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Research Article

Intravenous Ondansetron, Nefopam, and Paracetamol for Prevention of Post-Spinal Shivering During Caesarean Section: A Randomized, Controlled, Double-blind Study

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Abstract

Background: Shivering is a common complication of spinal anaesthesia, with an incidence of approximately 50%-60%, and is associated with increased perioperative morbidity. Although several pharmacological agents have been investigated for its antishivering prophylaxis, each has inherent limitations, and the optimal prophylactic agent remains a subject of ongoing debate. This study compared the anti-shivering efficacy of prophylactic intravenous paracetamol, ondansetron, and nefopam in obstetric patients undergoing spinal anaesthesia. *Methods:* Eligible obstetric patients were randomly allocated into four groups: Group P (paracetamol, n = 16), Group O (ondansetron, n = 16), Group N (nefopam, n = 16), and Group C (normal saline, n = 16). The primary outcome was the incidence of post-spinal shivering. Secondary outcomes included the severity of shivering, incidence of nausea, vomiting, hypotension, and perioperative haemodynamic variables. Continuous variables were analysed using one-way analysis of variance (ANOVA), while categorical variables were analysed using the chi-square test. A p-value of <0.05 was considered statistically significant. *Results:* No patient in the nefopam group developed shivering. The incidence of shivering was significantly lower in the ondansetron and nefopam groups than in the control group ($p < 0.001$), with nefopam demonstrating complete prophylaxis. Patients who developed shivering in the ondansetron group predominantly experienced mild-to-moderate shivering, whereas those in the paracetamol and control groups mainly exhibited moderate-to-severe shivering, with the difference being statistically significant. The incidence of nausea, vomiting, hypotension, and the perioperative trends in heart rate, mean arterial pressure, and peripheral oxygen saturation were comparable across all study groups. *Conclusion:* Prophylactic intravenous nefopam demonstrated the greatest efficacy in preventing post-spinal shivering in obstetric patients undergoing spinal anaesthesia, followed by ondansetron and paracetamol. Nefopam may therefore be considered a superior prophylactic agent for the prevention of post-spinal shivering in this patient population.

Keywords

Nefopam, Ondansetron, Paracetamol, Post-spinal Shivering, Spinal Anaesthesia, Obstetric Patients

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1. Introduction

Spinal anaesthesia remains the anaesthetic technique of choice for parturients undergoing lower-segment caesarean section (LSCS) because of its rapid onset, reliable sensory blockade, and favourable maternal and neonatal outcomes [1]. However, despite these advantages, it is commonly associated with complications such as hypotension, bradycardia, and post-spinal shivering [2].

Shivering is an involuntary, rhythmic, oscillatory muscular activity that occurs as a physiological response to hypothermia and serves to increase metabolic heat production [3, 4]. Following spinal anaesthesia, the reported incidence of shivering ranges from 50% to 60% [2, 4]. Although its exact pathophysiology remains incompletely understood, several mechanisms have been proposed, including redistribution of core body heat secondary to peripheral vasodilation below the level of the block, uninhibited spinal reflexes, increased sympathetic activity, and postoperative pain [5-7].

Post-spinal shivering is more than a source of patient discomfort. It significantly increases metabolic rate, oxygen consumption, and carbon dioxide production, thereby predisposing patients to myocardial ischaemia, hypoxaemia, and lactic acidosis. In addition, shivering may aggravate postoperative pain, impair wound healing, and interfere with electrocardiographic, pulse oximetry, and non-invasive blood pressure monitoring, making perioperative management more challenging [3, 4, 8]. Consequently, effective prevention of perioperative shivering remains an important component of quality obstetric anaesthetic care.

Both pharmacological and non-pharmacological strategies have been employed to prevent perioperative shivering. Non-pharmacological measures include warming intravenous fluids, forced-air warming devices, radiant heat, and optimization of operating room ambient temperature. Pharmacological agents that have demonstrated varying degrees of efficacy include pethidine, tramadol, dexamethasone, low-dose ketamine, clonidine, nefopam, ondansetron, and paracetamol.

