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Research Article

Intrathecal Ketamine Added to Bupivacaine for Prevention of Post-Spinal Shivering in Elective Cesarean Delivery: A Double-Blind Randomized Clinical Trial

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ABSTRACT

Background: Post-spinal shivering is a common complication during cesarean delivery under spinal anesthesia, occurring in 30-50% of parturients. Shivering increases oxygen consumption, interferes with monitoring, and negatively impacts maternal satisfaction. Intrathecal ketamine, an NMDA receptor antagonist, may provide anti-shivering benefits while avoiding systemic side effects. The objective is to evaluate the efficacy and safety of intrathecal ketamine (0.1 mg/kg) combined with bupivacaine in reducing post-spinal shivering during elective cesarean sections.

Methods: This parallel-group, double-blind, randomized clinical trial enrolled 100 ASA II parturients undergoing elective cesarean section under spinal anesthesia. Patients were randomized to receive either intrathecal bupivacaine 12.5 mg plus ketamine 0.1 mg/kg (Group A, n=50) or bupivacaine 12.5 mg alone (Group B, n=50). Primary outcomes included shivering incidence and severity using the Bedside Shivering Assessment Scale. Secondary outcomes included block characteristics, time to the first analgesic request, and adverse events.

Results: Intraoperative shivering was significantly reduced in the ketamine group (10% vs. 40%; $p<0.001$; OR=0.167, 95% CI: 0.056–0.492), representing an 83% relative risk reduction. Time to first analgesic request was prolonged in Group A (145 vs. 125 minutes; $p<0.001$). Motor block duration, PONV incidence, and patient satisfaction were comparable between groups. No neurological complications were observed during the two-month follow-up.

Conclusion: Intrathecal ketamine (0.1 mg/kg) significantly reduces post-spinal shivering incidence and severity while prolonging postoperative analgesia without increasing adverse effects, representing an effective non-opioid adjuvant for obstetric spinal anesthesia.

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Introduction

Post-spinal shivering is a well-known and uncomfortable complication of neuraxial anesthesia, particularly in obstetric practice. It´s incidence after spinal anesthesia for caesarean delivery have been quoted as being approximately 30% to over 50%. [1-2]. Inhibition of simply shivering causes whole body oxygen consumption, CO2 production cardiac workload to increase, which could all be clinically significant in parturients with limited or compromised cardiopulmonary reserve. Furthermore, intense shivering can disrupt noninvasive monitoring by influencing accurate blood pressure and pulse oximetry readings and unfavorably impact the overall birth experience along with maternal satisfaction. [2-3].

The pathophysiology of post-spinal shivering is multifactorial and not completely understood, but redistribution hypothermia, impairment of thermoregulatory vasoconstriction below the block, anxiety, and cold fluid or ambient exposure have all been implicated [3–5]. Numerous pharmacologic and non-pharmacologic strategies have been evaluated, including forced-air warming, warmed intravenous fluids, intrathecal or systemic opioids, 5-hydroxytryptamine receptor antagonists, α2 agonists, and N-methyl-D-aspartate (NMDA) receptor antagonists [2-3]. However, none of these approaches have emerged as a universally preferred anti-shivering modality in obstetric anesthesia, and each carries a distinct profile of adverse effects such as hypotension, oversedation, pruritus, or nausea and vomiting [6].

Ketamine, a phencyclidine derivative and non-competitive NMDA receptor antagonist, has gained attention as an anti-shivering agent because it modulates thermoregulatory pathways while preserving airway reflexes and sympathetic tone. Intravenous ketamine, at low doses, has been shown in randomized trials and a recent scoping review to reduce the incidence and/or intensity of perioperative shivering in patients receiving spinal anesthesia, including parturients undergoing cesarean delivery, with acceptable hemodynamic stability [6–9]. Nevertheless, concerns about psychomimetic reactions and neurotoxicity, as well as variability in effective dose ranges, have limited the widespread adoption of systemic ketamine solely for shivering prophylaxis in routine obstetric practice [10].

Intrathecal administration of ketamine offers a theoretically attractive alternative, allowing lower systemic exposure while targeting spinal NMDA receptors involved in nociception and possibly thermoregulation [11]. Previous studies have demonstrated that adding 0.1 mg/kg intrathecal ketamine to bupivacaine can prolong sensory and motor block and significantly delay the time to the first postoperative analgesic request without increasing neurological or psychotomimetic complications at this dose [12-13]. Despite these encouraging analgesic data, the potential role of intrathecal ketamine specifically in preventing post-spinal shivering during cesarean section has not been adequately investigated, and existing work on perioperative shivering has focused mainly on opioids, pethidine, and systemic ketamine rather than neuraxial ketamine [3,6].

