Prevention of post-anaesthetic shivering under subarachnoid block for lower limb surgeries: A randomised controlled study comparing nefopam and tramadol

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Abstract

Objectives: Shivering is one of the frequent, undesirable and unpleasant effects of spinal anaesthesia that can be prevented by several means including, pharmacological and non-pharmacological methods.
Methods: Patients between 18 and 65 years were randomly assigned into two groups (A or B). Group A patients received intravenous 0.3mg/kg nefopam while Group B patients received intravenous 0.5mg/kg tramadol just before the institution of subarachnoid block. The parameters assessed were: the incidence of post-spinal anaesthetic shivering, its' severity, and the side-effects of the two drugs. Changes in haemodynamic parameters, temperature, peripheral arterial oxygen saturation and temperature were also evaluated.
Results: Thirty- four patients (100%) in group A and twenty-eight patients (82.35%) in group B, were shivering-free. Thus, only six patients (17.65%) in Group B shivered intra-operatively; p= 0.025, which is statistically significant. The severity of post-anaesthetic shivering was assessed to be grade 2 in three patients (8.82%), while it was grade 1 in the remaining three patients (8.82%). Four patients experienced nausea in group B, but none in group A; p = 0.114. No episode of vomiting was observed in both groups.
Conclusion: Nefopam is better than tramadol for the prevention of intraoperative shivering under spinal anaesthesia.

Prévention des frissons post-anesthésiques sous bloc sous-arachnoïdien pour les chirurgies des membres inférieurs : une étude contrôlée randomisée comparant le néfopam et le tramadol

Résumé
Objectif de l'étude : Les frissons sont l'un des effets fréquents, indésirables et désagréables de la rachianesthésie qui peut être évité par plusieurs moyens, notamment des méthodes pharmacologiques et non pharmacologiques.
Méthode de l'étude : Les patients âgés de 18 à 65 ans ont été répartis au hasard en deux groupes (A ou B). Les patients du groupe A ont reçu 0,3 mg/kg de néfopam par voie intraveineuse tandis que les patients du groupe B ont reçu 0,5 mg/kg de tramadol par voie intraveineuse juste avant l'institution du bloc sous-arachnoïdien. Les paramètres évalués étaient : l'incidence des frissons post-anesthésie rachidienne, leur gravité et les effets secondaires des deux médicaments. Les modifications des paramètres hémodynamiques, de la température, de la saturation artérielle périphérique en oxygène et de la température ont également été évaluées.
Résultat de l'étude : Trente-quatre patients (100 %) du groupe A et vingt-huit patients (82,35 %) du groupe B n'avaient aucun frisson. Ainsi, seuls six patients (17,65 %) du groupe B ont frissonné en peropératoire ; p = 0,025, ce qui est statistiquement significatif. La sévérité des frissons post-anesthésiques a été évaluée au grade 2 chez trois patients (8,82 %), tandis qu'elle était au grade 1 chez les trois patients restants (8,82 %). Quatre patients ont présenté des nausées dans le groupe B, mais aucun dans le groupe A ; p = 0,114. Aucun épisode de vomissement n'a été observé dans les deux groupes.
Conclusion: Le néfopam est meilleur que le tramadol pour la prévention des frissons peropératoires sous anesthésie rachidienne.

Mots-clés : Bloc sous-arachnoïdien, prophylaxie anti-frisson, néfopam, tramadol

INTRODUCTION

Shivering is one of the common complications that is observed following the subarachnoid block. It occurs in a wide range, from 8.8% to 60.0% of patients (1, 2). Post-anaesthetic shivering increases metabolic oxygen consumption, lactic acidosis, risk of hypoxaemia, catecholamine release as well as intraocular and intracranial pressure. This makes it to be detrimental to patients with low cardiopulmonary reserve. Shivering may interfere with intra-operative haemodynamic monitoring, by causing the involuntary movement of muscles (3, 4).

The subarachnoid block (SAB) is one of the preferred choices of anaesthesia for lower limb surgeries worldwide because of reduced intraoperative blood loss, incidence of deep venous thrombosis and the provision of superior pain relief, among others.(5).

Several techniques have been used in the past to control shivering. This can either be non-pharmacological interventions such as the use of warming (devices) or pharmacological interventions (3, 6). Pharmacological interventions have been found to be superior to non-pharmacological because they are efficient, simple, readily available and cost effective (6).

Previous studies have evaluated the use of different drugs for the treatment of post-spinal anaesthetic shivering but very few studies have been done on its prevention. The ideal drug for the prevention of post-spinal anaesthetic shivering is yet to be found (1, 7). However, some drugs have been in use such as pethidine, tramadol, clonidine, neostigmine, ketamine and doxapram ketanserin and dexmedetomidine (3).

Pethidine is the most common intravenous drug used for the treatment and prevention of shivering. However, there is increased awareness of pethidine adverse effects such as hypotension, respiratory depression, pruritus and drowsiness (8). The irregular availability of opioids, especially in a developing country like Nigeria, also limits its use.

Tramadol reduces both the thresholds of shivering and vasoconstriction, nefopam significantly reduced only the shivering threshold. This means that the patient who received tramadol is more likely to shiver, while patients who received nefopam would experience little or no shivering because only the shivering threshold is reduced; there is no alteration in sweating and vasoconstriction threshold.

Nefopam is a recently introduced, safe, non-opioid, non-sedative (benxazocine) compound that is readily available, cheap, with good analgesic properties and very few side effects such as sweating and dry mouth. Nefopam acts by inhibiting the synaptic reuptake of dopamine, norepinephrine and serotonin in an amphetamine-like fashion (9).

Kim et al (10), in their study revealed that nefopam can be a good substitute for meperidine for the prevention of shivering during spinal anaesthesia with more stable haemodynamics. Tramadol a weak opioid had also been used for prevention and treatment of shivering under spinal anaesthesia in some studies, however nausea, vomiting and dizziness limit its use (8).

