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Research Article

A Randomized, Double-Blind Clinical Trial Comparing Prophylactic Intravenous Paracetamol and Intravenous Meperidine for Shivering During Cesarean Delivery Under Spinal Anesthesia

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Abstract

Background: Shivering is a distressing and common complication of spinal anesthesia for cesarean delivery (CD), with reported incidence rates of up to 55%. It increases maternal metabolic demand, thereby posing risks for patients with cardiopulmonary conditions. Although meperidine is an effective and well-established prophylactic agent, its use is limited by opioid-related adverse effects. Intravenous (IV) paracetamol is a non-opioid alternative that may reduce shivering by centrally modulating the thermoregulatory set point.

Objectives: This randomized, double-blind clinical trial compared the prophylactic efficacy of intravenous paracetamol and intravenous meperidine in preventing shivering during CD under spinal anesthesia.

Methods: In this randomized, double-blind clinical trial, 151 patients undergoing CD under spinal anesthesia were allocated to receive 1 g IV paracetamol (PARA), 0.3 mg/kg IV meperidine (MEP-IV), or normal saline (CTL) preoperatively. The primary outcomes were the incidence and intensity of shivering, assessed using a 4-point scale. Secondary outcomes included shivering onset time, hemodynamic stability (including mean arterial pressure [MAP] and heart rate [HR]), and adverse events. Longitudinal hemodynamic data were analyzed using repeated-measures analysis of variance.

Results: The overall incidence of shivering did not differ significantly among the groups (P = 0.146), with rates of 49.0% in the PARA group, 33.3% in the MEP-IV group, and 49.0% in the CTL group. Although IV paracetamol did not significantly reduce the overall incidence of shivering compared with meperidine or placebo, it was associated with a delayed onset and lower shivering severity.

Conclusions: Intravenous paracetamol may represent a potential non-opioid option for managing shivering during CD under spinal anesthesia.

Keywords: Shivering, Cesarean Section, Spinal Anesthesia, Paracetamol, Meperidine, Obstetric Anesthesia

1. Background

Shivering is a common and distressing complication during cesarean delivery performed under spinal anesthesia, with reported incidence rates as high as 35% - 55% (2-4). This phenomenon results from involuntary muscle activity triggered by neuraxial-induced vasodilation, which causes redistribution of heat from the core to the peripheral compartments and alters the hypothalamic thermoregulatory set point (5, 6). Although shivering is often transient, it increases maternal oxygen consumption and carbon dioxide

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production and may complicate intraoperative monitoring, particularly in patients with limited cardiopulmonary reserve (7, 8).

The global increase in cesarean delivery rates and the widespread preference for spinal anesthesia, because of its rapid onset and favorable safety profile, have increased the clinical importance of effective perioperative thermoregulation (9). Various pharmacologic agents have been investigated to prevent or treat perioperative shivering, including opioids, α_2-adrenergic agonists, N-methyl-D-aspartate receptor antagonists, and serotonergic agents (10-12).

Among these agents, meperidine is considered one of the most effective pharmacologic options for shivering prevention. Its anti-shivering properties are believed to be mediated through κ-opioid receptor agonism and modulation of thermoregulatory pathways within the central nervous system (6, 13). However, opioid use in obstetric anesthesia remains limited because of potential adverse effects, such as nausea, vomiting, pruritus, and possible neonatal respiratory depression (14).

Paracetamol, also known as acetaminophen, is a potential non-opioid alternative with a well-established safety profile. Its thermoregulatory effect is thought to be mediated through central cyclooxygenase inhibition and modulation of the hypothalamic thermoregulatory set point, which may influence perioperative shivering without causing sedation or respiratory depression (15, 16). Several studies have reported beneficial effects of IV paracetamol in reducing perioperative shivering in different surgical populations (17-19).