Given the high burden of post-spinal shivering in cesarean patients, its adverse physiologic and experiential consequences, and the absence of a clearly superior prophylactic regimen tailored to obstetric anesthesia, further research on spinal adjuvants is warranted. Building on prior evidence that intrathecal ketamine at 0.1 mg/kg is safe and enhances postoperative analgesia when combined with bupivacaine. The primary outcome was the incidence of post-spinal shivering in the operating room, defined as the occurrence of any shivering (Grade ≥1 on the Bedside Shivering Assessment Scale) during the intraoperative period. Secondary outcomes included the following: (1) severity of shivering graded using the BSAS scale; (2) duration of shivering episodes; (3) incidence and severity of shivering in the post-anesthesia care unit (PACU); (4) time to first postoperative analgesic request; (5) sensory and motor block characteristics; (6) hemodynamic parameters including blood pressure and heart rate variations; (7) adverse events including postoperative nausea and vomiting; and (8) patient satisfaction scores.

Methods

A parallel-group randomized double-blind clinical trial was conducted between September to December 2025, to evaluate the efficacy and safety of intrathecal ketamine 0.1 mg/kg as adjuvant with hyperbaric bupivacaine 12.5 mg (Group B) against bupivacaine 12.5 mg alone (Group A) in parturients undergoing elective cesarean section under spinal anesthesia. The study protocol received approval from the national ethics committee (IR.SBMU.MSP.REC.1404.255) and the Iranian Registry of Clinical Trials (IRCT20120910010800N14), and written informed consent was obtained from all participants prior to enrollment.

Design and setting Sample size was determined on the primary outcome of shivering incidence during intraoperative period. Low-dose IV ketamine (0.2mg/kg) administered to 123 parturients with spinal anesthetic for cesarean delivery in a randomized, double-blind trial reduced shivering from 70.7% in the saline control group patient group to 41.5% [14]. Based on this precedent we estimated that a baseline shivering rate of >70% provided adequate power to detect an approximate 25% absolute risk reduction in shivering with ketamine. Using a two-tailed statistical power of 80% and type I error rate of

0.05, calculating a 25% absolute reduction in shivering incidence with ketamine administration it was determined that the minimum required sample size exceeded 200 patients. Both study groups were 1:1 allocated to receive atorvastatin or placebo (50 subjects per group) having included a dropout rate of approximately 20% and powered the primary analysis, thus sample size was set to be 100 patients.

Computer generated permuted blocks were used for randomization. An independent statistician, who was not involved in patient recruitment, treatment administration or outcome assessment, randomised data in a 1:1 ratio. The treatment allocation was concealed by opaque sealed envelopes numbered sequentially prepared by the same independent biostatistician. Eligible patients were assigned consecutive study numbers in the order they were enrolled on the day of surgery after informed consent was provided by study personnel. The randomization code in the envelope was opened only at the time of drug preparation.

Blinding was achieved through a double-dummy design. All study syringes were prepared by an anesthesiologist who had no involvement in patient care, intraoperative management, data collection, or outcome assessment. The preparer first drew the weight-based ketamine dose for the ketamine group and the bupivacaine-only solution for the control group and then added sterile normal saline to each syringe to achieve an identical final volume of 2.8 mL in both groups. The appearance, volume, and labeling of the syringes were fully standardized to ensure visual indistinguishability. Neither the participants nor the study personnel involved in the care, data collection, or outcome assessment were aware of treatment allocation throughout the study period. The randomization code remained sealed with the independent statistician and was opened only after all data analysis had been completed and the final study report was prepared.

The study included women older than 18 years who had been scheduled for an elective cesarean delivery with spinal anesthesia. Only ASA physical status II patients were included. Participants had to weigh more than 50 kg. Participants were required to be normal and competent to understand consent. This study was conducted in singleton pregnancies with vertex presentation of the fetus in the final weeks of pregnancy (38–42 weeks gestation), and all participants needed to have sufficient command of the English language both to understand procedures relating to the study, as well as to communicate with staff undertaking data collection during their labour. Standard preoperative laboratory parameters with normal limits (hemoglobin level, platelet count and coagulation profile) were needed to guarantee the safety of spinal anesthesia. Finally, participants had to be able and willing to comply with study protocols and follow-up as required.