Nefopam is a centrally acting, non-opioid, non-sedative analgesic with established anti-shivering properties [3, 8]. Its thermoregulatory effect is thought to result from inhibition of the synaptic reuptake of serotonin, noradrenaline, and dopamine, thereby lowering the shivering threshold through central thermoregulatory pathways [8]. Ondansetron, a selective 5-hydroxytryptamine type-3 ($5\text{-}HT_3$) receptor antagonist widely used for the prevention of postoperative nausea and vomiting, has also been shown to reduce the incidence of shivering following both spinal and general anaesthesia [6]. Although its precise mechanism remains unclear, it is believed to exert its anti-shivering effect through modulation of serotonergic pathways within the preoptic anterior hypothalamus, the principal centre for thermoregulation [6].

Paracetamol reduces shivering by lowering the hypothalamic thermoregulatory set point through central inhibition of prostaglandin synthesis, thereby decreasing the threshold for shivering [9].

Previous studies comparing pharmacological agents for the prevention of post-spinal shivering have reported inconsistent findings. Anup et al [7] demonstrated that tramadol was more effective than ondansetron, whereas Ramadan et al [10] reported that meperidine was superior to both nefopam and ondansetron. In contrast, Lakhe et al [11] found that ondansetron, low-dose ketamine, and tramadol produced comparable anti-shivering effects following spinal anaesthesia.

Despite these reports, evidence directly comparing the prophylactic anti-shivering efficacy of intravenous ondansetron, nefopam, and paracetamol remains limited. To the best of our knowledge, no previous study has directly compared these three agents in obstetric patients undergoing caesarean section under spinal anaesthesia. Therefore, this study aimed to compare the prophylactic anti-shivering effects of intravenous ondansetron, nefopam, and paracetamol in parturients undergoing elective caesarean section under spinal anaesthesia.

2. Subjects and Methods

This prospective, randomized, double-blind, controlled comparative study was conducted at the Federal Teaching Hospital Owerri following approval from the institution's Human Research and Ethics Committee. It was registered with Pan Africa Clinical Trial Registry with number PACTR202604906314523. Written informed consent was obtained from all participants before enrolment.

A total of 64 ASA physical status II and III parturients aged 20-40 years who were scheduled for elective caesarean section under spinal anaesthesia were recruited for the study. Patients were excluded if they declined participation, had a body mass index (BMI) ≥ 35 kg/m^2, had a known hypersensitivity to any of the study medications, required conversion to general anaesthesia, or had emotional or psychiatric disorders that could interfere with study participation or assessment.

2.1. Randomization and Blinding

Participants were randomly allocated into four equal groups (n = 16 each) using a sealed opaque-envelope randomization technique: Group O: Ondansetron 4 mg intravenously, Group N: Nefopam 0.15 mg/kg intravenously, Group P: Paracetamol 1 g intravenously, Group C: Control (100 mL normal saline). Each study drug was diluted to a total volume of 100 mL and administered intravenously over an appropriate period, 10 minutes before induction of spinal anaesthesia. Both the participants and the investigators responsible for data collection and outcome assessment were blinded to treatment allocation throughout the study.

2.2. Anaesthetic Technique

Standard anaesthetic monitoring, including electrocardiography, non-invasive blood pressure measurement, pulse oximetry, and heart rate monitoring, was instituted before commencement of the procedure. Spinal anaesthesia was performed at either the L3-L4 or L4-L5 intervertebral space using a 27-gauge pencil-point spinal needle. Following confirmation of free flow of cerebrospinal fluid, 2 mL of 0.5% hyperbaric bupivacaine was administered intrathecally under aseptic conditions. Following the block, patients were positioned supine with left uterine displacement to minimize aortocaval compression. Operating room temperature was maintained at approximately 22 ℃ throughout the procedure, and supplemental oxygen at 2-5 L/min was administered via face mask.

2.3. Data Collection

Heart rate (HR), mean arterial pressure (MAP), and peripheral oxygen saturation (SpO_2) were recorded at baseline, every 5 minutes during the first 15 minutes following spinal anaesthesia, and subsequently at 15-minute intervals until completion of surgery. Shivering was assessed using the validated Crossley and Mahajan five-point grading scale. The primary outcome measure was the incidence of post-spinal shivering. Secondary outcome measures included the onset and severity of shivering, haemodynamic changes, and drug-related adverse effects.

