebo-controlled fashion. Group O4 (n=27) patients received 4mg
intravenous ondansetron, group O8 (n=27) received 8mg intravenous ondansetron while group C (n=28) received placebo normal saline. The study drugs were given immediately before induction of general anaesthesia. For every patient, general anaesthesia was induced with propofol-fentanyl regimen and maintained with isoflurane-oxygen-nitrous oxide mixture. At the end of surgery, the patients were monitored for shivering in the recovery room. The recorded incidences of shivering per group were 33% for group O4, 15% for group O8 and 57% for group C. The results showed that ondansetron 8mg was statistically superior to saline placebo in preventing post-anaesthetic shivering (p=0.003). Ondansetron 4mg was not statistically superior to placebo in preventing post-anaesthetic shivering (p=0.13). The authors concluded that 8mg single bolus intravenous ondansetron, given prophylactically prior to induction of general anaesthesia, significantly reduced the incidence of post-anaesthetic shivering in adult patients. The study revealed that serotonergic pathways have a role in the regulation of post-anaesthetic shivering. However, it was carried out on patients undergoing general anaesthesia. The pathophysiology and prevalence of shivering are not exactly similar in general and regional anaesthetic cases. The use of fentanyl as part of induction regimen has also confounded the result of the research since intravenous fentanyl has been proven to possess anti-shivering effects.

Kelsaka and co-researchers studied the efficacy of intravenous ondansetron compared to pethidine in preventing shivering among patients undergoing lower limb orthopaedic surgeries under spinal anaesthesia. Seventy-five patients were randomized into three groups in double-blind, placebo-controlled design. The patients were aged 20-60 years and were ASA physical status I or II. Groups O, M and C patients were given 8mg intravenous ondansetron, 0.4mg/kg intravenous pethidine (meperidine) and placebo normal saline respectively. The study drugs were given just before induction of spinal anaesthesia. The patients were then observed for shivering. The reported incidences of shivering in the groups were 8% in the ondansetron group, 8% in the pethidine group and 36% in the...
placebo group with p < 0.05. Body temperature was best preserved in ondansetron group and least in the pethidine group. However the pethidine group had the best haemodynamic profile as there were no records of hypotension or bradycardia in group M. Twelve percent of patients in ondansetron group had bradycardia. Hypotension and bradycardia occurred in 12% and 28% respectively in the placebo group. The authors concluded that ondansetron and pethidine were equally effective in preventing post-spinal shivering. This study by Kelsaka and colleagues\textsuperscript{27} lent more credence to the positive anti-shivering potency of ondansetron.

A study comparing ondansetron against tramadol for preventing shivering among women undergoing elective caesarean section under spinal anaesthesia was conducted by Ejiro and colleagues.\textsuperscript{52} Ninety ASA I or II patients (aged 18-45 years) undergoing elective caesarean deliveries under sub-arachnoid block were randomized by Ejiro and co-workers\textsuperscript{52} into three groups of 30 each. Group 1 patients received 0.5mg/kg tramadol; group 2 patients received 4mg of ondansetron while group 3 patients received placebo normal saline. The study drugs were administered to the patients 2 minutes after an established spinal anaesthesia. The patients were observed for shivering and adverse effects of the study drugs. The reported incidences of shivering in the study were 16.7% in tramadol group, 20.0% in ondansetron group and 53.3% in placebo group (P=0.003). Nausea and vomiting were recorded in 7 patients in tramadol group, 1 patient in ondansetron group and 2 patients in the saline group (P=0.031). The patients in ondansetron group reported the highest rate of satisfaction with the anti-shivering prophylaxis (76.7% versus 70% in tramadol group and 26.7% in placebo group). The researchers concluded that 4mg ondansetron was comparable to 0.5mg/kg tramadol in preventing shivering but that ondansetron could be preferable to tramadol because it offered a better anti-emetic property and a better patient satisfaction.
Ejiro and co-workers\textsuperscript{52} chose to give the study drugs after two minutes of establishing spinal anaesthesia. The reason for this was not stated. However, this time lag must have decreased the ability of the drugs to give satisfactory prophylaxis against shivering. This may be the reason that Kelsaka and colleagues\textsuperscript{27} achieved a better quality of anti-shivering prophylaxis with their study drugs than Ejiro and co-researchers.\textsuperscript{52} It would have been better if the drugs were given immediately after depositing the local anaesthetic in the intra-thecal space or even just before that.

Ejiro and colleagues\textsuperscript{52} recruited only elective caesarean section cases and excluded emergency cases for the study. The reason for this may be because of the uncertainty surrounding the relationship between labour pains and shivering. Generally, pain has been established as a risk factor for shivering.\textsuperscript{53} However, some researchers have suggested that labour pain has some protective effects against shivering probably due to increased heat production from labour activity as well as due to some unidentified fetoplacental products that have thermogenic functionality.\textsuperscript{54}

Browning and co-researchers\textsuperscript{24} did not demonstrate any statistical difference in prevention of shivering between ondansetron and saline placebo in Australian women undergoing caesarean section under combined spinal-epidural anaesthesia. The study was a prospective, randomized, placebo-controlled trial. One hundred and eighteen women undergoing elective caesarean section were randomized into groups O and S. Patients in group O (n=58) were given intravenous ondansetron 8mg while those in group S (n=60) were given saline placebo. The drugs were given prior to induction of combined spinal-epidural anaesthesia. The results showed no statistical differences between the groups in body temperature changes, incidence of nausea and vomiting, incidence of headache, and newborn APGAR scores. Shivering occurred in 41\% of patients in group O versus 47\% in group S (p=0.548). The authors concluded that intravenous ondansetron 8 mg before performing combined spinal-epidural (CSE) anesthesia in women undergoing elective caesarean delivery does not decrease the incidence or
severity of shivering. The researchers added fentanyl (15 micrograms) in the heavy bupivacaine given intrathecally in all patients. Intrathecal fentanyl has been noted to have anti-shivering effects. It is possible that the presence of fentanyl might have masked the possible differences in outcome of shivering between the study groups.

The mechanism by which ondansetron prevents shivering may be explained by the biogenic amine theory of central thermoregulation as proposed by Feldberg and Myers. Feldberg and Myers proposed that the balance of serotonin (5HT3) and norepinephrine in the pre-optic region of the anterior hypothalamus controls the body temperature set point. Subsequently, Feldberg and Myers discovered that when injected directly into the rat brain, serotonin (5HT3) caused shivering, vasoconstriction and subsequent increase in core temperature. Norepinephrine, they discovered, had opposite effect; that is, it attenuated the serotonin-induced hyperthermia. Ondansetron is a serotonin (5HT3) receptor antagonist. Its anti-shivering property may be connected to its ability to antagonize serotonin function in the central nervous system.

More recent studies tend to show that serotonin and norepinephrine inputs may be responsible for short- and long-term thermoregulatory adaptive modifications of shivering threshold. The fact that tramadol prevents reuptake of norepinephrine by nerve cell terminals may also be responsible for the antishivering properties of tramadol.