Exclusion criteria included contra-indications to spinal anesthesia such as coagulopathy (platelet count less than 100,000/μL, international normalized ratio greater than 1.5 or active anticoagulants therapy), local infection on the site of planned injection, patient refusal for spinal anesthesia The study did not include cesarean deliveries that were performed in an emergency setting. Participants with a BMI more than 45 kg/m² or clinically significant obesity that may interfere with spinal anesthesia were excluded from the study. Regarding allergies, any recognized hypersensitivity or history of an allergic response to local anesthetics (particularly bupivacaine) or ketamine was an exclusion criterion. Patients with the presence of important cardiovascular disease such as uncontrolled systemic arterial hypertension and diabetes (before pregnancy), coronary artery disease, heart failure or cardiac arrhythmias were excluded from participating. Individuals with psychiatric disorders requiring ongoing medication, particularly those affecting cognitive function or cooperation during the surgical procedure, were not eligible. Patients taking medications that could influence shivering mechanisms, including but not limited to tramadol, pethidine, ondansetron, or other anti-shivering agents within 24 hours before surgery, were excluded. Patients with preoperative core temperature abnormalities (temperature less than 36°C or greater than 38°C) or active infection were not considered for enrollment. Those with a history of chronic pain conditions requiring regular analgesic therapy or those taking opioid medications were excluded due to potential confounding effects on analgesic outcomes. Patients with a history of substance abuse were not eligible for participation. Cases that received misoprostol were excluded from the study. Surgery lasting more than 90 minutes was another reason for exclusion from the study. Finally, patients with multiple gestations (twins or higher-order pregnancies) or non-vertex fetal presentations requiring special delivery considerations were excluded from the study.

The spinal anesthesia was regularized as follows: a combination of the study drugs was injected into subarachnoid space at either L3-L4 or L4-L5 interspace with 25-gauge Quincke needle. After randomisation all patients underwent the same preoperative protocols, including IV fluid preloading 10 mL/kg body weight of crystalloid solution and standardized monitoring (non-invasive BP every 5 minutes, continuous ECG and pulse oximetry). The ambient temperature of the operating room was held between 22 and 24°C, and all intravascular fluid was warmed to 37°C with fluid warmers in order to minimize triggers of thermal stress and shivering. Hypotension was defined as systolic blood pressure less than 90 mmHg or a reduction of more than 20% from baseline; boluses of intravenous ephedrine and/or additional fluids were given whenever indicated. The primary outcome measure was the incidence of

shivering occurring during the intraoperative period. Post-spinal shivering was assessed every 15 minutes until 3 hours post-spinal anesthesia with the Bedside Shivering Assessment Scale (BSAS), a five-point simple and validated scale (scale ranges from 0-4) [17]. Scores based on visible muscular activity were as follows: 0 = no shivering; 1 = mild fasciculations of face or neck only; 2 = moderate tremor of limbs or truncal muscles, both arms and both feet or limbs; 3 = gross muscular activity involving one muscle group and most [7]4 = intense or violent whole body shivering interfering with monitoring or care.15 Intraoperatively, shivering was evaluated at intervals and recorded using the maximum score [10]; this sum was used for analysis. Secondary outcome measures were: incidence of shivering in the PACU; duration and severity of shivering during intraoperative period and in the PACU; time to first postoperative analgesic request (defined as the interval from spinal drug administration to first-request for pain relief medicine); sensory and motor block characteristics (assessed by regular intervals with validated dermatomal testing and standardized motor function scales); hemodynamic parameters including variations in blood pressure and heart rate; postoperative nausea and vomiting requiring antiemetic intervention (yes/no); patient satisfaction scores on 5-point Likert scale ranging from very dissatisfied to very satisfied. A trained research personnel conducted all outcome assessments blinded to treatment allocation during the entire study period reducing measurement bias. All patients were followed up in 2 months after surgery for serial neurological examinations to check new sensory, motor or sphincter deficits or neuropathic symptoms.

A Shapiro–Wilk test was used to assess the data distribution normality. Categorical variables were reported as frequencies and percentages, while continuous variables were presented as the mean ± standard deviation (SD) or median with interquartile range (IQR), depending on the distribution of data.

Group comparisons were conducted using chi-square tests for categorical outcomes, and independent samples t-tests or Mann-Whitney U tests as appropriate for continuous variables. A statistical significance level of less than 0.05 was set for all analyses. Statistical Analysis SPSS version 29.0 was used for the statistical analyses and tests in two-sided significance level were performed.