Recent clinical investigations have further explored pharmacologic strategies for shivering prevention in perioperative and obstetric anesthesia. For example, dexmedetomidine has been evaluated for its efficacy in reducing postoperative shivering through central α_2-adrenergic mechanisms (1). Comparative studies have also examined the balance between efficacy and systemic safety when using intrathecal meperidine versus IV acetaminophen for shivering prophylaxis in obstetric spinal anesthesia. Additionally, corticosteroids such as dexamethasone have recently been investigated as potential adjunctive agents for shivering prophylaxis in obstetric patients. These studies highlight the ongoing search for effective and safer pharmacologic strategies for shivering prevention.

2. Objectives

The present study was designed as a randomized, double-blind clinical trial to compare the prophylactic efficacy of IV paracetamol and IV meperidine in preventing shivering during elective cesarean delivery under spinal anesthesia. Secondary objectives included the evaluation of hemodynamic stability, time to shivering onset, adverse effects, and maternal satisfaction.

3. Methods

3.1. Study Design and Setting

This randomized, double-blind clinical trial was conducted at Shahid Beheshti Hospital, Isfahan, Iran. The trial was registered with the Iranian Clinical Trial Registration Center (IRCT20240524061880N1) and approved by the Ethics Committee of Isfahan University of Medical Sciences (IR.MUI.MED.REC.1403.062). Written informed consent was obtained from all participants before enrollment after an explanation of the study design, objectives, and pain scoring system, with assurances of data confidentiality.

3.2. Inclusion and Exclusion Criteria

The inclusion criteria were pregnant women classified as American Society of Anesthesiologists physical status II, aged 18 - 45 years, who were scheduled for elective cesarean section under spinal anesthesia.

The exclusion criteria were cardiovascular, pulmonary, hepatic, or renal disease; psychiatric disorders; diabetes mellitus; thyroid dysfunction; baseline body temperature outside the range of 36.5°C - 37.5°C on admission; a known history of alcohol or substance abuse; use of vasodilator drugs; anticipated need for intraoperative blood transfusion; receipt of labor analgesia or other medications potentially affecting thermoregulation; inadequate spinal block, defined as a bilateral sensory level below T4 or T5; and intraoperative complications requiring medications outside the study protocol.

3.3. Randomization and Blinding

Participants were randomized using the Sequence Generator tool in blocks of 15 eligible patients. Drug allocation was concealed using coded, identical syringes prepared by an anesthesiologist who was not otherwise

involved in patient care. The anesthesiologist who administered the spinal and IV medications, the anesthetists who recorded outcomes, and the biostatistician who performed the data analysis were all blinded to group allocation.

3.4. Sampling Method and Sample Size Calculation

The sample size was estimated based on previously reported differences in shivering incidence between the intervention and control groups. Assuming a reduction in shivering incidence from approximately 55% in the control group to 30% in the intervention group, with a significance level of $\alpha = 0.05$ and a statistical power of 80%, the minimum required sample size was calculated as 40 participants per group. To improve statistical reliability and account for possible dropouts, recruitment continued until 151 patients were included in the study.

3.5. Anesthetic Management and Interventions

All patients adhered to preoperative fasting guidelines. Standard monitoring, including electrocardiography, noninvasive blood pressure, and pulse oximetry (SpO_2), was applied. Intravenous fluid preloading was initiated with lactated Ringer solution at 15 mL/kg over 30 minutes, followed by maintenance at 5 mL/kg. Metoclopramide, 10 mg, was injected intravenously over 30 seconds.

Spinal anesthesia was performed using a 26-gauge Quincke needle at the L3-L4 or L4-L5 interspace via the paramedian approach, with the patient in a sitting position. After spinal drug injection, patients were immediately positioned supine with a left uterine displacement wedge, and urinary catheterization was performed.

Patients were randomly assigned to 1 of 3 groups:

- MEP-IV group: Ten minutes before spinal injection, patients received 10 mg meperidine diluted in normal saline and infused intravenously over 10 minutes. The spinal injection consisted of 2.5 - 3 mL (12.5 - 15 mg) hyperbaric bupivacaine.