There is dearth of local study that compares the effects of nefopam and tramadol as prophylaxis for shivering during subarachnoid block in Nigeria. This study therefore intends to compare the effect of nefopam versus tramadol as prophylactic agents for shivering under subarachnoid block in lower limb surgeries.

MATERIALS AND METHODS

This was a randomised double-blinded study. The study was conducted between March 2018 and January 2019 after ethical approval was obtained from the institution's Health Research Ethical (Committee).

The study population were adult patients aged between 18 years and 65 years with body mass-index 25-29kg/m^2 in the surgical specialty wards who were scheduled for elective lower limb orthopaedic surgery lasting less than three hours duration.

The eligible patients listed above were randomly assigned to either of two groups (Group A and B), for corresponding interventions. The formula (11) used for sample size (N) calculation was:

$$N = 2x\,(Z_\alpha + Z_\beta)^2 \times p\,(1-p)\,/\delta^2$$

According to a published study by (Bilotta et al) (12), the standard deviation (SD) =Type 1 error of rate of 5% at 99% confidence interval, where: Z_α = 1.96, the desired type II error rate of 5% (Z_β) =0.84. Provision for attrition rate of 10% was made and the minimum sample size required was 68. Each group consisted of 34 patients.

The patients were randomised into two groups A and B by a research assistant who is a Resident doctor in Anaesthesia using balloting technique. Each patient chose her group by picking from an opaque large envelope containing smaller envelopes. Each of the smaller envelopes contained a folded labelled paper. The folded paper had a number inscribed on it. The research assistant who was not involved in the study recorded the numbers. Those with even numbers were allocated to Group A (Drug A),

while those with odd numbers were assigned to Group B (Drug B)

The smaller envelopes were presented to the nurse Anaesthetist who was responsible for the preparation and coding of the study drugs. The drug coding, decoding, and preparation were done by a research assistant (a nurse anaesthetist who did not have any other role in the study). One ampoule of the original ACUPAN® contains nefopam hydrochloride (drug A) 10mg/ml (i.e 20mg per 2ml) while one ampoule of original TRAMADOL® contains tramadol hydrochloride (drug B) 50mg/ml (i.e 100mg in 2ml). The two study drugs were colourless and transparent. Drug A was prepared by diluting 0.3mg/kg of nefopam hydrochloride with normal saline to make up to 10ml solution using10ml syringe. While 0.5mg/kg of tramadol hydrochloride was also diluted with normal saline to make up to 10ml solution using 10ml syringe to ensure blinding and labelled as Drug B. Since the drugs doses were in mg/kg, the weight of each patient was communicated to the research assistant preparing the drugs. Only the research assistant who was not involved in any other way in the study recorded group randomisation, while drug coding and decoding were done separately. The principal investigator and the patients were blinded to the study drugs.

All the patients scheduled for elective lower limb surgeries were reviewed in the surgical specialty wards a day before surgery during pre-anaesthetic visit. Detailed history and physical examination were conducted on each patient. The patient's socio-demographics data (height, body weight, body mass index, religion and educational status) were obtained.

A multi- parameter monitor (Model G3D, Gulfex Medical and Scientific Company, England) was attached to the patient (in supine position) to measure base line vital signs and for continuous monitoring. The vital signs monitored included: non-invasive blood pressure (NIBP), electrocardiograph (ECG), pulse rate (PR), arterial oxygen saturation (SPO_2), respiratory rate (RR) and body temperature. Body temperature in degree Celcius (^oC) was monitored with the non-contact infrared thermometer (Model name: Diode Laser DT- 8806C).

Each patient had a size 18-gauge cannula inserted into the dorsum of the two hands. All patients were pre-loaded with 10 ml/kg of Ringer's lactate or Normal Saline (stored at room temperature (23^0C) about 15minutes before the establishment of the subarachnoid block. All subsequent intravenous fluids were warmed at room temperature (23^0C), but the cross-matched blood were warmed to body temperature (36.5 - 37^0 C) before administration. The operating theatre in which this study was performed was maintained at constant humidity (70%) and an ambient temperature of 23^oC for all the patients.

The research assistant picked randomly one of the two labelled syringes (that contained the study drugs A or B) from the set of sealed envelopes, removed the label and handed the syringe over to the principal investigator when the subarachnoid block was to be established. The principal investigator then administered either of the two study drug intravenously over a period of twenty (20) minutes (timed by stop watch) through a continuous push just before subarachnoid block was instituted. The spinal anaesthesia technique was performed by the most experienced anaesthetist in the team to reduce the bias of possibility of inter-person skill variability to bearest minimum. The labels were kept and patient's identification numbers were recorded in a code note book by the research assistant. The actual group each patient belonged to was revealed at the end of the data collection for subsequent analysis. The time of administration of the study drugs were noted as t_0. Spinal anaesthesia was established in sitting position with the patient's hips flexed and knees in extended position on the operating table. Aseptic protocol was duly observed. The skin and the subcutaneous tissues at the identified level L_3- L_4 or L_4 - L_5 was infiltrated with a fixed dose 20mg (2ml) of 1% plain lidocaine. Spinal anaesthesia was performed using 25- Gauge Quicke spinal needle through a midline approach at the level L_3-L_4 or L_4 -L_5 0.5% fixed dose 15mg hyperbaric bupivacaine was injected into the subarachnoid space after a free flow of cerebrospinal fluid. No neuraxial adjuvant was added. The subarachnoid injectate used was 0.5% Marcain by Astra Zenecca, Levent, Istanbul. The time of this intrathecal injection was noted as t_1 in minutes. The spinal needle was removed and sterile adhesive dressing was applied over the puncture site. The patient was positioned supine on the operation table with shoulder and head resting on a pillow and remained in this position for at 10 minutes. Sensory block was assessed along the mid-axillary line and the outer aspect of the thigh at 5, 10 and 15 minutes using response to alcohol swab while motor blockade was assessed using Bromage Scale (13) as described in table 1.