Attention to the potential strategic utility of ondansetron in obstetrics regional anaesthesia was rekindled after a study, done in Poland by Owkzuk and colleagues, demonstrated that ondansetron, given prophylactically before induction of spinal anaesthesia, also attenuated the fall in systolic and mean blood pressures.

During caesarean section under spinal anaesthesia, three cardinal challenges are nausea and vomiting (due to anaesthesia and surgical stimulation plus emetogenic effect of agents like oxytocin,
ergometrine and other drugs), hypotensive response to sub-arachnoid block, and post-spinal shivering. It is therefore worthwhile to compare the anti-shivering property of drugs such as ondansetron (which appears to have a triple action of controlling nausea and emesis, attenuating hypotensive response to sub-arachnoid anaesthesia and reducing the incidence and severity of shivering) against that of tramadol which has a long-established anti-shivering efficacy.
JUSTIFICATION FOR THE STUDY

The ideal anti-shivering agent to be used during sub-arachnoid block for caesarean section should be affordable, available and able to prevent shivering in nearly 100% of the parturients with no adverse effects to both the mother and the new born. Unfortunately, none of the drugs used so far is ideal.

Tramadol is the drug commonly used in the control of post-spinal shivering in most hospitals in the South-Eastern part of Nigeria. It is has a proven anti-shivering property. Although it has less side effect profile compared with pethidine and other opioids, studies have shown that tramadol induces a dose-dependent nausea and vomiting.

Unlike tramadol, ondansetron is a known anti-emetic drug with a wide therapeutic index. This implies that ondansetron is essentially devoid of serious side effects, even in amounts higher than the recommended clinical doses. Studies have also demonstrated that ondansetron, given before induction of spinal anaesthesia, attenuates the hypotensive response to spinal block. These positive attributes of ondansetron could be very useful in the care of patients undergoing caesarean section under spinal anaesthesia. However, studies on the effectiveness of ondansetron as an anti-shivering agent have yielded inconsistent results.

This study was chosen to compare the anti-shivering activity of ondansetron against that of tramadol, which is a drug with a proven anti-shivering effectiveness, among women undergoing elective or emergency caesarean section under spinal anaesthesia.
CHAPTER 3
METHODOLOGY

STUDY LOCATION

The study was carried out at the University of Nigeria Teaching Hospital (UNTH) Enugu, which is a 700-bedded tertiary hospital located in Ituku-Ozalla Enugu, Enugu state in the South-Eastern part of Nigeria. It serves Enugu and the majority of the other four south-eastern states of Nigeria.

STUDY POPULATION

Pregnant women at term who presented for elective or emergency caesarean section were recruited for the study.

STUDY DESIGN

This was a prospective, double-blind, placebo-controlled study with patients randomly allocated to three groups namely saline (S) group, tramadol (T) group and ondansetron (O) group.

ETHICAL CLEARANCE/APPROVAL

This was obtained from the Health Research Ethics Committee of the institution. Also written, informed consent was obtained from patients who volunteered to participate in the study.

DURATION OF STUDY

This study was conducted over a period of 14 months.

SAMPLE SIZE ESTIMATION

Setting the power of study at 80%, the confidence level at 95% and the degree of precision at 10%, the sample size was calculated based on the 15% shivering incidence as recorded by Sule et al in their Jos study. The formula used was that for comparison of groups in an experimental study and is stated below:

\[ n = \frac{2z^2 pq}{d^2} \]

where \( n \) = desired sample size (when reference population is greater than 10,000)
\( z = \) the standard normal deviate, usually set at 1.96 which corresponds to 95% confidence level

\( P = \) proportion in the target population estimated to have a particular characteristic (15% of patients shivered in JUTH study i.e 0.15)

\( q = 1.0 - p = 1 - 0.15 = 0.85 \)

\( d = \) degree of precision desired, set at 10% (i.e 0.1) considering limitations of time, resources and subjects, and wishing to conclude that an observed difference of 0.10 or more is significant at the 0.05 level.

The sample size was thus: \( 2 \times (1.96)^2 \times 0.15 \times 0.85 \times (0.1)^2 = 97.96 \), approximately 98.

This showed that a calculated sample size of approximately 33 per group would allow detection of differences between groups with a power of 80%. Thus a total of 99 patients aged 18-45 years were needed for the study. However, an additional 10% was added to this in order to make up for attrition. Ten percent of 99 is 9.9, approximately 10. Therefore, a total of 109 patients were studied.

**INCLUSION CRITERIA**

i. Women aged 18-45 years with term singleton pregnancy who presented for elective or emergency caesarean section.

ii. American Society of Anesthesiologists’ (ASA) physical status grade I or II

**EXCLUSION CRITERIA**

i. Patients who declined to give consent

ii. Patients with contraindications to spinal anaesthesia such as hypovolaemia, coagulopathy, allergy to local anaesthetic agents, raised intra-cranial pressure, fixed cardiac output states, patient refusal, local sepsis around the site of injection

iii. Patients with abnormal psychological profile

iv. Patients with initial body temperature less than 36 or more than 38 degrees celsius
v. Patients with severe systemic diseases such as diabetes mellitus, hypertension, renal insufficiency, hyperthyroidism or peptic ulcer disease
vi. Patients who had blood transfusion before or during surgery
vii. Patients on long term phenothiazines or monoamine oxidase inhibitors or anti-arrhythmic drugs.
viii. Patients with compromised cardiorespiratory condition
ix. Patients who received tramadol for labour pains prior to surgery
x. Patients with eclampsia.

SAMPLING PROCEDURE AND INTERVENTION

After obtaining ethical approval from the (UNTH) institutional research ethics committee and written informed consent from the patients, 109 obstetric patients scheduled for elective or emergency caesarean section under spinal anaesthesia were recruited for the study. The patients were recruited by simple random sampling. Every term pregnant woman who presented to the UNTH obstetric department for elective or emergency caesarean section within the period of the study, and who satisfied the criteria for recruitment, had a chance to participate.

During the pre-operative visit, the patient’s clinical history was taken, physical examination of the patient was conducted and the results of relevant investigations (full blood count, urinalysis, obstetric ultrasound scan and serum electrolytes) were reviewed. She was then acquainted with the proposed study, after which her informed consent was obtained.

Consented patients were randomly allocated to 3 groups according to the study drugs, namely Tramadol 50mg group (Group T), Ondansetron 4mg group (Group O) and Saline 4ml group (Group S). To accomplish this randomization while keeping both the researcher and the patient blinded, pieces of papers were labeled with one of the letters S, T or O and packaged in small uniform non-transparent envelopes such that each envelope contained one piece of labeled paper. Equal numbers of these small
envelopes were shuffled and gathered into a big envelope in batches. Each patient picked a small envelope from inside the big envelope and this determined the group allocation of the patient. An anaesthetic resident doctor then subsequently prepared the study drug according to the patient’s group allocation. For each patient, the appropriate study drug was prepared and diluted to a volume of 4ml (in a 5ml syringe). The researcher was unaware of the patients’ group allocation until the end of total sample collection.