- PARA group: Ten minutes before spinal injection, patients received 1 g paracetamol diluted in normal saline and infused intravenously over 10 minutes. The spinal injection consisted of 2.5 - 3 mL (12.5 - 15 mg) hyperbaric bupivacaine.

- Control group: Ten minutes before spinal injection, patients received normal saline infused intravenously over 10 minutes. The spinal injection consisted of 2.5 - 3 mL (12.5 - 15 mg) hyperbaric bupivacaine.

3.6. Monitoring and Outcome Assessment

Core body temperature was monitored intraoperatively using a tympanic thermometer (OMRON Gentle Temp 520). Operating-room temperature and humidity were maintained within standard institutional ranges, and supplemental oxygen was provided via a face mask according to routine obstetric anesthesia practice.

The following data were recorded:

- Anesthetic block characteristics: Time to peak sensory block, highest sensory block level assessed by pinprick sensation, duration of sensory block defined as the time to 2-segment regression, and complete motor block assessed using the modified Bromage criteria grade 4 (18).

- Hemodynamics and temperature: MAP, HR, and tympanic body temperature were recorded at baseline, 60 minutes after the intervention, and every 15 minutes during recovery.

- Shivering assessment: Shivering was assessed by a blinded observer using the validated 4-point scale described by Sai and Chu, 2006 (19): Grade 0, no shivering; grade 1, peripheral vasoconstriction without visible shivering; grade 2, muscle activity in 1 muscle group; grade 3, muscle activity in more than 1 muscle group but not generalized; and grade 4, generalized shivering involving the whole body.

- Rescue treatment and adverse events: Active warming with standard forced-air warmers was initiated for shivering grades 1 and 2. If shivering persisted or progressed to grade 3 or higher, IV meperidine was administered as rescue therapy. The need for rescue meperidine was recorded. Hypotension was treated with IV ephedrine. The need for ephedrine and other adverse events, including nausea, vomiting, and bradycardia, was recorded.

- Patient satisfaction: Patient satisfaction was assessed postoperatively using an 11-point numeric rating scale, ranging from 0, indicating completely dissatisfied, to 10, indicating completely satisfied.

Patients were closely monitored for potential adverse drug reactions, including nausea, vomiting,

hypotension, bradycardia, and respiratory depression. If nausea or vomiting occurred, antiemetic therapy was administered. Hypotension was treated with IV ephedrine and fluid administration, whereas bradycardia was managed with atropine when clinically indicated. All adverse events were documented and managed according to standard institutional protocols.

3.7. Statistical Analysis

Data were analyzed using SPSS version 26.0 (IBM Corp). Continuous variables, including age, MAP, and temperature, are expressed as mean ± SD and were analyzed using 1-way analysis of variance for normally distributed data or the Kruskal-Wallis test for nonnormally distributed data, with Tukey post hoc analysis for significant findings. Categorical variables, including shivering incidence and medication use, were compared using the χ^2 test or Fisher exact test and are reported as frequencies and percentages. Longitudinal changes in vital signs were evaluated using repeated-measures analysis of variance. Multivariable logistic regression was used to identify shivering risk factors, and adjusted odds ratios with 95% confidence intervals were reported. A 2-tailed α level of 0.05 defined statistical significance.

4. Results

4.1. Participant Flow and Group Allocation

The study enrolled 151 participants: 49 patients (32.5%) in the PARA group, 51 (33.8%) in the MEP-IV group, and 51 (33.8%) in the control group (Figure 1).

4.2. Demographic and Baseline Characteristics

The mean age was years. Age, height, weight, and body mass index did not differ significantly among the 3 groups. However, statistically significant baseline imbalances were observed. Gravidity was significantly lower in the control group than in the other 2 groups (P = 0.018). Gestational week was also significantly lower in the PARA group than in the control group but did not differ from that in the MEP-IV group (Table 1).