Bromage score before and at the end of the surgery were noted. Thereafter patient was placed in the position for operating procedure.

Surgery was allowed to commence once the desired level of block had been reached T_{8-} T_{10} dermatome. Meanwhile, the vital signs (non-invasive blood pressure, pulse rate and body temperature) were measured every two minutes for the first ten minutes after the spinal anaesthesia was established and at five minutes interval till the end of surgery but the peripheral oxygen saturation and respiratory rate were monitored continuously throughout the surgery. The non-invasive blood pressure, pulse rate and body temperature were documented every two minutes for the first ten minutes, then at fifteen minutes interval for the first ninety minutes and subsequently every thirty minutes till end of the surgery.

Intra-operatively, all the patients were covered with a single layer of drape leaving the neck and head exposed. No active warming devices were used. A stop watch was used to note the time of first appearance of shivering and for continuous monitoring. The severity of the shivering was assessed using Bed-side Shivering Assessment scale (BSAS) (6, 14). Shivering scores (by BSAS) and sedation scores (by four-point sedation scale) were recorded at interval of 2 minutes for the first 10 minutes and at 15, 30, 45, 60, 75, and 90 minutes after subarachnoid block and thereafter every 30 minutes till the end of surgery. The Bed-side Shivering Assessment Scale is as follows:

Grade 0: None: shivering noted on palpation of the masseter muscle, neck and chest wall.

Grade 1: Mild: shivering localized to the neck and or thorax only.

Grade 2: Moderate: shivering involving gross movement of the upper extremities in addition to the neck and thorax.

Grade 3: Severe: shivering in the face, head, upper and lower extremities. The researcher recorded the time at which shivering started, the duration of shivering (in minutes) and the shivering grade.

Supplemental 100% oxygen was administered at 2L/min via nasal prongs to the subjects that developed episodes of shivering during surgery or in the immediate post-operative period. For shivering Grade 2 or such lasting more than five minutes, low-dose intravenous 0.02mg/kg midazolam up to a maximum dose of 0.04mg/kg was administered. The non-pharmacological treatment for shivering was applied if required which includes the covering the chest of patient with warm blanket and or warming of intravenous fluids.

The outcome of prophylaxis was recorded by the researcher as effective if there is no shivering (primary outcome) or non-effective when there is: (i) incidence of shivering, (ii) incidence of side- effects of study drugs (secondary outcome).

The side effects of study drugs considered in this study included: pain on injection, nausea, vomiting, respiratory depression and hypotension. All monitoring was done by the principal- investigator who was also the attending anaesthetist. The duration of the surgery was recorded. All patients were transferred to the recovery room where their vital signs (PR, NIBP, RR, SPO_2, body temperature) were monitored till when discharged to the ward in stable clinical state.

Statistical analysis:

Data analysis was done using Statistical Package for the Social Science (SPSS) for Windows software, version 20.0 (IBM SPSS Inc., Chicago, IL, USA). All the data were complete.

Comparison was made between Group A and B. Demographic data was compared between the two groups to see any significant difference. Continuous variables were presented in means and standard deviation and comparison made with Student's t- test. Categorical variables were presented in proportion (percentages) and comparison made with the Chi–square test was used to test for the significance of difference between categorical variables. A p value< 0.05 was considered to be statistically significant and Null hypothesis was rejected.

RESULTS

A total of sixty-eight patients were recruited for the study and all patients completed the study.

The patients' demographic characteristics were comparable in the two groups (Table II). All the patients had the intended surgery. The most common indication was open reduction and internal fixation with plate and screw or intramedullary locked nail (ORIF) for closed lower limb fractures with a frequency of 19 (28%) as illustrated in Table III. The average duration of the surgery in the nefopam group (A) was 71.44 ± 38.77mins and tramadol group (B) was 85.59 ± 42.91mins with a t-test = 0.251 and a p-value = 0.81. This is not statistically significant.

The haemodynamic parameters (pulse rates, systolic blood pressure, diastolic blood pressure, mean arterial blood pressure) were

within normal limits and comparable (p= 1.000) between the two groups. Although hypotension was noticed in five patients (7.35%) during the surgeries, it was transient in nature and there was no statistically significant alteration in the overall haemodynamic parameters of the patients p= 1.000. The pre-operative base line vital signs in both groups described and the comparative intraoperative mean vital signs for Group A and B is illustrated in Figure 1 to 4.

The maximum height of block before the surgical incision in both groups was T_8 and all the patients in both groups had a Bromage score of IV (i.e unable to move both legs or feet, with complete-100% motor block) before the start of the surgery. There were no statistically significant differences in these figures in both groups.

There is no incidence of shivering in group A patients but six patients (17.65%) in group B, had episodes of shivering, out of which four patients (11.76%) were males while two 5.88% were female, p-value 1.000. This is not statistically significant.

Even though, more males shivered than females, there was no statistically significant difference between both genders (p-value =1.000). The mean time interval between of the administration of study drug (t_0) to onset of shivering in the tramadol group, was 33.67 ± 15.28 minutes. The mean shivering duration was 12.33 ± 4.03 minutes

The comparison of the incidence and severity of post spinal anaesthetic shivering following subarachnoid block in both groups is shown in Table IV.

Among those patients that shivered in group B, the severity of post-anaesthetic shivering was assessed to be grade 2 (two) in three patients (8.82%), while it was grade 1 in the remaining three patients (8.82%). Overall, shivering prophylaxis was effective in 62 patients (91%) and not-effective in 6 (9%). None of the patients in both groups experienced shivering in the post-anaesthetic care unit.

All the six patients in group B who developed episodes of shivering received 100% intranasal oxygen at 6L/min via face mask.

The side-effects evaluated in this study included nausea, vomiting and hypotension as shown in Table V. None of the patients in both groups had respiratory depression. There was no statistically significant difference in the post-operative vital signs readings between the two groups.

