

**COMPARISON OF INTERVENTIONAL USE OF TRAMADOL AND
PETHIDINE FOR THE MANAGEMENT OF SHIVERING DURING SPINAL
ANAESTHESIA**

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DECLARATION

I hereby declare that this research work is original. This work has not been submitted to any college for the award of a fellowship, neither has it been submitted to any medical journal for the purposes of publication.

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DEDICATION

This work is dedicated to the Almighty God for His infinite grace and my parents, late
Mr. George Ukpabio and Mrs Emma Ukpabio.

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LIST OF ABBREVIATIONS

%	-	Percentage
µg	-	Microgramme
ASA	-	America Society of Anesthesiologists
DBP	-	Diastolic Blood Pressure
IV	-	Intravenous
kg	-	kilogram
MAP	-	Mean Arterial Pressure.
mg	-	Milligramme
mmHg	-	Millimetre mercury
°C	-	Degree Centigrade
SBP	-	Systolic Blood Pressure
SD	-	Standard Deviation
SpO ₂	-	Peripheral Oxygen saturation
SPSS	-	Statistical Package for Social Sciences

SUMMARY

Back ground:

Shivering occurring under spinal anaesthesia is uncomfortable for patients and places the body under physiologic stress. It can increase oxygen consumption, metabolic rate and cause artifacts on the monitor. The incidence of shivering has been found to be quite high, approximating 40-60% in different studies. In lower limb orthopaedic surgery, regional anaesthesia provides useful benefits such as reduced incidence of peri-operative deep vein thrombosis and better postoperative pain relief compared with general anaesthesia. The deleterious effect of shivering warrant a prompt and rapid control on occurrence.

Aim and Objective:

This study compared the effectiveness of intravenous 0.35 mg kg⁻¹ pethidine and intravenous 0.25 mg kg⁻¹ tramadol in abolishing shivering in patients undergoing spinal anaesthesia for lower limb orthopaedic surgery.

Patients and Methods:

This was a prospective, randomised, double-blinded study conducted in 100 ASA grade I and II eligible patients aged between 15 and 65 years of age who were scheduled for lower limb orthopaedic surgery and shivered during spinal anaesthesia.

All the patients had preloading with warmed normal saline administered at a dose of 10 ml kg⁻¹. Spinal anaesthesia was induced in the sitting position with 3 mls of 0.5% hyperbaric bupivacaine before being positioned for surgery. When shivering occurred, the patients were given either intravenous 0.35 mg kg⁻¹ pethidine or intravenous 0.25 mg kg⁻¹ tramadol based on the group allocation; taking notice of a change in the intensity or disappearance of shivering as well as haemodynamic parameters such as non-invasive

blood pressure, pulse rate, peripheral oxygen saturation and temperature at intervals. Also noted were time to disappearing and recurrence of shivering as well as outcomes such as level of sedation, nausea and vomiting.

Results:

A total of 100 patients met the inclusion criteria and participated in the study out of 394 consecutive patients. The incidence of shivering was 25.38%. Complete disappearance of shivering occurred in 41(82%) patients in the tramadol group compared to 34(68%) in the pethidine group ($p=0.0059$). Recurrence of shivering after treatment was seen in 10(20%) patients in tramadol group compared to 6(12%) in the pethidine group ($p=0.555$). The most common side effect noted was nausea occurring in 16(32%) patients in the tramadol group compared to 26(52%) of the pethidine group ($p=0.149$). A total of 17(34%) patients in the tramadol group had sedation compared to 6(12%) in the pethidine group ($p=0.285$).

There were no significant differences in the mean arterial pressures, heart rate and axillary temperature of the two groups.

Conclusion:

The result of this study revealed that intravenous 0.25 mg kg^{-1} tramadol use for abolishing spinal anaesthesia induced shivering is as effective as intravenous 0.35 mg kg^{-1} pethidine in lower limb orthopaedic surgery, however its use is associated with more sedation.

CHAPTER ONE

INTRODUCTION

Shivering can be defined as a physiological response to hypothermia with the involuntary use of striated muscle contractions to produce heat.¹ It may occur following both general and central neuraxial anaesthesia. Prolonged impairment of thermoregulatory autonomic control under anaesthesia along with the cold environment of the operating room contribute to the fall of core body temperature and hence shivering. Shivering during neuraxial anaesthesia is a common and distressing side-effect. In temperate regions of the world, studies have shown that it develops in up to 55% of patients.² A study by Kolawole and Bolaji on subarachnoid block for lower abdominal and lower limb surgery reported an incidence of 8.18%.³

Spinal and epidural anaesthesia cause shivering by producing vasodilatation thus enhancing core-to-peripheral redistribution of heat, loss of thermoregulatory vasoconstriction below the level of blockade and decreased vasoconstriction threshold.^{4,5,6} Other known causes of shivering include blood transfusion reactions, drug reactions and pre-existing high grade fever. Perioperative hypothermia, however, is the most common cause of shivering.

Patients who shiver have increased oxygen consumption predisposing them to hypoxaemia, which could lead to delayed discharge from post anaesthesia care unit. The use of oxygen therapy is therefore advocated.^{2, 4} Shivering movements during central neuraxial anaesthesia may interfere with blood pressure, electrocardiogram and pulse oximetry monitoring. Apart from being an uncomfortable experience with a potential for reducing patient's satisfaction, its deleterious effects warrant prompt control on occurrence.

Non pharmacological measures of managing shivering involve the use of additional drape covers and blankets. These have been shown to reduce the intensity of

shivering and constitute one of the principal management for centers in Ilorin and Benin.³

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Numerous drugs have been used in the interventional management of shivering, with pethidine being one of the most effective and widely used.⁷ Intravenous tramadol, a centrally acting analgesic with weak opioid agonist properties, has also been useful in the treatment of shivering.⁸

The aim of this study was to compare the interventional use of tramadol and pethidine as anti-shivering agents for spinal anaesthesia induced shivering.

Relevance of Study

Spinal anaesthesia is a safe and increasingly popular anaesthetic technique. The effective care of patients under regional anaesthesia can be a challenge especially in resource poor setting where limited option of drugs to use exists.

Shivering occurring intraoperatively can be distressing. The non availability of opioids is a major factor in managing spinal anaesthesia induced shivering. Opioids, being controlled by the government regulations are not readily available.

Tramadol, though a weak opioid is commonly available. Its lack of addiction aids its availability as it is not subject to strict control.

Spinal anaesthesia is increasingly being used for lower limb and lower abdominal operative procedures in the sub region^{3,4}. The planning and execution of an anaesthetic care protocol that achieves better comfort for the patient is desirable.

AIMS AND OBJECTIVES

Aim of Study

To compare the effectiveness of tramadol and pethidine in abolishing spinal anaesthesia induced shivering in patients scheduled for lower limb orthopedic surgery.

Specific Objectives

- 1) To determine the incidence of shivering under spinal anaesthesia in patients undergoing lower limb orthopedic surgery.
- 2) To compare the efficacy of tramadol and pethidine in abolishing shivering during spinal anaesthesia using cessation and reoccurrence in shivering as measurable variables.
- 3) To compare the side-effect profile of tramadol and pethidine used in abolishing shivering using nausea, vomiting, pruritus and sedation as measurable variables.
- 4) To identify the proportion of patients with effective response to the study drugs.

Null Hypothesis

Tramadol is as effective as pethidine in abolishing shivering during spinal anaesthesia in patients undergoing lower limb orthopedic surgery

Alternative Hypothesis

Tramadol is not as effective as pethidine in abolishing shivering during spinal anaesthesia in patients undergoing lower limb orthopedic surgery.

CHAPTER TWO

LITERATURE REVIEW

Central neuraxial anaesthesia (epidural and subarachnoid) is a popular and safe anaesthetic technique for elective and emergency surgical procedures. The reason for this could be because it requires fewer drugs and equipment, making it attractive for resource poor environment. It is also very useful for pain management in the immediate post-operative period.

One of the common complications of this technique is shivering, reported to occur with an incidence of 39% - 57%.^{2, 9, 10, 11} This range of incidences was observed in studies done in temperate climate consisting of a variety of surgical procedures. In tropical climates, a study by Edomwonyi et al⁴ reported an incidence of 23.5% in parturients following caesarean section. Kolawole et al³ in another study reported an incidence of 8.18%. The difference in the incidences may be attributed to different sample population, one being parturients and the other non parturients.

Horn *et al*¹² established two distinct types of shivering. The majority is associated with cutaneous vasoconstriction and relates to thermoregulatory shivering. The minority is associated with cutaneous vasodilatation and relates with non-thermoregulatory shivering. Thermoregulatory shivering is thought to occur as a physiological response to hypothermia. This response is mediated in the hypothalamus which acts as a thermostat.

