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Research Article

Maximum Efficacy vs. Systemic Safety: Intrathecal Meperidine Versus Intravenous Acetaminophen for Shivering Prophylaxis in Obstetric Spinal Anesthesia

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ABSTRACT

Background: Shivering is a common and distressing complication of spinal anesthesia for cesarean section. While intrathecal meperidine is an effective prophylactic agent, its side effect profile prompts the search for alternatives. Intravenous acetaminophen has been proposed as a potential option due to its central antipyretic effect, but its efficacy compared to meperidine remains unclear. This study aimed to compare the efficacy and safety of prophylactic intrathecal meperidine versus intravenous acetaminophen for preventing shivering during cesarean section under spinal anesthesia.

Methods: In this triple-blind randomized controlled trial, 151 parturient (ASA II) scheduled for elective cesarean section under spinal anesthesia were allocated to three groups: 1) PARA group (n=49): received 1 g IV acetaminophen; 2) MEP-IT group (n=49): received 0.1 mg/kg intrathecal meperidine; 3) Control group (n=51): received placebo. The primary outcome was the incidence of clinically significant shivering (Grade ≥2). Secondary outcomes included shivering onset time, hemodynamic parameters, and adverse effects.

Results: The incidence of shivering was significantly lower in the MEP-IT group (24.5%) compared to both the PARA and control groups (49% each; P<0.0001). Shivering onset occurred significantly earlier in the PARA group (median: 5 minutes) than in the MEP-IT and control groups (median: 45 minutes; P<0.001). The PARA group exhibited a pronounced and sustained reduction in mean arterial pressure (MAP) and required vasopressor support more frequently (43%) than the control group (19%).

Conclusion: Intrathecal meperidine is highly effective for shivering prophylaxis. Our

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study showed that although intrathecal meperidine is more effective than intravenous pracetamol in preventing shivering after spinal anesthesia, paracetamol not only has no preventive effect compared to the control group, but also has higher hypotension and calls for additional studies.

Introduction

Over recent decades, global cesarean section (CS) rates have risen substantially in both developing and developed countries. A combination of maternal, fetal, medical, social, and even medicolegal factors appears to be driving this global trend [1-2]. Given this increase, greater attention must be paid to maternal outcomes, particularly given the elevated risks of mortality and morbidity associated with the procedure [3]. Notably, these adverse outcomes are not only caused by the surgical intervention itself but can also be attributed to the chosen anesthetic method, the physiological changes of pregnancy, and the mother's pre-existing medical status [4]. Spinal anesthesia is the preferred technique for elective CS due to its reliability, rapid onset, and avoidance of airway manipulation [5-6]. Despite its favorable safety profile, spinal anesthesia is frequently complicated by shivering, an involuntary muscular activity representing a common and distressing adverse effect [7-8]. Postoperative shivering is a thermoregulatory response of the body that occurs due to peripheral vasodilation caused by sympathetic stimulation.it caused redistrubution of central to peripheral heat [9-10]. This self-regulatory response in the body lowers the shivering threshold and reduces temperature, preventing a rapid response to the body's environmental temperature. [11-12]. Although usually benign, shivering significantly elevates metabolic demands, increasing oxygen consumption by up to 400-500%, which can be critical in a parturient with cardiorespiratory disease [13-14]. Furthermore, it compromises the reliability of clinical monitoring and may exacerbate patient discomfort. It may also adversely affect surgical outcomes by exacerbating wound pain, impairing wound healing, and prolonging recovery room stay [10]. The incidence of shivering after neuraxial anesthesia is high, averaging approximately 55% [15]. Several risk factors have been identified, with preoperative anxiety, emergency procedures, and patient transfer between cold environments significantly increasing shivering risk during cesarean sections [16].

The management of post-anesthetic shivering involves non-pharmacological methods (e.g., warming blankets) and various pharmacological agents [9]. Despite the positive effects of these methods, their use in practice is difficult and costly. [17]. Among pharmacological strategies, a diverse range of agents is employed. These include opioids, N-methyl-D-aspartate (NMDA) receptor antagonists, magnesium sulfate, α2 agonists, and other centrally acting drugs [11]. Intrathecal pethidine (meperidine) remains the most effective opioid for treating established shivering, with demonstrated superiority over other opioids like morphine and fentanyl. Its unique anti-shivering action is attributed to agonist activity at κ-opioid receptors and central anticholinergic effects [18]. The dose of 0.1 mg/kg intrathecal meperidine was selected as a maximum effective prophylactic dose in previous literature, known for its potent anti-shivering efficacy [7,19]. However, its use is constrained by a well-documented side effect profile, most notably respiratory depression (potentiated by other sedatives), nausea, vomiting, and pruritus [20]. The pursuit of an effective agent with a more favorable safety profile is therefore a clinical priority.

