# Comparison of pentazocine and pethidine for the treatment of shivering following subarachnoid block

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## Abstract

Pethidine is one of the known drugs for treating post-spinal shivering; however, it is a controlled drug. Pentazocine, a specific kappa agonist, is widely available in West Africa and is not yet a controlled drug. A randomized, double-blind trial was performed to compare the efficacy of pentazocine and pethidine for the treatment of post-spinal shivering. One hundred ASA I and II patients undergoing surgeries below the umbilicus under spinal anesthesia were studied. Patients who developed shivering after the administration of intrathecal bupivacaine for spinal anesthesia were randomly allocated to 2 groups to receive either Intravenous (IV) pethidine 25 mg (n=50) - group A, or IV pentazocine 30 mg (n=50) - group B. The time from the administration of the study drug to the reduction and complete disappearance of shivering, recurrence of shivering, and other adverse effects were determined. The two study groups did not differ significantly regarding patient characteristics. The difference between the mean time of administration of the study drug to the complete disappearance of shivering in group A (9.23±2.18 minutes) and B (6.70±1.15 minutes) was statistically significant ($p<0.05$). The onset of action was faster with pentazocine (94.04±16.20 seconds) compared with pethidine (151±34.01) ($p<0.05$). The pentazocine group had a higher recurrence of shivering than the pethidine group (30.8% *vs* 13.0%), though this difference was not statistically significant ($p=0.14$). Three patients (13.04%) had a recurrence of shivering in the pethidine group compared to 8 patients (30.77%) in the pentazocine group. There was no significant difference between the groups in terms of sedation, pulse rates, nausea, perioperative tympanic temperatures, and mean arterial pressures. No vomiting or respiratory depressions were observed. Pentazocine 30 mg and pethidine 25 mg were both equally effective in the treatment of shivering following subarachnoid block. Though pentazocine had a faster onset of action and abolished shivering earlier than pethidine, the rate of recurrence of shivering after treatment was however higher with pentazocine than with pethidine.

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## Introduction

Shivering is an involuntary oscillatory muscular activity which augments metabolic heat production above the basal level and is elicited when the preoptic region of the hypothalamus is cooled.[1] The incidence of shivering during Subarachnoid Block (SAB) is 40-60% in temperate countries and it is a common presentation during SAB. Crowley and Buggy,[1,2] in a broad sample of 21 studies, found the median incidence of shivering related to neuraxial anesthesia in the control groups to be 55%.

Shivering is an unpleasant and undesirable complication in the perioperative period as it leads to increased oxygen consumption, generalized muscle pains, and overall increased risk of hypoxia and its sequelae.[2,3] Apart from causing discomfort and exacerbat-

ing post-operative pain, post anesthetic shivering has been shown to increase catecholamine release, cardiac output, heart rate, blood pressure, and intra-ocular pressure.[1] It also commonly interferes with routine patient monitoring.

It is, therefore, imperative to treat or prevent postoperative shivering, provided the interventions are sufficiently simple and free of major side effects. Non-pharmacologic and pharmacologic approaches have been used to treat the shivering that occurs following SAB with varying degrees of success. These include the use of warm blankets, radiant heaters, and warm infusion fluids[3,4,] as well as the use of opioid analgesics like pethidine,[5] tramadol,[6,7] clonidine,[6] nalbuphine[4,] and ketamine.[8] However, only one documented study has been found on the use of pentazocine, a commonly used and widely available agonist/antagonist opioid analgesic in Nigeria, for the relief of shivering during SAB at a dose of 7.5 mg.[9] Terasako *et al*.[9] in their study compared the effect of pentazocine, pethidine and placebo for the treatment of shivering following SAB and concluded that 7.5 mg pentazocine given intravenously was not a form of treatment. The most popular method of treating shivering is by intravenous administration of low-dose pethidine (25 mg). Pethidine is, however, a controlled drug and is not readily available in our environment. Pentazocine is an agonist-antagonist like nalbuphine which has been found to be effective in the treatment of shivering following subarachnoid block.[10] This study seeks to compare the effectiveness of 25 mg pethidine with the commonly available pentazocine (30 mg) as a treatment option for shivering following SAB.