The mean volume of the total intravenous crystalloids administered in the first hour were comparable between the two groups and did not differ significantly between the two groups (i.e nefopam group =1441.18 ± 250.00 ml, tramadol group =1311.76 ± 318.87 ml, p-value = 0.07).

Table VI: shows the immediate postoperative mean vital sign at post anaesthetic care unit (PACU). The mean duration of stay in the recovery room in minutes was not statistically significantly different between the nefopam (66.71 ± 7.23mins) group and the tramadol (66.29 ± 6.29mins) group, with p-value = 0.16.

DISCUSSION

This study showed that both intravenous 0.3mg/kg nefopam and 0.5mg/kg tramadol were effective anti-shivering prophylactics, however, nefopam significantly reduces the incidence of shivering more than tramadol. Similarly, Bilotta et al (12) reported that the incidence of shivering among those that received nefopam were significantly lower (6%) than in those who received tramadol (24%) or placebo (57%). This was similar to Osaheni et al (14) study that compared intravenous 0.15mg/kg nefopam and intravenous 1mg/kg tramadol for the prevention of shivering during spinal anaesthesia in myomectomy surgery. They found that 15% of patients in tramadol group shivered compared to 5% of patients in the nefopam group. However, in this study, no incidence of shivering was recorded in the nefopam group while six (17.65%) patients experienced shivering in the tramadol group. This may probably due to higher dose (0.3mg/kg) of nefopam that was used in this study compared to 0.15mg/kg which was used in the study by Bilotta et al and Osaheni et al. (12, 14).

The report from Kim et al (10) also agreed with the findings in this study in that, there was no incidence of intraoperative shivering among patients that received intravenous nefopam even though lower dose nefopam was used (0.15mg/kg). The commonly reported side effects of nefopam are sweating, nausea, tachycardia and pain at injection, among others (12, 14, 15) In the study by Kim et al (10), there was no incidence of sweating nor tachycardia in both groups. Furthermore, although the incidence of nausea was not statistically significant between the two groups, Kim et al (10) observed that nausea was more frequently in the meperidine group than the nefopam group (7/33 vs 1/32 respectively) and it was not correlated with the sensory block levels. In this study also, sweating, tachycardia nausea and pain at injection were not observed among those that

received intravenous 0.3mg/kg nefopam, however four (11.8%) patients among those that received intravenous 0.5mg/kg tramadol experienced nausea.

When considering the relationship between the incidence of shivering and the types of surgical procedures and gender, studies have shown that shivering is more common, more severe and prolonged in the obstetric population who had caesarean sections (4, 16). This may be probably due to the fact that pregnancy is associated with a higher vascular sympathetic tone and as such pharmacological sympathectomy is likely to cause a more profound vasodilatation, and marked heat loss. This has been linked to shivering (17). Sule et al (18) reported that female patients experienced shivering more than their male counterparts with a male to female ratio of 1:1.74. However, in this study, among the six patients that shivered in group B, more males (11.76%) as compared to (5.88%) females and this could be probably be due to the fact that there were more males in the study population.

With reference to the severity of shivering, out of the six patients that shivered in this study, shivering grade 2 was observed in three patients (5.88%), while the remaining three patients had a shivering score of 1. The study by Tobi et al (8) showed that all the six patients in the 0.5mg/kg tramadol group, experienced shivering grade one. Osaheni et al (14) reported different level of shivering among their study subjects. Three patients (7.5%) had grade two shivering in the tramadol group but there is no occurrence of grade two shivering in nefopam group. The proportion of patients that had grade one shivering were comparable in both groups five patients (12.5%) in the tramadol group and two patients (5.0%) in the nefopam group. It is worthy of note here that these results could not be compared to the study by Tobi et al (8) because different shivering scale was used.

Tobi et al (8) and Shukla et al (19) reported different time of onset and duration of shivering. This could probably be due to the differences in the time of measurement of shivering in the two studies. Furthermore, the time of occurrence of shivering was monitored in minutes. This was taken as the time interval between the admnistration of local anaesthetic into subarachnoid space to the first appearance of shivering. Our study showed that most episodes of shivering occurred within the first thirty minutes of anaesthesia. Also it was observed that the decrease in core temperature was more dramatic in the first 15 minutes of the spinal anaesthesia. This is the critical period for fixing and onset of spinal anaesthesia. It is known that the maximum core-to- peripheral redistribution of heat following subarachnoid block takes place in the first hour. This might have been probably due the substantial heat loss from the skin below the level of block before the compensatory mechanism of vasoconstriction above the level of block is maximally activated.

In this study, result obtained from haemodynamic parameters (pulse rate, systolic blood pressure, diastolic blood pressure and mean arterial pressure), respiratory rate and peripheral arterial oxygen saturation were comparable between the two groups and there was no evidence of bradycardia nor tachycardia. Even though hypotension was noticed in five patients (7.35%), in both groups, this was transient. There was a corresponding slight decrease from the base line vital signs in all the haemodynamic parameters assessed but no statistically significant differences in the two groups.

A previous study had reported stable haemodynamic variables when nefopam, tramadol and placebo were used (12). Shukla et al (19) used both intravenous clonidine (0.5µg/kg) and intravenous tramadol (0.5mg/kg) to effectively treat patients with post-spinal anaesthesia shivering with no statistically significant differences, with respect to the heart rate, mean blood pressure, axillary temperature and oxygen saturation between the two groups. We reported similar haemodynamic stability in our two groups. However, whereas Shukla et al (19) focused on the intervention or the treatment of postspinal anaesthetic shivering, this study emphasised the use of anti-shivering prophylaxis.

