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Comparison of Intravenous Nefopam and Intravenous Tramadol for Shivering Prophylaxis in Patients Undergoing Myomectomy under Spinal Anaesthesia

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ABSTRACT

BACKGROUND: Post Anaesthetic Shivering (PAS) is an inadvertent complication of subarachnoid block. Nefopam and tramadol are among the pharmacological agents used for the treatment of PAS. We thus studied the effects of nefopam in comparison with tramadol as shivering prophylaxis in patients undergoing surgery under subarachnoid block. METHOD: Following Institutional Research and Ethics Committee approval, eighty ASA I or II patients scheduled for elective myomectomy under subarachnoid block were enrolled into two groups (nefopam and tramadol). Nefopam group received intravenous nefopam 0.15 mg/kg while Tramadol group received intravenous tramadol 1mg/kg15 minutes before the establishment of subarachnoid block. Both groups were evaluated at five minute intervals for 90 minutes for shivering, changes in haemodynamic parameters, temperature, arterial oxygen saturation (Sp02), nausea and vomiting. Data was analyzed using IBM SPSS version 20. RESULTS: The demographic characteristics, body mass index, baseline blood pressure, pulse rate, oxygen saturation, and intraoperative characteristic of patients in both groups were similar. The overall incidence of shivering was 10%. More patients in the tramadol group shivered compared to the nefopam group [six (15%); versus two (5%); P = 0.132] but patients in the tramadol group had more grade one shivering. The level of satisfaction with shivering prevention was higher with nefopam patients. CONCLUSION: Intravenous nefopam has relatively superior shivering prophylactic properties when compared to intravenous tramadol with delayed onset and severity of shivering.

INTRODUCTION

Subarachnoid block is the anaesthetic technique of choice for the surgical management of uterine fibroid. It is however associated with postanaesthetic shivering (PAS)[1]which some patients have described to be worse than the pain of surgery itself. [2] The mechanism by which subarachnoid block causes shivering is not fully understood. However, shivering results from a central hypothalamic reduction in core temperature by 0.5^{o}C proportional to the level of block. This results in hypothermia, vasoconstriction and shivering. [3]

Various pharmacological agents have been tried for the reduction of post-anaesthetic shivering (PAS) with varying degrees of success[4]. Pethidine has remained the gold standard of treatment but its use is associated with respiratory depression, sedation, pruritus, and postoperative nausea and vomiting.[5] Clonidine is another potent anti-shivering agent with side effects, such as sedation and hypotension while ketamine causes hallucination, sedation, and dissociative phenomenon.[2] As a result, the search for an ideal prophylactic agent is necessary especially as PAS still remains a problem despite the availability of these interventions.

Tramadol is a mild mu (μ) opioid receptor agonist, which mediates shivering by regulating body temperature through serotoninergic pathway. Although it is readily available in our environment, it increases the risk of postoperative nausea and vomiting (PONV).[2,3] The efficacy of tramadol in comparison with other anti-shivering drugs for the treatment and prevention of shivering has been demonstrated in the literature. For example, Ejiro and co-workers[6] found its efficacy to be similar to that of ondansetron.

Similarly, nefopam a central analgesic with morphine sparing-effects[3] has also been shown to be efficacious in the management of PAS. [7] However, pain at injection site has been reported with its use. Tramadol and nefopam have similar pathways of reducing shivering but unlike tramadol, nefopam does not cause sedation. Few studies have compared nefopam with tramadol. We thus sought to determine the prophylactic anti-shivering effect of intravenous nefopam compared with intravenous tramadol.

METHODS

ETHICAL APPROVAL: This study was approved by the Institution's Review Board or Ethics Committee of the University of Benin Teaching Hospital, Benin City, Nigeria, with

reference number, Adm/E22/A/vol.V11/1188. Written informed consent was obtained from each patient enrolled for the study.

DESIGN OF STUDY: This study was a prospective randomized controlled clinical trial. SETTING: This study was conducted at the University of Benin Teaching Hospital (UBTH) Benin City, Edo State.

INCLUSION CRITERIA: patients of ASA I or II physical status, scheduled for myomectomy were enrolled for this study.

EXCLUSION CRITERIA: patients' refusal, patients with known allergy to study medication, repeat myomectomy, patients with mental disorder who cannot cooperate for SAB, previous history nausea and/or vomiting, patients with contraindications to SAB, history of fever, inadequate or failed SAB and conversion to general anaesthesia.