2.4. Sample Size Determination

The sample size was calculated using WINPEPI software (Version 11.65) based on the findings of Lakhe et al. [11], who reported a mean onset of shivering of 21 ± 1.15 minutes in the ondansetron group and 13 ± 9.62 minutes in the control group. Assuming a study power of 90%, a 95% confidence level, and a type I error (α) of 0.05, the minimum required sample size was estimated to be 16 participants per group, giving a total sample size of 64 patients.

2.5. Statistical Analysis

Data were analysed using IBM Satistical Package for Social Sciences (SPSS) Statistics version 25.0 (IBM Corp., Armonk, NY, USA). Continuous variables were tested for normality and presented as mean ± standard deviation (SD) or median (interquartile range), as appropriate. Comparisons of normally distributed continuous variables among the four groups were performed using one-way analysis of variance (ANOVA), while the independent-samples *t*-test was used for comparisons between two groups. Non-normally distributed variables were analysed using the Kruskal-Wallis test for multiple-group comparisons and the Mann-Whitney U test with Bonferroni correction for pairwise comparisons. Categorical variables were analysed using the Chi-square test or Fisher's exact test where appropriate. A two-tailed *p*-value <0.05 was considered statistically significant.

3. Results

A total of 64 parturients completed the study, with 16 participants allocated to each of the four study groups. There were no protocol deviations or withdrawals.

3.1. Baseline Characteristics

The demographic characteristics and surgical profiles of the participants were comparable across the four groups. There were no statistically significant differences in age, body mass index (BMI), or duration of surgery (all $p > 0.05$), indicating that the study groups were well matched at baseline (Table 1).

Table 1. *Comparison of the demographic variables and surgery profile of the patients among the groups.*

Variable	Paracetamol	Ondansetron	Nefopam	Control	F	P value
Age	31.44 ±4.38	29.88 ±6.32	29.19 ±5.61	31.06 ±6.90	0.503	0.68
BMI	31.44 ±3.28	30.69 ±3.05	30.31 ±3.44	30.81 ±3.44	0.320	0.81
Duration of surgery	52.00 ±8.96	58.25 ±11.24	55.94 ±10.92	57.81 ±12.55	1.054	0.446

3.2. Incidence of Post-Spinal Shivering

The incidence of post-spinal shivering differed significantly among the study groups ($p < 0.001$). Shivering occurred in all patients (100%) in the control group, compared with 15 patients (93.8%) in the paracetamol group, 5 patients (31.3%) in the ondansetron group, and none of the patients (0%) in the nefopam group (Table 2).

Table 2. Comparison of the incidence of shivering between the groups.

Variable	Paracetamol	Ondansetron	Nefopam	Control	Pvalue
Incidence of Shivering	15 (93.5%)	5 (31.3%)	0 (0%)	16 (100%)	0.000
Odds ratio	0.9375	0.028	0.0		

3.3. Onset of Shivering

There was a statistically significant difference in the onset of shivering among the study groups (Kruskal-Wallis test, $p < 0.001$). Pairwise comparisons with Bonferroni correction demonstrated that prophylactic administration of nefopam and ondansetron significantly prevented or delayed the onset of shivering compared with paracetamol (both $p = 0.003$). No statistically significant difference was observed between the paracetamol and control groups ($p > 0.05$) (Tables 3 and 4).

Table 3. Comparison of the Onset of Shivering among the groups[1].

Variable	Paracetamol	Ondansetron	Nefopam	Control	Statistic	Pvalue
Onset of Action	24.5 (19.25, 32.75)	0.0 (0.0, 14.0)	0.0 (0.0, 0.0)	22.5 (22.0, 23.75)	38.345	<0.000

Table 4. Comparison of the Onset of Shivering among the groups.

Variable	Paracetamol	Ondansetron	Nefopam
Mean Rank	17.84	10.72	0.0
Mann-whitney u	106.500	35.500	0.00
P value	0.423	0.000	0.000
P value with Bonferroni correction	1.269	0.003*	0.003*

* significant

3.4. Severity of Shivering

The severity of post-spinal shivering varied significantly among the study groups ($p < 0.001$). No patient in the nefopam[1] group developed shivering. In the ondansetron group, shivering was predominantly mild to moderate, whereas patients in the paracetamol group experienced mainly moderate-to-severe shivering. In contrast, severe shivering predominated in the control group, with most patients experiencing Grade 3 or Grade 4 shivering (Table 5).