The higher incidence of hypotension can cause more shivering following spinal blockade of many segments. Vasopressors are often needed for the prevention of spinal anaesthesia- induced hypotension, despite the use of intravenous fluid preloading. Prophylactic intravenous ephedrine in doses of 5mg and above has been used successfully to prevent this condition (8, 20, 21). Also prophylactic intravenous ephedrine 3mg is as effective as 6mg in reducing the incidence and severity of spinal anaesthesia-induced hypotension during lower limb and lower abdominal (general) surgeries (20). In this study, the overall incidence of hypotension was five (7.35%) probably because of adequate preloading with 10ml/kg crystalloids and

ensuring a level of blockage below the dermatomal level of T_4.

Nefopam had been safely used in different doses (0.05mg/kg, 0.1mg/kg, 0.15mg/kg, 0.2mg/kg and 0.3mg/kg) for anti-shivering prophylaxis in several studies (9, 14, 22), but fewer studies[13, 22] had investigated it's side-effects. Pain at injection site was the only adverse effects of nefopam that was noted with the incidence of 6% (3/50) in the study by Hatem et al (23) and 15.6% in the study by Yeon et al (10). Slow injection of diluted study drugs administered over 15 minutes helped to prevent this experience in this study. Pain at injection site was not experienced in the study by Osaheni et al (14) and in this study. Episodes of intraoperative tachycardia and hypotension were reported in both groups in the study by Osaheni et al (14), however, more patients had tachycardia in nefopam group (11.84%), compared to the tramadol group (8.68%). They also found that there were no significant differences in the occurrence of hypotension in both groups, Significant differences in pulse rates were observed at 25, 40, 50, and 90 minutes post spinal anaesthesia. Furthermore, they reported episodes of bradycardia only among 2.6% of patients in the tramadol group whereas none in the nefopam group. This finding was contrary to this study, where none of the patient in both groups experienced bradycardia nor tachycardia. Variations in the type of surgery and blood loss which were not stressed in these two studies may account for the differences.

Finally Alfonsi et al (15) demonstrated that nefopam is a unique drug, in that, whilst most anti-shivering drugs reduce both the thresholds of shivering and vasoconstriction, nefopam significantly reduced only the shivering threshold. This does not mean that the patient is more prone to shivering, instead, patients who received nefopam would experience little or no shivering because only the shivering threshold is reduced; there is no alteration in sweating and vasoconstriction threshold. The anti-shivering effects of nefopam could be due to its action on numerous sites which are involved in the control of the thermoregulatory shivering (23, 24).

CONCLUSION

Both nefopam and tramadol are effective for anti-shivering prophylaxis. However, nefopam is more effective than tramadol for the prevention of intraoperative shivering under spinal anaesthesia.

Intravenous nefopam at a dose of 0.3mg/kg is superior to 0.5mg/kg intravenous tramadol as anti-shivering prophylaxis in terms of its efficacy, minimal side-effects and patient's satisfaction.

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REFERENCES

1. Arina Q, Novi E, Rosuliana I, Amartha MB, Wahyu C. Management of shivering in post-spinal anaesthesia using warming blankets and warming fluid therapy. Journal Ners 2019; 14(3): 305-9. https://doi.org/10.20473/jn.v14i3.17166
2. Lopez MB, Postanaesthetic shivering from pathophysiology to prevention. Rom J of Anaesth and Intensive Care. 2018; 25 (1): 73-81. https://doi.org/10.21454/rjaic.7518.251.xum
3. Obasuyi BI, Alagbe-Briggs OT, Echem RC. Choice of anaesthesia for orthopaedic surgeries in developing country: How appropriate? J Med Sci 2013; 4(3):101-102.
4. Javaherforoosh F, Akhondzadeh R, Aein KB, Olapour A, Samimi M. Effects of Tramadol on Shivering Post-spinal Anaesthesia in Elective Cesarean Section. Park J Med Sci.2009; 25 (1): 12-17.
5. Dorre N. The Post-anaesthetic Care unit In: Miller RD, editor. Miller's Anaesthesia. 7th ed. Philadephia, USA: Churchill Livingstone; 2010. p. 2707-2718. *DOI:* 10.1213/ane.0b013e3181b7c799
6. Saurabh S, Deepak D, Sadhan S, Jagdeep SB, Josemine D, Puja D. Comparison of three different Fluid warming Techniques used to Maintain Euthermia in patients who underwent Caesarean Section: A Retrospective Audit. Journal of Obstetric Anaesthesia and Critical Care 2019; 9 (1): 35-39. *DOI:* 10.4103/joacc.JOACC_52_18
7. Yang Zhou, Abdul M, Yuan H, He L, Hui Lian G, Xing Gao, Ming-Sheng D, Jun-Li Cao. Efficacy and Safety of Prophylactic use of Ketamine for prevention of Postanaesthetic shivering: A Systematic Review and Meta- Analysis. BMC Anesthesiology 2019; 19:245. https://doi.org/10.1186/s12871-019-0910-8
8. Tobi KU, Imarengiaye C, Edomwonyi NP. Tramadol effects on perioperative shivering in lower limb orthopaedic surgeries under spinal anaesthesia. J West Afr Coll Surg. 2012; 2(2): 63-79.
9. Piper SN, Rohm KD, Suttner SW, Maleek WH,

Kranke P, Boldt J. A comparison of nefopam and clonidine for the prevention of post-anaesthetic shivering: A comparative, double-blind and placebo-controlled dose-ranging study. Anaesthesia 2004; 59; 559-564. https://doi.org/10.1111/j.1365-2044.2004.03734.x