All the patients were pre-medicated with intravenous ranitidine 50mg and metoclopramide 10mg on arrival in the operating theatre. The baseline vital signs were taken namely: tympanic membrane temperature using digital infrared ear thermometer (ThermoBuddy, HuBDIC200, Korea); non-invasive blood pressure, mean arterial pressure, pulse rate and oxygen saturation using a multi-parameter monitor (Mindray PM-7000, Shenzhen Mindray Biomedical Electronics Ltd, China). The operating room temperature was maintained between 24-26 degrees celsius by adjusting the temperature setting of the air conditioner while measuring the ambient temperature with a wall thermometer (kadio3806, China). Tympanic membrane temperature of less than 36.5 °C was defined as hypothermia.

Intravenous access was obtained using two size 16 Gauge intravenous cannulae. One of the intravenous lines was dedicated to fluid infusion and the other to drug administration. An anaesthetic machine with oxygen supply, airway devices, laryngoscope and resuscitation drugs were available in the theatre. Each patient was preloaded with 20ml/kg normal (0.9%) saline at room temperature over 10-15 minutes prior to induction of spinal anaesthesia. The fluid infusion was subsequently reduced and regulated as required.

Spinal anaesthesia for all patients was done by the researcher. After placing the patient in the sitting position with feet on a stool, cleaning the back with antiseptics and locating the lumbar spinal interspaces, subarachnoid anaesthesia was instituted at either L3/4 or L4/5 interspaces. Hyperbaric
bupivacaine (Marcaine®, AstraZeneca), 5mg/ml, 12.5mg was injected through a 25G Quincke spinal needle (Taechang Ltd, China). The patient was then positioned supine with head and shoulders supported on a pillow and tilted to a 15 degrees left lateral position.

Just after the intrathecal injection, the study drug was given as a single intravenous bolus by an anaesthetic resident doctor. Both the patient and the researcher were blinded to the nature of the particular study drug administered since the solutions of saline, tramadol and ondansetron were all clear and transparent.

Patients in group S were given 4ml 0.9% saline intravenously. Patients in group T were given 50mg of Tramadol (Pauco pharmaceuticals, Nigeria) made up in 4ml volume, intravenously. Patients in group O received 4mg of ondansetron (Vomistat, LINCOLN parenteral Ltd Gujarat, India) made up in 4ml volume, intravenously. The pulse rate, mean arterial pressure (MAP) and peripheral oxygen saturation were recorded at 5 minutes’ intervals while tympanic membrane temperatures were recorded at 10 minutes’ intervals throughout surgery.

All patients were covered with one layer of sterile surgical drapes over the chest, thighs and legs during the operation. Sensory block level was assessed with alcohol swab test at 5 minutes’ intervals. The presence of shivering was observed and recorded by the researcher (who was blinded to the nature of the study solution administered). Shivering was graded according to the scale validated by Tsai and Chu³⁷ as follows:

grade 0 = no shivering,
grade 1 = piloerection or peripheral vasoconstriction but no visible shivering,
grade 2 = muscular activity in only one muscle group,
grade 3 = muscular activity in more than one muscle group but not generalized,
grade 4 = shivering involving the whole body.
If after spinal anaesthesia and concomitant administration one of the study drugs, grade 3 or 4 shivering was noted, the prophylaxis was regarded as ineffective and intravenous pethidine 12.5 mg was administered as a rescue drug.

Patients were also monitored for hypotension, bradycardia, sedation, nausea and vomiting. Hypotension, defined as a decrease in mean arterial blood pressure by more than 20% from baseline value, was treated by crystalloid (normal saline) infusion and if necessary ephedrine was administered in 6mg intravenous boluses. The total volume of crystalloid used was recorded. The amount of ephedrine given in each group was also recorded. Bradycardia, defined as pulse rate less than 60 beats/minute, was also promptly treated with intravenous atropine once it occurred. The researcher also assessed the degree of sedation on a five-point scale:

1 = fully awake and oriented,
2 = drowsy,
3 = sleepy but rousable to verbal command,
4 = sleepy but rousable to mild physical stimulation, and
5 = sleepy and not rousable by mild physical stimulation.

Other side effects, including headache, were noted as they occurred.

As the head of the baby was delivered, the nose, mouth and pharynx were suctioned with a bulb syringe. After the rest of the body was delivered, the umbilical cord was clamped and cut. The neonate was then handed over to the neonatologist who placed the baby under the radiant warmer with a tilt in a slight trendelenburg position. The body was then dried with a sterile towel. At this point, the neonate was evaluated and the one-minute APGAR score was taken concurrently with as much resuscitation as was needed. The APGAR score was taken by the neonatologist who was otherwise unaware of the study solutions given. Neonates with APGAR scores 8-10 were regarded as vigorous and needed only gentle
stimulation (such as flicking the feet, rubbing the backs or additional drying of the bodies). Neonates with APGAR scores 7 or less were regarded as depressed or asphyxiated and for these ones, more resuscitation was needed including further suctioning of the oropharynx and stomach, blowing 100% oxygen across the face, chest compression (if the heart rate was less than 60 beats/minute) or even positive pressure ventilation as the case required.

Immediately after the delivery of the baby, oxytocin 5iu intravenous bolus was given (to the mother) followed by slow infusion of 25iu in 500ml normal saline. At the end of the surgery, the patient was moved to the recovery room where her vital signs (pulse rate, blood pressure and body temperature) continued to be monitored.

STATISTICAL ANALYSIS

Data were collected with forms designed for the study. Statistical analyses were done using Statistical Package for Social Sciences 20.0 (SPSS Inc., Chicago, IL., U.S.A). Demographic characteristics (namely age, weight, gravidity, exigency of surgery and total operating times) were compared across the groups using Kruskal-Wallis test. Analyses of Variance (ANOVA) with Tukey post hoc test were applied to compare the study groups in terms of the baseline vital signs, baseline operating room temperatures, volumes of intravenous fluid, prevalence of hypothermia and grades of shivering. Incidences of bradycardia and hypotension as well as the cumulative ephedrine consumption, the spinal sensory block levels, the APGAR scores of the newborn and the prevalence of drug side effects (sedation, headache, nausea and vomiting) were compared across the groups using chi-square tests. Paired-sample T-test was applied to analyze the within-group changes in the operating room temperatures (ORT). Between-group differences in the frequency of shivering were analyzed using the Independent-samples Mann-Whitney U test. Results were displayed in tables and graphs and P values less than 0.05 were considered to be statistically significant.
CHAPTER 4

RESULTS

One hundred and nine patients were enrolled for this study. Nine patients were excluded from the analysis because five patients had unexpected need for blood transfusion; three patients had inadequate spinal block and had to be converted to general anaesthesia; one patient was too apprehensive and had to be sedated with diazepam. A total of 100 patients completed the study (33 in group S, 33 in group T and 34 in group O).

The three groups were comparable with respect to age, weight, gravidity, exigency of surgery, total operating time and total volumes of intravenous fluid (table I). They were also statistically similar in terms of the baseline vital signs (pulse rate, mean arterial blood pressure, tympanic membrane temperature, peripheral oxygen saturation) and baseline operating room temperatures (table II). The peak sensory block levels (table III) and the APGAR scores of the newborn (table IV) were statistically comparable among the groups.