STUDY POPULATION: Eighty (80), 40 per group ASA I or II female patients, scheduled for elective myomectomy under subarachnoid block, were enrolled into the study.

PREOPERATIVE REVIEW: All eligible patients scheduled for myomectomy under SAB had a preoperative visit a day before planned surgery. The study protocol was explained to all eligible patients and a written informed consent was obtained. The height and weight of each patient were taken and recorded. General and systemic examinations were done. Ease of endotracheal intubation was evaluated using Mallampati score. Basic investigations including haemoglobin concentration, urinalysis, electrolyte, urea and creatinine were done for all patients. Patients were fasted overnight from 10 pm for uniformity. Each patient was given 10mg metoclopramide, 150mg tablet ranitidine and 10 mg diazepam orally the night before and on the morning of surgery.

RANDOMIZATION: The patients were randomized into nefopam (N) and tramadol (T) group by balloting technique. Each patient chose her group by picking from an opaque large envelope containing folded labeled paper which could either be "N" or "T" group. These labeled papers were presented to a second anaesthetist who was responsible for the preparation and coding of the study drugs. In the theatre, pre-checked functional anaesthetic machine and other ancillary equipments were made available. Operating room temperature was monitored with a Brannan® wall thermometer (Brannan and Sons, Cumbria England). Intraoperative patient monitoring was done with Edan® multiparameter monitor (Edan

instruments GmbH, Germany, M8B). Baseline temperature, pulse rate, blood pressure oxygen saturation (SpO2), electrocardiography (ECG) were obtained and recorded. Thereafter, each patient's circulation were preloaded with warm 15mls/kg 0.9% normal saline after intravenous access had been established with size 16G intravenous cannula on the non-dominant upper limb.

PROCEDURE: A second anaesthetist was responsible for the preparations and coding of the study drugs. Each drug was drawn into a 20 ml syringe and was made up to 20ml with the addition of sterile water. The appropriate code and patient identification number were recorded in a code notebook. The syringe that was presented to the principal investigator bore only the code number. Group N syringe contained nefopam 0.15mg/kg (Acupan,®Biocodex, France.NAFDAC reg. N 04- 5504)while group T syringe contained tramadol 1mg/kg(Tramal,® Grunenthal, Germany. NAFDAC reg. N 04-0483). The principal investigator administered the drugs intravenously over 15 minutes while the patient's circulation was being preloaded with 15mL/kg of 0.9% normal saline. The principal investigator also assessed for shivering. The actual group each patient belonged to was revealed at the end of surgery for subsequent analysis. Subarachnoid block was performed with the patient in the sitting position with the knee and hip flexed,and the flexed knee higher than the hip. The lower back was aseptically prepared with chlorhexidine and methylated spirit. L3/L4 or L4/L5 inter-vertebral spaces were located and infiltrated using 2mls of2% plain lidocaine. The subarachnoid space was accessed using 25G pencil point (Whitacre) spinal needle. Correct placement of spinal needle in the subarachnoid space was confirmed by the presence of clear, free, flowing cerebrospinal fluid. Thereafter, a 3.0ml (15mg) of inthrathecal 0.5% heavy bupivacaine (at room temperature) with 25mg of pethidine was deposited into the subarachnoid space. The patient was returned to supine position with a pillow placed under the head and shoulder to prevent excessive rostra spread of LA. A block height of T6 was required for the surgery. This was ascertained from loss of skin sensation to cold cotton wool swab soaked with methylated spirit. Intravenous fluid (0.9% normal saline) was administered at 10ml/kg for the first one hour thereafter at 5mL/kg/h. On-going fluid loss was corrected to meet a urinary output of 0.5ml – 1ml/kg/h. Monitoring of blood pressure, oxygen saturation, respiratory rate, shivering, nausea, vomiting, pain, and sedation were done every 5 minutes intra-operatively and every 15 minutes post operatively for 45 minutes until patient was discharged to the ward. Onset of shivering, duration, and grade was assessed using Tsai and Chu scale[8] [0 – no shivering; 1 –presence of piloerection or peripheral