10. Kim YA, Kweon TD,Kim M, Lee HI,Lee YJ, Lee KY Comparison of meperidine and nefopam for prevention of shivering during spinal anaesthesia. Korean J Anaesthesiol. 2013; 64 (3): 229-233. https://doi.org/10.4097/kjae.2013.64.3.229
11. Baoliang Z. How to calculate sample size in randomised controlled trial? J Thorac Dis. 2009; 1(1): 51-54.
12. Bilotta F, Pietropaoli P,Sanita R, Liberatori G, Rosa G. Nefopam and Tramadol for the Prevention of Shivering During Neuraxial Anaesthesia. Regional Anaesthesia and Pain Medicine. 2002; 27(4): 380-384. https://doi.org/10.1053/rapm.2002.33563
13. Sanga M, Banach J, Ledvina A, Modi NB, Mittur A. "Pharmacokinetics, metabolism and excretion of nefopam, a dual reuptake inhibitor in healthy male volunteers".Xenobiotica 2016; 46 (11): 1001-1016. https://doi.org/10.3109/00498254.2015.1136989
14. Osaheni O, Amadasun FE., Tobi KU. Comparison of Intravenous Nefopam and Intravenous Tramadol for Shivering Prophylaxis in Patients Undergoing Myomectomy under Spinal Anaesthesia. IJSRM 2018; 10 (2): 172-185.
15. Alfonsi P, Adam F, Passard A, Guignard B, Sessler DI. Nefopam, a Non-sedative Benzoxazocine Analgesic, Selectively Reduces the Shivering Threshold. Anesthesiology 2004; 100 (1): 37-43. https://doi.org/10.1097/00000542-200401000-00010
16. Tsen LC, Hepner DL. Needles used for spinal anaesthesia. Exp Rev Med Devices; 2006; 3:499-508. https://doi.org/10.1586/17434440.3.4.499
17. Ejiro BA, Edomwonyi NP, Imarengiaye CO. Ondasetron versus Tramadol in the Prevention of Post anaesthetic shivering following Caesarean Section under Spinal Anaesthesia. Afr J of Anaesth and Int Care. 2014; 14(1): 16-11. https://doi.org/10.4314/AJAIC.V14I1
18. Sule AZ, Isamade ES, Ekwempu CC. Spinal Anaesthesia for lower abdominal surgery; A Review of 200 cases. Nig. J Surg Res. 2005; 7 (1-2): 226-230. https://doi.org/10.4314/njsr.v7i1.12287
19. Shukla U, Malhotra K, Prabhakar TA. A Comparative Study of the effect of clonidine and tramadol on post-spinal anaesthesia shivering. Clin Invest. 2011; 55(3): 242-246. Doi: 10.4103/0019.5049.82666.
20. Okubuiro EO, Onajin-Obembe BO, Ebirim LH. A comparison of haemodynamic effect of Low effect of Low doses of prophylactic IV Ephedrine in Spinal Anaesthesia for lower abdominal surgery. AJAIC 2017; 17 (1): 1-6.
21. Chinadoti T, Tritrakan T. The prospective study of hypotension and bradycardia during spinal anaesthesia with bupivacaine: Incidence and risk factors part two. J Med Assosc Thai. 2007; 90(3): 492-501.
22. Bilotta F, Sanita R, Liberatori G, Larosa I, Rosa G. Nefopam or tramadol in the prevention of shivering during subarachnoid or epidural anaesthesia. Eur J Anaesthesiol 2001; 18(Suppl.): 79-80. https://doi.org/10.1097/00003643-200100001-00282
23. Hatem SM. Dexmedetomidine versus Nefopam for the management of post-spinal anaesthesia shivering: A randomised double-blind controlled study. Egyp J Anaesth 2015; 31: 315-320. https://doi.org/10.1016/j.egja.2015.06.004
24. Evans MS, Lysakowski C, Tramer MR. Nefopam for the Prevention of Postoperative Pain: Quantitative Systematic Review. Br J Anaesth. 2008; 101 (5): 610-617. https://doi.org/10.1093/bja/aen267

Table I: Bromage Score[13] Grade Criteria Degree of motor block

Grade	Criteria	Degree of motor block
I	Free movement of the legs and feet	Nil (0%)
II	Just able to flex the knees with free movement of feet	Partial (33%)
III	Unable to flex knees, but with free movement of feet	Almost complete (66 %)
IV	Unable to move legs or feet	Complete (100%)

Table II: Patients demographics characteristics

Patients Parameters	Group A (Nefopam) N=34; Mean ±SD	Group B (Tramadol) N=34; MEAN ± SD	p-value
Age	41.76± 12.70	40.71 ± 13.22	0.26 *
Body Weight (kg)	68.09 ± 3.01	67.33 ± 3.17	0.31 *
Height (m)	1.63 ± 0.03	1.62 ± 0.03	0.19 *
Body Mass Index (Kgm$^{-2)}$	25.67 ± 0.74	25.46 ± 1.06	0.36 *
	Group A (Nefopam) Frequency (%)	**Group B (Tramadol) Frequency (%)**	**p-value**
Gender Ratio			
Male	24 (70.6)	22 (64.7)	0.64 *
Female	10 (29.4)	12 (35.3)	
Total	34 (100)	34 (100)	

*not significant

Table III: Frequency distribution of lower limbs surgeries performed

Surgical Procedures	Frequency (%)
Open reduction and internal fixation + Plate and Screw or intramedullary locked nail	19 (28%)
Split thickness skin grafting	16 (24%)
Open reduction and external fixation + K-wire	8 (12%)
Screw/ Plate removal or adjustment and fixing	7 (10%)
Ankle arthrodesis	6 (9%)
Close reduction and manipulation under anaesthesia	4 (6%)
Corrective Osteotomy	3 (4%)
Sequestrectomy	3 (4%)
Below knee amputation	1 (1.5%)
Hermiarthroplasty	1 (1.5%)
TOTAL	68 (100)

Table IV: incidence and severity of postoperative shivering following subarachnoid block in both groups

	Group A (Nefopam) Frequency (%)				Group B (Tramadol) Frequency (%)			
BSAS	0	1	2	3	0	1	2	3
Male	24 (70.6)	0 (0)	0(0)	0(0)	18 (52.93	2 (5.88)	2 (5.88)	0
Female	10 (29.4)	0 (0)	0(0)	0 (0)	1(2.94)	1(2.94)	1(2.94)	0
Total	34 (100)	0(0)	0 (0)	0 (0)	28(82.33)	3 (8.82	3(8.82)	0

Key: BSAS =Bedside Shivering Assessment Scale
Grade 0: None: shivering noted on palpation of the masseter muscle, neck and chest wall.
Grade 1: Mild: shivering localized to the neck and or thorax only.
Grade 2: Moderate: shivering involving gross movement of the upper extremities in addition to the neck and thorax.
Grade 3: Severe: shivering in the face, head, upper and lower extremities.