Table 5. Comparison of the degree of shivering between the groups.

Degree of Shivering	Paracetamol	Ondansetron	Nefopam	Control	Pvalue
0	1 (6.3%)	11 (68.8%)	16 (100%)	0 (0%)	
1	2 (12.5%)	1 (6.3%)	0 (0%)	0 (0%)	0.000
2	6 (37.5%)	4 (25%)	0 (0%)	1 (6.3%)	

[1] * p - value from Kruskal Wallis test

Degree of Shivering	Paracetamol	Ondansetron	Nefopam	Control	Pvalue
3	7 (43.8%)	0 (0%)	0 (0%)	10 (62.5%)	
4	0 (0%)	0 (0%)	0 (0%)	5 (31.3%)	

Grades 1 &2 are mild and moderate shivering, grades 3 &4 are severe shivering.

3.5. Adverse Effects

The incidences of nausea, vomiting, and hypotension were comparable among the four groups, with no statistically significant differences observed ($p > 0.05$). Overall, all three study medications were well tolerated, and no serious drug-related adverse events were recorded during the study period (Table 6).

Table 6. *Comparison of the side effects between the groups.*

Variable	Paracetamol	Ondansetron	Nefopam	Control	P value
Nausea	6 (37.5)	2 (12.5%)	2 (12.5%)	4 (25%)	0.26
Vomiting	3 (18.8%)	1 (6.3%)	0 (0%)	1 (6.3%)	0.25
Hypotension	1 (6.3%)	5 (31.3%)	3 (18.8%)	5 (31.3%)	0.26

3.6. Haemodynamic Parameters

The trends in heart rate and mean arterial pressure remained comparable throughout the intraoperative period among all study groups. No statistically significant intergroup differences were observed at any measurement point ($p > 0.05$), indicating that the study medications did not adversely affect haemodynamic stability (Figures 1 and 2). Similarly, peripheral oxygen saturation remained stable throughout the perioperative period, with no significant differences observed among the four groups (Figure 3).