## Materials and Methods

This randomized, prospective, comparative, and double-blinded study was carried out at Aminu Kano Teaching Hospital, Kano North West Nigeria, in 100 ASA I and II patients of either sex aged between 18 and 65 years. Patients who were scheduled for urological, gynecological, lower limb orthopedic, and general surgery elective procedures under SAB and lasting less than 2 hours were chronologically recruited into this study. Patients who had hypersensitivity to the study drugs, obstetric patients, patients with a body mass index ≥35kg/m$^2$, addicts, or patients on long-term opioid therapy were excluded from the study. Institutional ethical committee approval was sought and approval was obtained.

All patients were reviewed a day before surgery to assess their fitness to undergo anesthesia. Pre-assessment included history taking, examination, and review of investigations such as Full Blood Count (FBC), Urea, Electrolytes and Creatinine (U/E/Cr), urinalysis, and Fasting Blood Sugar (FBS). The study was explained to the patients, and informed consent was taken for participation. All patients were weighed, and their height was taken. No premedication was administered, and all patients were asked to fast overnight. On the morning of surgery, the temperature of the operating room was kept at 26°C[11] by setting the theatre air conditioners and monitoring with Comark instrument WT4 wall thermometer; the anesthetic machine in the operating theatre was checked, and all resuscitation equipment and drugs were kept handy.

On arrival of the patients in the theatre, baseline vital signs were recorded using a multi-parameter monitor (DASH 4000 GE; GE Healthcare, Chicago, USA). These include Pulse Rate (PR), Non-Invasive Blood Pressure (NIBP) with Mean Arterial Pressure (MAP), Electrocardiogram (ECG), Peripheral Oxygen Saturation (SpO□) and peripheral body temperature. The core temperature (tympanic) was recorded using an electronic thermometer (Braun thermoscan ear thermometer IRT 4520; Braun, Melsungen, Germany). An appropriately sized IV cannula was inserted followed by a 20mls/kg normal saline preload at room temperature 20-30 minutes before SAB.

Scrubbed and using an aseptic technique with the patient in a sitting position, a skin wheal was raised with 2mls of 1% plain lidocaine, and a lumbar puncture was performed by the researcher between the 3$^{rd}$ and 4$^{th}$ lumbar intervertebral space with a 25G pencil point (Whitacre; Becton Dickinson, Franklin Lakes, USA) spinal needle. With free flow of cerebrospinal fluid, 3mls of 0.5% heavy bupivacaine (Marcaine Spinal Heavy %0.5 aspen) at room temperature was injected into the subarachnoid space. Patients were made to lie supine immediately after injection, with a pillow under the shoulder to control the cephalad spread of the local anesthetic. The appropriate level of sensory block (target level of $T_8$-$T_{10}$) was ensured, as well as the establishment of a motor block. Pulse rate, NIBP, MAP, SpO□, ECG, and temperature were monitored immediately after the institution of the SAB and subsequently at 5-minute intervals till the end of surgery into the recovery period until discharge to the ward. The time of onset of shivering (measured with Time Timer Watch Plus), as well as temperatures (peripheral and core), were recorded. Movements ranging from mild fasciculation and visible tremors to gross muscular activity were regarded as shivering. All consenting patients who shivered after the institution of the block were randomly assigned into one of two groups: A (pethidine group) and B (pentazocine group), using a sealed envelope technique in a double-blinded manner. Those in group A received 25 mg IV pethidine, and those in group B received 30 mg IV pentazocine. Both drugs were made up to 5 ml with water for injection in two different syringes by the assisting anesthetist, who did not further participate in the study. The researcher was blinded to the contents of the syringe till the patient was discharged to the ward. Patients were monitored, and the effect of treatment was documented. The time of onset of shivering, time of onset of reduction in shivering, and time from treatment to disappearance of shivering were noted and recorded. All the patients who developed intraoperative hypotension (a drop of 20% MAP from baseline) responded well to increased fluid therapy with 0.9% saline. No patient developed hypotension to warrant treatment with ephedrine. Patients who developed nausea and vomiting were to be treated with IV metoclopramide 10 mg, but no vomiting was recorded. Nausea spontaneously resolved with the correction of mild hypotension using intravenous fluids. Bradycardia (heart rate of less than 60 beats per minute) was to be treated with atropine 0.5 mg IV, but none of the patients developed bradycardia. Patients' sedation was graded using the Campbell scale,[12] with 1 being wide awake; sedated, easily arousable was graded as 2, drowsy and difficult to arouse was 3 and unarousable was 4. Patients with $SpO_2$ of less than 94% received oxygen 100% at 4 L/min via nasal prongs. Postoperatively, recovery nurses continued monitoring patients until complete block regression.