4.3. Hemodynamic Changes

Vital signs, including MAP and HR, were assessed at baseline and at 1, 3, 15, 30, 45, and 60 minutes after the intervention. The corresponding data are summarized in Table 2.

Over time, MAP decreased significantly in all 3 study groups (Figure 2). However, the reduction was more pronounced in the PARA group, with significantly lower values at 1, 45, and 60 minutes after the intervention (Table 2).

Repeated-measures analysis of variance for HR did not reveal statistically significant differences in HR changes over time among the groups (P = 0.823). The MEP-IV and control groups showed reductions in HR after the intervention, whereas the PARA group showed a transient increase followed by a progressive decline (Figure 3).

Analysis of MAP over time did not show a significant overall difference among the 3 groups (P = 0.09). However, pairwise comparisons revealed statistically significant differences between the PARA group and the control group. As shown in Figure 2, the PARA group exhibited a more pronounced decrease in MAP over time than did the control group.

4.4. Shivering Outcomes and Temperature

Shivering time in the PARA group was significantly shorter than that in the other 2 groups (P = 0.001). Temperature comparisons revealed significant baseline differences among the groups (P < 0.0001): The PARA group was warmer than the MEP-IV group, which was warmer than the control group. Pairwise comparisons showed a significant difference between the PARA and control groups (P < 0.0001), but no significant differences between the PARA and MEP-IV groups (P = 0.083) or between the MEP-IV and control groups (P = 0.175). During shivering, temperature differences were no longer significant overall (P = 0.122), with identical values in each group and no significant pairwise differences (Table 3).

4.5. Demographic and Clinical Associations With Shivering

Associations between demographic and clinical variables and shivering incidence and shivering intensity were analyzed independently in each group. Because no participants in the PARA group had shivering intensity grade 3 or 4, a comprehensive analysis of the effects of the studied variables on shivering intensity in this group was not feasible.

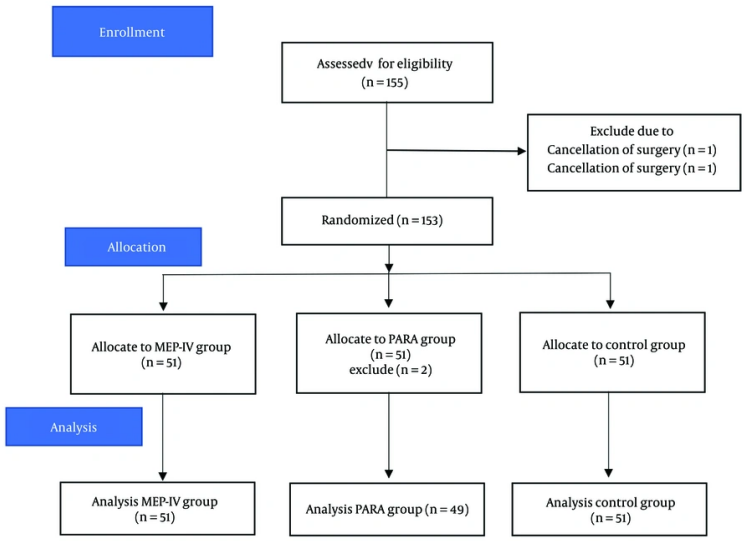

Figure 1. The Study Process According to the CONSORT Flow Diagram

Table 1. Comparison of Demographic Characteristics Among the 3 Study Groups [a]

Variables	PARA (n = 49)	MEP-IV (n = 51)	Control (n = 51)	P-Value
Age (y)	31.98 ± 5.66	31.2 ± 5.52	33.1 ± 5.84	0.240
Height (cm)	160.86 ± 9.94	162.63 ± 5.96	160.2 ± 14.7	0.555
Weight (kg)	80.59 ± 13.25	79.12 ± 13.32	78.43 ± 13.37	0.711
BMI	31.19 ± 5.1	29.79 ± 3.94	33.22 ± 25.4	0.209
Gravidity	2.37 ± 1.23	2.25 ± 0.12	1.76 ± 0.71	0.009
Pregnancy week	36.22 ± 2.55	37.06 ± 2.79	37.51 ± 1.15	0.018

[a] Values are expressed as mean ± SD. Abbreviation: BMI, Body Mass Index.