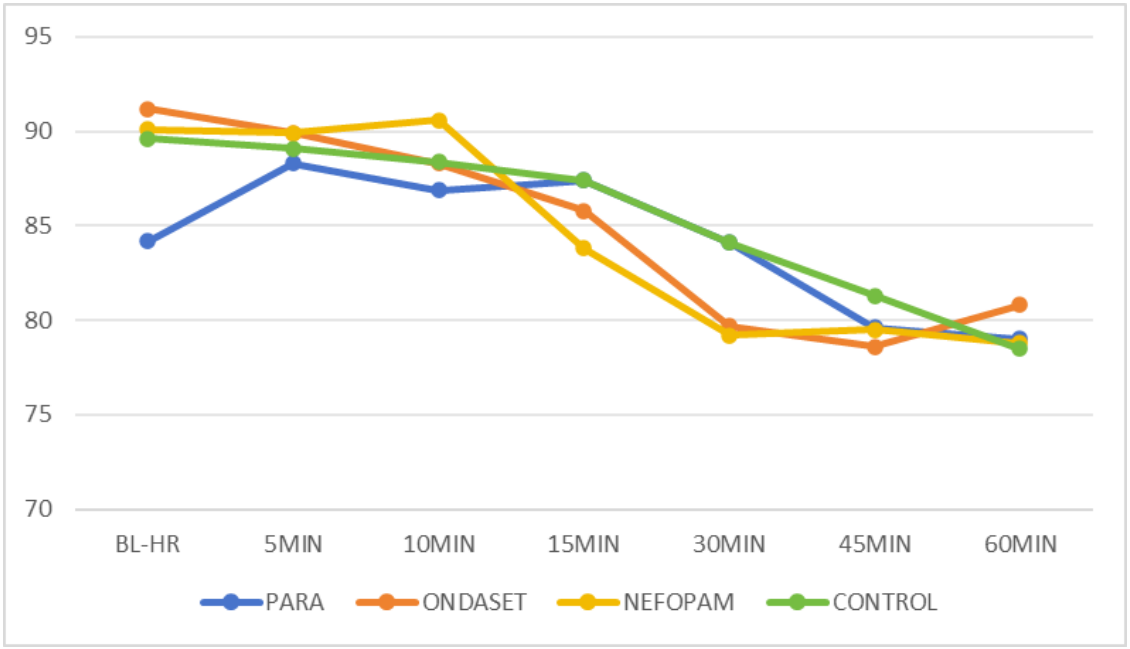

Figure 1. *Comparison of the trend of the mean pulse rate over time among the groups.*

