ORIGINAL ARTICLE

# Intravenous Nefopam versus Tramadol for Prevention of Misoprostol-Induced Shivering during Caesarean Section under Spinal Anaesthesia: A Randomized Double-Blind Controlled Trial

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**ABSTRACT**

**Background:** Misoprostol-induced shivering is a common and distressing adverse effect among women undergoing caesarean section under spinal anaesthesia. Although both tramadol and nefopam have been used for shivering prevention, evidence comparing their effectiveness in obstetric patients receiving misoprostol remains limited. **Methods:** This randomized double-blind controlled trial enrolled 100 parturients undergoing elective caesarean section under spinal anaesthesia. Participants were randomly assigned to receive either intravenous tramadol 1 mg/kg (Group T, n=50) or intravenous nefopam 0.15 mg/kg (Group N, n=50) following administration of misoprostol. The primary outcome was the incidence of shivering. Secondary outcomes included shivering severity, time to onset of shivering, haemodynamic parameters, adverse effects, and rescue therapy requirements. **Results:** Baseline demographic and perioperative characteristics were comparable between groups. Shivering occurred in 20 patients (40%) in the tramadol group and 10 patients (20%) in the nefopam group (p=0.028). Moderate-to-severe shivering was significantly less frequent among patients receiving nefopam (p=0.041). The mean time to onset of shivering was significantly longer in the nefopam group (26.4 ± 6.1 minutes) than in the tramadol group (18.6 ± 5.2 minutes; p<0.001). Nausea occurred more frequently with tramadol (28% vs 12%; p=0.041), whereas tachycardia was more common with nefopam (24% vs 6%; p=0.012). Rescue therapy was required less frequently in the nefopam group (4% vs 16%; p=0.046). **Conclusion:** Intravenous nefopam was more effective than tramadol in preventing misoprostol-induced shivering during caesarean section under spinal anaesthesia. Nefopam reduced shivering incidence and severity, delayed symptom onset, and decreased rescue therapy requirements while maintaining acceptable haemodynamic stability.

**Key words:** Nefopam; Tramadol; Misoprostol; Shivering; Caesarean section.

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## Introduction

Shivering is a common and clinically significant complication of spinal anaesthesia, particularly during caesarean section. The reported incidence ranges from 40% to 70%, largely due to neuraxial blockade, perioperative heat loss, and physiological changes associated with pregnancy.[1-3] Although shivering is a protective thermoregulatory response, it may result in increased oxygen consumption, carbon dioxide production, metabolic demand, catecholamine release, and maternal discomfort. In obstetric patients, severe shivering may interfere

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with monitoring, surgical conditions, and early mother–infant interaction.[1-3]

The mechanism of shivering during spinal anaesthesia is multifactorial. Sympathetic blockade causes peripheral vasodilation and redistribution of heat from the core to peripheral tissues, resulting in impaired thermoregulation and a reduction in core temperature.[4,5] Additional factors such as exposure to a cool operating theatre environment, administration of unwarmed intravenous fluids, and evaporative heat loss further increase the risk of perioperative shivering.[2,4] Consequently, shivering remains one of the most frequent adverse effects encountered during caesarean section under spinal anaesthesia.

The widespread use of misoprostol in obstetric practice has introduced an additional challenge. Misoprostol, a synthetic prostaglandin $E_1$ analogue, is commonly used for the prevention and treatment of postpartum haemorrhage because of its effectiveness, low cost, and stability at room temperature.[6] However, shivering and pyrexia are among its most frequently reported adverse effects.[7] Misoprostol-induced shivering is believed to occur through central thermoregulatory mechanisms involving hypothalamic prostaglandin receptors, resulting in an elevation of the thermoregulatory set point.[8] Consequently, shivering may occur even in the absence of significant hypothermia.

Because non-pharmacological measures alone are often insufficient, pharmacological prophylaxis plays an important role in shivering prevention. Various agents have been evaluated, including opioids, $\alpha_2$-adrenergic agonists, N-methyl-D-aspartate receptor antagonists, and centrally acting analgesics.[9] Tramadol is one of the most commonly used agents because of its availability and proven efficacy. Its anti-shivering effect is attributed to weak μ-opioid receptor agonism and inhibition of serotonin and norepinephrine reuptake.[10] However, tramadol is frequently associated with adverse effects such as nausea, vomiting, dizziness, and sedation.