vasoconstriction; 2 – muscular activity in one muscle group only; 3 – muscular activity in greater than one muscle group but not generalized; 4- shivering involving the whole body]. Grade three shivering and above was managed with IV pethidine 0.25mg/kg. Visual analogue scale in centimeters was used to assess pain [VAS: 0 – no pain; 10 – worst imaginable pain]. Analgesia was administered using intravenous pentazocin 1mg/kg when pain score was greater than. The level of sedation was assessed using Ramsey sedation scale[9] [1 – Anxious, agitated, restless; 2- oriented, calm and cooperative; 3 – respond to command only; 4 – brisk response to loud voice and light glabellar tap; 5 – sluggish to no response to light glabellar tap or loud auditory stimulus; 6 – no response to pain]. The severity of Nausea and vomiting was assessed using numeric scoring system for postoperative nausea and vomiting – PONV [0 – no nausea and vomiting; 1 – nausea but no vomiting; 2 – vomited once; 3 – two or more episodes of vomiting]. [10]Nausea was defined as a feeling of vomiting reported by the patient while vomiting is the rhythmic movement of the anterior abdominal wall associated with the ejection of vomitus.[11]Retching is the observed rhythmic movement of anterior abdominal wall without ejection of stomach content. Nausea or vomiting was treated with intravenous metoclopramide 10mg stat. Retching was considered as vomiting. A systolic blood pressure decrease greater than 20% from the baseline value was considered as hypotension. Hypotension was treated initially with 20mL/kg of 0.9% normal saline or with ephedrine boluses in 3mg aliquots. Patient satisfaction was measured using a three-point scale where 0 is not satisfied, 1 is satisfied and 2 is most satisfied.[12] The first preoperative haemodynamic parameter reading obtained before initiation of subarachnoid block was regarded as the baseline vital sign. Baseline vital sign consist of pulse rate, systolic blood pressure, diastolic blood pressure, mean arterial blood pressure and oxygen saturation. Time to shivering or onset of shivering was defined as the time from establishment of subarachnoid block to the time patient started shivering. This study ended immediately the patient left the recovery room for the ward. Other routine postoperative care was however continued in the ward.

DATA ANALYSIS: Data entry and analysis was done using IBM Statistical Package for Social Sciences (SPSS version 20.Chicago, Il, USA).Parametric data such as BMI, heart rate, mean arterial, systolic and diastolic blood pressure, duration of surgery, were summarized as mean and standard deviation while categorical data were summarized as counts and percentages. Comparison of parametric data was done with independent student's T- test. Categorical data such as ASA status, grades of shivering were analyzed using chi-squared test

or Fisher's exact test where appropriate. P value less than 0.05 was considered statistically significant. 9

RESULTS

Eighty-four (84) patients were enrolled in this study but only eighty patients participated in the study. Four patients were excluded from this study after enrolment, two from each group for study protocol violation. Table 1 shows similarity in the demographic characteristics of patients in both tramadol (T) and nefopam (N) groups. Both groups had similar mean age (P = 0.17), parity (p = 0.659) educational status (P = 0.05) and symphysis fundal height (p = 0.65).

Table 1: Socio-demographic and preoperative characteristics of patients

Parameter	Tramadol Group N = 40	Nefopam Group N = 40	P value	Level of significance
Age (years)	37.10 ± 4.18	35.9 ± 3.24	0.170	NS
Secondary education	7(17.5%)	6(15%)	0.500	NS
Tertiary Education	33(82.5%)	34(85%)	0.500	NS
Weight (kg)	71.95±15.89	74.94 ± 12.13	0.350	NS
Height (meters)	1.65±0.07	1.59 ± 0.14	0.21	NS
BMI(Kg/m^2)	26.56 ± 4.58	28.23 ± 3.20	0.064	NS
ASA 1(%)	11(27.5%)	7 (17.5%)	0.211	NS
ASA 2(%)	29 (72.5%)	33 (82.5%)	0.210	NS
SFH (Weeks)	19.50 ± 3.64	20.95 ± 3.27	0.659	NS
Parity	30 ± 516	25 ± 494	0.659	NS
PCV(%)	34.83 ± 2.34	35.43 ± 2.15	0.236	NS

NS – No significant difference. P > 0.05

SFH - symphysiofundal height

Preoperative packed cell volume (P = 0.236), ASA classification (ASA 1: P = 0.211; ASA 2: P = 0.211), weight (p = 0.35) and height (p = 0.21), BMI (P = 0.064) were also similar. The incidence of shivering in this study was 10% (Table II).