The hypothalamus contains neurons which are sensitive to changes in skin and blood temperatures. These temperature regulating centers are found in the anterior portion of the hypothalamus called the preoptic area. It receives input from peripheral and central thermoreceptors. These areas include the skin surface, deep abdominal and thoracic tissues, the brain and spinal cord. Afferent signals of temperature from the head and neck reach the hypothalamus through the trigeminal nucleus. The temperature sensory signals

from the preoptic area and those from the periphery are combined in the posterior hypothalamus to control heat producing and conserving response in the body.⁵ These responses include noradrenaline release from sympathetic fibres to constrict skin blood vessels, piloerection to trap air close to the skin and adrenaline release from the adrenal medulla to increase thermogenesis.¹³ The mechanism for non-thermoregulatory shivering is not fully known.

Although there are no studies to show documented risk factors for intraoperative shivering under neuroaxial anaesthesia, there is weak evidence to support the association of risk factors such as the level of neuroaxial block, gender and age with hypothermia.^{2, 14, 15} There are also, documented risk factors for shivering postoperatively after general anaesthesia. They include younger age, hypothermia, prolonged surgery and orthopaedic endoprosthetic surgery.^{1, 14}

Anaesthesia and surgery contribute to substantial loss of heat in the operating theater.¹⁶ The hypothermia typically results from heat loss due to a combination of radiation, convection, conduction and evaporation mechanisms.¹⁷ The thermoregulatory system coordinates defenses against cold and heat to maintain internal body temperature within a narrow range, thus optimizing normal physiologic and metabolic functions. Both general and regional anaesthesia are known to affect the efficiency of this homeostatic thermoregulatory system and may result in different degrees of perioperative hypothermia.¹⁸

The shivering occurring postoperatively after general anaesthesia is commonly associated with halothane leading to the coinage of the term, "halothane shakes". This in no way disparages the contribution of other risk factors such as American Society of Anesthesiologists' physical status classification of the patients on account of shivering in response to normothermic or hyperthermic patients, surgical procedures where major body

cavities are exposed, the use of cold intravenous fluids, volume of intravenous replacement, duration of anaesthesia or surgery and ambient operating room temperature.^{18, 19}

Crowley and Buggy² posited in a review article that though some predisposing factors are common to shivering under general and neuraxial anaesthesia, the threshold for shivering to occur under neuraxial anaesthesia may be less for males relative to females and also this threshold tends to increase with age. The reason females may be less prone to shivering could be as a result of having more body fat than males and consequently they are more resistant to hypothermia.

Shivering under anaesthesia is often not considered an important intraoperative adverse event. In a survey of 33 clinical problems, physician anaesthetists ranked shivering eighth when the frequency was considered and twenty-first when asked about the importance of preventing this complication.²⁰ However shivering increases oxygen consumption by 200% - 500%⁵ and may consequently cause hypoxaemia. Hypoxaemia in patients with reduced cardiorespiratory reserves can increase morbidity and sometimes mortality.

Other reported consequences of shivering include raised carbon dioxide production, lowered mixed venous oxygen saturation and lactic acidosis.^{14,21} It also causes difficulty in the ability to correctly measure haemoglobin oxygen saturation using the peripheral pulse oximetry and accuracy with non-invasive blood pressure measurement.^{7,22,23} Giving unreliable measurements could be harmful in haemodynamically unstable or even stable patients.

The temperature regulatory system is usually divided into three components: thermosensors and afferent neural pathways, integration of thermal inputs and effector pathways for autonomic and behavioural regulation. The majority of ascending afferent

pathways terminate in the reticular formation and hypothalamus. Multiple inputs from various thermosensitive sites are integrated within the spinal cord. The effector pathway uses skin vasomotor activity, shivering and sweating. Although shivering can be independently initiated by cold sensitive spinal neurones in some species, supraspinal facilitation is necessary in humans.¹ The efferent shivering pathway starts at an area between the anterior and posterior hypothalamus and makes multiple connections with the reticular formation in the mesencephalon, pons and medulla before it ends at the alpha motor neurones. Heat loss is normally regulated without the response of shivering. This is because thermoregulatory vasoconstriction decreases cutaneous heat loss and constrains metabolic heat to the core thermal compartment. Thermoregulatory shivering is thus, a last resort mechanism that is activated when behavioural compensation and maximal cutaneous vasoconstriction are insufficient to maintain core temperature. Thermoregulatory shivering is principally mediated via bioamines such as serotonin and noradrenaline, peptides and cholinergic receptors.¹

The shivering that occurs during spinal anaesthesia is accompanied by central hypothermia and peripheral vasoconstriction above the level of block, and is thus primarily thermoregulatory mediated.^{1, 13} Preganglionic sympathetic blockade and skeletal muscle paralysis occur below the level of block.

Non pharmacologic methods have been useful in the management of shivering. Warming humidified inspired gases and insulating the patient's environment have been particularly studied. Pflug *et al*²⁴ demonstrated that active warming abolished shivering. To achieve this, inspired gases were humidified and warmed to 42 ó 47 °C and the patients were insulated with blankets. Mekajavic and Eiken²³ reported that radiant heat applied to the facial area reduced shivering. Although only seven subjects were studied, all had observed inhibition of shivering suggesting that the trigeminal region contributes to overall

thermoregulatory response. Kolawole and Bolaji³ in their prospective observational study used additional drape covers to reduce the intensity of shivering.

Edomwonyi et al⁴ in another prospective observational study used additional drapes and oxygen therapy to manage shivering. The study population were all parturients. They showed a higher incidence of shivering in those who had spinal anaesthesia as opposed to those who had general anaesthesia. Body temperature is often not monitored in patients undergoing regional anaesthesia, therefore anaesthesiologists are usually unable to accurately estimate the hypothermic state of their patients.²⁵ This makes significant, undetected hypothermia more likely and increases the chances of shivering occurring under regional anaesthetic technique.

Radiant heating and insulating drape cover are non pharmacological methods of managing shivering. While these methods may still continue to be employed, pharmacological methods are more popular for the therapeutic management of shivering.¹³ There are in existence efficient drugs for ameliorating shivering and they act on one or more ways on thermoregulatory shivering. Pethidine is an opioid that possesses anti-shivering effect. It has different pharmacological properties which include mu and kappa agonism, alpha 2 adrenoceptor agonism and an anticholinergic effect. A combination of all these pharmacological properties of pethidine contributes to its anti-shivering effect.¹

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A meta-analysis by Kranke *et al*²⁰ analysed data from 20 randomized comparative clinical trials to ascertain the relative efficacy of pharmacological intervention that was used in the treatment of shivering. This meta-analysis consisted of 944 patients receiving interventions of meperidine (pethidine), morphine, fentanyl, ketanserin, clonidine, methylphenidate, doxapram, nefopam, lidocaine, tramadol and magnesium. All the studies

were done for patients undergoing general anaesthesia except two that had neuraxial (spinal and epidural) anaesthesia.

The active intervention doses most often tested, included intravenous pethidine 25 mg^{26,27,28}, intravenous morphine 2.5 mg²⁶, intravenous fentanyl 25 g²⁶, intravenous alfentanil 250 g^{27,28}, intravenous tramadol 50 mg²⁹, intravenous clonidine 150 g^{30,31}, intravenous lidocaine 50 mg³², intravenous doxapram 100 mg^{33,34} and intravenous magnesium 30 mgkg⁻¹.³⁵ Since many of these interventions were tested in one small trial, undue weight could not be given to their antishivering efficacy, only interventions that were used in at least two randomised trials were analysed. A statistical significant difference between the intervention and placebo was assumed when 95% of confidence interval (CI) of the relative risk (RR) did not include 1. This was because all combined data were clinically and statistically homogenous ($P > 0.1$) so a fixed effect model was used by the authors of the meta-analysis. All the interventions in at least two randomised trials were analysed and found to be statistically more significant than placebo. These interventions included pethidine, clonidine, alfentanil and doxapram.

Some of the pertinent trials include one by Mercadante et al³⁰ where shivering in 60 parturients who received epidural analgesia for labour pains were randomised and treated with intravenous clonidine 150 ug, intravenous pethidine 50 mg and placebo. Twenty patients each had these study drugs administered. There was no increased incidence of side effects such as pruritus, nausea and vomiting among the treatment groups. The focus of the authors was on the response of intervention after treatment rather than the incidence of shivering, hence they did not control factors that might influence the incidence of shivering such as the temperature of epidural drug used and the temperature of intravenous fluids. Clonidine was observed to be as effective as pethidine (p value > 0.05), though causing a greater reduction in heart rate.

A trial by Pauca et al²⁶ randomised 100 consecutive patients who shivered after general or regional anaesthesia in the recovery room following intra-abdominal procedures to receive intravenous morphine 2.5 mg, intravenous fentanyl 25 ug, intravenous pethidine 25 mg and placebo. The duration of surgery was less than 120 minutes, the difference noted with respect to cessation of shivering for pethidine at 20 minutes after injection was highly significant (p value < 0.001). The study involved patients who had both general or regional anaesthesia without any consideration that heat loss may be more in one group since patients who have regional anaesthesia tend to shiver above the level of the block. Furthermore no valid consent were obtained from the patients selected for the study as it was the authors opinion that it was too cumbersome to do so, constituting a breach of ethical protocol. It was concluded that morphine and fentanyl were not effective in treating shivering (P value > 0.05).