Intravenous acetaminophen (paracetamol) presents a compelling alternative. Intravenous acetaminophen (paracetamol) has been an effective analgesic for many years [21]. It exerts its effects through its central antipyretic effect in the hypothalamus. This action is mediated by cyclooxygenase inhibition and prostaglandin E2 reduction [22]. Intravenous injection of 1 g of paracetamol has been studied as a prophylactic for postoperative pain [23]. In some studies, the preventive effect of rectal acetaminophen on postoperative shivering has been suggested to be due to its inhibitory effect on hypothermia. [17].

Based on this rationale, we designed the present study to directly compare the efficacy of prophylactic intravenous acetaminophen with that of the established gold standard, intrathecal meperidine, for the prevention of shivering in patients undergoing elective CS under spinal anesthesia. Therefore, we conducted this study with the aim of hemodynamic stability and side effects in different intervention groups.

Methods

A randomized, triple-blind, controlled clinical trial was conducted at Beheshti Hospital in Isfahan, Iran, between 2023 and 2024. The study protocol received approval from the Ethics Committee of Isfahan University of Medical Sciences (IR.MUI.MED.REC.1402.440) and was prospectively registered in the Iranian Registry of Clinical Trials (IRCT20240221061070N5). All participants provided written informed consent prior to enrollment.

Participants

Consisted of 151 pregnant women aged 18–45 years with ASA physical status II who underwent elective cesarean delivery under spinal anesthesia. Patients were

excluded if they had evidence of systemic infection or local infection at the puncture site, underlying thyroid, cardiovascular, or pulmonary disease, coagulation disorders, neurological or psychiatric conditions, a history of alcohol or substance abuse, a body mass index greater than 35 kg/m², abnormal baseline body temperature (>38°C or <36.5°C), use of medications influencing thermoregulation or vasodilation, or known hypersensitivity to paracetamol or meperidine. Participants were excluded from further analysis if the surgical duration exceeded 120 minutes or if spinal anesthesia was insufficient, defined as failure to achieve a sensory block to the T8 dermatome or a complete motor block (Bromage score of 3). Minor intervention-related adverse effects, including nausea, vomiting, or pruritus, were managed with standard symptomatic treatment and did not necessitate withdrawal. In cases where inadequate spinal anesthesia required conversion to general anesthesia, the participant was withdrawn, and the reason was recorded.

Sample Size and Sampling Method

Sample size was calculated using a two-proportion comparison formula based on previous studies, assuming P1 = 0.64, P2 = 0.38, $\alpha = 0.05$ (Z = 1.96), and power = 80% ($\beta = 0.84$). Accordingly, 30 participants were required for each group, yielding a total sample size of 90. Sampling was performed using simple randomization via computer-generated sequences (Random.org). During the study, we expanded the sample to 151 participants to improve the robustness of our findings and to allow for more sophisticated subgroup analyses.

Randomization and Blinding

Randomization was accomplished using random number sequences generated on Random.org and placed into sealed, opaque envelopes. An independent nurse not involved in patient management opened the envelopes and prepared the allocated intervention.

The trial was triple-blind, meaning that patients, anesthesiologists, surgeons, and the investigators responsible for outcome assessment were unaware of group assignments.

Interventions

Participants were assigned to one of three groups:

1. **Intravenous paracetamol group (PARA)** (n = 49): 1 g paracetamol diluted in 100 mL normal saline administered over 15 minutes.
2. **Intrathecal meperidine group (MEP-IT)** (n = 49): 0.1 mg/kg intrathecal meperidine (maximum total dose 10 mg) was mixed with the bupivacaine, followed by 100 mL normal saline infused intravenously over 15 minutes [7,19].
3. **Control group** (n = 53): 100 mL intravenous normal saline with no active drug. Patients in this group received only the 12.5 mg hyperbaric bupivacaine intrathecally.

All study medications were prepared by the hospital pharmacy to ensure uniformity and administered by a nurse who had no role in further patient management or outcome assessment.

Anesthesia Protocol and Monitoring

Routine intraoperative monitoring was instituted for all patients and consisted of continuous three-lead electrocardiography, intermittentinvasive blood pressure measurement, and pulse oximetry. Prior to spinal anesthesia, a crystalloid preload was administered using Ringer's solution at a dose of 10 mL/kg over 30 minutes. Oxygen supplementation was delivered throughout the procedure at a flow rate of 5 L/min via a face mask.

Spinal anesthesia was performed in the sitting position at the L4-L5 interspace using a paramedian approach. A 26-gauge Quincke spinal needle was used to inject 12.5 mg (2.5 mL) hyperbaric bupivacaine at a rate of 0.2 mL/s. Sensory block level was targeted between T4 and T8. Patients who failed to achieve an adequate block (sensory block below T8 or incomplete motor block) were converted to general anesthesia and excluded.