Patient demographics, treatment and effect of treatment, and unwanted effects such as hypotension, nausea, recurrence, and sedation were recorded. The data obtained was analyzed using the Statistical Package for Social Sciences (SPSS) version 18.0 for Windows statistical software. An inter-group comparison of shivering between the pentazocine and pethidine groups was done. P value <0.05 was considered statistically significant. Student's t-test was used for the analysis of continuous variables, and the Chi-square test for categorical variables. Values were expressed as numbers, means, and standard deviations, and the results were presented in the form of tables and graphs.

## Results

Demographic parameters (Table 1) showed the mean age in the pethidine group (group A) and pentazocine group (group B) to be 33.3±11.2 years and 36.5±14.2 years, respectively, with no statistical difference between the two groups (p=0.21). The mean height of group A was 1.70±0.05 m, and group B was 1.72±0.05 (p=0.10). The mean Body Mass Index (BMI) for group A was 24.90 kg/m$^2$, and 24.31 kg/m$^2$ for group B.

Twenty-three (23) patients who developed shivering were recruited into group A and received IV pethidine, and 26 received IV pentazocine in group B.

As shown in Table 2, the time from administration of the treatment drug to the onset of reduction in shivering in both groups showed a statistically significant difference. For group A, it was 151.85±34.01 sec, and for group B, 94.04±16.20 sec (p=0.001). The time from administration of the treatment drug to when shivering disappeared completely was significantly different for both groups. Shivering stopped faster in the pentazocine group, as shown in Table 2. Group A had a mean time of 9.23±2.18 minutes, and for B, 6.70±1.15 minutes (p-value=0.001) which is statistically significant. The recurrence of shivering occurred in 3 patients (13.04%) in group A and 8 patients (30.77%) in group B, with a p-value of 0.14, which was also statistically insignificant. Table 3 shows the side effects of treatment in the two groups. Hypotension following SAB occurred in 20 patients (20.0%): 5(21.74%) of these patients who developed shivering were in group A and 6 (23.06%) in group B. The difference was not statistically significant (p-value=0.91). Nausea was found in 4 patients (17.39%) in group A and 5 patients (19.23%) in group B with p-value = 1.0, which is statistically insignificant. Sedation was found in 3 patients (13.04%) in group A and 9 patients (34.62%) in group B (p=0.08). However, three patients (13.04%) in the pethidine group and eight (30.40%) in the pentazocine group had recurrences of shivering after successful initial treatment. Figure 1 shows the mean core temperature changes in both groups. These were comparable at varying time intervals.

## Discussion

Results obtained from this study show that pentazocine and pethidine are both effective in the treatment of shivering following subarachnoid block. However, pentazocine had a shorter onset of action and abolished shivering faster than pethidine. Studies have tested the efficacy of a large variety of drugs to prevent shivering in normothermic or hypothermic surgical patients. Park *et al.*[13] identified meperidine (pethidine), tramadol, clonidine, nefopam, and ketamine as the most frequently studied and efficacious medications for this purpose. As the incidence of hypotension is high during regional anesthesia, hypotensive agents such as clonidine may, however, not be appropriate in preventing shivering. In addition, pethidine and tramadol may cause nausea, vomiting, and respiratory depression during and after regional anesthesia. The hypertensive and tachycardiac effects of ketamine limit its use.