The results showed no statistically significant correlations between any evaluated demographic or clinical variables and shivering incidence or shivering intensity in any of the 3 groups, as detailed in Table 4. These findings suggest that participant demographic and clinical characteristics did not notably affect shivering responses.

5. Discussion

Shivering remains a common complication of neuraxial anesthesia for cesarean delivery. This randomized, double-blind trial compared the prophylactic efficacy of IV paracetamol with that of IV meperidine for the prevention of shivering during cesarean delivery under spinal anesthesia.

In our study, the overall incidence of shivering did not differ significantly among the 3 groups. Although the incidence was numerically lower in the meperidine group, this difference did not reach statistical significance. These findings are generally consistent with previous reports describing the anti-shivering properties of meperidine, which are believed to result from its central opioid and adrenergic effects on thermoregulatory pathways (6, 13, 20).

Despite the lack of a significant reduction in the overall incidence of shivering, IV paracetamol appeared to modify the clinical characteristics of shivering. In

Table 2. Changes in Mean Arterial Pressure and Heart Rate Among the 3 Groups Over Time [a]

Variables and Time	Groups			P-Value			
	PAR	MEP-IV	Control	Three-Group	PARA vs. MEP-IV	PARA vs. Control	MEP-IV vs. Control
Mean arterial pressure (min)							
Before	97.81 ± 14.87	96.14 ± 13.8	94.81 ± 12.7	0.555	0.546	0.280	0.629
1	81.35 ± 19.68	92.28 ± 19.8	93 ± 13.2	0.003 [b]	0.036 [b]	0.021 [b]	0.934
3	75.92 ± 15.52	80.0 ± 18.7	75.7 ± 16.3	0.345	0.941	0.224	0.201
15	77.95 ± 13.79	78.72 ± 14.9	82.1 ± 11.3	0.261	0.774	0.125	0.187
30	77.2 ± 14.98	83.43 ± 13.8	80.96 ± 13.7	0.048 [b]	0.029 [b]	0.187	0.384
45	77.59 ± 12.48	85.07 ± 11.4	81.52 ± 12.8	0.007 [b]	0.002 [b]	0.092	0.146
60	79.04 ± 10.91	82.23 ± 11.2	82.64 ± 12	0.027 [b]	0.007 [b]	0.116	0.284
P-value for comparison over time	< 0.0001 [b]	0.013 [b]	< 0.0001 [b]	0.090 [c]	0.061 [c]	0.045 [b, c]	0.542 [c]
Before vs. 1	-16.46 (-21.85 to -11.07) [b]	-3.86 (-23.37 to 15.39)	-1.82 (-3.67 to 0.031)	-	-	-	-
Before vs. 3	-21.89 (-27.38 to -16.39) [b]	-16.09 (-21.33 to -10.84) [b]	-19.14 (-23.55 to -14.73) [b]	-	-	-	-
Before vs. 15	-19.86 (-25.85 to -13.86) [b]	-17.41 (-22.13 to -12.69) [b]	-12.72 (-17.71 to -7.73) [b]	-	-	-	-
Before vs. 30	-20.61 (-26.54 to -14.68) [b]	-12.71 (-16.7 to -8.76) [b]	-13.85 (-18.79 to -8.91) [b]	-	-	-	-
Heart rate (min)							
Before	99.38 ± 16.86	103.1 ± 18.1	102.5 ± 16.1	0.500	0.272	0.358	0.843
1	101.6 ± 20.74	98.27 ± 21.0	101.69 ± 17	0.628	0.401	0.981	0.287
3	102.4 ± 22.82	96.82 ± 19.85	92.12 ± 26.42	0.019 [b]	0.202	0.028 [b]	0.286
15	99.22 ± 19.95	92.25 ± 18.6	94.0 ± 19.7	0.182	0.309	0.181	0.731
30	94.1 ± 15.95	96.35 ± 15.22	94.96 ± 17.8	0.730	0.493	0.794	0.665
45	90.27 ± 12.98	91.45 ± 13.2	88.14 ± 13.1	0.435	0.652	0.418	0.246
60	85.98 ± 13.17	87.94 ± 14.31	89.2 ± 12.3	0.478	0.462	0.229	0.662
P-value for comparison over time	< 0.0001 [b]	< 0.0001 [b]	< 0.0001 [b]	0.823 [c]	0.833 [c]	0.545 [c]	0.684 [c]
Before vs. 1	2.22 (-4.45 to 8.9)	-4.83 (-12.38 to 2.78)	-0.82 (-4.17 to 2.52)	-	-	-	-
Before vs. 3	3.02 (-11.51 to 0.49)	-6.28 (-13.45 to 0.48)	-10.39 (-18.5 to -2.27) [b]	-	-	-	-
Before vs. 15	-0.143 (-6.72 to 6.43)	-10.85 (-14.15 to -2.3) [b]	-8.51 (-13.84 to -3.18) [b]	-	-	-	-
Before vs. 30	-5.26 (-11.05 to 0.52) [b]	-6.75 (-11.4 to -1.83) [b]	-7.54 (-12.42 to -2.67) [b]	-	-	-	-