Table 2: Incidence and duration of shivering

Parameter	Tramadol N = 40 Mean ± SD	Nefopam N = 40 Mean ± SD	P value	level of significance
Pulse rate (beat/min)	86.48 ±9.36	87.30 ±10.60	0.71	NS
Systolic blood pressure (mmHg)	121..03±9.28	120.08 ± 9.51	0.65	NS
Diastolic blood pressure (mmHg)	77.90 ± 9.00	74.38 ± 11.51	0.13	NS
MAP (mmHg)	91.93 ± 8.91	88.20 ±10.20	0.09NS	
$Sp0_2$ (%)	96 -100%	96 – 100%	0.687	NS

Values are expressed as number and percentages.

NS - Not significant (Fisher's Exact test).P > 0.05

Six patients (15%) shivered in the tramadol group compared to two patients (5%) in the nefopam group although there was no statistical significant difference. (P = 0.132). The duration of shivering was also similar in both groups (P = 0.807). Three patients (7.5%) had grade two shivering in tramadol group (figure 1). There was no occurrence of grade two shivering in nefopam group. The proportion of patients that had grade one shivering were comparable in both groups {five (12.5%) in tramadol group and two (5.0%) in nefopam group. P = 0.90}.

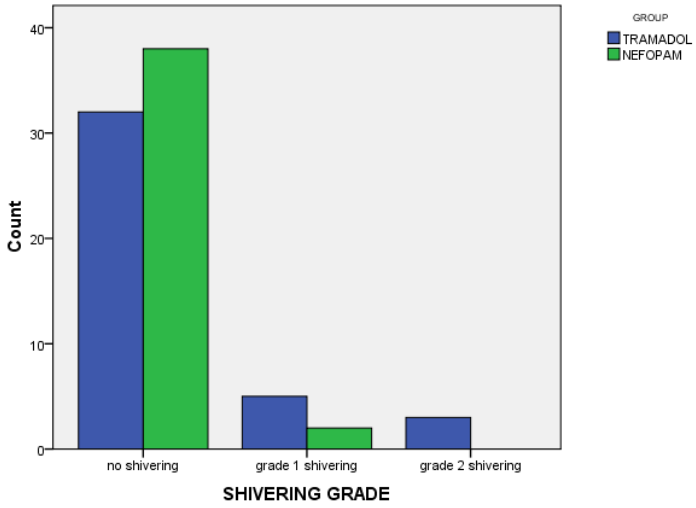

Figure 1: Shivering grades.

Count = number of patients.

Grade 0 : Shivering – tramadol 32 (80%), Nefopam 38 (95%) P=0.09 (not significant).

Grade 1: Tramadol 5 (12.5%), Nefopam 2 (5.0%). P = 0.09 (not significant).

Grade 2: Tramadol 3(7.5%). Nefopam – 0(0%).

Figure 2 illustrates the onset of shivering in a survival analysis plot. Shivering occurred earlier in tramadol group compared to nefopam group (20 minutes versus 85 minutes). The vertical-axis (cumulative survival proportion) refers to the proportion of patients in the study that have not shivered at a particular point. The horizontal -axis reflects the time shivering occurred. At the beginning of the study, the cumulative proportion of patient that did not shivered was 1.0. The proportion of patients in the nefopam group that did not shiver remains at 1.0 until the 85th 10 minute when the proportion reduced because two patients shivered. The censor symbol (crucifix) depicts the end of the study and the proportion of patient that have shivered at the 90th minute. Similar pattern was observed in the tramadol group. However, shivering occurred earlier in the tramadol group. The proportion of those that did not shiver therefore was less than 1.0 at the commencement of the graph. Subsequently, shivering episodes occurred at the 25 minutes, 75 minutes and at the 90th minute respectively. A crucifix (censor) also represents the proportion of patients in whom shivering was observed.