As shown in table V, 16 (48.5%) of the 33 patients in the placebo group had shivering. This was the highest among the three groups. Thirteen (39.4%) of the 33 patients in the tramadol group had shivering. Shivering was recorded in only 2 (5.9%) of the 34 patients in the ondansetron group. The differences in incidence of shivering were statistically significant between groups S and O ($p=0.000$) and groups T and O ($p=0.001$) but not between groups S and T ($p=0.460$). The overall incidence of shivering in this study was 31%. Of the 13 patients that shivered in group T: 8 had grade 2 shivering while 5 had grade 3 shivering (table VI). Of the two patients that shivered in group O: 1 patient each had grade 1 and grade 2 shivering respectively (table VI). In contrast, all the 16 cases of shivering in the placebo group were grade 3 (table VI).
Incidence of hypotension and cumulative ephedrine consumption across the study groups are shown in table VII. Hypotension occurred most in placebo group and least in tramadol group. Hypotension was noted in 18(54.5%) patients in group S, 13(39.4%) patients in group T and 17(50.0%) patients in group O. Though more patients had hypotension in group O than in group T, patients in group O had the fastest response to fluid boluses. Consequently, cumulative ephedrine consumption was least in group O (42mg) compared to groups S (102mg) and T (54mg). Of the 18 patients who had hypotension in group S, 12(66.7%) needed ephedrine to control their hypotension while in 6 (33.3%) hypotension was treated with fluid resuscitation alone. Of the 13 patients that had intra-operative hypotension in the tramadol group, 7(53.8%) needed ephedrine while 6(46.2%) did not. In the Ondansetron group, 5(29.4%) out of the total of 17 cases of intra-operative hypotension needed ephedrine while 12(70.6%) responded to fluid resuscitation alone. The differences across the groups were not statistically significant in terms of incidence of intra-operative hypotension (p=0.449), proportion that required ephedrine (p=0.105) and the cumulative amount of ephedrine consumed (p=0.301).

Intra operative bradycardia occurred in 4 (12.1%), 1 (3.0%) and 2 (5.9%) of patients in groups S, T and O respectively as shown in table VII. There was no statistically significant differences in occurrence of bradycardia across the three groups (p=0.334).

The incidence of side effects (sedation, headache, nausea and vomiting) among the study groups is shown in table VIII. The highest incidence of sedation was observed in group T (11, 33.3%). There were equal incidences of sedation (6 patients each) in both the S and O groups. This amounts to 18.2% of patients in group S and 17.6% of patients in group O. The differences in the incidence of sedation were not statistically significant among the groups (P=0.226).
Five (15.2%) patients complained of headache in the O group while only 1 (3.0%) patient had similar complaint from the T group. All patients in group S were headache-free. A statistically significant difference exists ($p=0.027$) when the numbers that had headache were compared among the study groups.

There was no incidence of nausea and vomiting in the ondansetron group. Six (18.2%) and 5 (15.2%) patients in Group S and Group T respectively had nausea without retching or vomiting. The highest incidence of vomiting was recorded in group T (6, 18.2%) followed by Group S (2, 6.0%). There were statistical differences among the groups when compared for nausea ($p=0.038$) and vomiting ($p=0.021$)

Compared to the baseline, the mean operating room temperatures (ORT) did not change significantly at 10, 20, 30, 40, 50 and 60 minutes within each group (table IX). Intra-operatively, there was significant drop in the mean tympanic membrane temperature (TMT) compared to the baseline in all the groups. The drop was more precipitous in groups S and O than in group T (fig. 1). However, an interesting pattern was observed in group O as the core temperature dropped to its nadir in 40 minutes, after which it was seen to have started rising towards the baseline (fig. 1). Body core temperature was, however, better preserved in the tramadol group compared to the ondansetron and placebo groups. As shown in figure 2, the least incidence of intra-operative hypothermia was recorded in group T (4, 12.1%) compared to group O (7, 20.6%) and group S (14, 42.4%).
<table>
<thead>
<tr>
<th></th>
<th>Group S (N=33)</th>
<th>Group T (N=33)</th>
<th>Group O (N=34)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age in years</strong></td>
<td>33.4±5.1</td>
<td>31.5±4.7</td>
<td>31.3±6.0</td>
<td>0.264</td>
</tr>
<tr>
<td>(Mean±SD*)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Weight in kg</strong></td>
<td>76.7±4.2</td>
<td>78.5±6.3</td>
<td>77.2±5.4</td>
<td>0.628</td>
</tr>
<tr>
<td>(Mean±SD*)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Gravidity</strong></td>
<td>6/27</td>
<td>5/28</td>
<td>4/30</td>
<td>0.765</td>
</tr>
<tr>
<td>(Primigravida/Multigravida)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Surgical exigency</strong></td>
<td>13/20</td>
<td>16/17</td>
<td>12/22</td>
<td>0.537</td>
</tr>
<tr>
<td>(Elective/Emergency)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Operating time in minutes</strong></td>
<td>74.06±11.25</td>
<td>81.33±11.77</td>
<td>76.15±11.28</td>
<td>0.053</td>
</tr>
<tr>
<td>(Mean±SD*)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Intravenous fluid volume in litres</strong></td>
<td>3.036±0.253</td>
<td>2.991±0.206</td>
<td>3.121±0.225</td>
<td>0.053</td>
</tr>
<tr>
<td>(Mean±SD*)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*SD = Standard Deviation
Table II: Baseline vital signs and baseline operating room temperature

<table>
<thead>
<tr>
<th></th>
<th>Group S (N=33)</th>
<th>Group T (N=33)</th>
<th>Group O (N=34)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pulse rate in beats/min</strong></td>
<td>87.79±13.14</td>
<td>88.73±12.29</td>
<td>93.79±14.76</td>
<td>0.278</td>
</tr>
<tr>
<td>(Mean±SD*)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Mean arterial pressure in mmHg</strong></td>
<td>89.91±8.80</td>
<td>87.67±6.23</td>
<td>89.76±3.29</td>
<td>0.339</td>
</tr>
<tr>
<td>(Mean±SD*)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Tympanic temperature in °C</strong></td>
<td>37.05±0.30</td>
<td>37.09±0.30</td>
<td>37.01±0.29</td>
<td>0.521</td>
</tr>
<tr>
<td>(Mean±SD*)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>SPO₂ in %</strong></td>
<td>96.33±1.32</td>
<td>96.33±2.10</td>
<td>96.29±1.59</td>
<td>0.995</td>
</tr>
<tr>
<td>(Mean±SD*)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Operating room temperature in °C</strong></td>
<td>24.01±0.42</td>
<td>24.12±0.60</td>
<td>24.10±0.40</td>
<td>0.659</td>
</tr>
<tr>
<td>(Mean±SD*)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*SD = Standard Deviation
Table III: Peak sensory block levels compared across the study groups