[a] Values are expressed as mean ± SD or mean difference (95% CI). Abbreviations: CI, confidence interval; MEP-IV, intravenous meperidine; PARA, intravenous paracetamol.

[b] Comparison over time between groups.

[c] Significant at the 0.05 level.

particular, the paracetamol group demonstrated a significantly delayed onset of shivering, and no cases of severe shivering, defined as grade 3 or 4, were observed. These findings support the proposed mechanism by which paracetamol acts through central inhibition of cyclooxygenase pathways and modulation of the hypothalamic thermoregulatory set point (15, 16).

Recent clinical studies have investigated additional pharmacologic strategies for shivering prevention in perioperative settings. For example, dexmedetomidine has been reported to reduce postoperative shivering through its central α_2-adrenergic effects (1). Comparative investigations have also examined the relative efficacy and systemic safety of intrathecal meperidine and IV acetaminophen in obstetric spinal anesthesia. In addition, recent research has explored dexamethasone as a potential adjunctive agent for shivering prophylaxis in obstetric patients. These

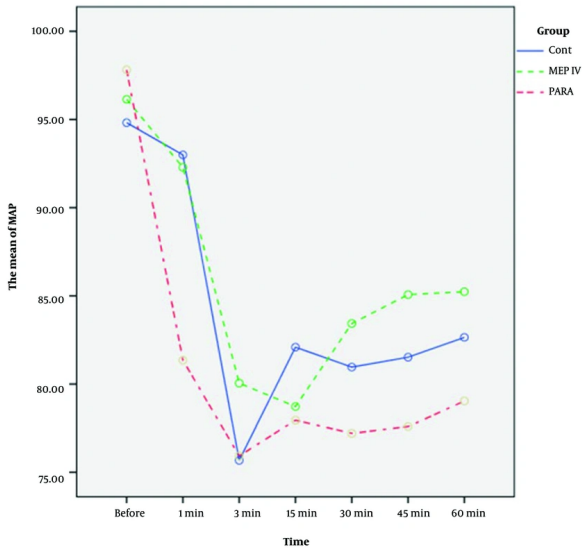

Figure 2. Changes in Mean Arterial Pressure Over Time by Study Group

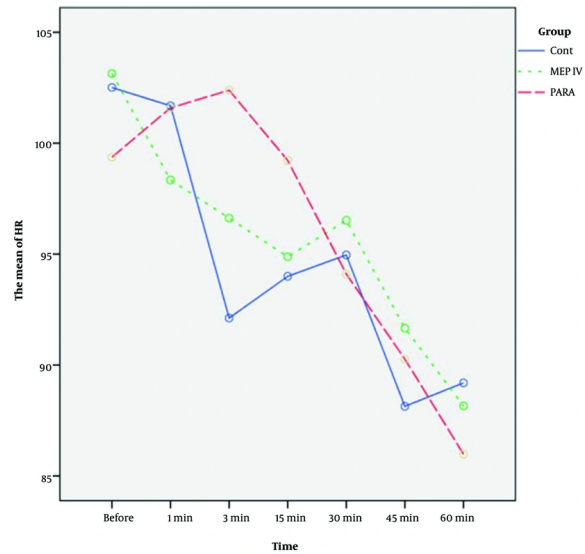

Figure 3. Changes in Mean Heart Rate Over Time by Study Group

studies highlight the growing interest in opioid-sparing strategies for shivering management.

Regarding hemodynamic variables, HR did not differ significantly among the groups during the study period. A more pronounced early reduction in MAP was observed in the paracetamol group. However, this decrease was transient, clinically well tolerated, and did not lead to increased vasopressor requirements.

Table 3. Clinical Characteristics Related to Shivering Among Patients in the 3 Treatment Groups [a]

Variables	Groups			P-Value			
	PARA	MEP-IV	Control	Three-Group	PARA vs. MEP-IV	PARA vs. Control	MEP-IV vs. Control
Shivering							
Yes	24 (49)	17 (33.3)	25 (49)	0.146	0.105	0.998	0.159
No	25 (51)	34 (66.7)	26 (51)				
Shivering intensity							
No to mild shivering (grade 0 - 1)	35 (71.4)	36 (70.6)	37 (72.5)	0.976	0.926	0.901	0.826
Moderate to very severe shivering (grade 2 - 4)	14 (28.6)	15 (29.4)	14 (27.5)				
Time of shivering, median (IQR)	5 (0, 45)	45 (37.5, 60)	45 (33.75, 45)	< 0.001	< 0.001	< 0.001	0.091