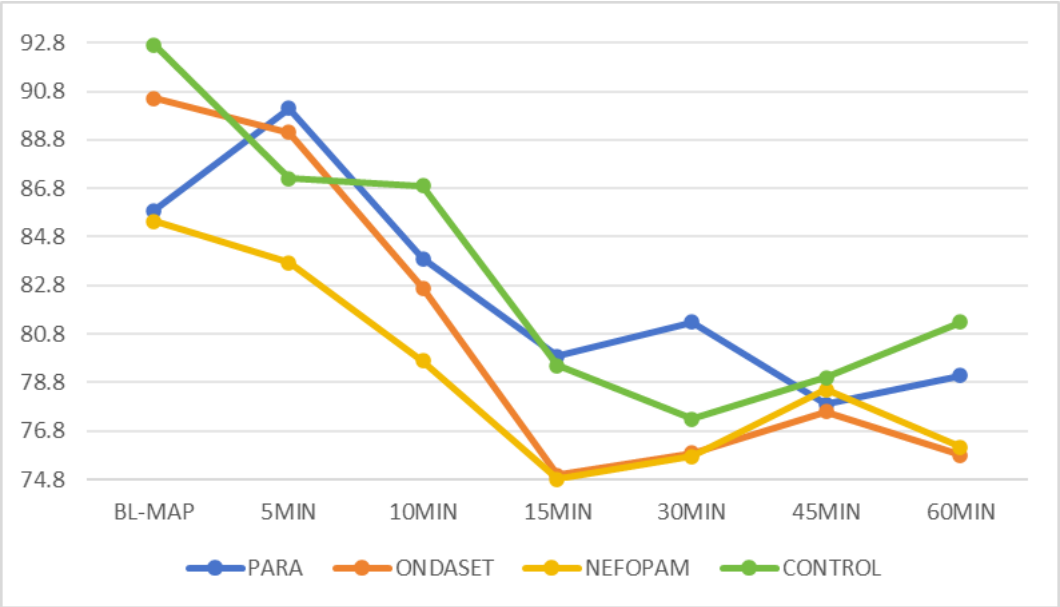

Figure 2. *The trend of the mean MAP over time between the groups.*

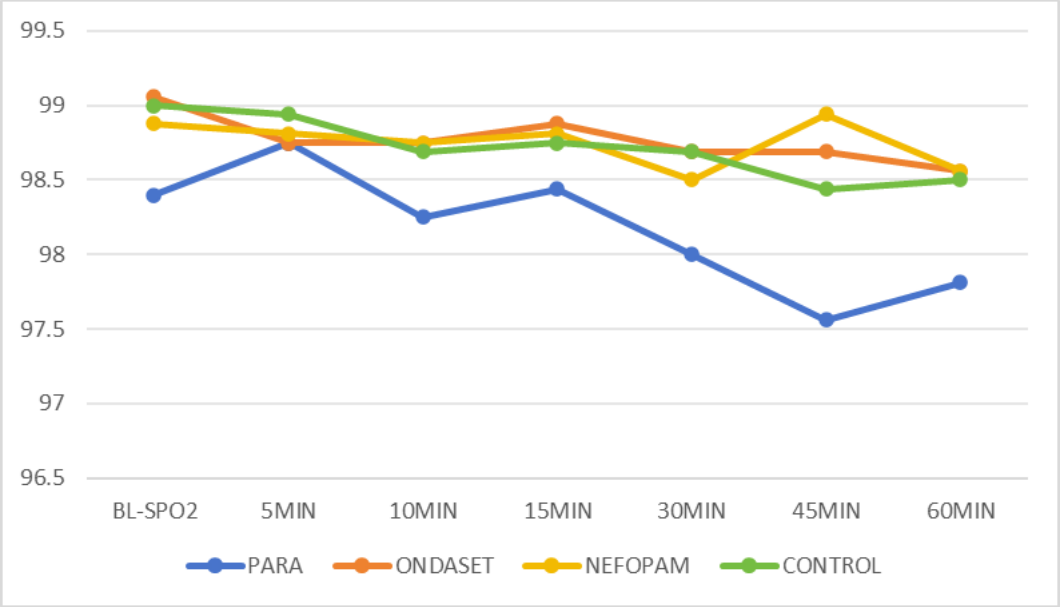

Figure 3. *Comparison of the trend of the mean SPO_2 between the study groups.*

4. Discussion

The present study demonstrated that prophylactic administration of ondansetron, nefopam, and paracetamol reduced the incidence and severity of post-spinal shivering in parturients undergoing elective caesarean section under spinal anaesthesia. Among the three agents evaluated, nefopam exhibited the greatest prophylactic anti-shivering efficacy, followed by ondansetron, while paracetamol showed the least effectiveness.

No patient in the nefopam group developed post-spinal shivering, whereas shivering occurred in 31.3%, 93.8%, and 100% of patients in the ondansetron, paracetamol, and control groups, respectively. These findings demonstrate the superior efficacy of nefopam in preventing post-spinal shivering. Furthermore, the calculated odds ratio suggests that prophylactic ondansetron markedly reduced the likelihood of shivering compared with the control group, whereas paracetamol offered only minimal protection.

The findings of the present study are consistent with those reported by Tohme et al. [12] and Lakhe et al. [11], both of whom demonstrated superior anti-shivering efficacy with nefopam and ondansetron. However, unlike Tohme et al. [12] who reported a 16% incidence of shivering in the nefopam

group, no episode of shivering was observed among patients who received nefopam in the present study. This difference may be attributable to methodological variations between the studies. Tohme et al. used either hyperbaric or isobaric bupivacaine without clearly specifying the dose administered, whereas the present study employed a standardized dose of 2 mL of 0.5% hyperbaric bupivacaine. Hyperbaric bupivacaine provides a more predictable spread of sensory blockade than the isobaric formulation and may therefore influence the occurrence of post-spinal shivering [13].

Another possible explanation for this discrepancy relates to the timing of nefopam administration. In the study by Tohme et al., [12] nefopam was administered 30 minutes before spinal anaesthesia, whereas in the present study it was given 10 minutes before the block. Considering the relatively rapid onset and limited duration of action of nefopam, administration closer to the time of spinal anaesthesia may have optimized its prophylactic effect [14].

The incidence of shivering observed in the ondansetron group was comparable to that reported by Lakhe et al., [11] probably because both studies employed similar dosing regimens. In contrast, Majeed et al. [15] reported that paracetamol substantially reduced the incidence of post-spinal shivering. The higher incidence observed in the present study may reflect differences in study populations. While Majeed et al. investigated non-obstetric female patients, the present study was conducted exclusively among obstetric patients. Pregnancy is associated with physiological changes that influence the spread of intrathecal local anaesthetic, potentially increasing the likelihood of post-spinal shivering [13].

The incidence of shivering in the control group was 100%, which is higher than the 50-60% incidence commonly reported following neuraxial anaesthesia [2, 4]. Nevertheless, similar incidences have been reported by Majeed et al. [15]. These findings further emphasize the profound disruption of thermoregulation caused by spinal anaesthesia, primarily through peripheral vasodilatation and redistribution of core body heat.

The present study also demonstrated that nefopam was significantly more effective than both ondansetron and paracetamol in preventing and delaying the onset of post-spinal shivering. These findings are consistent with those of Lakhe et al. [11]. Although Lakhe et al. reported their data using mean ± standard deviation, whereas the present study employed median and interquartile range because of the non-normal distribution of the data, both studies reached similar conclusions regarding the superior prophylactic efficacy of nefopam. This consistency strengthens the validity of the present findings despite differences in statistical methodology.