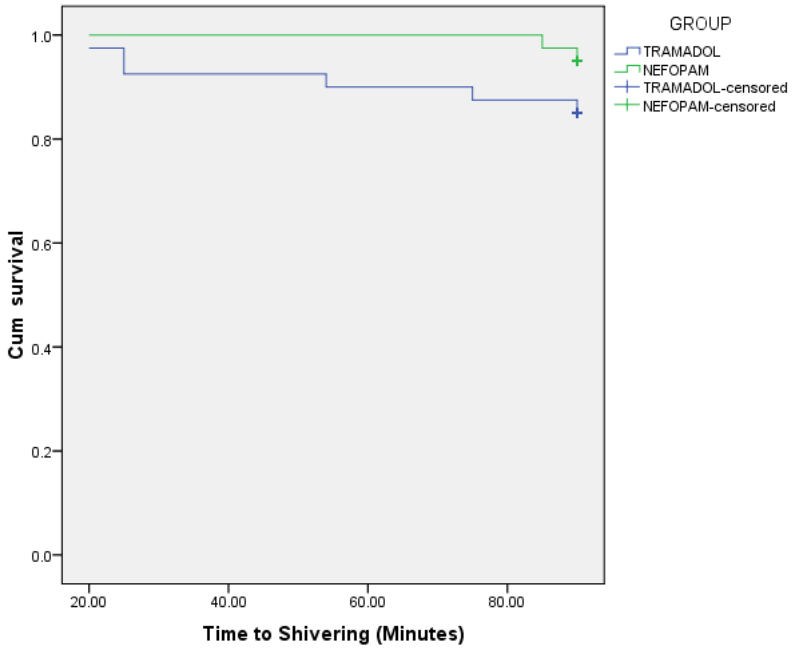

Figure 2: Shivering onset time.

Cum survival (cumulative survival) – Refers to the Proportion of patients that have not yet shivered at a particular point in time.

Censored - Refers to the proportion of patients that shivered at the end of the study.

Time to shivering(minute): tramadol – 20, 25, 25, 54, 75, 90; nefopam-85, 85.

Table III shows the incidence of side effects. More patients had tachycardia in the nefopam group (11.84%), compared to the tramadol group (8.68%).(P = 0.0516). A significant difference in pulse rate was observed (Table VI) at 25th minute (P = 0.004), 40th minute (P = 0.042), 50 minute (P = 0.023), and 90th minute (P = 0.027) respectively. Bradycardia occurred only in the tramadol group (2.76%).

Table 3: Incidence of side effects

Parameter	Tramadol Group N = 40	Nefopam Group N = 40	P value	Level of significance
Shivered	6(15%)	2(5%)	0.132	NS
No-shivering	34(85%)	38(95%)	0.132	NS
Duration of shivering(min)	10 ± 0.01	11± 0.01 0.807		NS
Overall shivering incidence	8(10%)			

* = total number of readings.

NS – No significant difference. P > 0.05

Occurrence of hypotension was similar in both groups (P =1.0000). None of the patient had nausea, vomiting, itching or pain at the site of injection of the study drugs. The bars in figure 3 illustrate the degree of satisfaction of patients in both groups. The degrees of satisfaction were comparable in both groups. None of the patients were dissatisfied (not satisfied) with the prevention of postanaesthetic shivering. Seven (17.5%) patients in tramadol group and 4 (11%) patients in nefopam group were satisfied with the degree of prevention of shivering in this study (P = 0.25) while thirty-six (32.2%) patients in nefopam group and thirty-three (42.5%) in tramadol groups were more satisfied.

Table 4: Baseline vital sign.

Parameter	Tramadol Group N = 40 (percent)	Nefopam Group N = 40 (percent)	P value	Level of significance
Episodes of tachycardia	66/760*(8.68)	90/760*(11.84)	0.0516	NS
Episodes of bradycardia	21/760*(2.76)	-	-	-
Episodes of hypotension	4/760*(0.53)	5/760*(0.66)	1.000	NS
Nausea	-	-	-	-
Vomiting	-	-	-	-
Pain at injection site	-	-	-	-
Itching	-	-	-	-
Sedation	-	-	-	-

NS – no significant difference. P > 0.05

Table 5: Intraoperative pulse rate pattern.

Parameter	Time(min)	Tramadol N = 40 Mean ± SD	Nefopam N= 40 Mean ± SD	P value	Level of significance
Pulse rate	25	79.55 ± 17.67	89.40 ± 11.75	0.004	Significant
Pulse rate	40	81.25 ± 13.82	87.23 ± 12.08	0.042	Significant
Pulse rate	50	79.70 ± 14.39	86.78 ± 12.87	0.023	Significant
Pulse rate	90	78.95 ± 12.12	85.28 ± 12.90	0.027	Significant