Nefopam (Acupan) is a centrally acting non-opioid analgesic that has emerged as a promising alternative for shivering prevention. It inhibits the reuptake of serotonin, norepinephrine, and dopamine, thereby modulating central thermoregulatory pathways without opioid receptor activation.[11] Previous studies have demonstrated that nefopam effectively reduces perioperative shivering and may be associated with fewer gastrointestinal adverse effects than tramadol.[12,13]

Despite the availability of both agents, evidence directly comparing nefopam and tramadol for the prevention of misoprostol-induced shivering during caesarean section under spinal anaesthesia remains limited. Most previous studies have involved mixed surgical populations, while data specifically addressing obstetric patients receiving misoprostol are scarce.[12,14] This evidence gap is particularly relevant in low-resource settings where misoprostol is widely used and access to active warming devices may be limited.

Therefore, this randomized double-blind controlled trial was designed to compare the efficacy and safety of intravenous nefopam and intravenous tramadol for the prevention of misoprostol-induced shivering among parturients undergoing caesarean section under spinal anaesthesia. The primary outcome was the incidence of shivering, while secondary outcomes included shivering severity, time to onset, haemodynamic changes, adverse effects, and rescue therapy requirements.

## Methods

### Study Design and Setting

This randomized double-blind controlled trial was conducted in the obstetric operating theatres of a tertiary healthcare institution in northern Nigeria. The study was conducted and reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) 2010 guidelines.[15] Ethical approval was obtained from the Institutional Research Ethics Committee before commencement of the study. Written informed consent was obtained from all participants before enrolment.

### Study Population

The study population consisted of term parturients scheduled for elective caesarean section under spinal anaesthesia. Eligible participants were women aged 18–40 years with singleton pregnancies at a gestational age of 37–42 weeks and classified as American Society of Anesthesiologists (ASA) physical status II.

Patients with known hypersensitivity to tramadol, nefopam, or misoprostol, pre-existing fever (temperature >38°C) or hypothermia (<36°C), seizure disorders, significant cardiovascular or neurological disease, thyroid dysfunction, chronic

opioid use, or contraindications to spinal anaesthesia were excluded. Patients requiring conversion to general anaesthesia or experiencing major intraoperative complications were excluded from the final analysis.

**Sample Size Determination**

The sample size was calculated using the formula for comparison of two independent proportions. Based on previous studies reporting a reduction in shivering incidence from 50% in patients receiving tramadol to 25% in those receiving nefopam, a minimum sample size of 45 participants per group was required to achieve 80% power at a 5% level of significance. To compensate for possible attrition, 50 participants were recruited into each group, giving a total sample size of 100 parturients.[16]

**Randomization and Blinding**

Participants were randomly assigned in a 1:1 ratio to either the tramadol group (Group T) or the nefopam group (Group N) using a computer-generated randomization sequence with block sizes of four. Allocation concealment was achieved using sequentially numbered opaque sealed envelopes prepared by an independent investigator.

The study medications were prepared in identical 10 mL syringes by an anaesthetist not involved in patient management or data collection. Both participants and investigators responsible for drug administration, outcome assessment, and data analysis were blinded to treatment allocation throughout the study.

**Anaesthetic Technique**

On arrival in the operating theatre, baseline measurements of heart rate, non-invasive blood pressure, peripheral oxygen saturation, and axillary temperature were recorded. An 18-gauge intravenous cannula was inserted, and patients received 10 mL/kg of crystalloid solution before spinal anaesthesia.

Under aseptic conditions, spinal anaesthesia was performed at the L3–L4 or L4–L5 interspace using a 25-gauge Quincke spinal needle. Hyperbaric bupivacaine 0.5% (10–12 mg) was administered intrathecally. Following the procedure, patients were positioned supine with left uterine displacement and received supplemental oxygen at 3–5 L/min via facemask. Surgery commenced after confirmation of a sensory block level of at least T6.

**Intervention Protocol**

Following delivery of the neonate, umbilical cord clamping, and administration of 600 µg sublingual misoprostol, participants received the allocated study medication.

Group T received intravenous tramadol 1 mg/kg, while Group N received intravenous nefopam (Acupan) 0.15 mg/kg. The study drugs were diluted with normal saline to a total volume of 10 mL and administered slowly over 2–3 minutes. The selected doses were based on previous studies demonstrating efficacy in preventing perioperative shivering while minimising adverse effects.[10,12]

**Intraoperative Management**

Operating theatre temperature was maintained between 22°C and 24°C throughout the study period. Intravenous fluids were administered at room temperature, and active warming devices were not used to standardise environmental thermal exposure.

Hypotension, defined as a reduction in systolic blood pressure greater than 20% from baseline or a systolic blood pressure below 90 mmHg, was treated with intravenous ephedrine in 5–10 mg increments. Bradycardia, defined as a heart rate below 50 beats per minute, was treated with intravenous atropine 0.6 mg.