A study by Kizilirmak et al³⁵ randomised 75 patients who had general anaesthesia and shivered during recovery to receive intravenous pethidine 0.5 mg/kg, intravenous magnesium sulphate 30 mg/kg and placebo. The mean duration of surgery was a 100 minutes. The types of surgeries done were not stated and all the studied patients had distal oesophageal temperature monitoring in the postoperative recovery period. Most patients would find that level of monitoring invasive, uncomfortable and undesirable . Each of the intervention and control groups had 25 patients. Findings showed that the patients in the pethidine and magnesium sulphate groups had significantly shorter duration of shivering than placebo (p value < 0.01). Both pethidine and magnesium sulphate were just as effective (p value > 0.05), though the duration of shivering with pethidine was shorter.

A study by Lyons et al²⁷ randomised 51 patients who shivered after general anaesthesia during recovery to receive intravenous alfentanyl 250 ug, intravenous pethidine 25 mg and placebo. The types of surgery done and their estimated duration were

not stated. This information would give an indication of susceptibility to hypothermia and consequently shivering. The interventional group had 18 patients each while the placebo had 15. All study groups should have been allotted same number of patients to help further reduce bias. Both alfentanil and pethidine proved significantly better than placebo (p value < 0.005). There was a highly significant incidence of reshivering associated with alfentanil (p value < 0.005).

Some of the studies discussed above pooled shivering due to both regional and general anaesthesia. Most however, studied shivering occurring in the recovery room. This study intends to investigate shivering as a result of spinal anaesthesia occurring in the operating room in lower limb orthopedic surgeries.

Findings in the meta-analysis by Kranke *et al*²⁰ showed that only one study of the twenty analysed included either tramadol or pentazocine. Pethidine was used in five of the trials. Efficacy was established in this meta-analysis for pethidine, clonidine, alfentanil and doxapram. No conclusion could be drawn with regards to the efficacy of tramadol or pentazocine possibly because they were not as widely used.

Tramadol is a centrally acting analgesic with weak affinity for mu opioid receptors and even weaker affinity for delta and kappa opioid receptors. It can be administered intravenously to provide pain relief and it also has anti-shivering properties.⁷ It inhibits the neuronal re-uptake of norepinephrine and 5-hydroxytryptamine.¹ In a study conducted by Chan *et al*¹⁰, intravenous tramadol given at a dose of 0.25 mg/kg and 0.5 mg/kg to 12 patients in each group effectively controlled shivering during caesarean delivery under spinal and epidural anaesthesia compared to normal saline placebo in 12 patients (p value < 0.001). In this double blind randomised study, increasing the dose to 0.5 mg/kg did not improve its therapeutic effect. There was no explanation as to why a lower dose of 0.25 mg/kg was more effective than a higher dose of 0.5 mg/kg. It is possible that since the

focus of the authors was on response to drugs after treatment rather than the incidence of shivering, the methodology and the sample size of 12 will limit how the study can be extrapolated.

Tramadol is also more readily available especially in comparison to the less available and more controlled pethidine. Its distinct pharmacodynamic advantage in the treatment of shivering is in its weak sedating and respiratory depressing potential³⁶. This fact was observed when Tsai et al³⁷ compared intravenous tramadol 0.5 mgkg⁻¹, intravenous amitriptyline 20 mgkg⁻¹ and intravenous pethidine 0.5 mgkg⁻¹ for treatment of post epidural shivering in 45 parturients scheduled for elective caesarean section. In this randomised study, 15 parturients each were administered these drugs as treatment for shivering. There was a significantly more frequent incidence (33%) of sedation in the pethidine group when compared with tramadol (7%) and amitriptyline (0%) (p value < 0.01). Sedation in obstetric patients may prevent early maternal-child bonding. For such a moderate dose of intravenous pethidine 0.5 mgkg⁻¹ to cause such significant side effects as reported is worrisome as this may limit its use in parturients. It is possible that the sample size was not large enough resulting in such large differences in sedation.

Some authors have investigated the prophylactic control of shivering with success. Eberhart *et al*¹⁴ studied how prophylactic control of core temperature helped reduce the occurrence of shivering. In their observational prospective study, 1000 patients who had general anaesthesia were observed in the post anaesthesia care unit. The type of surgeries which would suggest susceptibility to hypothermia and shivering were not stated. The procedures lasted for an average duration of 70minutes. A significant independent risk factor identified for shivering was hypothermia (p value < 0.0001). However it was noted that most of the patients were admitted into the post anaesthesia care unit hypothermic with a mean core body temperature of 35.8⁰C. Eleven percent had a core temperature of

less than 35°C. This seems to correlate with 116 patients (11.6%) that shivered in the study. The relative short duration of only one hour in the post anaesthesia care unit where the patients were assessed may account for this incidence.

Najafianaraki et al³⁸ evaluated the effect of warm and cold intrathecal bupivacaine on shivering under spinal anaesthesia. Seventy eight parturients for spinal anaesthesia were randomly assigned to receive either intrathecal heavy bupivacaine at 23 °C or at 4 °C. The two groups consisted of 39 parturients each. Incidence of shivering with warm bupivacaine was 8% while incidence with cold bupivacaine was 39% (p value = 0.002). The methodology showed study was a randomised double blinded clinical one. The operating room temperature was maintained at 23 °C, intravenous fluids administered at a temperature of 37 °C and supplemental oxygen therapy was used for all participants. The methodology, however, would have been better without the use of intrathecal fentanyl in all participants. This is because, being an opioid, fentanyl could confound the results of the study. Fentanyl is a phenylpiperidine derivative³⁹, being in the same class of compounds from which pethidine is derived. There was no mention of any intervention for shivering in their methodology.

Some investigators studied the effects of proven antishivering agent used intrathecally as prophylaxis. Roy *et al*⁴⁰ established the efficacy of intrathecal pethidine in a randomised prospective double blinded study. They studied 40 parturients for elective operative delivery under spinal anaesthesia. Twenty patients each were randomised to receive either intrathecal pethidine 0.2 mg/kg or an equivalent volume of saline in the spinal injectate of heavy bupivacaine and morphine. It was found that the incidence of shivering was less in the pethidine group (p value < 0.02). All subjects in their study were parturients and the use of hyperbaric bupivacaine 0.75% (10.5mg) may actually be a contributory reason for the high incidence of shivering of 85% noticed. This could possibly

be a result of direct stimulation of injected concentration of bupivacaine causing shivering. All intravenous fluids used for preloading were warmed to 37°C and oxygen therapy was administered to all participants. Also a sample size of 20 participants per group seemed inadequate in the study design.

Usta *et al*⁴¹ investigated the use of dexmedetomidine for the prevention of shivering during spinal anaesthesia. The study was prospective, randomised and double blinded. The methodology for arriving at the sample size was not clear and seemed to be based on a preliminary study by the authors. In comparing a sample size of 30 participants of two groups, they reported it effectively decreased the incidence and severity of shivering related to spinal anaesthesia with 10% shivering in dexmedetomidine group compared with 56% in the control. Their findings revealed very high statistical significance with a *p* value = 0.001. The operating room temperature was maintained at 21 °C and intravenous fluids administered at room temperature, however no mention was made of the type or duration of surgeries. This could introduce bias as these factors can predispose to hypothermia and cause shivering in either of the study groups.

On the contrary to dexmedetomidine, Browning *et al*⁴² investigated and reported that ondansetron does not prevent or decrease shivering intensity under neuraxial anaesthesia. This study consisted of a sample size of two groups of 60 parturients each for elective operative delivery under combined spinal epidural anaesthesia. The women received either intravenous ondansetron 8 mg or saline before combined spinal epidural anaesthesia. Both ondansetron and placebo groups had a similar incidence of 40% shivering, thus did not differ statistically (*p* value = 0.54). Participants who shivered were administered intravenous clonidine 30 ug with good effect. All participants received intravenous fluids at room temperature. The authors were of the opinion that it was

possible that ondansetron did have antishivering properties but their study had insufficient power to detect it in spite of the seemingly large sample size.

Jeon *et al*⁹ reported that intrathecally injected clonidine did not reduce the incidence of shivering. One hundred and fifty orthopaedic patients for spinal anaesthesia using 12-15 mg hyperbaric bupivacaine were randomly assigned to receive either intrathecal clonidine 150 ug, intravenous clonidine 1 ug/kg or saline as placebo. The incidence of shivering with placebo and intrathecal clonidine was 40% and 34% respectively while incidence with intravenous clonidine was 8%, significantly lower than the other groups (p value < 0.01). Ambient temperature of operating room was 23 °C. All fluids were administered at room temperature, and patients were completely covered with drapes except for the head and neck area. Although the types of orthopedic surgery done were not mentioned, endoprosthetic procedures could theoretically cause hypothermia and account for the difference.¹⁴ Furthermore the authors opined that clonidine injected intrathecally could be responsible for those group of patients being more hypothermic by inhibiting transmission of afferent thermal skin signals at the level of the spinal cord.