Temperature before intervention	37.11 ± 0.17	37.02 ± 0.26	36.94 ± 0.14	< 0.0001	0.083	< 0.0001	0.175
Temperature during shivering	36.98 ± 0.23	36.97 ± 0.21	36.85 ± 0.18	0.122	0.998	0.493	0.137

[a] Values are expressed as No. (%) or mean ± SD. Abbreviations: IQR, interquartile range; MEP-IV, intravenous meperidine; PARA, intravenous paracetamol.

Therefore, the observed change in MAP should be interpreted cautiously and does not appear to compromise the overall hemodynamic safety profile of IV paracetamol.

Baseline temperature imbalances among groups represent an important limitation of the present study and may have influenced the observed incidence of shivering. Although temperatures during shivering episodes were not significantly different, the baseline differences suggest the possibility of imperfect randomization or environmental influences. Additionally, baseline differences in gravidity and gestational week were observed among groups. However, multivariable analysis did not demonstrate a significant association between these variables and shivering outcomes.

Overall, our findings suggest that IV paracetamol may represent a useful non-opioid option for perioperative shivering management. Although it did not significantly reduce the overall incidence of shivering, its association with delayed onset and lower shivering severity may provide clinically relevant benefits.

5.1. Limitations

Several limitations of this study should be acknowledged. First, baseline differences in body temperature were observed among the study groups, which could potentially influence the incidence of shivering. These differences may reflect environmental factors or imperfect randomization. Second, baseline imbalances in gravidity and gestational age were identified among groups. Although no significant associations were found between these variables and shivering outcomes, they remain potential confounding factors. Finally, the study was conducted at a single center, which may limit the generalizability of the findings to other populations or clinical settings.

5.2. Conclusions

Although IV paracetamol did not significantly reduce the overall incidence of shivering compared with meperidine or placebo, it was associated with delayed onset and lower severity of shivering. These findings suggest that IV paracetamol may serve as a potential non-opioid option for shivering management during cesarean delivery under spinal anesthesia, although further studies are warranted.