Table V: The side –effects of the study drugs

Side-Effects	Group A (Nefopam) Frequency (%)	Group B (Tramadol) Frequency (%)	x^2-value	p-value
Nausea				
Yes	0 (0)	4 (11.8)	4.25	0.114 *
No	34 (100)	30 (88.2)		
Vomiting				
Yes	0 (0)	0 (0)	0	0
No	34 (100)	34 (100)		
Pain on injection				
Yes	0 (0)	0 (0)	0	0
No	0 (0)	0 (0)		
Hypotension				
Yes	2 (5.9)	3 (8.8)		
No	32 (94.1)	31(91.2)	0.22	1.000*
Respiratory depression				
Yes	0 (0)	0 (0)	0	0
No	0 (0)	0 (0)		

*** not significant**

Table VI: Immediate post-operative mean vital signs at post anaesthetic care unit (at least 2hours monitoring)

Clinical Parameters	Group A (Nefopam) Mean ± S.D.	Group B (Tramadol) Mean ± S.D.	t-test	p-value
Pulse Rate/ min	87.73 ± 16.50	84.05 ± 14.32	5.213	0.43 *
Systolic Blood Pressure (SBP) (mmHg)	132.83 ± 12.06	128.30 ± 10.18	2.608	0.57 *
Diastolic Blood Pressure(DBP) (mmHg)	76.64 ± 5.20	76.25 ± 8.89	1.242	0.25 *
Mean Arterial Pressure	85.69 ± 15.10	71.26 ± 13.90	1.343	1.50 *
Respiratory Rate/ min	12.36 ± 2.12	12.88 ± 2.50	1.251	0.32 *
Temperature (°C)	37.03 ± 2.07	37.05 ± 2.40	5.655	0.30 *
Peripheral Arterial Oxygen Saturation (SPO2 %)	98.33 ± 11.48	97.28 ± 1.32	3.840	0.60 *

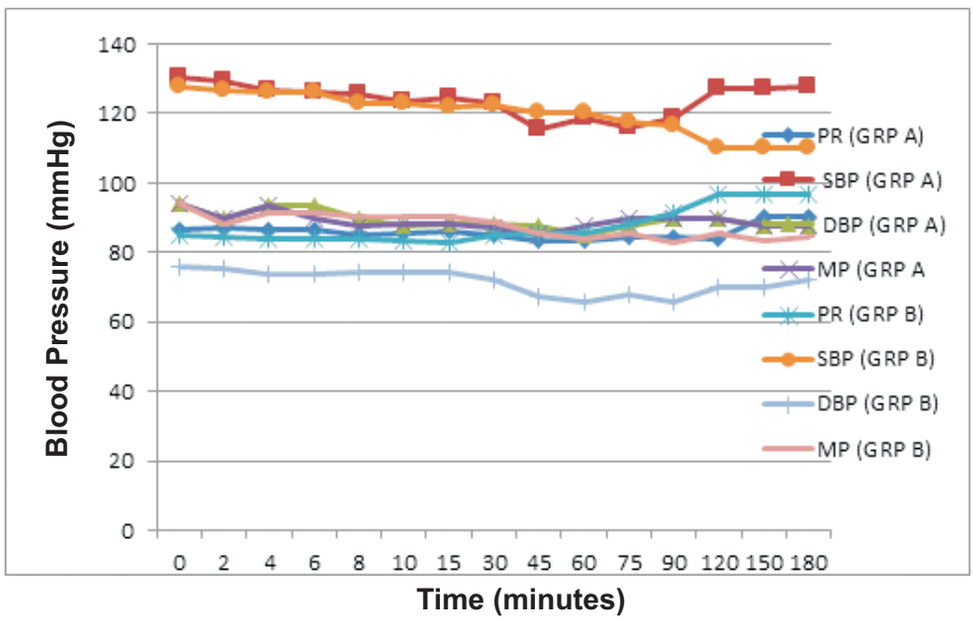

Figure 1: Showing preoperative baselines and comparative intraoperative mean haemodynamic monitoring (Group A and B)

KEY

PR= Pulse rate
SBP= Systolic Blood Pressure
DBP= Diastolic Blood Pressure
MP =Mean Arterial Blood Pressure
GRP A= Nefopam group
GRP B= Tramadol group