Other studies have compared the efficacy of pharmacological agents in reducing shivering.^{7, 43, 44} Bilotta *et al*⁴³ evaluated nefopam and tramadol in prevention of shivering under neuraxial anaesthesia. Ninety orthopaedic cases under epidural and spinal anaesthesia were randomly allocated into one of three groups to receive either intravenous nefopam 0.15 mg/kg, tramadol 0.5 mg/kg or saline placebo prior to anaesthesia induction. The incidence of shivering with placebo and intravenous tramadol was 57% and 24% respectively while the incidence with intravenous nefopam was 6%. The findings revealed that though shivering reduction with nefopam was statistically significant (p value < 0.05) compared to tramadol, it was very highly significant (p value < 0.01) compared to saline. All fluids were administered at room temperature. The relative antishivering potency of

nefopam could be explained by its longer duration of action and also possibly the fact that the tested dose of intravenous tramadol 0.5 mg/kg used may not have been adequate for all the patients it was used for. .

In another study of 75 orthopaedic cases, Kelsaka et al⁴⁴ compared ondansetron and pethidine for the prevention of shivering in patients under spinal anaesthesia. All the surgeries were elective orthopaedic that utilized tourniquets. Twenty-five patients each were randomly allocated to receive either intravenous ondansetron 8 mg, pethidine 0.4 mg/kg or saline placebo prior to induction of anaesthesia. Their results showed ondansetron and pethidine to have similar effect in preventing spinal induced shivering when administered prior to the spinal anaesthesia. The incidence of shivering with placebo was 36% while the incidence of 8% was observed with both ondansetron and pethidine. Their findings contradicted those of Browning et al⁴² who reported that ondansetron did not prevent or decrease shivering intensity in their study. The difference in sample population may account for this contradiction as Kelsaka et al⁴⁴ used predominantly male patients while Browning et al⁴² used patients.

Mohta et al⁷ studied the effect of various doses of tramadol, comparing these with pethidine in the treatment of shivering. This study evaluated shivering observed after general anaesthesia. One hundred and sixty five patients were randomly assigned to receive intravenous tramadol in doses of 1, 2 and 3 mg/kg, pethidine 0.5 mg/kg or saline placebo at the time of wound closure. Incidence of shivering (42%) was highest with saline placebo (p value < 0.005), incidence with increasing doses of tramadol was 9%, 6% and 3% respectively. Incidence of shivering with pethidine was 12%. The three tramadol groups and the pethidine group were statistically comparable to each other with respect to demographic profile, duration of anaesthesia and temperature of operating room (p value > 0.05). Tramadol at the dose of 2 mg/kg was concluded as having the best combination

of antishivering and analgesic action without excessive sedation. The sample size for this study appeared adequate but the infusions used were administered at room temperature, which can predispose to hypothermia and shivering.

This study compares the interventional use of tramadol and pethidine for the management of shivering occurring during spinal anaesthesia.

CHAPTER THREE

PATIENTS AND METHODS

Study Setting

The study was carried out in the Department of Anaesthesia, University of Calabar Teaching Hospital, Cross River State in Southern Nigeria.

Study Population

Patients of American Society of Anesthesiologists (ASA) classes I or II status scheduled for elective lower limb orthopaedic surgery under spinal anaesthesia were recruited into the study after obtaining an informed written consent (see appendix 1).

Inclusion Criteria

1. Patients between ages 15 and 65 years of age scheduled for elective lower limb orthopaedic surgeries
2. American Society of Anesthesiologists class I or II patients

Exclusion Criteria

1. Age more than 65 years and less than 15 years of age
2. Hypersensitivity to pethidine, tramadol or bupivacaine
3. Patients with contraindications to spinal anaesthesia
 - a. Patient's refusal
 - b. Infection at site of injection
 - c. Hypovolemia
 - d. Coagulopathy
 - e. Neurological disease
 - f. Increased intracranial pressure
4. Body temperature less than 36.5°C or more than 38°C
5. Surgical procedures that could not be completed with subarachnoid block alone

Sample Size Determination

The minimum sample size for the study was calculated using the formula for comparative population study⁴⁸ and response rate of 50% for pethidine from a previous study⁴⁹;

$$n = \frac{p(1-p) [Z + Z_{\beta}]^2 \times 2}{d^2}$$

where

n = desired sample size in study population

P= Proportion of patients with effective response in 15 minutes when administered intravenous pethidine after shivering under neuroaxial anaesthesia⁴⁹

Z = standard normal deviate at 95% confidence level =1.96

Z_β = 80% power of the test =0.84

d=difference to be detected at the end of study (P_A-P_B)=30%=0.3

P_A=Proportion of shivering participants from previous study (pre-intervention) =42% = 0.42

P_B=Estimate of expected shivering control from previous study (post-intervention) =12% = 0.12

$$n = \frac{0.5(1 - 0.5) \times [1.96 + 0.84]^2 \times 2}{(0.42 - 0.12)^2} = 43.5$$

Assuming 15% (0.15x43.5=6.5) of patients opting out of study, desired sample size was (43.5+6.5) =50.

Therefore, the actual minimum sample size was 50 each for the pethidine group as well as the tramadol group making a total of 100.

Study Design

The study was a prospective randomised double blinded comparative study. It was conducted over a period of six months (May 2015 to November 2015). An approval was

obtained from the University of Calabar Hospital Research and Ethical Committee. Only patients who met the inclusion criteria were recruited into the study. The patients and principal investigator were blinded to the study drug. The randomisation was done prior to the eligible participant enrolment. A randomisation schedule was prepared using computer generated odd and even numbers and placed in a sealed envelope. A third party was co-opted and had custody of the allocations in a sealed envelope without the principal investigator being aware of who received what intervention until after assessment of treatment. This third party was responsible for preparation of the study drugs.

The patients were reviewed a day prior to surgery. During the review, the procedure of planned surgery, regional anaesthetic technique and study was explained to the patient (see appendix 1). The effect of the drugs to be used was explained to the patient. After taking a history and carrying out a systemic physical examination, the patient's age, weight and height were recorded. Findings of the systemic examination and vital signs (pulse, blood pressure, respiratory rate, temperature) were also recorded. They were classified using the ASA physical health status classification. Full blood count, serum electrolyte, urea and creatinine, urinalysis were requested for and results reviewed. Their written informed consent was obtained.

In the theatre, a standard multimodal monitor (DASHTM4000; General Electric, Freiburg, Germany) was used for non-invasive blood pressure monitoring and peripheral arterial oxygen saturation monitoring. Also monitored were the electrocardiogram and the axillary temperature. An anaesthetic machine with oxygen source, laryngoscope with different sizes of blades, several sizes of cuffed endotracheal tubes as well as resuscitation drugs such as ephedrine, atropine and adrenaline were made available. The patient's baseline blood pressure, pulse rate, oxygen saturation and axillary temperature were taken and recorded. An intravenous line was secured with an 18G cannula using normal saline

infusion. All preloading fluids were warmed to body temperature of 37 °C and administered at a dose of 10 mlkg⁻¹.

The patients were placed in a sitting position. Under asepsis, routine cleaning of lumbar region was carried out using a solution of povidone iodine only. A skin weal was raised with 1% lidocaine using a 25G hypodermic needle, then other layers were infiltrated at lumbar vertebrae 3-4 or 4-5 interspace. Spinal anaesthesia was performed with a 25G Quincke bevelled spinal needle using the same space. The dose of 0.5% bupivacaine (Duracaine Heavy, Myungmoon Pharm., Seoul, Korea) 15mg or 3mls was injected intrathecally. Dressing was applied to the punctured site. The patients were slowly returned to the supine position with head and shoulders supported on a pillow. The patient was positioned for the surgery.

Following confirmation of spinal block by loss of sensory sensation to pain using pin prick up to a minimum level of T6, surgery was allowed to start. Two consecutive assessments were made thereafter to ascertain maximum level of block height. The blood pressure comprising the systolic blood pressure (SBP), mean arterial blood pressure (MAP) and diastolic blood pressure (DBP), pulse rate, oxygen saturation and axillary temperature were monitored every 5 minutes for 30 minutes, then every 10 minutes till the end of surgery. Patients were observed for shivering. The time and vital signs at onset of shivering were noted.

Hypotension was considered as a reduction of up to 20% of baseline mean arterial blood pressure⁵¹ and was treated using intravenous ephedrine 6mg aliquot boluses. Surgery was allowed to proceed when sensory block height of T6 was achieved. Shivering was graded with a scale similar to that validated by Crossley and Mahajan⁵⁰ as follows:

0= No shivering

- 1= Piloerection or peripheral vasoconstriction but no visible shivering
- 2= Muscular activity in only one muscle group
- 3= Muscular activity in more than one muscle group but not generalized shivering
- 4= Shivering involving the whole body

Only patients with Grades 2, 3 and 4 shivering for at least a minute were defined to have shivered.