Operating and recovery room temperatures were maintained at 23-25°C with 60-70% humidity. Core temperature was measured using a tympanic thermometer, and peripheral (axillary) temperature was recorded simultaneously.

1. Grade 0 (None): No shivering observed.
2. Grade 1 (Mild): Localized, fine shivering limited to the neck and/or chest.
3. Grade 2 (Moderate): Visible shivering involving the upper limbs, in addition to the neck and chest.
4. Grade 3 (Severe): Generalized, coarse shivering involving the trunk, upper limbs, and lower limbs.

If shivering of grade ≥2 occurred after delivery, treatment was initiated per study protocol.

Outcome Measures

- **Primary Outcome:** The incidence of clinically significant shivering, defined as Grade 2 or 3, requiring rescue intravenous meperidine. Rescue meperidine was administered as a 12.5 mg IV bolus, repeated after 10 minutes if shivering persisted.

- **Secondary outcomes**: Measures focused on perioperative shivering characteristics, including the time to onset and severity graded on a 0–3 scale. Hemodynamic and physiological variables, namely mean arterial pressure, heart rate, peripheral oxygen saturation, and both core and peripheral temperatures, were recorded throughout the study period. Episodes of clinically significant hypotension were documented, defined as a reduction in mean arterial pressure greater than 20% from baseline or an absolute value below 65 mmHg, along with

the requirement for vasopressor support using intravenous ephedrine (10 mg). Patient satisfaction was evaluated using a validated 7-point Likert scale [24]. In addition, adverse events such as nausea, vomiting, pruritus, and sedation were systematically recorded.

Sedation was evaluated at 15-minute intervals using a four-level scoring system, ranging from fully awake and alert (Grade 1) to unarousable (Grade 4), with intermediate grades reflecting responsiveness to verbal or physical stimulation. [25].

Statistical Analysis

Data were analyzed using SPSS 26.0 (IBM Corp.). Continuous variables (e.g., age, MAP, temperature) are expressed as mean ± SD and analyzed using one-way ANOVA (normal distribution) or the Kruskal-Wallis test (non-normal distribution), with Tukey post-hoc analysis for significant findings.

Categorical variables (e.g., shivering incidence, medication use) were compared using χ^2 or Fisher's exact tests and reported as frequencies (%). Longitudinal vital sign changes were evaluated using repeated measures ANOVA. Multivariable logistic regression identified shivering risk factors, reporting adjusted ORs with 95% CIs. A two-tailed α level of 0.05 defined statistical significance.

Results

A total of 151 participants were enrolled in this study, with the following group distribution: 49 (32.5%) in the intravenous paracetamol (PARA) group, 49 (32.5%) in the intrathecal meperidine (MEP-IT) group, and 53 (35.1%) in the control group (Figure 1).

The mean ± SD age of participants was 32.09 ± 5.7 years (range: 18 to 45 years). Age distribution did not differ significantly among the three groups (P=0.201). Similarly, no significant differences were observed in height (P=0.414), weight (P=0.640), or BMI (P=0.230) among the groups.

However, gravidity was significantly lower in the control group compared to the other two groups (P=0.008), and gestational age was significantly lower in the PARA group compared to both other groups (P=0.001) (Table 1).

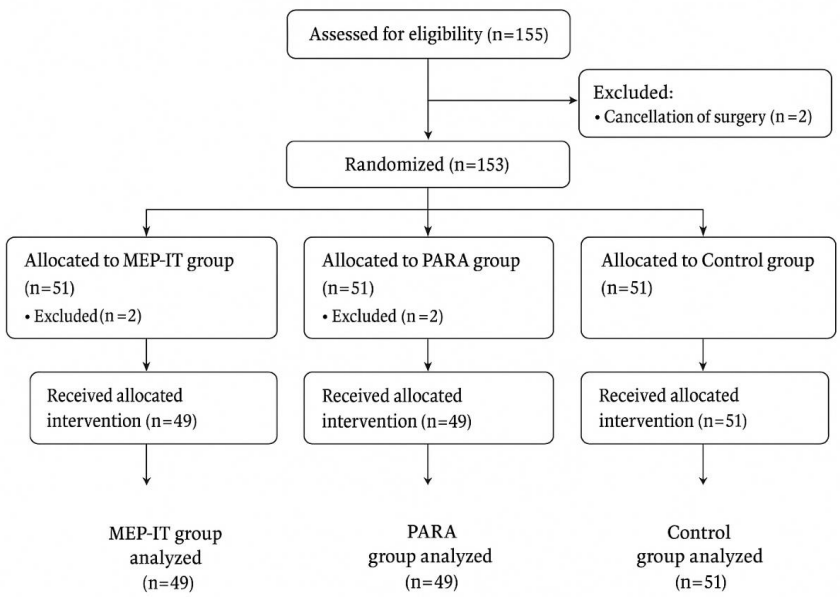

Figure 1- Participant flow diagram according to the CONSORT statement (Abbreviations: PARA, Intravenous Paracetamol group; MEP-IT, Intrathecal Meperidine group)