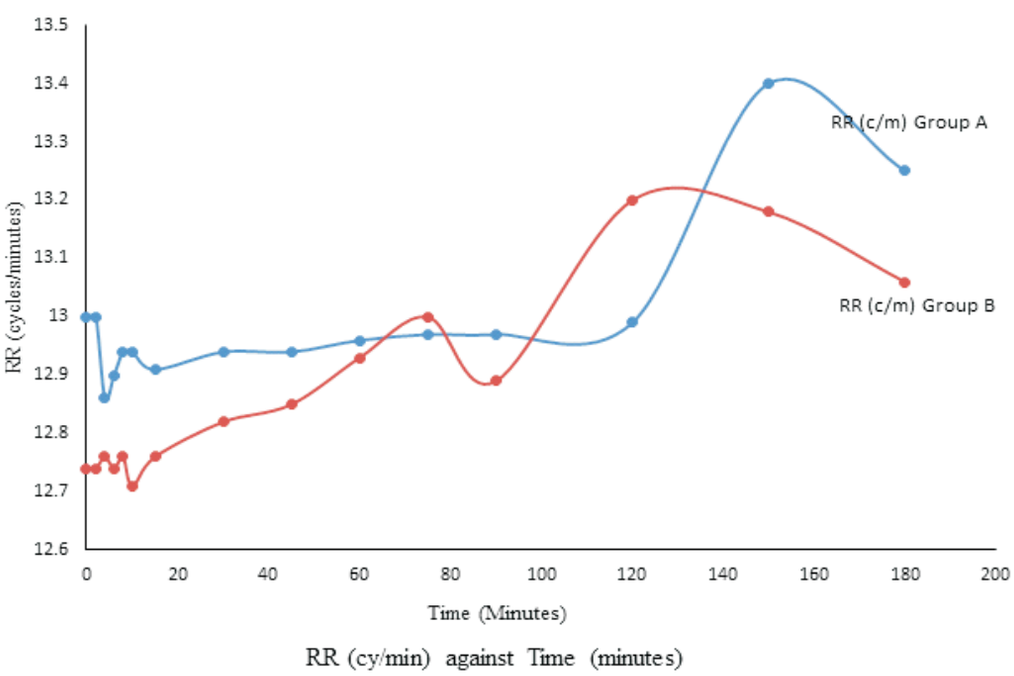

Figure 2: Preoperative baseline and comparative intraoperative respiratory rates monitoring for group A and B

Group A: …… Nefopam
Group B ……. Tramadol
RR ……. Respiratory rates

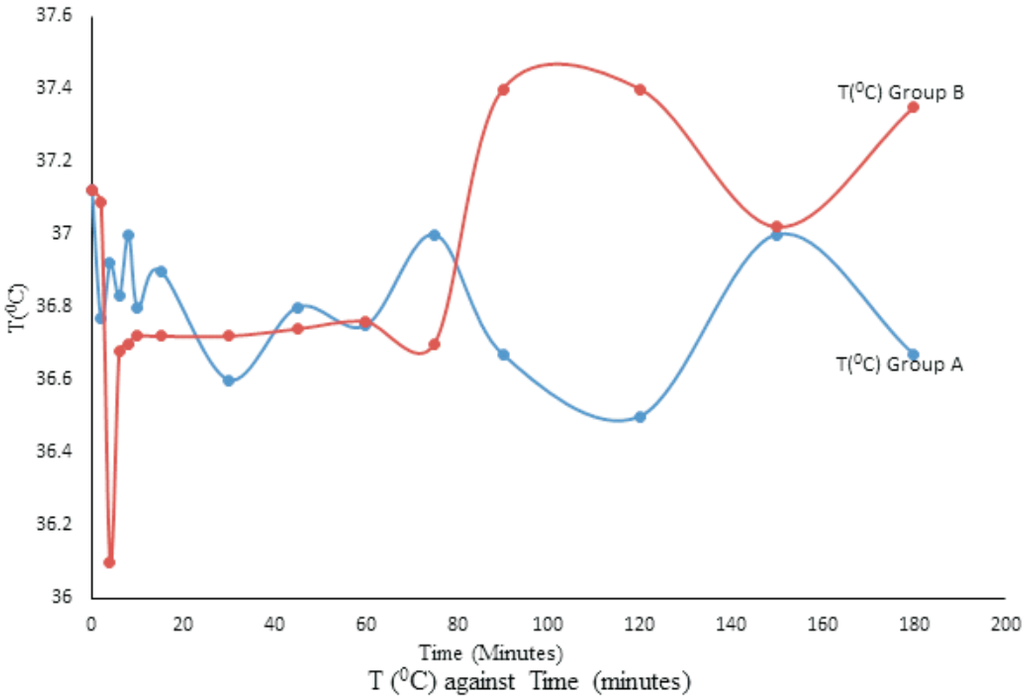

Figure 3: Preoperative baseline and comparative intraoperative body temperature monitoring

Group A ……. Nefopam
Group B …….. Tramadol
T^0C ……. Temperature in degree Cencius

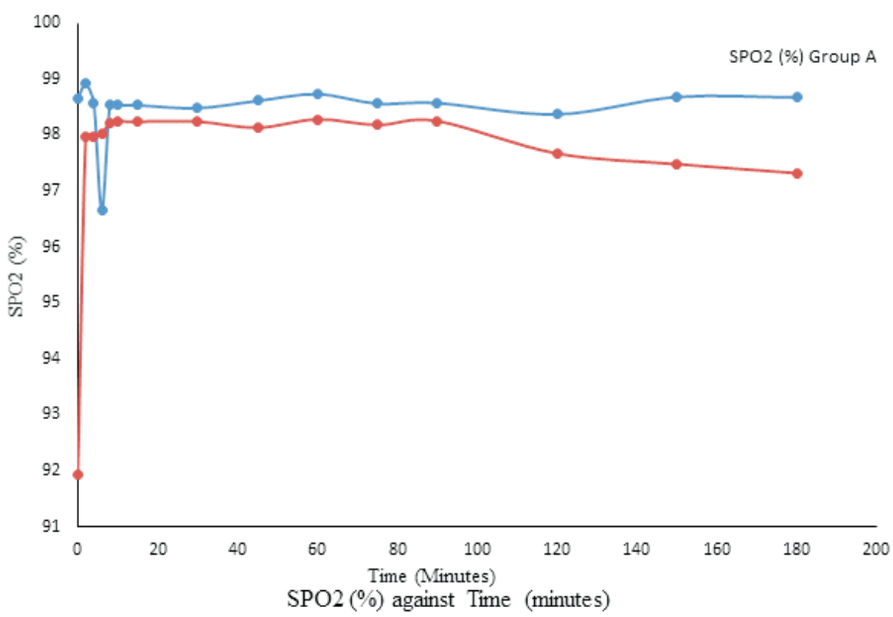

Figure. 4: Preoperative base line and comparative intraoperative peripheral arterial oxygen saturation monitoring for group a and b

Group A ……. Nefopam
Group B ……. Tramadol
SPO2 …… Peripheral Arterial Oxygen Saturation