Patients who shivered were treated with oxygen therapy via nasal prongs with flow rate of 2L min^{-1} and randomised into one of two groups using computer generated random numbers. The Group P received 0.35 mgkg^{-1} of pethidine (Pethidine Injection BP, Martindale, Essex, United Kingdom) intravenously and the Group T received 0.25 mgkg^{-1} tramadol (Tramal®, Grünenthal, Aachen, Germany) intravenously.

Nausea, when it occurred, was managed by intravenous metoclopramide 10mg. Sedation was graded using a scale similar to one used by Maheshwari et al⁵¹ as follows:

- 0= Alert
- 1= Arousal to voice
- 2= Arousal to gentle tactile stimulation
- 3= Arousal to vigorous tactile stimulation
- 4= No awareness

Patients with Grade 1 and 2 were defined after 10 minutes of interventional treatment to have mild sedation while patients with Grade 3 and 4 after 10 minutes of interventional treatment were defined to have heavy sedation. When sedation occurred and was associated with an peripheral oxygen saturation (SpO_2) of less than 95%, it was treated with oxygen administration by face mask with flow rate of 5L min^{-1} using rebreathing facemask

Shivering refractory to initial drug intervention was treated with a intravenous rescue repeat dose of 0.35 mgkg^{-1} for the pethidine group and 0.25 mgkg^{-1} for the tramadol group.

A refractory shivering was defined as shivering occurring with no improvement up to 10 minutes after intervention⁵², as assessed by patient. Partial improvement was defined as shivering occurring up to 10 minutes after intervention with reduction in intensity, also as assessed by patient. Marked improvement was defined as cessation of shivering in 10 minutes after intervention. An effective response to both drug was defined as those with partial and marked improvement.

Data Collection

Primary outcome measures included:

1. Proportion of patients that shivered in both groups
2. Proportion of tramadol and pethidine groups that had cessation of shivering and reoccurrence in shivering as measurable variables.

Secondary outcome measures included assessment of effects such as:

1. Side effect profile such as nausea, vomiting, pruritus and sedation.
2. Proportion of patients with effective response.

Patients characteristics, incidence of shivering, management and outcome of side effects were documented.

Data Analysis

The data collected were entered into a spread sheet package and analysed using the Statistical Package for the Social Sciences (SPSS) version 21. The frequency tables were generated. Numerical data were expressed as mean \pm standard deviation. Categorical data were expressed as frequency and percentages. Data were presented in tables and charts. Independent Student's T-test was used for inferential analysis of data variables such as

age, weight and duration of surgery. Chi-square test was used for test of significance for categorical variables. A p value < 0.05 was considered significant.

CHAPTER FOUR

RESULTS

One hundred patients shivered and were recruited during the study period. For the minimum sample size of 100 patients, a total of 394 consecutive patients were administered sudarachnoid blocks.

Of the 100 patients that were analysed, 59 were males and 41 were females. The sex distribution and ASA class distribution between the two groups were identical with 27 males and 23 females in the tramadol group while the pethidine group had 16 males and 9 females respectively as shown in Table 1.

The two groups were statistically similar with respect to age, weight and height with mean age of 34.28 (\pm 15.69) years and 44.18 (\pm 14.86) years in the tramadol and pethidine groups respectively. There was no statistically significant difference between the ages in both groups ($p = 0.760$). The indications for surgery for both pethidine and tramadol groups are represented in Table 1.

The mean values of the vital signs of the study population monitored at the onset of shivering are shown in Table 2. During the period of shivering, the mean systolic and diastolic blood pressure did not statistically differ and showed a slight increase. The range of mean systolic blood pressures during the perioperative period (before the block and after the block) was 101-127 mmHg and 103-118 mmHg for tramadol and pethidine respectively (p value = 0.055). The mean pulse rate at the onset of shivering was 73(\pm 15.9) bpm and 92(\pm 12.15) bpm for the tramadol and pethidine groups respectively It did not differ statistically, the p value was 0.06. The trend of pulse monitored for both groups perioperatively showed a slight increase (Figure 1).

The mean peripheral oxygen saturation at the onset of shivering showed a reduction from the baseline pre-operative values. The values at the onset of shivering were 96.4(\pm 2.1953) % and 93.3(\pm 2.03) % for tramadol and pethidine groups respectively.

37(74%) of those in the tramadol group had no need for rescue repeat drug while 28(56%) in the pethidine group had no need for rescue repeat drugs (aTable 4)

The mean correlation coefficient for pulse rate of tramadol and pethidine groups showed a positive correlation (Figure 1) while the mean correlation coefficient for axillary temperature of tramadol and pethidine showed a negative correlation (Table 2).

The effect of shivering on some haemodynamic variable between the tramadol and pethidine group caused a temporal period of no correlation apparent in the correlation graph of the mean arterial pressure and peripheral oxygen saturation (Figures 3 and 4).

Time of Occurrence and Reoccurrence of Shivering

Table 3 shows that most episodes of shivering in the two groups 33(66%) in tramadol and 27(54%) in pethidine occurred with an intensity of grade three shivering. This was not statistically significant p value 0.344.

Table 5 shows that most episodes of shivering occurred within twenty minutes of administration of spinal anaesthesia in both the tramadol and pethidine group. Table 6 shows how the outcome of intervention after treatment occurred. In the tramadol group, 3(6%) patients had partial improvement in and 7(14%) compared with 5(10%) patients in the pethidine group (p values 0.411). Comparatively in the tramadol group, 41(82%) patients had cessation of shivering compared with 34(68%) patients in the pethidine group (p values 0.059).

Table 7 shows re-occurrence of shivering with 10(20%) of the tramadol group having a re-occurrence of shivering and only 6(12%) of the pethidine group having a re-occurrence. (p value 0.555)

Complications of Treatment

A total of 16 (32%) patients in the tramadol group developed nausea while 4 (8%) patients vomited as opposed to (52%) patients having nausea in the pethidine group and 7(14%) patients vomiting. These differences were not statistically significant p values 0.149 and 0.171 respectively (Table 8). Only 1(2%) patient developed pruritus in the tramadol group, while 4(8%) patients had pruritus in the pethidine group. A comparative higher incidence of mild and heavy sedation was observed in tramadol group (10/17) as compared with the pethidine group (4/6). These differences however were not statistically significant p values 0.259 and 0.285 respectively (Table 8).

Table 1a: Socio-demographic characteristics of the Patients

Variables	No. of Patients		P Value	significance
	Tramadol (n=50)	Pethidine (n=50)		
Mean Age(in years) ±SD	34.28± 15.69	44.18± 14.86	0.760	*NS
Mean Weight(in Kg) ±SD	64.64±9.145	6.7±11.10	0.345	*NS
Sex : Male	27(54%)	32(64%)	0.051	*NS
Female	23(46%)	18(36%)	0.174	*NS
Sex Ratio: M:F	27:23	16:9		
Mean Height (metre)± SD	1.38±.49	1.50±0.027		*NS
ASA Classification				
I	27 (54%)	37 (74%)	0.051	*NS
II	23 (46%)	13 (26%)	0.285	*NS
ASA I:II Ratio	27:23	37:13		

Table 1b: showing indications for surgeries

Indication Number (%)	No. of Patients	
	Tramadol (n=50)	Pethidine (n=50)
Amputation	7 (14%)	6 (12%)
Debridement	10 (20%)	11 (22%)
Open Reduction & fixation	6 (12%)	10 (20%)
Others	27 (54%)	23 (46%)

Table 2: Vital signs of study group at onset of shivering

Operational Vital Signs	Tramadol Group (n=50)	Pethidine Group (n=50)	P Value	significance
SBP (mmHg)±SD	130.64±10.087	133.07±10.13	0.155	NS*
DBP(mmHg)±SD	86.09±7.56	85.05±10.40	0.249	NS*
MAP(mmHg)±SD	68.184±8.39	66.741±8.54	0.574	NS*
PULSE(bpm)±SD	102.62±9.18	98.03±5.02	0.535	NS*
SpO ² ± SD	96.14±2.195	93.3±2.03	0.470	NS*
Axillary Temp(⁰ C)	36.22±2.667	36.9±1.62	0.055	NS*
Volume of Fluid(l)	3.76±0.114	3.20±0.123	0.719	NS*
Estimated Blood loss (ml)	821.59±33.95	919.29±24.64	0.674	

*NS = Not significant

SBP = Systolic blood pressure

MAP = Mean arterial pressure

SpO₂ = Peripheral Oxygen saturation

Table 3: Incidence / Grade of shivering

Incidence/grade of shivering	Tramadol Group (n=50)	Pethidine Group (n=50)	P Value	
0				
1	-	-		
2	-	-		
3	33(66%)	27(54%)	0.344	NS*
4	17(34%)	23(46%)	0.741	NS*

Table 4: Administration of repeat rescue drugs

Administration of repeat drugs	Tramadol Group (N=50)	Pethidine Group (N=50)	P Value	significance
Yes	13(26%)	22(44%)	0.285	*NS
No	37(74%)	28(56%)	0.076	*NS