Pethidine is the most widely used drug for the treatment of postoperative shivering. Ejiro *et al.*[5] reported pethidine to be the gold standard for the treatment of shivering following subarachnoid block. Previous studies by Casey *et al.*[14] and Leslie *et al.*[15]

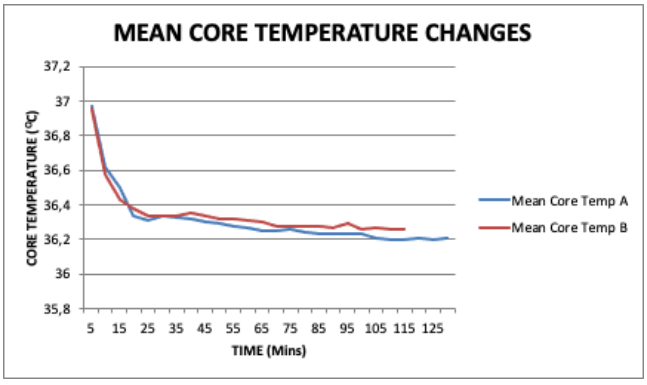


**Figure 1.** Mean intraoperative core temperatures in groups A and B.

**Table 1.** Patients' characteristics (mean ± Standard Deviation, SD).

| Patients' demographics | Group A n=50 | Group B n=50 | T test | p |
|---|---|---|---|---|
| Age (years) | 33.3±11.2 | 36.5±14.2 | -1.25 | 0.21 |
| Weight (kg) | 71.4±8.04 | 70.9±10.7 | 0.22 | 0.76 |
| Height (m) | 1.70±0.05 | 1.72±0.05 | 2.36 | 0.1 |
| BMI (kg/m$^2$) | 24.9±2.86 | 24.31±2.78 | 1.04 | 0.30 |

**Table 2.** Times of onset of reduction, and treatment to reduction of shivering (mean ± Standard Deviation, SD).

| | Group A n=23 | Group B n=26 | p |
|---|---|---|---|
| Onset of reduction of shivering (sec) | 151±34.01 | 94.04±16.20 | <0.0001 |
| Disappearance of shivering (min) | 9.23±2.18 | 6.70±1.15 | <0.0001 |

**Table 3.** Patients' characteristics (mean ± Standard Deviation, SD).

| Side effects | Group A n=23 | | Group B n=26 | | Test | p-value |
|---|---|---|---|---|---|---|
| Hypotension | 5 | 18 | 6 | 20 | $X^2$=0.013 | 0.91 |
| Nausea | 4 | 19 | 5 | 21 | Fisher's exact test | 1.0 |
| Sedation | 3 | 20 | 9 | 17 | $X^2$=3.07 | 0.08 |
| Recurrence | 3 | 20 | 8 | 18 | $X^2$=2.20 | 0.14 |

have also found it to be effective in the treatment of PAS. The mean onset time of reduction of shivering after pethidine administration was found to be 151.85±34.01 seconds in this study. An onset time of 5 minutes has also been reported by Philip *et al*.[16] when they compared the effectiveness of pethidine and tramadol for controlling shivering during epidural anesthesia. The wide difference between this present study and that by Philip *et al.* could be attributed to the difference in operating room temperatures.