Significant- Significant difference. P < 0.05

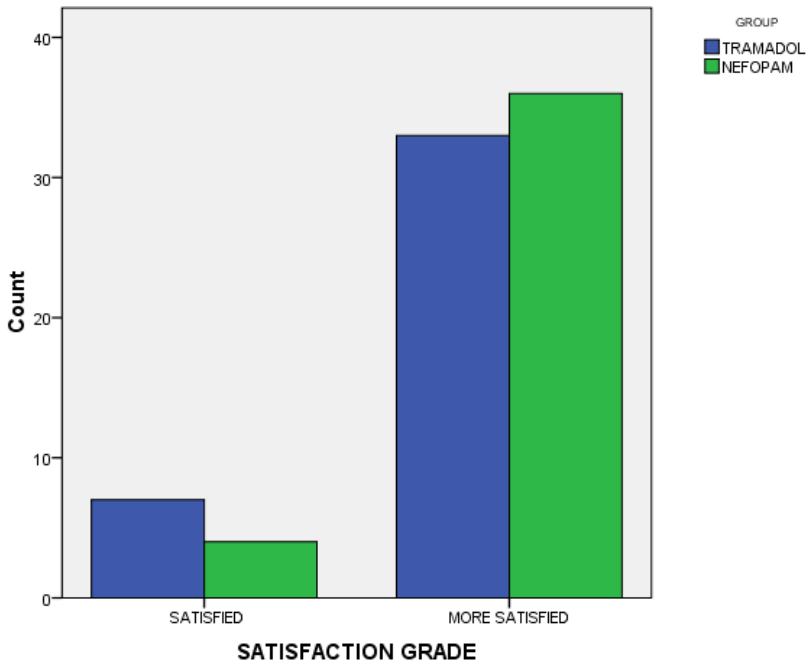

Figure 3: Satisfaction grade.

Counts - number of patients

Not satisfied – Tramadol: nil; Nefopam: nil

Satisfied – tramadol 7(17.5%); nefopam 4(11%). P = 0.25 (NS)

More satisfied – tramadol 33 (42.5%); nefopam 36 (32.2%) p = 0.25% (NS).

DISCUSSION

The overall occurrence of shivering in this study was 10% which is low compared with reports from other studies[13,14, 15,16] . This observed variations resulted from differences in methodology. Some of these studies reported the incidence of shivering following neuroaxial block without any prophylaxis while others included a placebo group. Although the use of placebo in clinical research in the presence of other clinical equivalence has been discouraged[1718], nevertheless, a placebo controlled study has its own merits.[19,20]

In most clinical research involving placebo control, the overall incidence of shivering tends to be high. Stating these values as incidence of shivering when comparing equivalent intervention could be misleading. Other reasons for the low incidence of shivering in this

study include the use of warm intravenous fluid, warming of intrathecal injection to room temperature before it was administered, [21]the use of a pharmacological antishivering prophylaxis (tramadol or nefopam), [22] premedication with anxiolytic agent like diazepam,[23] controlled operating room temperature,[22]and the addition of pethidine to subarachnoid bupivacaine.[24,25]

Chun et al[26] investigated patients who had transurethral prostatectomy under subarachnoid block with or without addition of pethidine. The incidence of shivering was lower in the group who had combination of 8mg 0.5% hyperbaric bupivacaine with pethidine compared to those that did not. Although, this research involved elderly males that are prone to shivering, [27], it however buttressed the fact that the addition of pethidine to inthrathecal bupivacaine does reduce the incidence of shivering. [12] The incidence of shivering in the tramadol group in this study is comparable to the result obtained by Tobi and colleagues[16] however they could not demonstrate a clear difference with the use of 0.5 mg/kg of tramadol for prevention of shivering compared with placebo.

Another study[6] using the same dose of tramadol (0.5 mg/kg) in patients who had ceasarean delivery demonstrated a statistical difference between tramadol and ondansetron for prevention of shivering. The low incidence of shivering in the nefopam group that was observed in our study is comparable to the findings of Bilotta and colleagues[15] while Manal and colleagues [28]on the other hand, reported a higher incidence of shivering in patients who received nefopam compared to our study. This difference could be explained by the mean age of the patients which was higher when compared to the mean age of our patients. It has been established that older patients shiver more. [27] Nevertheless, nefopam was more effective in preventing postanaesthetic shivering compared to the combination of ketamine and midazolam.

Although nefopam and tramadola share similar pathways of action like inhibition of reuptake of monoamines[29]nefopam differs due to its antagonist activity at the NMDA receptor. This is a similar pathway by which ketamine and magnesium exert their antishivering effects.[30]In addition, nefopam does not impair vasoconstriction compared to tramadol[31]and tramadol exert its effects through opioid receptors. However, the effect of tramadol on kappa receptors responsible for the control of shivering is weak.[32]These slight differences could explain the clinical superiority of nefopam over tramadol as postanaesthetic shivering prophylactic agent. Previously, it has been documented that female patients experienced shivering more than

their male counterparts[33]with a male to female ratio of 1:1.74. Although there are no clinical trials that have shown the relationship between postanaesthetic shivering and gender,[22] Crowley et al[22] in a review article on shivering and neuroaxial anesthesia also observed that the incidence of shivering in most reports appear higher in the female population.