Table 1- Comparison of demographic characteristics between the three study groups

Variables	PARA (n=49)	MEP-IT (n=49)	Control (n=51)	P value
	Mean ± SD			
Age (years)	31.98 ± 5.66	34.14 ± 6.32	33.1 ± 5.84	0.201
Height (cm)	160.86 ± 9.94	162.41 ± 6.0	160.2 ± 14.7	0.414
Weight (kg)	80.59 ± 13.25	78.08 ± 16.01	78.43 ± 13.37	0.640
BMI	31.19 ± 5.1	29.55 ± 5.67	33.22 ± 25.4	0.230
Gravid	2.37 ± 1.23	2.08 ± 0.86	1.76 ± 0.71	0.008*
Pregnancy week	36.22 ± 2.55	37.10 ± 1.04	37.51 ± 1.15	0.001**

Abbreviations: PARA, Intravenous Paracetamol group; MEP-IT, Intrathecal Meperidine group. Note: Data are presented as mean ± SD. * Statistically significant at the 0.05 level; ** Statistically significant at the 0.01 level).

Hemodynamic parameters are summarized in Table 2. Mean arterial pressure and heart rate were comparable across groups at baseline. Analysis revealed a significant group × time interaction for mean arterial pressure ($P < 0.0001$). Following the intervention, the PARA group experienced an early and marked decline in MAP that became evident at the first minute and persisted throughout the 60-minute observation period. In contrast, changes in MAP in both the MEP-IT and control groups were modest during the early phase and did not reach statistical significance. Between-group comparisons demonstrated significant differences in MAP at 1, 3, and 60 minutes ($P < 0.05$ for all), with consistently lower values observed in the PARA group compared with the other two groups, particularly during the initial post-intervention period. Heart rate also changed significantly over time within each group ($P < 0.0001$). In the PARA group, HR showed a brief, non-significant increase during the first few minutes, whereas a gradual decline in HR was observed in both the MEP-IT and control groups. This decrease reached statistical significance from minute 3 onward in the MEP-IT group. Significant inter-group differences in HR were noted at 1, 3, and 15 minutes ($P < 0.05$), mainly reflecting higher HR values in the PARA group compared with the MEP-IT group during this interval.

Shivering outcomes differed notably among the study groups. The overall incidence of shivering was markedly lower in the MEP-IT group, affecting 24.5% of patients, whereas nearly half of the participants in both the PARA and control groups experienced shivering (49% in each group; $P < 0.0001$).

In addition to differences in incidence, the temporal pattern of shivering varied across groups. Shivering developed much earlier in the PA group, with a median onset time of 5 minutes, while onset was substantially delayed in both the MEP-IT and control groups (median: 45 minutes; $P < 0.001$). Core body temperature measurements showed that patients in the MEP-IT group had lower baseline temperatures prior to intervention and maintained lower core temperatures during shivering episodes compared with the other groups ($P < 0.0001$ and $P = 0.011$, respectively). Despite these differences in incidence, timing, and temperature profiles, the intensity of shivering did not differ significantly among the three groups. (Table 3).

Table 2- Changes in MAP and HR between the three groups over time

Variable	Time	Group (Mean ± SD)			P value Comparison between groups			
Mean Arterial Pressure (mmHg)		PARA	MEP-IT	Control	Three groups	PARA & MEP-IT	PARA & Cont	MEP-IT & Cont
	Before	97.81 ± 14.87	98.03 ± 15	94.81 ± 12.7	P = 0.439	P = 0.979	P = 0.280	P = 0.239
	1 min	81.35 ± 19.68	98.02 ± 14.41	93.00 ± 13.2	P < 0.0001*	P < 0.0001*	P = 0.021*	P = 0.040*
	3 min	75.92 ± 15.52	85.98 ± 17.33	75.70 ± 16.3	P = 0.002*	P = 0.008*	P = 0.224	P = 0.003*
	15 min	77.95 ± 13.79	82.80 ± 12.21	82.10 ± 11.3	P = 0.117	P = 0.168	P = 0.125	P = 0.761
	30 min	77.20 ± 14.98	82.12 ± 12.3	80.96 ± 13.7	P = 0.180	P = 0.232	P = 0.187	P = 0.655
	45 min	77.59 ± 12.48	82.47 ± 10.36	81.52 ± 12.8	P = 0.078	P = 0.101	P = 0.092	P = 0.661
	60 min	79.04 ± 10.91	85.52 ± 9.71	82.64 ± 12.0	P = 0.015*	P = 0.012*	P = 0.116	P = 0.193
	P value (over time)	P < 0.0001*	P < 0.0001*	P < 0.0001	P = 0.098^	P = 0.054^	P = 0.045*	P = 0.633^
	Mean diff (95% CI) before vs. 1 min	-16.46 (-21.85, -11.07)*	-0.14 (-0.006, 0.33)	-1.82 (-3.67, 0.031)				
	Mean diff (95% CI) before vs. 3 min	-21.89 (-27.38, -16.39)*	-12.05 (-16.53, -7.55)*	-19.14 (-23.55, -14.73)*				
	Mean diff (95% CI) before vs. 15 min	-19.86 (-25.85, -13.86)*	-15.22 (-18.93, -11.51)*	-12.72 (-17.71, -7.73)*				