*NS= statistically not significant

Table 5: Onset of shivering after spinal anaesthesia

After SAB (Minutes)	Tramadol Group (n=50)	Pethidine Group (n=50)	P Value	
5	22	13	0.161	*NS
10	8	11	0.100	*NS
15	13	18	0.102	*NS
20	4	1	0.305	*NS
30	3	2	0.092	*NS
40	7	4	0.208	

* NS = not significant

Table 6: Outcome of intervention administered

10 mins After SAB	Tramadol Group (N=50)	Pethidine Group (N=50)	P Value	significance
No Improvement	6 (12%)	11(22%)	0.183	NS*
Partial Improvement	3 (6%)	5(10%)	0.411	NS*
Marked Improvement	41(82%)	34(68%)	0.059	NS*

Table 7: Reoccurrence of shivering

After Subarachnoid block (Minutes)	Tramadol Group (n=50)	Pethidine Group (n=50)	P Value	
30	3(6%)	2(4%)	0.092	*NS
40	7(14%)	4(8%)	0.208	*NS
Total	10(20%)	6(12%)	0.555	

*NS = not significant

Table 8: Complications seen in patients

Complications	Tramadol Group (N=50)	Pethidine Group (N=50)	p Value	significance
Nausea	16(32%)	26(52%)	0.149	*NS
Vomiting	4(8%)	7(14%)	0.171	*NS
Pruritus	1(2%)	4(8%)	0.350	*NS
Hypotension	2(4%)	3(6%)	0.128	*NS
Somnolence				
Mildly sedated	10(20%)	4(8%)	0.259	*NS
Heavily sedated	17(34%)	6(12%)	0.285	*NS

*NS = Not significant

Figure 1: Baseline and trends in pulse rate (*mean/SD*)

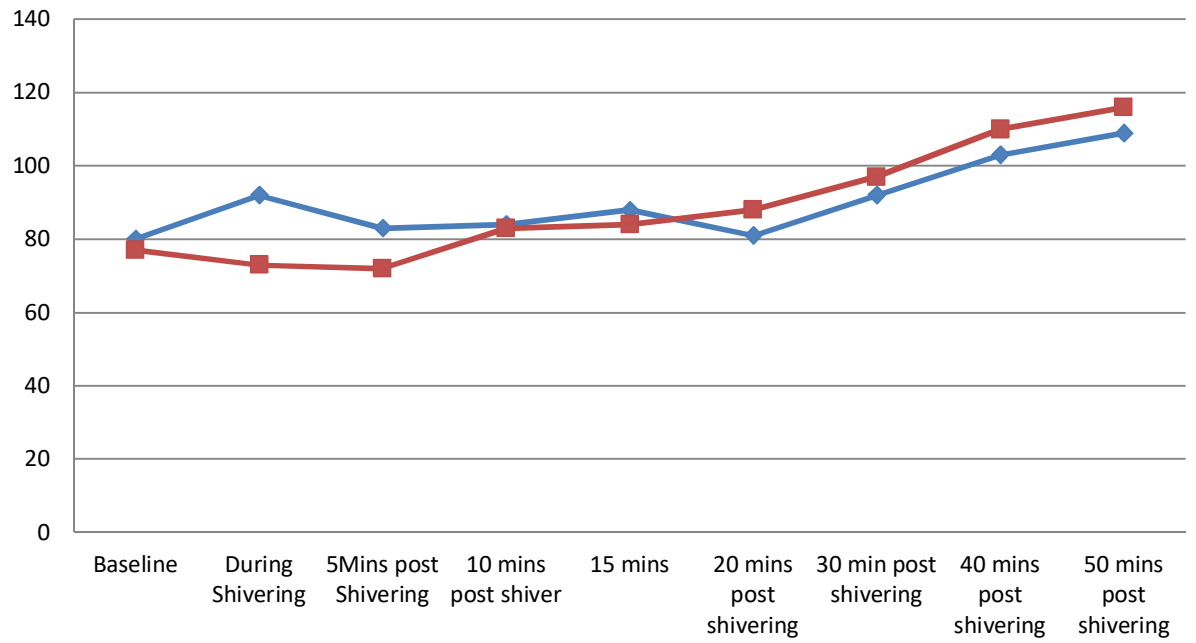


Figure 2: Mean correlation coefficient for MAP at different time intervals for the 2 groups

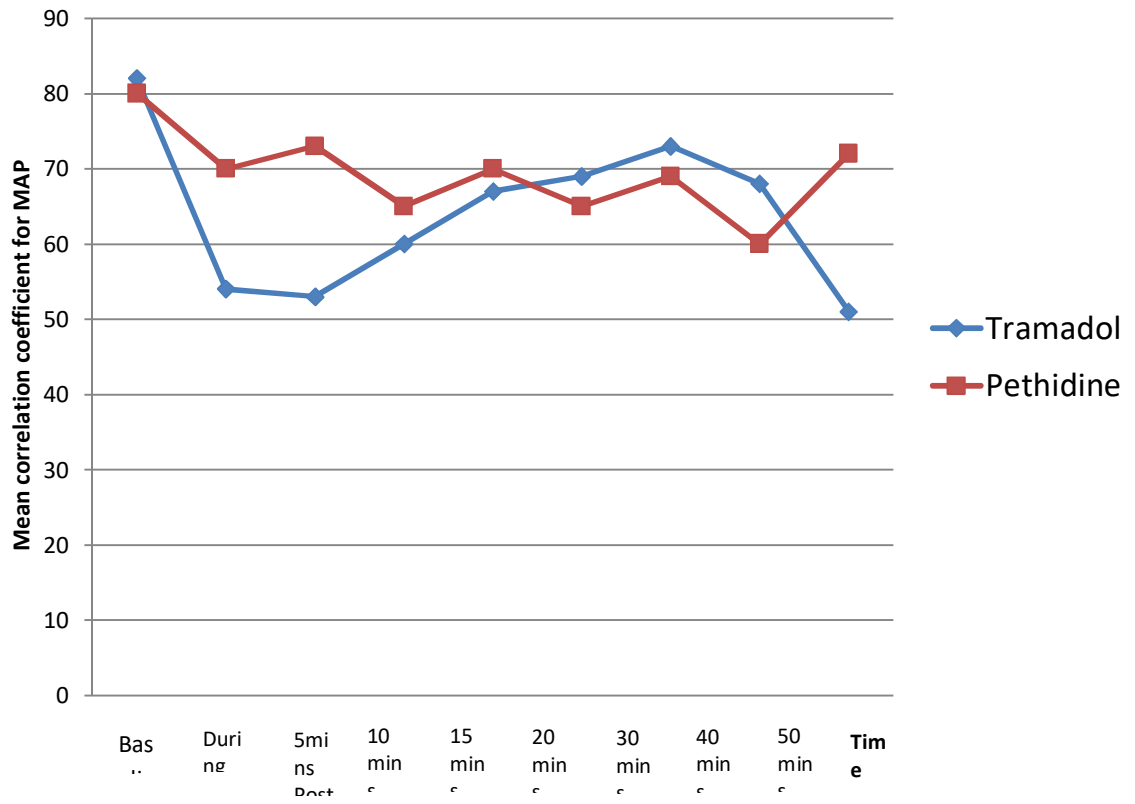
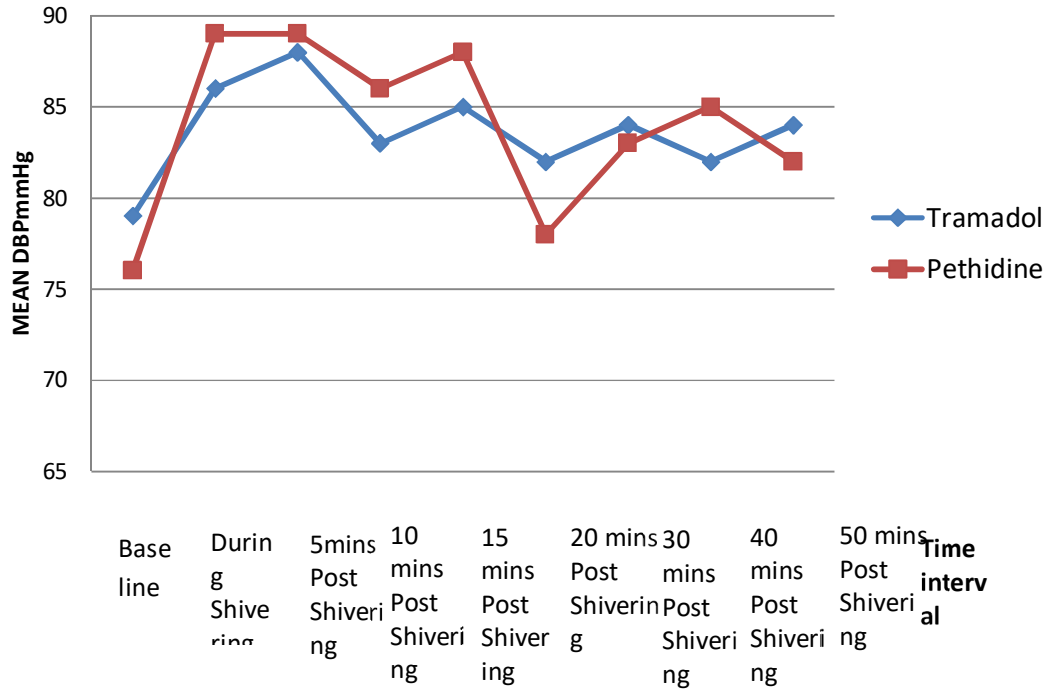


Figure 3: Mean DBP at different time intervals for the 2 groups



CHAPTER FIVE

DISCUSSION

This study compared the effectiveness of intravenous tramadol 0.25 mgkg^{-1} and intravenous pethidine 0.35 mgkg^{-1} for the abolishing of spinal anaesthesia induced shivering in patients scheduled for lower limb orthopedic surgeries. It showed that there was cessation of shivering in more patients in the tramadol group 41(82%) compared to the pethidine group 34(68%) though the difference was not statistically significant ($p=0.059$).