Results

Regarding the primary outcome, the incidence of post-spinal shivering in the operating room was significantly lower in the ketamine group (Group A: 10%, 5/50) compared to the control group (Group B: 40%, 20/50), with Fisher's exact test demonstrating a statistically significant difference ($p < 0.001$). This represents an approximately 83% relative risk reduction in shivering with intrathecal ketamine. The overall mean ± standard deviation (SD) of age was 31.51 ± 6.14 years (95% CI: 30.29–32.73). The age range extended from 18 to 46 years with a median of 32 years, demonstrating a near-normal distribution. The independent samples t-test revealed no significant difference between the two groups ($t(98) = -1.33$, $p = 0.188$; mean difference = -1.62 years; 95% CI -4.05 to 0.81; Cohen's $d = -0.27$) (Table 1). The overall mean height of participants was 163.23 cm ± 6.06 cm, showing a normal distribution. The independent samples t-test revealed no significant difference ($t(98) = 0.21$, $p = 0.831$; mean difference = 0.26 cm; 95% CI -2.16 to 2.68; Cohen's $d = 0.04$). The median (IQR) body weight was 81.00 (18.00) kg for Group B and 81.00 (20.75) kg for Group A. The Mann-Whitney U test revealed no significant difference ($U = 1190.0$, $Z = -0.414$, $p = 0.681$; median difference = 0 kg; effect size $r = -0.041$). The BMI data showed a non-normal distribution in Group A. Participants in Group B had a median (IQR) BMI of 30.30 (5.66) kg/m², while those in Group A had a median (IQR) of 30.16 (6.68) kg/m². The Mann-Whitney U test showed no significant difference between groups ($U = 1143.0$, $p = 0.463$, $r = -0.074$) (Table 1). Among participants, 15 (15%) had a history of hypertension. In Group B, 6 patients (12%) were hypertensive, while 9 patients (18%) had hypertension in Group A. The difference was not statistically significant ($\chi^2 = 0.71$, $p = 0.401$; Fisher's exact $p = 0.577$; $\varphi = 0.084$). The distribution of gestational diabetes mellitus was identical between groups, with 10 patients (20.0%) in each arm ($\chi^2 = 0.00$, $p = 1.000$; Fisher's exact test; $\varphi = 0.000$) (Table 2). A total of 22 participants (22%) were nulliparous, and 78 (78%) had at least one prior delivery. The distribution of previous delivery history was similar between groups (Mann-Whitney $U = 1206.5$, $Z = -0.32$, $p = 0.754$; median = 1 in both groups; effect size $r = -0.032$) (Table 2).

As shown in (Table 3), the overall incidence of shivering in the operating room was 25% (n = 25). A significant difference was observed between groups: shivering occurred in 40% of Group B (20 of 50) compared with 10% in Group A (5 of 50). Fisher's exact test demonstrated a statistically significant reduction ($p < 0.001$; $\varphi = 0.346$). The odds of shivering were markedly lower in Group A (OR = 0.167, 95% CI 0.056–0.492), representing an approximate 83% reduction in shivering risk. Among the parturients studied, 75% exhibited no shivering (Grade 0), while 13%, 10%, and 2% demonstrated mild (Grade 1), moderate (Grade 2), and severe shivering (Grade 3), respectively. There was no report of Grade 4 shivering.

Table 1- Baseline Demographic Characteristics

Variable	Bupivacaine (n=50)	Ketamine + Bupivacaine (n=50)	P value	Effect Size (95% CI)
Age (years) Mean ± SD	30.70 ± 6.34	32.32 ± 5.88	0.188[a]	Cohen's d = -0.265 (-0.658, 0.129)
Weight (kg) Median (IQR)	81.00 (18.00)	81.00 (20.75)	0.681[b]	r = -0.041
Height (cm) Mean ± SD	163.36 ± 5.59	163.10 ± 6.55	0.831[a]	Cohen's d = 0.043 (-0.349, 0.435)
BMI (kg/m²) Median (IQR)	30.30 (5.66)	30.16 (6.68)	0.463[b]	r = -0.074

[a] Independent samples t-test (for normally distributed data). [b] Mann-Whitney U test (for non-normally distributed data). BMI = Body Mass Index; CI = Confidence Interval; IQR = Interquartile Range; SD = Standard Deviation. Effect size interpretation: negligible (|r| < 0.10), small (0.10–0.29), medium (0.30–0.49), large (≥ 0.50)

Table 2- Obstetric History

Variable	Bupivacaine (n=50)	Ketamine + Bupivacaine (n=50)	P value	Effect Size
Number of Previous Deliveries - Median (IQR)	1.00 (1.00)*	1.00 (2.00)*	0.754[a]	r = -0.032
History of Diabetes- n (%)	10 (20.0%)	10 (20.0%)	1.000[b]	φ = 0.000
History of Hypertension- n (%)	6 (12.0%)	9 (18.0%)	0.577[b]	φ = 0.084