	Mean diff (95% CI) before vs. 30 min	-20.61 (-26.54, -14.68)*	-15.91 (-20.63, -11.17)*	-13.85 (-18.79, -8.91)*				
Heart rate	Before	99.38 ± 16.86	99.35 ± 16.17	102.5 ± 16.1	P = 0.573	P = 0.998	P = 0.358	P = 0.330
	1 min	101.6 ± 20.74	97.17 ± 19.91	101.69 ± 17.0	P = 0.004*	P = 0.002*	P = 0.981	P = 0.230
	3 min	102.4 ± 22.82	92.41 ± 15.66	92.12 ± 26.42	P < 0.0001*	P < 0.0001*	P = 0.028*	P = 0.987
	15 min	99.22 ± 19.95	91.37 ± 16.55	94.0 ± 19.7	P < 0.0001*	P < 0.0001*	P = 0.181	P = 0.689
	30 min	94.10 ± 15.95	92.73 ± 14.12	94.96 ± 17.8	P = 0.108	P = 0.608	P = 0.794	P = 0.544
	45 min	90.27 ± 12.98	87.80 ± 13.22	88.14 ± 13.1	P = 0.109	P = 0.114	P = 0.418	P = 0.897
	60 min	85.98 ± 13.17	87.33 ± 12.76	89.2 ± 12.3	P = 0.065	P = 0.285	P = 0.229	P = 0.458
	P value (over time)	P < 0.0001*	P < 0.0001*	P < 0.0001*	P = 0.362^	P = 0.432^	P = 0.545^	P = 0.482^
	Mean diff (95% CI) before vs. 1 min	2.22 (-4.45, 8.90)	-2.18 (-10.35, 5.28)	-0.82 (-4.17, 2.52)				
	Mean diff (95% CI) before vs. 3 min	3.02 (-11.51, 0.49)	-6.94 (-11.33, -2.79) *	-10.39 (-18.50, -2.27) *				
	Mean diff (95% CI) before vs. 15 min	-0.14 (-6.72, 6.43)	-7.98 (-12.73, -3.48) *	-8.51 (-13.84, -3.18) *				
	Mean diff (95% CI) before vs. 30 min	-5.26 (-11.05, 0.52)	-6.62 (-11.80, -1.00) *	-7.54 (-12.42, -2.67) *				

Data are presented as Mean ± SD. PARA, Intravenous Paracetamol group; MEP-IT, Intrathecal Meperidine group; Cont, Control group; MAP, Mean Arterial Pressure. *Statistically significant at the 0.05 level; ^P value for the group × time interaction effect.

Table 3- Clinical characteristics related to shaving in patients in the three treatment groups

Variable	**Group**			**P value Comparison between groups**			
	PARA	MEP-IT	Control	Three groups	PARA & MEP-IT	PARA & Cont	MEP-IT & Cont
Shivering							
- Yes	24 (49.0%)	12 (24.5%)	25 (49.0%)	P < 0.0001*	P = 0.012*	P = 0.998	P = 0.013*
- No	25 (51.0%)	37 (75.5%)	26 (51.0%)				
Shivering intensity							
- No to mild (grade 0-1)	35 (71.4%)	43 (87.8%)	37 (72.5%)	P = 0.653	P = 0.843	P = 0.901	P = 0.080
- Moderate to very severe (grade 2-4)	14 (28.6%)	6 (12.2%)	14 (27.5%)				
Time of shivering (min)	5 (0, 45)	45 (30, 56.25)	45 (33.75, 45)	P < 0.001*	P < 0.001*	P < 0.001*	P = 0.962
Temperature before intervention (°C)	37.11 ± 0.17	36.78 ± 0.15	36.94 ± 0.14	P < 0.0001*	P < 0.0001*	P < 0.0001*	P < 0.0001*
Temperature during shivering (°C)	36.98 ± 0.23	36.63 ± 0.31	36.85 ± 0.18	P = 0.011*	P < 0.0001*	P = 0.021*	P = 0.001*

Abbreviations: PARA, Intravenous Paracetamol group; MEP-IT, Intrathecal Meperidine group; Cont, Control group; IQR, Interquartile Range. Note: Data are presented as Mean ± standard deviation, Number (%), or median (IQR) as appropriate. * Statistically significant at the 0.05 level.