**Outcome Measures**

The primary outcome was the incidence of shivering occurring intraoperatively and within 60 minutes following administration of the study drug.

Secondary outcomes included shivering severity, time to onset of shivering, haemodynamic changes, temperature changes, adverse effects, and rescue therapy requirements.

Shivering severity was assessed using a validated four-point scale:

Grade 0: No shivering.

Grade 1: Piloerection or peripheral vasoconstriction without visible muscular activity.

Grade 2: Visible muscular activity confined to one muscle group.

Grade 3: Visible muscular activity involving more than one muscle group.

Axillary temperature was recorded at baseline and at 15-minute intervals throughout the observation period. Adverse effects, including nausea, vomiting, tachycardia, dizziness, and sweating, were documented.

Patients who developed Grade 3 shivering received intravenous pethidine 25 mg as rescue therapy.

Data Collection and Monitoring

Data were collected by a trained investigator who was blinded to group allocation. Continuous monitoring was maintained intraoperatively and during the first 60 minutes of postoperative recovery. All observations were recorded using a standardized data collection form.

**Statistical Analysis**

Data were analysed using Statistical Package for the Social Sciences (SPSS) version 25. Continuous variables were expressed as mean ± standard deviation and analysed using the Student's t-test or Mann–Whitney U test as appropriate. Categorical variables were presented as frequencies and percentages and analysed using the Chi-square test or Fisher's exact test.

Relative risks (RRs) and corresponding 95% confidence intervals (CIs) were calculated for categorical outcomes. A p-value of less than 0.05 was considered statistically significant.

**Results**

Participant Flow

A total of 112 parturients were assessed for eligibility during the study period. Twelve women were excluded, including eight who did not meet the inclusion criteria and four who declined participation. The remaining 100 eligible participants were randomized equally into the tramadol (n = 50) and nefopam (n = 50) groups. All randomized participants received the allocated intervention, completed follow-up, and were included in the final analysis. No participant was lost to follow-up or excluded from analysis (Figure 1).

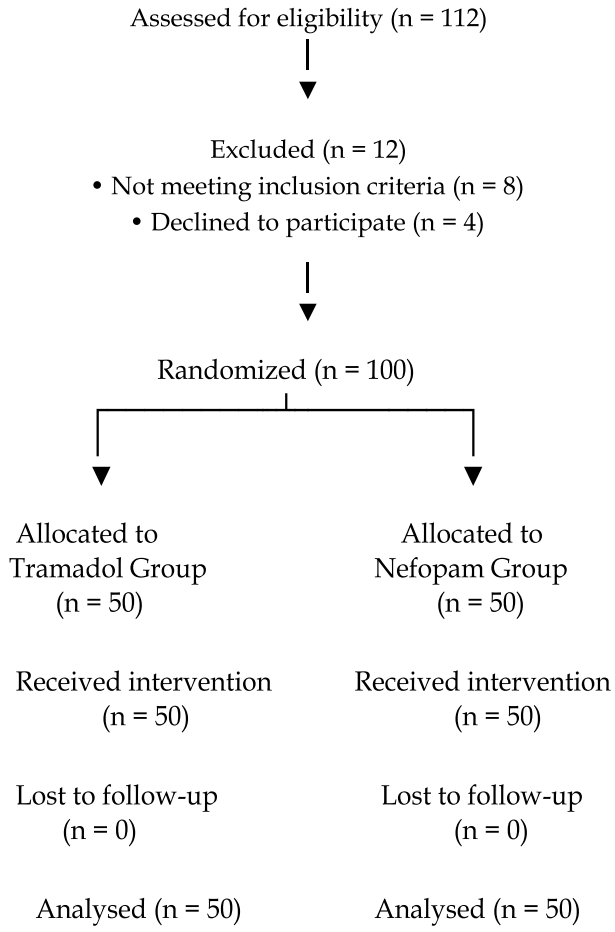


**Figure 1. CONSORT flow diagram showing participant enrolment, randomization, allocation, follow-up, and analysis.**

**Baseline Characteristics**

The baseline demographic and perioperative characteristics were comparable between the two groups. No statistically significant differences were observed in age, weight, gestational age, duration of surgery, or baseline axillary temperature (Table 1).