Shivering in the present study occurred earlier in tramadol group compared with nefopam group. While this finding is comparable with some studies,[6,16]Bilotta and colleagues [15] observation seems to differ. This difference in shivering onset time could have resulted from the differences in the point of measurement. Nevertheless, the study shows that the onset of shivering is delayed when nefopam is used as pre-treatment of postanaesthetic shivering compared to tramadol.

The incidence of significant side effects such as sedation, nausea, vomiting, and pain at the site of injection or postdural puncture headache was negligible in this study. While this finding is heartwarming, previous studies had reported[15] nausea and vomiting in both nefopam and tramadol group and injection pain in the nefopam group. Postoperative nausea and vomiting (PONV) occurred in the aforementioned study because antiemetic prophylaxis was not given. Furthermore, slow injection of diluted study drugs helped to prevent the experiences of injection pain, nausea and vomiting in our study.

More patients in the nefopam group rated shivering prophylaxis more satisfactory although it was however not statistically significantly different between the two groups. These observations reflect the satisfaction of the majority of patients who did not shiver. It underscores the value of proper preoperative education. Moreover, high score is usually associated with single item question that is used in point scale.[34]

CONCLUSION

Nefopam appears to be relatively superior to tramadol in the prevention, onset and severity of intraoperative postanaesthetic shivering.

LIMITATIONS

It would have been clinically expedient to monitor the core temperature in this study. This, however, was not possible in our setting. The lack of statistical difference in the incidence of shivering may be related to the sample size.

REFERENCES

1. Jean-Denis R. Postoperative shivering. Anaesthesiology Rounds 2004; 3(6):122
2. Sessler D. Temperature and Monitoring.Miller RD (editor). Miller's Anaesthesia. 7th edition, Pennsylvania Churchill Livingstone. 2009:1533-1556
3. Bhattacharya KP, Bhattacharya L, Rajnish KJ, Ramesh CA. Post Anaesthesia Shivering(PAS) - A Review. Indian J Anaesth. 2003; 47(2):88- 93
4. Longnecker D, Brew LD, Newman FM, Zapol MW. Anaesthesiology. McGraw Hill Medical. 2008; 2013 – 2017.
5. Igbal A, Ahmed A, Rudra A, et al. Prophylaticgranisetronvspethidine for the prevention of postoperative shivering. A randomized control trial. Indian J Anaesth. 2009; 53(3):330 – 334.
6. Ejiro BA, Edomwonyi NP, Imarengiaye CO. Ondansetron versus tramadol in the prevention of postanaesthesia shivering following caesarean section under spinal anaesthesia. Afr J of Anaesth and Int Care. 2014; 14(1):6 – 11.
7. Abdelrahman RS. Prevention of shivering during regional anaesthesia. Comparison of midazolam, midazolam plus ketamine, tramadol and tramadol plus ketamine. life science journal 2012; 9(2):132-139.
8. Tsai YC, Chu KS: A comparison of tramadol, amitriptyline, and meperidine for postepiduralanaesthetic shivering in parturient. AnesthAnalg 2001; 93: 1288–92 24
9. Atashkhoyi S, Negargar S. Effect of tramadol for prevention of shivering after spinal anaesthesia for cesarean section. Res. J. Biol. Sci. 2008; 3(12):1365-1369.
10. Rodes VA, McDaniel RW. Nausea, vomiting and retching: complex problems in palliative care. C A Cancer J Clin 2001; 51: 232 – 248.
11. Greenberger NJ. Approach to the patient with upper GI complaints. Porter RS, Caplan JN (editors). The Merck Manual of Diagnosis and Therapy. 19th edition. New Jersey, Merck Sharp and Dohme Corp. 2011: 70 – 83
12. Scardino M, Grapplolo G, Gurgone A, Mazziotta G, Et al. Single-shot epidural-spinal anaesthesia followed by oral oxycodone/naloxone and ketoprofen combination in patients undergoing total hip replacement: Analgesic efficacy and tolerability. Minerva Anesthesiol. 20`15; 81: 19 – 27
13. Alagbe-Briggs OT, Kushimo OT. Pattern of post-anaesthetic shivering at Lagos University Teaching Hospital Idi-Araba Lagos. Port Harcourt Med J. 2012: 6(4):412 – 421.
14. Edomwonyi NP, Ekwere IT, Egbekun R, Idehen HO, Sadiq A. Anaesthesia related ccomplications in oobstetrics patients. Afr J AnaesthInt Care 2005; 6(2): 8-13. 25
15. Bilotta F, Pietropaoli P, Sanita R, Liberatori G. Nefopam and Tramadol for the prevention of shivering during neuroaxial anesthesia. RegAnesth Pain Med 2002; 27:380 – 384.
16. Tobi KU, Edomwonyi NP, Imarengiaye CO. Tramadol effects on perioperative shivering in lower limb orthopedic surgeries under spinal anesthesia. West Afric. College of Surg J. 2012; 2(2) :46 – 62.
17. World Medical Association decleration of Helsinki. Bulletin of World Health Organization 2001; 79(4):373 – 374.
18. Senezam B. The decleration of Helsinki – the cornerstone of research ethics. Archieves of Onchology 200: 9(3):179-184
19. Temple R, Ellenberg SE. Placebo-controlled trials and active-control trails in the evaluation of new treatments. Part 1: Ethical and scientific issues. Annals of Internal Medicine 2000;133:455-463
20. Temple R, Ellenberg SE. Placebo-controlled trials and active-control trails in the evaluation of new treatments. Part 2: Practical issues and specific cases. Annals of Internal Medicine 2000;133:464-470
21. uggy DJ, Crossley AWA. Thermoregulation, mild perioperative hypothermia and postanaesthetic shivering. BJA 2000; 84:615 – 628. 26
22. Crowley JL, Buggy MD. Shivering and neuraxial anesthesia. RegAnesth Pain Med. 2008; 33:241-252.
23. Abdelrahman RS. Prevention of shivering during regional anaesthesia. Comparison of midazolam, midazolam plus ketamine, tramadol and tramadol plus ketamine. life sci J 2012; 9(2):132-139
24. Chun D, Kil KH, Kim H, Park C, Chung K. Intrathecalmeperidine reduces intraoperative shivering during transurethral prostatectomy in elderly patients. Korean J Anesthesiol. 2010; 59(6):389 – 393.