Multivariate Analysis

The association between demographic/clinical variables and shivering incidence and intensity was analyzed separately for each group.

It should be noted that since no participants in the PARA group exhibited grade 3-4 shivering intensity, a comprehensive analysis of factors affecting shivering intensity in this group was not feasible.

Clear differences were observed among the study groups with respect to shivering outcomes. The frequency of shivering was substantially reduced in the MEP-IT group, with 24.5% of patients affected, compared with an incidence of 49% in both the PARA and control groups (P < 0.0001).

The timing of shivering also varied between groups. Patients in the PARA group developed shivering shortly after the intervention, with a median onset time of 5 minutes, whereas shivering occurred considerably later in the MEP-IT and control groups (median: 45 minutes; P < 0.001). Analysis of temperature profiles revealed that core body temperature was lower in the MEP-IT group at baseline and remained lower during shivering episodes compared with the other groups (P < 0.0001 and P = 0.011, respectively). Despite these differences in incidence, onset, and temperature characteristics, the severity of shivering did not differ significantly among the three groups. (Figure 2) Line chart showing the trend of Heart Rate (HR) over time in the PARA, MEP-IT, and Control groups. Data are presented as the mean (Figure 3).

Table 4- The relationship between demographic and clinical variables with the incidence and shivering intensity by group

Group	Independent Variable	Shivering (Yes)		Shivering Intensity#	
		OR	95% CI	OR	95% CI
PARA	Age	1.068	0.962, 1.186	-	-
	BMI	1.013	0.907, 1.132	-	-
	Gravid	1.392	0.856, 2.264	-	-
	Pregnancy week	0.954	0.763, 1.195	-	-
	Changes MAP at 1 min$	1.025	0.991, 1.060	-	-
	Changes MAP at 3 min$	1.008	0.979, 1.039	-	-
	Changes MAP at 15 min$	1.017	0.988, 1.046	-	-
	Changes HR at 1 min$	1.016	0.990, 1.043	-	-
	Changes HR at 3 min$	0.993	0.968, 1.018	-	-
	Changes HR at 15 min$	1.027	0.997, 1.058	-	-
MEP-IT	Age	1.009	0.909, 1.121	0.927	0.734, 1.172
	BMI	1.007	0.896, 1.131	0.995	0.803, 1.231
	Gravid	1.352	0.635, 2.879	1.636	0.651, 4.111
	Pregnancy week	1.394	0.664, 2.928	3.895	0.564, 21.491
	Changes MAP at 1 min$	1.001	0.966, 1.038	0.927	0.690, 1.244
	Changes MAP at 3 min$	0.962	0.921, 1.006	0.975	0.910, 1.045
	Changes MAP at 15 min$	0.987	0.938, 1.038	1.054	0.949, 1.169
	Changes HR at 1 min$	1.003	0.978, 1.029	1.009	0.965, 1.054
	Changes HR at 3 min$	1.014	0.969, 1.060	0.991	0.921, 1.065
	Changes HR at 15 min$	1.019	0.977, 1.063	0.904	0.782, 1.045
Control	Age	1.026	0.93, 1.13	1.054	0.86, 1.28
	BMI	1.007	0.89, 1.13	0.861	0.62, 1.18
	Gravid	1.302	0.59, 2.87	0.223	0.02, 1.89
	Pregnancy week	1.184	0.72, 1.94	2.835	0.79, 18.59
	Changes MAP at 1 min$	1.004	0.92, 1.09	1.007	0.83, 1.21
	Changes MAP at 3 min$	1.012	0.98, 1.05	0.98	0.92, 1.06
	Changes MAP at 15 min$	0.993	0.96, 1.03	1.005	0.91, 1.06
	Changes HR at 1 min$	0.969	0.90, 1.02	1.008	0.90, 1.11
	Changes HR at 3 min$	0.996	0.981, 1.01	0.996	0.95, 1.04
	Changes HR at 15 min$	1.013	0.982, 1.04	1.02	0.96, 1.07

Abbreviations: PARA, Intravenous Paracetamol group; MEP-IT, Intrathecal Meperidine group; OR, Odds Ratio; CI, Confidence Interval; MAP, Mean Arterial Pressure; HR, Heart Rate. Notes: Analysis for shivering intensity compares moderate to very severe shivering (grade 2-4) to no or mild shivering (grade 0-1); $ Changes were calculated as the value at the specified time point minus the baseline value; Statistically significant at

the 0.05 level (for odds ratios where the 95% CI does not include 1); Dash (-) indicates that the analysis was not performed for that variable in the respective group.