**Table 1. Baseline Characteristics of Participants**

| Variable | Group T (n=50) | Group N (n=50) | p-value |
|---|---|---|---|
| Age (years) | 29.8 ± 4.2 | 30.1 ± 3.9 | 0.71 |
| Weight (kg) | 74.5 ± 8.1 | 75.2 ± 7.6 | 0.64 |
| Gestational age (weeks) | 38.5 ± 1.1 | 38.7 ± 1.0 | 0.33 |
| Duration of surgery (min) | 52.3 ± 6.8 | 51.6 ± 7.2 | 0.59 |
| Baseline temperature (°C) | 36.7 ± 0.3 | 36.6 ± 0.4 | 0.28 |

**Incidence and Severity of Shivering**

Shivering occurred in 20 patients (40%) in the tramadol group compared with 10 patients (20%) in the nefopam group. Nefopam significantly reduced the incidence of shivering compared with tramadol (RR 0.50, 95% CI 0.26–0.95; p = 0.028).

The distribution of shivering severity is presented in Table 2. Moderate-to-severe shivering occurred more frequently in the tramadol group than in the nefopam group. The overall difference in severity distribution was statistically significant (p = 0.041).

**Table 2. Severity of Shivering**

| Grade | Group T, n (%) | Group N, n (%) |
|---|---|---|
| 0 (No shivering) | 30 (60) | 40 (80) |
| 1 (Mild) | 8 (16) | 6 (12) |
| 2 (Moderate) | 7 (14) | 3 (6) |
| 3 (Severe) | 5 (10) | 1 (2) |

**Overall comparison: p = 0.041**

The mean time to onset of shivering was significantly longer in the nefopam group than in the tramadol group (26.4 ± 6.1 minutes versus 18.6 ± 5.2 minutes; p < 0.001).

**Haemodynamic Parameters**

Heart rate and mean arterial pressure measurements are shown in Table 3. Baseline values were similar between groups. Heart rate was significantly higher in the nefopam group at 30 and 60 minutes. Mean arterial pressure remained comparable throughout the study period.

**Table 3. Haemodynamic Parameters**

| Parameter | Group T | Group N | p-value |
|---|---|---|---|
| **Heart Rate (beats/min)** | | | |
| Baseline | 84 ± 9 | 83 ± 8 | 0.62 |
| 30 min | 85 ± 9 | 94 ± 10 | 0.003 |
| 60 min | 83 ± 8 | 91 ± 9 | 0.005 |
| **Mean Arterial Pressure (mmHg)** | | | |
| Baseline | 92 ± 8 | 91 ± 7 | 0.55 |
| 30 min | 90 ± 6 | 89 ± 7 | 0.61 |
| 60 min | 91 ± 7 | 90 ± 6 | 0.58 |

**Temperature Changes**

Axillary temperature decreased progressively in both groups during the perioperative period. At 60 minutes, the mean temperature was 36.1 ± 0.5°C in the tramadol group and 36.3 ± 0.4°C in the nefopam group. The difference between groups was not statistically significant (p = 0.07).

**Adverse Effects**

The incidence of adverse effects is presented in Table 4. Nausea occurred significantly more frequently in the tramadol group than in the nefopam group (28% vs 12%, p = 0.041). Tachycardia was more common in the nefopam group (24% vs 6%, p = 0.012). No significant difference was observed in the incidence of vomiting.

**Table 4. Adverse Effects**

| Outcome | Group T, n (%) | Group N, n (%) | p-value |
|---|---|---|---|
| Nausea | 14 (28) | 6 (12) | 0.041 |
| Vomiting | 10 (20) | 4 (8) | 0.089 |
| Tachycardia | 3 (6) | 12 (24) | 0.012 |

**Additional Outcomes**

Rescue therapy with intravenous pethidine was required in 8 patients (16%) in the tramadol group compared with 2 patients (4%) in the nefopam group (RR 0.25, 95% CI 0.06–0.98; p = 0.046).

**Discussion**

This randomized double-blind controlled trial demonstrated that intravenous nefopam was more effective than tramadol in preventing misoprostol-induced shivering among parturients undergoing caesarean section under spinal anaesthesia. Patients who received nefopam experienced a significantly lower incidence and severity of shivering, a longer time to onset of symptoms, and a reduced requirement for rescue therapy. These findings indicate that nefopam provides superior prophylactic control of shivering in obstetric patients receiving both spinal anaesthesia and misoprostol.

Shivering remains one of the most common complications of neuraxial anaesthesia. Spinal anaesthesia impairs thermoregulatory control through sympathetic blockade, peripheral

vasodilation, and redistribution of core heat from the central compartment to peripheral tissues, thereby lowering the thresholds for vasoconstriction and shivering.[17,18] The administration of misoprostol further increases the risk through prostaglandin-mediated effects on hypothalamic thermoregulation.[19,20] Consequently, the incidence of shivering observed in the tramadol group is consistent with rates previously reported among obstetric patients undergoing caesarean section under spinal anaesthesia.[21,22]

The principal finding of this study was the significantly lower incidence of shivering among patients receiving nefopam. This observation agrees with previous studies demonstrating the efficacy of nefopam in preventing perioperative shivering during both regional and general anaesthesia.[12,13] Nefopam exerts its anti-shivering effect through inhibition of serotonin, norepinephrine, and dopamine reuptake within the central nervous system, resulting in modulation of thermoregulatory pathways without opioid receptor activation.[11] The superior efficacy observed in the present study may therefore be attributed to its broader monoaminergic activity and direct effects on central thermoregulation.