25. Abdoreza NA, Kamran M. The effects of different doses of meperidine on shivering during delivery under spinal anesthesia. Int J Prev Med 2012; 3(10):706 – 712.
26. Chun D, Kil KH, Kim H, Park C, Chung K. Intrathecalmeperidine reduces intraoperative shivering during transurethral prostatectomy in elderly patients. Korean J Anesthesiol. 2010. 59(6):389 – 393
27. Frank MS, El-Rahmany, Cattaneo GC, Barnes RA. Predictor of hypothermia during spinal anesthesia. Anesthesiology. 2000; 92(5):1330 -1334.
28. Manal M K, Noha SH. Prevention of post spinal shivering by using ketamine plus midazolam in comparison with nefopam. Eg J Anaesth 2011; 27(1):1-5. 27
29. Alfonsi P. Postanaesthetic shivering. Epidemiology, pathophysiology and approaches to prevention and management.Minerva. 2003; 69: 438 – 441.
30. Alfonsi P, Adam F, Passard A, Guignard B, Sessler D I, Chauvin M. Nefopam, a nonsedativebenzoxazocin analgesic, selectively reduce the shivering threshold. Anaesth 2004;100(1): 37 – 43.
31. Bilotta F, Farri F, Giovanini F, Pinto G, Rosa G. Nefopam or clonidine in the pharmacologic prevention of shivering in patients undergoing conscious sedation for interventional neuroradiology. Anaesthesia. 2005; 60: 1124 – 128.
32. Javaherforoosh F, Akhondzadeh R, Aein KB, Olapour A, Samimi M. Effects of Tramadol on shivering post spinal anesthesia in elective cesarean section. Pak J Med Sci 2009; 25(1):12-17.
33. Sule AZ, Isamade ES, Ekwempu CC. Spinal anaesthesia for lower abdominal surgery: a review of 200 cases. Nig J Surg Res. 2005; 226-230.
34. Fung D. Measuring patient satisfaction with anaesthesia care: A review of current methodology. AnesthAnalg 1998; 84(5):1089 - 1098aAa 28 11 12 29 22 31 32