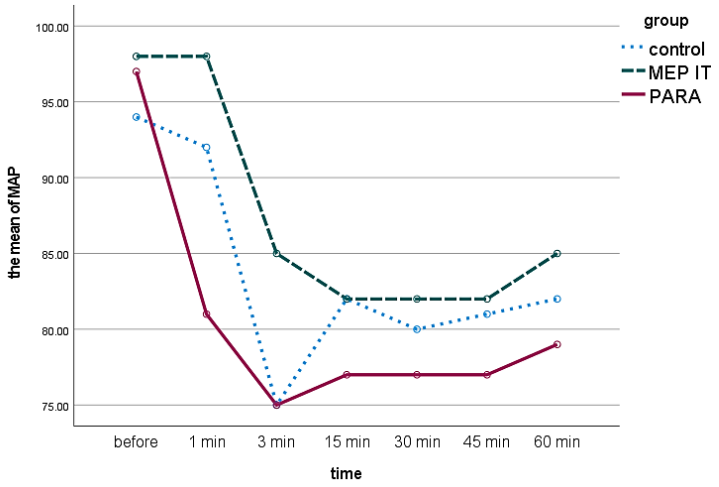

Figure 2- Changes in the mean of MAP over time by three groups.

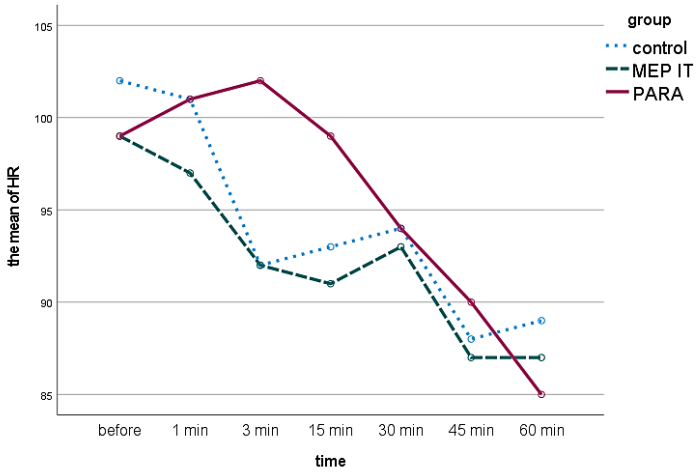

Figure 3- Changes in the mean of HR over time by three groups.

Discussion

This triple-blind randomized controlled trial demonstrated a clear divergence in the efficacy of the studied interventions for preventing shivering after spinal anesthesia for cesarean section. Our primary outcome reveals that intrathecal meperidine is a highly effective prophylactic agent, significantly reducing the incidence of shivering by half compared to both intravenous paracetamol and placebo (24.5% vs. 49% in each of the other groups, P<0.0001, (Table 3)). Furthermore, it delayed the onset of shivering considerably (median time: 45 minutes vs. 5 minutes in the paracetamol group, P<0.001, (Table 3)). Patients in the meperidine group exhibited significantly lower core body temperatures both prior to intervention and during episodes of shivering (P < 0.0001; Table 3), while nevertheless achieving more effective control of shivering. In addition to these findings, marked hemodynamic differences were identified between groups, as the paracetamol group experienced a significant and sustained decrease in mean arterial pressure (P < 0.0001; Table 2). Although heart rate changed significantly over time in all groups, these fluctuations did not appear to have a meaningful clinical relationship with the incidence or onset of shivering. Furthermore, multivariate analysis confirmed that none of the demographic or clinical variables predicted shivering incidence or severity in any treatment group (Table 4).

The strong anti-shivering effect of intrathecal meperidine observed in the present study is well aligned with prior neurophysiological and clinical findings. The approximately 50% reduction in shivering incidence corresponds with the documented ability of intrathecal opioids, including meperidine and fentanyl, to attenuate thermoregulatory responses [19,26–27]. In addition, the

substantial delay in shivering onset seen in the meperidine group supports a preemptive influence on central thermoregulatory control mechanisms [28–29]. Notably, this enhanced suppression of shivering occurred despite lower core body temperatures, a phenomenon previously reported by Matsukawa et al. and Alfonsi et al., and may indicate a dissociation between afferent thermal input and the shivering reflex, potentially mediated through modulation of the spinoreticular pathway. [18,30-31].