<table>
<thead>
<tr>
<th></th>
<th>Group S (N=33)</th>
<th>Group T (N=33)</th>
<th>Group O (N=34)</th>
<th>Chi-square</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>T3 Sensory level</td>
<td>1 (3%)</td>
<td>1 (3%)</td>
<td>0</td>
<td>1.051</td>
<td>0.591</td>
</tr>
<tr>
<td>T4 Sensory level</td>
<td>12 (36.4%)</td>
<td>10 (30.3%)</td>
<td>7 (20.6%)</td>
<td>2.065</td>
<td>0.356</td>
</tr>
<tr>
<td>T5 Sensory level</td>
<td>20 (60.6%)</td>
<td>21 (63.6%)</td>
<td>27 (79.4%)</td>
<td>3.153</td>
<td>0.207</td>
</tr>
<tr>
<td>T6 Sensory level</td>
<td>0</td>
<td>1 (3.0%)</td>
<td>0</td>
<td>2.051</td>
<td>0.359</td>
</tr>
</tbody>
</table>
Table IV: APGAR scores of the newborn compared across the study groups

<table>
<thead>
<tr>
<th></th>
<th>Group S (N=33)</th>
<th>Group T (N=33)</th>
<th>Group O (N=34)</th>
<th>Chi-square</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>APGAR 6</td>
<td>1 (3.0%)</td>
<td>0</td>
<td>0</td>
<td>2.051</td>
<td>0.359</td>
</tr>
<tr>
<td>APGAR 7</td>
<td>5 (15.2%)</td>
<td>3 (9.1%)</td>
<td>2 (5.9%)</td>
<td>1.644</td>
<td>0.440</td>
</tr>
<tr>
<td>APGAR 8</td>
<td>11 (33.3%)</td>
<td>8 (24.2%)</td>
<td>14 (41.2%)</td>
<td>2.174</td>
<td>0.337</td>
</tr>
<tr>
<td>APGAR 9</td>
<td>12 (36.4%)</td>
<td>13 (39.4%)</td>
<td>9 (26.5%)</td>
<td>1.369</td>
<td>0.504</td>
</tr>
<tr>
<td>APGAR 10</td>
<td>4 (12.1%)</td>
<td>9 (27.3%)</td>
<td>9 (26.5%)</td>
<td>2.807</td>
<td>0.246</td>
</tr>
</tbody>
</table>
Table V: Number of patients with shivering compared across the study groups

<table>
<thead>
<tr>
<th>Group</th>
<th>Number of patients with shivering</th>
<th>Mean rank</th>
<th>Sum of ranks</th>
<th>Man-Whitney U value</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>S VS T</td>
<td>16 (48.5%)</td>
<td>35.00</td>
<td>1155.00</td>
<td>495.00</td>
<td>0.460</td>
</tr>
<tr>
<td>S VS O</td>
<td>16 (48.5%)</td>
<td>41.24</td>
<td>1361.00</td>
<td>322.00</td>
<td>0.000</td>
</tr>
<tr>
<td>T VS O</td>
<td>13 (39.4%)</td>
<td>39.70</td>
<td>1310.00</td>
<td>373.00</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>2 (5.9%)</td>
<td>26.97</td>
<td>917.00</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table VI: Number of patients with different grades of shivering

<table>
<thead>
<tr>
<th>Grade</th>
<th>Group S</th>
<th>Group T</th>
<th>Group O</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 2</td>
<td>0</td>
<td>8 (24.2%)</td>
<td>1 (2.9%)</td>
<td>Group S vs Group T = 0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Group S vs Group O = 0.896</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Group T vs Group O = 0.005</td>
</tr>
<tr>
<td>Grade 3</td>
<td>16 (48.5%)</td>
<td>5 (15.2%)</td>
<td>1 (2.9%)</td>
<td>Group S vs Group T = 0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Group S vs Group O = 0.000</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Group T vs Group O = 0.376</td>
</tr>
</tbody>
</table>
Table VII: Intra-operative bradycardia, hypotension and cumulative ephedrine consumption compared across the study groups

<table>
<thead>
<tr>
<th></th>
<th>Group S (N=33)</th>
<th>Group T (N=33)</th>
<th>Group O (N=34)</th>
<th>Chi-square</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Incidence of bradycardia</strong></td>
<td>4 (12.1%)</td>
<td>1 (3.0%)</td>
<td>2 (5.9%)</td>
<td>2.194</td>
<td>0.334</td>
</tr>
<tr>
<td><strong>Incidence of hypotension</strong></td>
<td>18 (54.5%)</td>
<td>13 (39.4%)</td>
<td>17 (50%)</td>
<td>1.600</td>
<td>0.449</td>
</tr>
<tr>
<td><strong>Proportion of the hypotensive cases that required ephedrine</strong></td>
<td>12 (66.7%)</td>
<td>7 (53.8%)</td>
<td>5 (29.4%)</td>
<td>4.516</td>
<td>0.105</td>
</tr>
<tr>
<td><strong>Cumulative ephedrine consumption</strong></td>
<td>102mg</td>
<td>54mg</td>
<td>42mg</td>
<td>4.870</td>
<td>0.301</td>
</tr>
</tbody>
</table>
Table VIII: Prevalence of sedation, headache, nausea and vomiting compared across the groups

<table>
<thead>
<tr>
<th></th>
<th>Group S (N=33)</th>
<th>Group T (N=33)</th>
<th>Group O (N=34)</th>
<th>Chi-square</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sedation</td>
<td>6 (18.2%)</td>
<td>11 (33.3%)</td>
<td>6 (17.6%)</td>
<td>2.972</td>
<td>0.226</td>
</tr>
<tr>
<td>Headache</td>
<td>0</td>
<td>1 (3.0%)</td>
<td>5 (14.7%)</td>
<td>7.191</td>
<td>0.027*</td>
</tr>
<tr>
<td>Nausea</td>
<td>6 (18.2%)</td>
<td>5 (15.2%)</td>
<td>0</td>
<td>6.522</td>
<td>0.038*</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>2 (6.1%)</td>
<td>6 (18.2%)</td>
<td>0</td>
<td>7.773</td>
<td>0.021*</td>
</tr>
</tbody>
</table>

*Significant level at 0.05.
Table IX: Within-group changes in mean operating room temperatures compared to the baseline

<table>
<thead>
<tr>
<th>Time</th>
<th>Group S (N=33)</th>
<th>Group T (N=33)</th>
<th>Group O (N=34)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>24.012±0.417°C</td>
<td>24.115±0.602°C</td>
<td>24.100±0.405°C</td>
</tr>
<tr>
<td>10 minutes</td>
<td>24.070±0.257°C</td>
<td>24.121±0.360°C</td>
<td>24.000±0.319°C</td>
</tr>
<tr>
<td>20 minutes</td>
<td>24.139±0.252°C</td>
<td>24.133±0.401°C</td>
<td>24.024±0.324°C</td>
</tr>
<tr>
<td>30 minutes</td>
<td>24.118±0.198°C</td>
<td>24.073±0.379°C</td>
<td>24.015±0.322°C</td>
</tr>
<tr>
<td>40 minutes</td>
<td>24.152±0.224°C</td>
<td>24.139±0.401°C</td>
<td>24.076±0.355°C</td>
</tr>
<tr>
<td>50 minutes</td>
<td>24.091±0.227°C</td>
<td>24.270±0.382°C</td>
<td>24.094±0.342°C</td>
</tr>
<tr>
<td>60 minutes</td>
<td>24.118±0.280°C</td>
<td>24.246±0.431°C</td>
<td>24.053±0.323°C</td>
</tr>
</tbody>
</table>

*P value

0.052 0.295 0.191

Operating room temperatures are in degree Celsius. The values are presented as Mean±Standard Deviation.