This is similar to previous studies. Dhimar et al⁵³ in a randomized double blinded clinical trial compared the control of shivering under spinal and epidural anaesthesia with tramadol and pethidine. Sixty non parturients either received intravenous tramadol 1 mgkg^{-1} or intravenous pethidine 1 mgkg^{-1} . Marked improvement occurred more and earlier in the tramadol group than those who had pethidine ($p \text{ value} < 0.001$).

Mohta et al reported that intravenous tramadol 2 mgkg^{-1} had the best combination of antishivering and analgesic efficacy without excessive sedation in comparison with intravenous tramadol doses of 1 mgkg^{-1} , 3 mgkg^{-1} and pethidine 0.5 mgkg^{-1} .⁵⁴ However, when comparing antishivering and analgesic efficacy without the variable of sedation, intravenous tramadol 3 mgkg^{-1} was better than the intravenous tramadol 1 mgkg^{-1} , 2 mgkg^{-1} and pethidine 0.5 mgkg^{-1} ($p < 0.001$). Their study though prospective randomized and double-blinded studied 165 patients, each of which had shivering after general anaesthesia as opposed to this study.

Another possible difference observed in the efficacy of dose of tramadol in the above two studies and the index study could be due to the timing of the dose of tramadol. Mohta et al⁵⁴ gave the highest dose and this was at the end of surgery when the patients were likely to be more hypothermic. In this study, tramadol was given in less than two minutes when shivering was noticed. Dhimar et al⁵³ did not state when tramadol was administered after shivering started but observed the patients for shivering only frequently until the 5th minute after the neuroaxial block

when the patients were assessed every 10 minutes. It could be that giving tramadol earlier when shivering is noticed will make a much less effective dose available to counter shivering.

A study was done by Mahesh et al⁵⁵ to compare the effect of intravenous tramadol 1 mgkg⁻¹ and intravenous pethidine 0.5 mgkg⁻¹ in 40 patients undergoing various surgical procedures under neuroaxial block. In their study, both drugs were found to be effective in reducing shivering however, 19 patients in the tramadol group had control of shivering at the end of 5 minutes but there were no patients who had control of shivering at the end of 5 minutes in the pethidine group which was statistically significant (p value < 0.001). They reported a very high incidence of reoccurrence of shivering in the pethidine group (50%) compared to the tramadol group (10%) p value = 0.176. Their study was markedly different from my study where the reoccurrence of shivering was 12% for the pethidine group compared with 20% for the tramadol (p value = 0.555). This difference could be as a result of my sample size which was more than double those of Mahesh et al. Another reason for the higher reoccurrence in the tramadol group could be that the intrinsic potency of pethidine is higher.

In another study, Manouchehrian et al⁶⁴ compared the effect of intravenous tramadol 0.5 mgkg⁻¹ and intravenous meperidine 0.5 mgkg⁻¹ for the treatment of shivering following spinal anaesthesia in patients for elective caesarian section for 70 patients. It was found that the efficacy of abolishing shivering at 10 minutes after instituting the subarachnoid block to be 97.1% for the tramadol group and 88.5% for the pethidine group (p = 0.34). This correlated with this study where the efficacy at 10 minutes was 82% for the tramadol group and 68% for the pethidine group (p = 0.059). While these values correlated with what was obtained in my study, there was no mention of any reoccurrence of shivering in their study in spite of the fact that their study population was larger and consisted of parturients that are more prone to hypothermia.^{10, 11, 40}In addition, pregnancy states are associated with a larger vascular sympathetic tone and as such spinal anaesthesia induced sympathectomy is likely to cause a more profound vasodilatation, heat loss and consequent more attendant shivering.²

The overall incidence of shivering in Manouchehrian et al⁶⁴ study is 26.3%. This is low compared to the world wide incidence usually quoted as 39 ó 57%.^{10, 11} It however, agrees with previous reports of Edomwonyi et al⁵⁶ (29.8%) and Atashkhoyi⁵⁷ (33.3%). However, in these two studies, all the patients were parturients unlike this study.

In the study of Edomwonyi et al⁵⁶, the reason could be because of the temperate climate where the study was done and similar operating environment. For the second study, a lower room temperature of 20 ó 23°C was used, intravenous fluid was administered at room temperature in a subtropical environment. This contrasted with the ambient operating room temperature of this study where temperature ranged from 25 ó 27°C. This higher room temperature could even out the odds and could account for the similarity for incidences in spite of the differences in the study population.

Other authors have reported a lower incidence of shivering. Sule et al⁴⁵ reported an incidence of 15% for shivering in a review of 200 reported patients who had lower abdominal surgery under spinal anaesthesia. The fact that the incidence was low may be as a result of the study being retrospective and the authors failing to portray the total occurrence of shivering. Also, the authors indicated the shivering reported as being part of the overall complications and not setting out from the outset to establish it.

Although shivering may have beneficial thermoregulatory effect in health, it never-the-less places the body under increased physiological stress which may be disadvantageous.^{1, 2} Shivering movement during spinal anaesthesia could interfere with accurate monitoring of blood pressure and pulse oximetry.⁵⁹

In this study, shivering was noted to cause a slight tendency towards an increase of the systolic and diastolic blood pressure which was less for tramadol group than it was for pethidine group (Table 2) though these changes were not statistically significant (p value = 0.155 for mean SBP; p value = 0.249 for mean DBP).

In the study done by Dhimar et al⁵³, the reverse was the case as both parameters showed a slight decrease with respect to the preoperative values; this decrease being more in pethidine group than in tramadol group (p value \times 0.05). This dissimilarity may be because of the regional being done in Dhimar and colleagues studies using either of epidural or combined spinal epidural to institute the regional blockade. Although there was no statistical significance, the volume of fluid injected may be the reason for a more profound fall in the blood pressure as opposed to this study where a fixed dose of 15mg or 3mls of 0.5% heavy bupivacaine was used in all patients. Furthermore, the discomfort arising from the patients' shivering may be the reason for the apparent rise in the blood pressure noted in this study. This reason, may have also been present in Dhimar et al⁵³ but may have been offset by the temperature of injected epidural solution.

More marked changes were seen in the pulse oximetry monitoring where three reductions in oximetry reading was noted over the period monitored intraoperative for both the tramadol group and the pethidine group. The first of these three reduction changes correlated with the period within the first ten minutes, where most of the shivering in both study groups occurred (Table 5). The other two may have been accentuated by the occurrence of grade I shivering.¹ In Grade I shivering, there is the presence of piloerection and peripheral vasoconstriction without evidence of visible shivering, leading to some shutting of blood from the skin and periphery consequently causing aberration in oximetry readings.⁵⁹

Perioperative temperature monitoring is one of the very important aspects of care given to patients.^{25, 60} Although the gold standard for core temperature monitoring is the pulmonary artery, however this is very invasive. A useful none invasive monitor for core temperature is the tympanic probe.⁶⁰ Among the different types of site for monitoring of core temperature during neuraxial anaesthesia, rectal temperature appears to be the most accurate.⁶⁰ The rectal temperature probe may be undesirable to most patients because of its site. Patient under neuraxial anaesthesia would generally prefer to have their temperature monitored via the axillary or

forehead.²⁵ Axillary and forehead skin temperature however tend to be lower than the true core temperature by 1.5- 2.5°C.

In this study, the axillary temperature was used as a source of temperature monitoring because of the unavailability of the tympanic probe and also convenience for the patient. The trend of axillary temperature intraoperatively in both study groups showed a gradual reduction throughout the duration of the spinal anaesthesia. The gradual reduction was more for the pethidine group than the tramadol group. The reason tramadol group had a lower reduction in temperature may be as a result of its pharmacological property of inhibiting neuronal uptake of norepinephrine and causing an interference with cutaneous vasoconstriction.^{7, 29} This reduction was not statistically significant at different measured interval (Table 2). The values obtained from the axillary temperatures monitor may have been influenced by the spinal anaesthetic which causes a vasodilation below the level of block and a compensating cutaneous vasoconstriction above the level of the block.^{1, 25}.