Nefopam also significantly reduced the severity of shivering. This finding is clinically important because severe shivering increases oxygen consumption, carbon dioxide production, metabolic demand, and catecholamine release, all of which may adversely affect perioperative physiological stability.[24,25] Similar reductions in shivering severity have been reported in comparative studies evaluating nefopam against tramadol and other anti-shivering agents.[12,13]

Another important finding was the significantly longer time to onset of shivering among patients receiving nefopam. Delayed onset of shivering provides a longer period of maternal comfort during surgery and recovery. Previous studies have similarly reported prolonged shivering-free intervals among patients receiving nefopam compared with tramadol and other pharmacological interventions.[14,26]

Both study drugs maintained acceptable haemodynamic stability. Although heart rate was modestly higher among patients receiving nefopam, mean arterial pressure remained comparable between groups throughout the observation period. This finding is consistent with the sympathomimetic properties of nefopam resulting from norepinephrine reuptake inhibition.[11] The observed tachycardia was mild, transient, and did not require treatment. Similar haemodynamic findings have been reported in previous perioperative studies.[27]

The adverse-effect profile observed in this study favoured nefopam. Nausea and vomiting occurred more frequently among patients receiving tramadol, whereas nefopam was associated with a higher incidence of mild tachycardia. Reduced gastrointestinal adverse effects are particularly important in obstetric patients because postoperative nausea and vomiting may adversely affect maternal comfort, recovery, and early maternal–infant interaction. Previous systematic reviews have reported similar findings regarding the safety profile of nefopam and other anti-shivering agents.[5,9]

The reduced requirement for rescue therapy further supports the superior efficacy of nefopam. Patients receiving nefopam required significantly less rescue medication than those receiving tramadol, suggesting more sustained prophylactic control of shivering. Reduced use of rescue medication may simplify perioperative management and reduce overall drug exposure. Similar findings have been reported in studies evaluating pharmacological approaches to shivering prevention.[28,29]

From a broader clinical perspective, these findings are particularly relevant in low- and middle-income countries where misoprostol is widely used for the prevention of postpartum haemorrhage and access to active warming devices may be limited. Under such circumstances, nefopam represents a practical non-opioid alternative that can improve maternal comfort while maintaining safety. The increasing emphasis on opioid-sparing perioperative strategies further supports the use of nefopam in contemporary obstetric anaesthesia practice.[30]

The strengths of this study include its randomized double-blind design, adequate sample size, standardized anaesthetic protocol, and comprehensive assessment of efficacy and safety outcomes. However, several limitations should be acknowledged. The study was conducted at a single centre, which may limit generalizability. Axillary temperature measurements were used instead of invasive core temperature monitoring, and neonatal

outcomes were not assessed. In addition, long-term postoperative outcomes and cost-effectiveness analyses were beyond the scope of the study. Future multicentre studies incorporating neonatal outcomes and economic evaluations would further strengthen the evidence base.[31,32]

The findings of this study support the use of nefopam as an effective and well-tolerated non-opioid option for the prevention of misoprostol-induced shivering during caesarean section under spinal anaesthesia.

**Conclusion**

Intravenous nefopam demonstrated superior efficacy compared with tramadol for the prevention of misoprostol-induced shivering during caesarean section under spinal anaesthesia. Nefopam significantly reduced the incidence and severity of shivering, prolonged the time to onset, and decreased the requirement for rescue therapy. Although associated with a higher incidence of mild tachycardia, nefopam resulted in fewer gastrointestinal adverse effects and maintained acceptable haemodynamic stability. These findings support the use of nefopam as an effective non-opioid alternative for shivering prophylaxis in obstetric anaesthesia.

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**Conflict Of Interest**

The authors declare that they have no conflicts of interest.

**Ethical Approval**

Ethical approval for this study was obtained from the Institutional Research Ethics Committee before commencement of the study.

**Informed Consent**

Written informed consent was obtained from all participants before enrolment.

**Author Contributions**

All authors contributed substantially to the conception and design of the study, data collection, data analysis, interpretation of results, manuscript drafting, and approval of the final version of the manuscript.

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