*The p value is the lowest obtained within each study group when the mean operating room temperatures at intervals were compared to the respective baseline values.
Figure 1: Mean tympanic membrane temperatures at time intervals across the study groups.
Figure 2: Prevalence of intra-operative hypothermia across the study groups
CHAPTER 5

DISCUSSION

An important finding in this study was the effectiveness of ondansetron in preventing shivering after spinal anaesthesia for caesarean section. Only 2 (5.9%) of the 34 patients in group O shivered while 16 (48.5%) patients shivered in the control group ($P=0.000$). Kelsaka and co-workers$^{27}$ had recorded 8% and 36% incidences of shivering in the ondansetron and saline (control) groups respectively after spinal anaesthesia in non-obstetric patients. Although Kelsaka and colleagues$^{27}$ used 8mg intravenous ondansetron in that study (compared with 4mg in this study), a slightly higher percentage of patients in the ondansetron group had shivering (8% compared to 5.9% in this study). This may be due to their lower operating room temperature (21-22°C) compared to this study (24-26°C). This, however, has to be interpreted with caution since, contrary to expectation, a lower percentage of patients had shivering in their control group compared to the control group of this study (36% vs 48.5%).

The differences between the findings in the study by Kelsaka et al$^{27}$ and that of this study may also be due to the differences in patient population in the two studies (non-obstetric patients versus obstetric patients in this study). It may be that altered physiology of pregnancy increased the sensitivity of the patients to ondansetron in this study.

In the study by Shakya and co-workers$^{21}$ 10% incidence of post-spinal shivering was noted in the ondansetron group compared to 42.5% in the placebo group. As in this study, 4mg of intravenous ondansetron was used by Shakya and colleagues$^{21}$ and the operating room temperature was maintained at 24-26 °C. However, non-obstetric patients were the participants in the study by Shakya and co-researchers$^{21}$ unlike in this study where the participants were obstetric patients. There is an obvious
pattern of response to ondansetron when this study is compared side by side against the studies by Kelsaka et al.27 and Shakya et al.21 Kelsaka and colleagues27 used 8mg ondansetron in non-obstetric population and the recorded incidence of shivering was 8% in the ondansetron group. Shakya and co-workers21 used a lower dose (4mg) of ondansetron in non-obstetric patients and they noted a slightly higher (10%) incidence of shivering among patients given ondansetron. In this study, 4mg ondansetron was administered to obstetric patients and a lower incidence of 5.9% was recorded. The chronology of patient population, dose of ondansetron and the subsequent rate of shivering in the three different studies suggest a heightened sensitivity of obstetric population to intravenous ondansetron.

In this study, less number of patients shivered in the tramadol group (13; 39.4%) compared to the placebo group (16; 48.5%), but the difference was not statistically significant \( p=0.460 \). This is contrary to the findings in the study by Atashkhoyi and colleagues44 who observed that tramadol was statistically superior to placebo (28.57% versus 65.71% incidences of shivering, \( p=0.0001 \)) in preventing post-spinal shivering. However, Atashkhoyi and colleagues44 used 1mg/kg tramadol in that study unlike in this study where a uniform dose of 50mg tramadol was used irrespective of the patient’s weight. The weight-based dosing of tramadol might have contributed to the increased effectiveness of tramadol in prevention of shivering in their study.

This study demonstrated a statistically-significant difference in the incidence of shivering between tramadol and ondansetron groups. Compared to the Ondansetron group, more patients in the tramadol group had shivering (5.9% versus 39.4%, \( P=0.001 \)). Ejiro and co-workers52 recorded a different pattern of results in their study in which they compared the efficacy of tramadol and ondansetron in preventing shivering among women undergoing elective caesarean section under spinal anaesthesia. In their study, larger proportion of patients had shivering in the ondansetron group compared to tramadol group (20.0% versus 16.7%, \( P=0.003 \)). Unlike in this study where the study drugs
were administered to the patients just immediately after depositing the local anaesthetic into the intrathecal space, Ejiro and colleagues\textsuperscript{52} had a delay time of 2 minutes interval from the time of establishing spinal anaesthesia to the time of injecting the study drugs. The reason for this delay was not stated in that study. However, it is possible that this might have contributed to the differences in incidence of shivering between their study and this study.

All the patients in the study by Ejiro and co-researchers\textsuperscript{52} were elective caesarean section cases unlike this study in which both elective and emergency cases were recruited. In fact, in this study, 64.7\% of the patients in the ondansetron group and 51.5\% of those in the tramadol group had emergency caesarean section. Many of these emergency cases were already in labour. It has been suggested that labour has some protective effect on shivering by virtue of labour-induced increase in circulating levels of catecholamines and subsequent augmentation of metabolic heat.\textsuperscript{54} This could partly explain the lower incidence of shivering recorded in the ondansetron group in this study compared to the ondansetron group in the study by Ejiro and co-workers. However, despite the discrepancy in the incidences of shivering between the ondansetron groups of the two studies, the overall incidences of shivering were similar (31\% in this study, 30\% in the study by Ejiro and colleagues).

In this study, the mean core body temperatures dropped below the baseline values in all the groups with the steepest drop noted in the saline group. The drop in body temperature was least precipitous in the tramadol group. The drop in core body temperature during spinal anaesthesia could be attributed to a combined influence of the spinal anaesthesia and relatively cold operating room temperature on the patients’ body. With the interruption of the autonomic flow below the level of spinal block, there would be accompanying vasodilatation below the block. This causes heat redistribution from the core to the periphery and subsequent heat loss from the body. Heat loss to the environment was worsened by a relatively low operating room temperature.
It was observed that for the tramadol and placebo groups, the core body temperature dropped progressively below the baseline. For the ondansetron group, the downward trend in the mean body core temperature was arrested after 40 minutes. After 40 minutes, the temperature started to appreciate towards the baseline, an indication of recovery of the thermoregulatory system. It is not clear by what mechanism ondansetron influences the changes in thermoregulation during anaesthesia and surgery. However, serotonergic activity has been identified in the anatomic and physiologic pathways of both central and peripheral thermoregulation.\textsuperscript{61}

Overall, body core temperature was relatively better preserved in the tramadol group than the placebo and ondansetron groups in this study. Intra-operative hypothermia was recorded in only 12.1% of patients in tramadol group. In contrast, Gamal and Khalid\textsuperscript{62} recorded a higher incidence of hypothermia (60%) among patients given tramadol 1mg/kg prior to induction of spinal anaesthesia for elective caesarean section in an Egyptian hospital. The lower operating room temperature (of 22\textdegree C) in that study (compared to 24-26\textdegree C used in this study) could be the reason for the higher incidence of hypothermia.