With regard to shivering severity, no patient in the nefopam group developed shivering, while shivering in the ondansetron group was predominantly mild to moderate. In contrast, moderate-to-severe shivering was common in the paracetamol group, and severe shivering predominated in the control group. Consequently, clinically significant shivering requiring intervention occurred most frequently in the control and paracetamol groups. These observations are broadly consistent with the findings of Nallam et al. [16], who reported predominantly mild shivering among patients receiving ondansetron. The higher proportion of clinically significant shivering observed in the present study may be explained by the lower ondansetron dose (4 mg) compared with the 8 mg dose used by Nallam et al. Previous studies have suggested a dose-dependent anti-shivering effect of ondansetron, which may account for this difference [17-19].

Similarly, Esmat et al. [20] reported substantially lower rates of clinically significant shivering following prophylactic paracetamol administration than those observed in the present study. This discrepancy may again be explained by differences in patient populations, as their study included non-obstetric surgical patients, whereas the present investigation was limited to obstetric patients. Pregnancy-related physiological changes may increase susceptibility to post-spinal shivering by influencing the extent of sympathetic blockade and thermoregulatory responses [13].

The incidence of nausea, vomiting, and hypotension did not differ significantly among the four groups, although nausea and vomiting occurred more frequently in the paracetamol and control groups, while hypotension was more common among patients who received ondansetron. These findings differ from those of Tohme et al., [12] who reported higher incidences of nausea and vomiting in the nefopam group. Such differences may reflect variations in drug dosage and patient characteristics between the two studies. Pharmacologically, Nefopam inhibits the reuptake of serotonin, noradrenaline, and dopamine, and exhibits α_2-adrenergic and non-competitive NMDA receptor antagonist activity, leading to sympathomimetic and anticholinergic effects that reduce the likelihood of hypotension [21-23]. Conversely, Ondansetron, a selective 5-HT_3 receptor antagonist, effectively reduces the incidence of nausea and vomiting [24].

Haemodynamic variables, including heart rate, mean arterial pressure, and peripheral oxygen saturation, remained stable throughout the perioperative period in all study groups. These findings are consistent with previous studies demonstrating that nefopam, ondansetron, and paracetamol do not significantly compromise haemodynamic stability when administered prophylactically during spinal anaesthesia [20, 25, 26].

Collectively, the findings of the present study support previous evidence that ondansetron reduces post-spinal shivering through modulation of central serotonergic pathways, whereas the superior efficacy of nefopam is likely attributable to its inhibition of central monoamine reuptake and its direct effects on thermoregulatory pathways [11, 26-28]. Although paracetamol demonstrated comparatively lower efficacy, it still offers practical advantages because of its favourable safety profile, wide availability, and affordability, making it a reasona-

ble option in resource-limited settings where access to alternative agents may be limited.

The present study has some limitations. It was conducted at a single centre with a relatively modest sample size, which may limit the generalisability of the findings. In addition, continuous core temperature monitoring was not performed, precluding direct assessment of perioperative thermal changes. Future multicentre studies with larger sample sizes and continuous temperature monitoring are recommended to validate these findings and further define the comparative effectiveness of these pharmacological agents.

5. Conclusion

Prophylactic intravenous ondansetron, nefopam, and paracetamol reduced the incidence and severity of post-spinal shivering in parturients undergoing elective caesarean section under spinal anaesthesia, with nefopam demonstrating the greatest prophylactic anti-shivering efficacy, followed by ondansetron, while paracetamol offered a more modest but safe and accessible alternative, however, larger multicentre randomized controlled trials are needed to confirm these comparative benefits and safety profiles.

Abbreviations

ANOVA	Analysis of Variance
BMI	Body Mass Index
HR	Heart Rate
5-HT3	Hydroxytryptamine Type 3
LSCS	Lower Segment Caesarean Section
MAP	Mean Arterial Pressure
SPO2	Peripheral Oxygen Saturation
SPSS	Satistical Package for Social Sciences
SD	Standard Deviation

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Author Contributions

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Data Availability Statement

The data is made available from the corresponding author upon reasonable request.

Conflicts of Interest

The authors declare no conflicts of interest.

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