In contrast, prophylactic intravenous paracetamol, administered at the selected dose and timing, failed to demonstrate any advantage over placebo in the prevention of shivering and was associated with two notable and unanticipated findings. Most strikingly, the paracetamol group exhibited a markedly earlier onset of shivering compared with the control group (median 5 minutes versus 45 minutes), representing an approximately fourfold acceleration. This observation is both novel and clinically concerning. Although intravenous acetaminophen is known to reduce the shivering threshold through central mechanisms, the accelerated onset observed here may reflect paradoxical systemic effects, such as enhanced vasodilation or the influence of its metabolite AM404, potentially intensifying peripheral heat loss triggered by spinal anesthesia [32–33].

Pronounced hemodynamic instability was also evident in the paracetamol group, which demonstrated a significantly higher frequency of sustained hypotension necessitating vasopressor intervention compared with the control group (43% vs. 19%). This observation challenges the common assumption that intravenous acetaminophen is hemodynamically neutral. Possible mechanisms include direct vasodilatory effects mediated by its active metabolite AM404 through activation of TRPV1 channels or inhibition of L-type calcium channels in vascular smooth muscle [6,34]. Taken together, these findings underscore a clinically relevant safety interaction when intravenous acetaminophen is administered in conjunction with spinal anesthesia.

Disadvantageous profile of intravenous paracetamol: In marked contrast to the efficacy observed with intrathecal meperidine, the accelerated onset of shivering in the intravenous paracetamol group represents a paradoxical and highly novel safety signal. When considered alongside its lack of prophylactic benefit, these results suggest that the combined peripheral and central actions of paracetamol may be counterproductive within the neuraxial anesthesia setting. Spinal anesthesia induces shivering primarily by causing profound peripheral vasodilation, which rapidly dumps core heat, lowering the central core temperature. While paracetamol's central antipyretic action is meant to lower the shivering threshold to tolerate this temperature drop, its peripheral metabolites may exacerbate the initial heat loss. Specifically, the paracetamol metabolite and other active compounds are known to cause direct vascular relaxation and vasodilation by activating potassium channels in vascular smooth muscle [33-34]. By layering this drug-induced peripheral vasodilation onto the spinal-induced sympathetic blockade, IV paracetamol may have significantly increased the rate of core-to-peripheral heat redistribution, thereby accelerating the drop in core temperature below the (now lowered) shivering threshold. Thus, the drug did not just fail to prevent shivering—it appears to have triggered or accelerated the hypothermic process, resulting in significantly earlier shivering onset than in the control group, which received only the standard IV fluid bolus. This detrimental effect highlights that the peripheral actions of paracetamol, specifically on vascular tone, may dominate over its central thermoregulatory benefits when used during sympathetic blockade.

Although our result confirming the lack of efficacy of intravenous paracetamol is consistent with the findings of Rasoli et al., our study provides crucial new evidence of a detrimental effect: the drug paradoxically accelerates the onset of shivering, a concerning safety profile not previously reported [35].

Our results are consistent with prior studies that have questioned the prophylactic efficacy of intravenous acetaminophen in the prevention of neuraxial anesthesia–related shivering. However, the observed acceleration in shivering onset, together with the increased requirement for vasopressor support in the paracetamol group, constitutes a meaningful and novel contribution to the existing literature. Furthermore, multivariate analysis demonstrated that demographic and clinical variables were not independent predictors of shivering, supporting the interpretation that the observed differences were attributable to true pharmacological effects. Collectively, these findings support the generalizability of our results across a broad obstetric population [16,36].

Strengths and Limitations

The principal strengths of this study lie in its rigorous triple-blind design, an adequately powered sample size, and the direct comparison between a gold-standard intervention and a commonly employed alternative. One limitation was the baseline imbalance observed in gravidity and gestational age; however, multivariate analysis confirmed that these variables did not confound the primary outcome. In addition, the external validity of the findings is primarily applicable to ASA II parturients undergoing elective cesarean delivery.

Conclusion

Our results provide clear evidence that intrathecal meperidine is a highly effective prophylactic strategy against shivering following spinal anesthesia for cesarean

section. In contrast, prophylactic intravenous paracetamol, at the dose and timing used in this study, demonstrated no benefit over placebo and was associated with a significant and sustained decrease in arterial pressure. For reliable shivering prophylaxis, intrathecal meperidine should be considered a first-line pharmacological option. IV paracetamol should not be relied upon for preventing shivering in this context. Its role remains primarily for adjunctive analgesia. Clinicians should be aware of the potential for significant hypotension when administering IV paracetamol in conjunction with spinal anesthesia. Further studies are needed to elucidate the mechanism behind paracetamol's hemodynamic effects and to explore if alternative dosing regimens could prove effective for shivering prophylaxis.

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