When patients with normal body temperature are anaesthetised using spinal anaesthesia as in this index study with their skin exposed to the cold operating theatre, they ultimately become hypothermic due to heat loss from the core to the skin and environment by radiation, conduction and convection.^{2,5} Furthermore, the exposed surgery surfaces and the fact that on the average as my study showed a mean of 3-4 litres of fluid administered at room temperature will cause a predisposition to hypothermia and shivering to the patient.

The efficacy of pethidine and tramadol in abolishing shivering in clinical scenarios have been well documented.^{10, 37, 51, 61} In this study, 44(88%) patients in the tramadol group had cessation in their shivering after 10 minutes as opposed to 39(78%) in the pethidine group (Table 6.). These response rate correlate with those made by Maheshwari et al⁵¹ and those made by Pausawadi et al⁶¹ of 92% and 74% respectively, although higher doses of tramadol were used in their treatment of shivering.

The pethidine group had a response rate of 39(78%) patients comparable to observations made by Bhatnager et al⁶² and Wang et al⁶³ of 83% and 80% respectively. Also a higher dose of 0.5 mgkg⁻¹ pethidine was used in both studies in comparison to 0.35 mgkg⁻¹ pethidine used in this study.

This study had a reoccurrence of shivering after treatment with 10(20%) patients with the tramadol group and 6(12%) in the pethidine group (Table 7). This finding was in tandem with those of Maheshwari et al⁵² though in contrast with those of Tobi et al⁵² who observed no reoccurrence of shivering possibly because of their prior prophylactic use of tramadol in preventing shivering in the first place.

The reoccurrence rate of 12% for the pethidine group was at variance with some studies done with treatment of shivering using pethidine. Mahesh and Kaparti⁵⁵ reported a reoccurrence of shivering of 50% after pethidine while Wrench et al²⁸ reported a reoccurrence of 40%. Differences noted could be as a result of the studies done in temperate climate and also bias due to a small sample size.

The side effect profile of the two groups in my study showed that there was some haemodynamic stability. There was no incidence of hypotension in the two groups studied. The blood pressure and pulse rate in the first 20 minutes during the occurrence of most of the shivering actually marginally increased. The correlation coefficient for pulse rate for the two groups showed some interesting variance. The pulse rate for the pethidine group initially decreased marginally below that of the tramadol group from its baseline (Figure 1.). This is at variance with work done by Dhimar et al and Manouchehrian et al.^{53, 64} These two studies showed the pulse rate rise marginally during the first 10 minutes of onset of shivering. The plausible reason for this could be artificial correlates from the pulse oximetry reading as a result of the shivering.⁵⁹

On the other hand, tramadol group showed a steady rise and then at about 20 minutes post shivering, the reverse was the case; with pethidine having consistent higher pulse rates than tramadol.

This study reported a high incidence of nausea and vomiting for both study groups. Twenty(40%) patients in the tramadol group had nausea and vomiting while 33(66%) patients had nausea and vomiting in the pethidine group. p value = 0.149 for nausea and p value = 0.171 for vomiting. These results differ from studies by Dhimar⁵³ that showed the rate of nausea and vomiting of 2(6.66%) patients in the tramadol group and 6(20%) patients in the pethidine group. This marked difference could be as a result of the usual practice of preoperative antibiotic administration.⁶⁵ Antibiotics common in use include ceftriaxone¹⁷ which when administered potentiates emesis effect of the opiate study drug. Also, the low sample size of their study could account for the result.

CONCLUSION

The incidence of shivering under spinal anaesthesia in this study is 25.38%. Shivering is an unpleasant and significant cause of discomfort for patients under spinal anaesthesia. It is also a cause of interference for electrocardiogram and pulse oximetry monitoring. Tramadol is as effective in treating shivering as pethidine but at a dose of 0.5 mg/kg, it is associated with more reoccurrence of shivering.

LIMITATION OF STUDY

This study is only restricted to spinal anaesthesia and cannot be extrapolated to other regional technique like epidural and combined spinal epidural anaesthesia. This is because the volume of injectate can predispose to hypothermia and shivering.

Study is limited to patients undergoing shivering under spinal anaesthesia and receiving fixed doses of tramadol and pethidine for treatment. It could not assess the effectiveness of various doses in controlling shivering.

Lastly, an un-blinded observer collected all data which could create room for bias.

RECOMMENDATION

There is need to develop a protocol for the treatment of patients undergoing shivering under subarachnoid block considering the discomfort it poses to patients and potential harmful effect associated with it.

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APPENDIX I

INFORMATION TO PARTICIPANTS/INFORMED CONSENT

Dear Sir/ Madam,

I am a Senior Registrar in the Department of Anaesthesiology, University of Calabar Teaching Hospital, Calabar. I wish to inform you that you have been selected to take part in the study entitled "Comparison of interventional use of Tramadol and Pethidine for management of shivering during spinal anaesthesia." You are being asked to participate in this study because you are undergoing an operation under spinal anaesthesia. You were randomly assigned to one of two groups if you shiver in the operating room: Group P will receive an intravenous injection of 0.35mgkg^{-1} pethidine and Group T will receive an intravenous injection of 0.25mgkg^{-1} tramadol.

The medication was provided by the investigator and at no cost to you.

Purpose of study: The study is designed to compare which of the drugs is better in the management of shivering during spinal anaesthesia.

Statement of confidentiality: The information provided in this study shall be treated with utmost confidentiality. The investigator was the only person to have access to the questionnaire and data collected.

Benefits: The study when completed shall be of benefit and will help determine the most appropriate drug to use in the management of shivering during spinal anaesthesia.

Risk: There are minimal complications from subarachnoid block. The incidences of allergy to bupivacaine, pethidine or tramadol are minimal. You may feel drowsy or nauseous which was treated using oxygen and some drugs.

Refusal/ Withdrawal from the study: You are free to withdraw from the study if you so desire. Your refusal or withdrawal from the study will not in any way affect your management care in this hospital.

Compensation: There was no financial compensation if you decide to be included in this study.

CONSENT FORM

I Mr / Mrs / Miss....., having read and understood the above information, hereby accept to participate in the study "Comparison of interventional use of Tramadol and Pethidine for management of shivering during regional anaesthesia."

Signature or thumb prints.....
(Participant)

Date.....

Signature.....

Date.....

Dr. Ukpabio E. I. (Researcher)

Signature or thumb print

Date

APPENDIX II

DATA PROFORMA ON COMPARISON OF INTERVENTIONAL USE OF
TRAMADOL AND PETHIDINE FOR MANAGEMENT OF SHIVERING DURING
SPINAL ANAESTHESIA
BY DR UKPABIOE. I. DEPARTMENT OF ANAESTHESIA

1. A Patient Initial D Age (yrs): G Sex: .
B Type of Surgery: E Indication: H Weight(kg) .
C ASA Status . F Height(m) G Date of Surgery .
2. Operative vital signs Intraop vital signs after Administration of Anaesthesia
- Baseline 5min 10min 15min 20min 30min 40min 50min
- a. SBP, DBP, MAP
- b. Pulse
- c. SPO₂
- d. Temp
3. Did shivering occur? YES/NO If yes Grade of Shivering Time of
administration of LA Onset of shivering
(min) after admin of LA . Drug given for
shivering .. Administration of repeat drug YES/NO
Any Blood Transfused . Total
Fluid administered intraoperatively . Total Fluid
administered for preloading ..
- Intervention administered ..
- AFTER 5mins 10mins 15mins 20mins 30mins 40mins 50mins
- No improvement
- Partial (small) improvement

Marked improvement

4. Any Side-effects
 - a. Nausea
 - b. Vomiting
 - c. Pruritus
 - d. Hypotension
 - e. Somnolence
 - 1 Mildly sedated
 - 2 Heavily sedated
5. Management of Side-effects
6. Outcome of management

APPENDIX III

HEALTH RESEARCH ETHICS COMMITTEE
UNIVERSITY OF CALABAR TEACHING HOSPITAL

P. M. B. 1278, CALABAR, NIGERIA

CHIEF MEDICAL DIRECTOR:

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MBBCH, DA (WACS), DA (WFSA)

SECRETARY:

Ededet Eyoma Esq.
BA, LLB, BL, MPA, DIP-Comp. Sc, ANIM, AIHSAN

Our Ref: UCTH/HREC/003-R

17th Dec, 2014
Date: _____

Your Ref: _____

Dr. Ukpabio Esien Ita Ukpabio
Department of Anaesthesia
UCTH
Calabar.

Dear Dr. Ukpabio

RE: APPLICATION FOR EXTENSION OF ETHICAL CLEARANCE FOR PART II
DISSERTATION ON UCTH/HREC/33/408

Your request for Extension of Ethical approval for your study " COMPARISON OF INTERVENTIONAL USE OF TRAMADOL AND PETHIDINE FOR MANAGEMENT OF SHIVERING DURING REGIONAL ANAESTHESIA" is hereby approved.

Ethical approval for the study is hereby extended for a period of 12 months.

Prof. Martin Meremikwu
Chairman, UCTH HREC.