Footnotes

AI Use Disclosure: The authors declare that no generative AI tools were used in the creation of this article.

Authors' Contribution: M. S. contributed to the study concept and design, acquisition of data, analysis and interpretation of data, drafting of the manuscript, statistical analysis, and financial support. M. S., F. H., and Z. N. provided administrative, technical, and material support. F. H. critically revised the manuscript for important intellectual content. A. B. and F. H. supervised the study. Z. N. also contributed to financial support.

Table 4. Relationship Between Demographic and Clinical Variables and Shivering Incidence and Intensity by Group [a]

Groups and Independent Variables	Shivering (Yes)		Shivering Intensity	
	OR	95% CI	OR	95% CI
PARA				
Age	1.068	0.962 to 1.186	-	-
BMI	1.013	0.907 to 1.132	-	-
Gravidity	1.392	0.856 to 2.264	-	-
Pregnancy week	0.954	0.763 to 1.195	-	-
Changes in MAP at 1 min	1.025	0.991 to 1.060	-	-
Changes in MAP at 3 min	1.008	0.979 to 1.039	-	-
Changes in MAP at 15 min	0.017	0.988 to 1.046	-	-
Changes in HR at 1 min	1.016	0.990 to 1.043	-	-
Changes in HR at 3 min	0.993	0.968 to 1.018	-	-
Changes in HR at 15 min	1.027	0.997 to 1.058	-	-
MEP-IV				
Age	0.982	0.883 to 1.092	1.057	0.821 to 1.361
BMI	1.021	0.879 to 1.185	0.776	0.496 to 1.214
Gravidity	0.667	0.326 to 1.366	1.948	0.308 to 12.306
Pregnancy week	0.989	0.803 to 1.218	0.880	0.545 to 1.421
Changes in MAP at 1 min	1.003	0.995 to 1.013	0.997	0.979 to 1.015
Changes in MAP at 3 min	0.958	0.924 to 0.993 [b]	1.064	0.938 to 1.207
Changes in MAP at 15 min	0.998	0.963 to 1.033	1.034	0.941 to 1.136
Changes in HR at 1 min	1.020	0.994 to 1.047	1.027	0.969 to 1.088
Changes in HR at 3 min	1.010	0.984 to 1.036	1.088	0.974 to 1.215
Changes in HR at 15 min	0.980	0.948 to 1.012	0.981	0.913 to 1.054
Control				
Age	1.026	0.93 to 1.13	1.054	0.86 to 1.28
BMI	1.07	0.89 to 1.13	0.861	0.62 to 1.18
Gravidity	1.302	0.59 to 2.87	0.223	0.02 to 1.89
Pregnancy week	1.184	0.72 to 1.94	2.835	0.79 to 18.59
Changes in MAP at 1 min	1.004	0.92 to 1.09	1.007	0.83 to 1.21
Changes in MAP at 3 min	1.012	0.98 to 1.05	0.98	0.92 to 1.06
Changes in MAP at 15 min	0.993	0.96 to 1.03	1.005	0.01 to 1.06
Changes in HR at 1 min	0.969	0.90 to 1.02	1.008	0.90 to 1.11
Changes in HR at 3 min	0.996	0.981 to 1.01	0.996	0.95 to 1.04
Changes in HR at 15 min	1.013	0.982 to 1.04	1.02	0.96 to 1.07

[a] Abbreviations: BMI, body mass index; CI, confidence interval; HR, heart rate; MAP, mean arterial pressure; MEP-IV, intravenous meperidine; OR, odds ratio; PARA, intravenous paracetamol.

[b] Significant at the 0.05 level.

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Conflict of Interests Statement: The authors declare no conflict of interest.

Data Availability: The dataset presented in the study is available on request from the corresponding author during submission or after publication. The data are not publicly available due to privacy concerns.

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