In this study, the highest incidence of sedation was observed in the tramadol group. Eleven (33.3\%) of the 33 patients in the tramadol group had sedation compared to 6 patients each in the placebo and ondansetron groups. Neeharika\textsuperscript{63} reported a markedly higher incidence of sedation (56.7\%) among patients given intravenous tramadol for prevention of shivering during lower limb surgery under spinal anesthesia in India. The reason for this may be due to the relatively higher dose of tramadol (1mg/kg) used for that study. Using a low dose (0.5mg/kg) intravenous tramadol as prophylaxis against post-spinal shivering, Reda\textsuperscript{64} observed equal incidences of sedation (of 5\% each) in the tramadol and placebo groups. It is apparent, from the studies by Neeharika\textsuperscript{63} and Reda\textsuperscript{64}, that the sedative effect of tramadol is dose-dependent. However, all the patients that participated in the two studies were non-obstetric patients.
unlike in this study. Using a dose of 1mg/kg intravenous tramadol for prophylaxis against shivering among women undergoing caesarean section under spinal anaesthesia, Atashkhoyi and colleagues\textsuperscript{44} recorded 11.4\% sedation in the tramadol group compared to 5.71\% in the placebo group. In this study, a uniform dose of 50mg tramadol was used for all patients in the tramadol group. Accordingly, the incidence of sedation was expected to be lower than that observed by Atashkhoyi and colleagues.\textsuperscript{44} On the contrary however, the observed incidences of sedation were as high as 33.3\% in the tramadol group and 18.2\% in the placebo group. The overall high incidence of sedation in this study may be accounted for by the fact that over 50\% of patients had caesarean section under emergency conditions. Some of these women had been in labour pains for quite some time and when the pain of labour was finally relieved by spinal anaesthesia, they tended to relax and probably compensate for a rest that had hitherto been deprived them due to pain. Randomization is believed to have subjected all study groups to similar influence of this phenomenon. Yet, sedation occurred more in tramadol group (33.3\%) and less in ondansetron (17.6\%) and placebo (18.2\%) groups. This indicates that tramadol has an intrinsic tendency to cause more sedation than both ondansetron and saline placebo.

An outstanding adverse effect observed in the ondansetron group was mild headache which occurred in 5 (14.7\%) of patients in that group. Headache was also noted in 1 (3.0\%) patient in the tramadol group. These bouts of headache resolved spontaneously within minutes of onset without treatment. Veneziano and colleagues\textsuperscript{65} also noted mild and self-limiting headache as the most frequent side effect of ondansetron when used as anti-emetic agent in patients given cancer chemotherapy for gynaecological malignancies.

The mechanism by which ondansetron induces headache is not clear. Ondansetron is not absolutely a specific 5HT\textsubscript{3} receptor antagonist. It has, in addition, a weak antagonistic effect on 5HT\textsubscript{1}, 5HT\textsubscript{2} and 5HT\textsubscript{4} receptors.\textsuperscript{66} Ondansetron-induced headache has been linked to its antagonistic effects
on 5HT₁ receptors in susceptible individuals; susceptible individuals in this parlance being fasted persons, postoperative patients, and migraine sufferers.⁶⁷ However, Veneziano colleagues⁶⁵ observed that ondansetron-induced headache had no correlation to previous history of recurrent headache or migraine.

There was no record of nausea and vomiting in the ondansetron group in this study. Eleven (33.3%) patients had nausea in the tramadol group and out of this, 6 (18.2%) patients vomited. Eight (24.2%) patients had nausea in the placebo group and out of this number, 2 (6.0%) vomited while 6 (18.2%) did not. A fairly similar trend was observed by Sahoo and colleagues²⁶ in their study on pregnant women undergoing elective caesarean section under spinal anaesthesia. In their study, 7 (26.9%) out of 26 patients in the placebo group had nausea while only 1 (3.8%) of patients in the ondansetron group had nausea.

In this study, ondansetron group demonstrated a superior haemodynamic profile compared to the tramadol and saline groups since cumulative ephedrine consumption was lowest in ondansetron group (42mg) compared to tramadol group (54mg) and saline group (102mg). In agreement with the findings in this study, Sahoo and colleagues²⁶ had demonstrated that Ondansetron 4 mg, given intravenously 5 min before subarachnoid block reduced vasopressor use in parturients undergoing elective caesarean section. In their study, the cumulative phenylephrine consumption were 2mg in ondansetron group (n=26) and 11mg in the placebo group (n=26).

The occurrence of hypotension and bradycardia during spinal anaesthesia has been partly attributed to a sequence of events that culminate in the Bezold-Jarisch reflex (a reflex cardiovascular inhibition).⁶⁸,⁶⁹ Spinal anaesthesia blocks sympathetic flow and reflex vasoconstriction in the blocked segments. This induces venous pooling, creating a picture of hypovolaemia. There is subsequently a poor venous return. This leads to activation of cardiac mechanoreceptors in the Bezold-Jarisch reflex
The Bezold-Jarisch reflex (BJR) includes a paradoxically high vagal activity with an attendant hypotension and bradycardia. Serotonin released (by platelets) during low-volume states has been suggested as a possible trigger for Bezold-Jarisch reflex. The ability of ondansetron to antagonize the activity of serotonin on the serotonergic (5HT) receptors in the BJR pathway may explain its ability to attenuate the hypotensive and bradycardic response to spinal anaesthesia.
CONCLUSION:

This study demonstrated that Ondansetron is significantly superior to tramadol in preventing shivering under spinal anaesthesia in women undergoing caesarean section. Side effect profile was also better with ondansetron than with tramadol as fewer patients had sedation, nausea and vomiting in the ondansetron group. However, during spinal anaesthesia, body core temperature was better preserved with tramadol compared to ondansetron.

This study could not establish a direct causal relationship between core hypothermia and shivering during spinal anaesthesia.
RECOMMENDATION:

From this study, the following recommendations are hereby made:

1. Single bolus intravenous ondansetron should be used routinely as a regimen to prevent shivering in women undergoing caesarean section under spinal anaesthesia.

2. Prospective studies should be carried out in the same population to look for the minimum dose of ondansetron that could give a satisfactory anti-shivering effect without causing headache as side effect.

3. Prospective studies should be carried out to compare ondansetron versus tramadol in terms of efficacy in treatment of shivering during spinal anaesthesia in the same population.
LIMITATIONS OF THE STUDY

1. The exact temperature of the crystalloid infusion and hyperbaric bupivacaine used were difficult to monitor in the study. However, all crystalloids were not warmed and were kept outside the operating room until they were ready to be used. All hyperbaric bupivacaine were left in the body of the refrigerator in the theatre pharmacy until they were ready to be used when they were brought and used immediately.

2. Oxytocin which was a frequently used oxytocic agent in this study is emetogenic agent and it was difficult to differentiate vomiting caused by this drug from that of the study drugs, especially tramadol.
REFERENCES


46. Safavi M, Honarmand A, Rahmanikhah E, Badiei S, Attari M. Intrathecal meperidine versus intrathecal fentanyl for prevention of shivering in lower limb orthopaedic surgeries under spinal


APPENDIX I

PATIENT INFORMED CONSENT

Dear Patient,

You are being asked to participate in this research study. You will be made to understand enough, and in clear terms, the nature of the research to enable you make an informed judgment. You will then be, subsequently, asked to sign a consent if you wish to participate.