Pentazocine in this study showed a shorter onset of action in the reduction of shivering (94.04±16.20) compared to the timing seen in the pethidine group (151±34.01). Chowdry *et al*.[17] also reported a slower onset of reduction of shivering with the pethidine group when compared to nalbuphine. The time of complete disappearance of the shivering for pethidine was found to be 9.23±2.18 minutes. Similar results were found by Philip *et al*.[16] and Terasako *et al*.[9] Despite pethidine's efficacy in controlling shivering, recurrence after treatment is known to occur.[18-20] In this study, 13.04% (3 patients) of the patients who received pethidine and 30.77% (8 patients) in the pentazocine group had a recurrence of shivering after successful initial treatment. Higher incidences of recurrence after treatment with pethidine have been reported (34%,[17] 33%[16]). These higher incidences may be attributed to the lower operating room temperatures (22±1°C) used by Chowdry *et al*.[17] and Philip *et al*.[16] This present study was conducted in the tropics with higher ambient temperatures. Patients who had a recurrence of shivering after treatment were treated with additional drape covers and placed under a radiant heater in the recovery room.

The only study we found in the literature that compared pethidine with pentazocine reported the effect of pentazocine to have no statistical difference with normal saline and so concluded that Pentazocine 7.5 mg was not effective for the treatment of post-anesthetic shivering.[9] The dose of pentazocine used in the present study is, however, higher (30 mg). This could account for the effectiveness of pentazocine for the treatment of post-spinal shivering observed in this study. Comparing the effectiveness of pethidine and pentazocine for shivering control in this study, it was found that there was a statistically significant difference between pentazocine and pethidine both in the onset of reduction of shivering and the time of complete disappearance of shivering.

This study found no correlation between shivering and core temperature, and this finding is supported by the review of fifteen trials by Kranke *et al*.,[21] which also found no relationship between shivering and average core temperature.

Overall, intraoperative hypotension occurred in 20.0% of patients. The incidence of hypotension and nausea were similar in both study groups. Hypotension could have occurred as a result of vasodilatation from the spinal anesthesia, excessive intraoperative hemorrhage, or as a side effect of the treatment drugs. Honarmand[22] reported the incidence of hypotension to be 23% while comparing the prophylactic effect of midazolam, ketamine, and ketamine plus midazolam for the prevention of shivering during regional anesthesia. These are comparable with the 20.0% incidence of hypotension found in this study. Treatment of hypotension was done with rapid infusion of 0.9% saline while the nausea resolved with the return of blood pressure to normal. Since hypotension responded to an increase in vascular volume, it was probably due to the effect of spinal anesthesia.

Nausea occurred in 19.0% of patients in this study. The occurrence of nausea coincided with the time at which hypotension occurred and resolved when hypotension was corrected. Sule *et al*.[3] and Olanrewajo reported the incidence of nausea to be 17.5% and 20.0%, respectively. These are comparable to the mean incidence of 19.0% in this study. There was no significant difference in the occurrence of nausea between the two groups (19.23% for the pentazocine group and 17.39% for the pethidine group). The incidence of nausea reported by Honarmand[22] was, however, higher than that found in the present study. They found an incidence of nausea of 26.0% when they used ketamine for a similar study. Nausea and vomiting are known side effects of ketamine and could have accounted for the higher incidence.

Sedation occurred in 9 (34.62%) patients in the pentazocine group and 3 (13.04%) in the pethidine group. The incidence of sedation in the study by Saini[23] following intravenous pethidine for PAS was 10%, which is similar to the incidence of sedation in our pethidine group. Other side effects, such as vomiting, itching, bradycardia, or respiratory depression, were not observed.

## Conclusions

Pentazocine 30 mg and pethidine 25 mg are both effective in the treatment of shivering following subarachnoid block. Though pentazocine had a faster onset of action and abolished shivering earlier than pethidine, the rate of recurrence of shivering after treatment was, however, higher with pentazocine than with pethidine. Both drugs at these doses caused minimal side effects when used for the treatment of shivering following subarachnoid block.

### Recommendations

Pethidine remains one of the drugs of choice for the treatment of shivering post-subarachnoid block. A larger sample size should be studied by comparing pentazocine with pethidine so as to improve the sensitivity of the outcome. Pentazocine could be used for the treatment of shivering following subarachnoid block where pethidine is not available.

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