The research study is titled: comparison of intravenous tramadol versus ondansetron for preventing shivering during caesarean delivery under spinal anaesthesia. The purpose is to determine the relative efficacy each of tramadol and ondansetron for preventing spinal anaesthesia-induced shivering during caesarean section.

Your participation in this research is confidential; only the researcher will have access to your identity and information that can be associated with your identity. In the event that the research findings are published no personally-identifying information about you will be disclosed or divulged.

Benefits:

1. You will not be required to pay for the syringes and drugs used for the research study. The researcher will take care of them.

2. The results obtained will help provide a better care for other persons needing medical attention in the future.

There will be no additional charges to you for taking part in the study and taking part in the study will not expose you to additional risks aside those of anaesthesia and surgery. The choice to participate or not is voluntarily yours to make. If you decide not to participate, all the usual and customary care will still be made available to you without prejudice. If you agree to participate, you still maintain the prerogative to withdraw at any time or stage. The UNTH ethics committee, which is responsible for making sure
that researches are appropriate, has reviewed the nature and gamut of this study before its commencement.

RESPONSE:

I have read the above statements and understand the meaning in clear terms. I have also been able to ask questions and express concerns all of which have been appropriately and satisfactorily addressed by the researcher. The purpose, benefits and potential risks of the research study have been made clear to me. I hereby give my free, well-informed consent to be a participant in the study:

..............................................................................................................................................................

Name and Signature/thumb print of subject.

..............................................................................................................................................................

Name and signature of Researcher.

..............................................................................................................................................................

Name and signature/thumb print of witness.
APPENDIX II

DATA COLLECTION FORM

A. Biodata

Name:……………………………… Hospital number………………

Age:………………Marital status:………………Gravidity:………………

Gestational age:………………

B. Medications received before arriving at the theatre:……………………………………

C. Basic vital parameters:

Weight(Kg) …….. Temperature(°C)……………… Pulse Rate………………

Blood Pressure……………… Mean Arterial Blood Pressure………………

Peripheral oxygen saturation (SPO₂)………………

D. Vital signs and sensory level at 5 minutes intervals:

<table>
<thead>
<tr>
<th></th>
<th>0 min (Basic)</th>
<th>5 min</th>
<th>10 min</th>
<th>15 min</th>
<th>20 min</th>
<th>25 min</th>
<th>30 min</th>
<th>35 min</th>
<th>40 min</th>
<th>45 min</th>
<th>50 min</th>
<th>55 min</th>
<th>60 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulse rate (b/m)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood pressure (mmHg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean arterial pressure (mmHg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SpO₂ (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensory level</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
E. Tympanic temperature at 10 minutes intervals

<table>
<thead>
<tr>
<th>Temperature (°C)</th>
<th>0 minute (Basic)</th>
<th>10 minutes</th>
<th>20 minutes</th>
<th>30 minutes</th>
<th>40 minutes</th>
<th>50 minutes</th>
<th>60 minutes</th>
</tr>
</thead>
</table>

F. Shivering grade at 5 minutes intervals:

<table>
<thead>
<tr>
<th></th>
<th>5 min</th>
<th>10 min</th>
<th>15 min</th>
<th>20 min</th>
<th>25 min</th>
<th>30 min</th>
<th>35 min</th>
<th>40 min</th>
<th>45 min</th>
<th>50 min</th>
<th>55 min</th>
<th>60 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

G. Sedation score at 5 minutes intervals:

<table>
<thead>
<tr>
<th></th>
<th>5 min</th>
<th>10 min</th>
<th>15 min</th>
<th>20 min</th>
<th>25 min</th>
<th>30 min</th>
<th>35 min</th>
<th>40 min</th>
<th>45 min</th>
<th>50 min</th>
<th>55 min</th>
<th>60 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
H. Vasopressor (ephedrine) use

<table>
<thead>
<tr>
<th>Amount</th>
<th>Time given</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

I. Total IV Fluid Volume


J. Other adverse effects.

Nausea……………

Vomiting…………..

Others indicate……………

…………….

……………..

K. Total Operating Time


L. APGAR Score of Newborn

<table>
<thead>
<tr>
<th></th>
<th>1 minute</th>
<th>5 minute</th>
<th>10 minute</th>
<th>15 minute</th>
</tr>
</thead>
<tbody>
<tr>
<td>APGAR Score</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
UNIVERSITY OF NIGERIA TEACHING HOSPITAL  
ITUKU-OZALLA, P.M.B. 01129, ENUGU, NIGERIA,  
TEL: 042-252022, 252573, 252172, 252134, Fax: 042-252665  
E-mail: cdunth@infoweb.abs.net

Prof. O. O. MBONU, MB (Lond.), FRCS(c), FWACS  
Chairman, U.N.T.H. Management Board

Barr. (Mrs.) M. U. OKONKWO, LLB. [Hons.], BL, MPA, MRISAN, PMI, FCMA  
Director of Administration/Secretary  
U.N.T.H. Management Board

Dr. A. U. MBAH, MD [LODZ], FNCP, FNIM, (KS)  
Chief Medical Director

Dr. C. C. AMAH, MBBS, FWACS, FICS, MNIM, MIP  
Chairman, Medical Advisory Committee

Date: 22nd November, 2013.

NHREC/05/01/2008B - FWA00002458 – IRB00002323

ETHICAL CLEARANCE CERTIFICATE

TOPIC: PREVENTION OF POST-ANAESTHETIC SHIVERING UNDER  
SUB-ARACHNOID BLOCK FOR CAESAREAN SECTION:  
A PROSPECTIVE, RANDOMISED, PLACEDBO-CONTROLLED  
STUDY COMPARING TRAMADOL VERSUS ONDANSETRON

BY: DR. NNACHETA, TIMOTHY EKENE

FOR: A DISSERTATION FOR PART II FELLOWSHIP EXAMINATION  
OF THE FACULTY OF ANAESTHESIA, NATIONAL  
POSTGRADUATE COLLEGE OF NIGERIA

This research project on the above topic was reviewed and approved by the University of Nigeria Health Research Ethics Committee. This certificate is valid for one year from date of issue.
Our Ref:  

DR NNACHETA T. EKENE  
DEPT OF ANAESTHESIA,  
UNTH,  
ENUGU

Date: 22/8/2014

Dear Sir/Madam,

RE: REGISTRATION OF TITLE OF DISSERTATION: ASSESSMENT OF PROPOSAL FOR THE PART II EXAMINATIONS IN THE FACULTY OF ANAESTHESIA

We wish to refer to your letter on the above subject matter and inform you that your proposal titled: “PREVENTION OF POST-ANAESTHETIC SHIVERING UNDER SUB-ARACHNOID BLOCK FOR CAESAREAN SECTION: A RANDOMISED, CONTROLLED STUDY COMPARING TRAMADOL VERSUS ONDANSETRON.” has been re-assessed.

You may now proceed with the study.

The attached are the comments and recommendations of the assessor(s) for guidance, in the conduct of your project. However, you are required to effect the corrections and submit four (4) corrected copies to the College for the records.

We wish you the best of luck.

Yours faithfully,

[Signature]

Mrs. E. A. Akpabio  
Examination Officer  
E-mail: adanmaakpabio@yahoo.com  
For: College Registrar