[a] Mann-Whitney U test (for non-normally distributed count data). [b] Fisher's Exact Test (for categorical variables). r = correlation coefficient for non-parametric tests. φ (phi coefficient) = effect size for 2×2 contingency tables. Effect size interpretation: negligible (|r| < 0.10), small (0.10–0.29), medium (0.30–0.49), large (≥ 0.50). IQR = Interquartile Range

Table 3- Shivering Outcomes in Operating Room and Recovery

Outcome	Bupivacaine (n=50)	Ketamine + Bupivacaine (n=50)	P value	Effect Size
Operating Room				
Shivering incidence n (%)	20 (40.0%)	5 (10.0%)	<0.001[a]	φ = 0.346
Shivering grade - Median (IQR)	0.00 (0.00)	0.00 (0.00)	<0.001[b]	r = -0.358
Shivering duration (min) - Median (IQR)	0.00 (20.00)	0.00 (0.00)	0.001[b]	r = -0.315
Grade distribution				
Grade 0 (None) n (%)	30 (60.0%)	45 (90.0%)	-	-
Grade 1 (Mild) n (%)	10 (20.0%)	3 (6.0%)	-	-
Grade 2 (Moderate) n (%)	8 (16.0%)	2 (4.0%)	-	-
Grade 3 (Severe) n (%)	2 (4.0%)	0 (0.0%)	-	-
Grade 4 (Very Severe) n (%)	0 (0.0%)	0 (0.0%)	-	-
Recovery Room				
Shivering incidence n (%)	15 (30.0%)	7 (14.0%)	0.090[a]	φ = 0.193
Shivering grade - Median (IQR)	0.00 (0.00)	0.00 (0.00)	0.055[b]	r = -0.192
Shivering duration (min) - Median (IQR)	0.00 (14.00)	0.00 (0.00)	0.018[b]	r = -0.231
Grade 0 (None) n (%)	35 (70.0%)	43 (86.0%)	-	-
Grade 1 (Mild) n (%)	6 (12.0%)	3 (6.0%)	-	-
Grade 2 (Moderate) n (%)	9 (18.0%)	4 (8.0%)	-	-
Grade 3 (Severe) n (%)	0 (0.0%)	0 (0.0%)	-	-
Grade 4 (Very Severe) n (%)	0 (0.0%)	0 (0.0%)	-	-

Data are presented as n (%) or median (IQR). [a] Fisher's Exact Test. [b] Mann-Whitney U test. φ = phi coefficient for 2×2 contingency tables. r = correlation coefficient. Effect size interpretation: negligible (|r| < 0.10), small (0.10–0.29), medium (0.30–0.49), large (≥ 0.50). IQR = Interquartile Range

The median and mode of the shivering grade were both 0. Comparison between the two treatment groups demonstrated a significant reduction in shivering severity among patients receiving ketamine. Mann–Whitney U analysis showed that the distribution of shivering grades differed significantly between groups ($U = 856.5$, $Z = -3.577$, $p < 0.001$; effect size $r = 0.358$). Patients in Group B had a higher mean rank (58.37) compared with those receiving ketamine + bupivacaine (42.63), indicating overall greater shivering severity in the control group.

An ordinal logistic regression model was used to adjust for baseline and intraoperative covariates ($\chi^2 = 84.498$, $df = 21$, $p < 0.001$; Nagelkerke $R^2 = 0.719$). Among the covariates, only a few variables reached statistical significance, such as diabetes history ($B = 3.881$, $p = 0.035$), motor block duration ($B = -0.098$, $p = 0.007$),

nausea treatment (B = 5.416, p = 0.007), vomiting treatment (B = -6.757, p = 0.015), fentanyl use (B = 5.594, p = 0.023), midazolam use (B = -18.364, p = 0.010), warmed IV fluids (B = 5.682, p = 0.009), and meperidine use (B = 5.267, p = 0.020). However, given the model instability and sparse data patterns (75% cells with zero frequencies), these findings should be interpreted with caution.

The duration of shivering in the operating room demonstrated a highly skewed distribution in both groups. The median duration was 0 minutes (IQR 20) in Group B compared to 0 minutes (IQR 0) in Group A. Although median shivering duration was zero in both groups due to the high proportion of non-shivering patients, the interquartile ranges differed substantially (20 minutes vs. 0 minutes), and the Mann-Whitney U test detected this distributional difference, (U = 913.5, Z = –3.149, p = 0.001; effect size r = -0.315), with Group B showing a higher mean rank (57.23 vs. 43.77), reflecting both greater incidence and longer duration of shivering episodes.

Exploratory univariate ANOVA modeling ($F(22,77) = 5.96$, $p < 0.001$; partial $\eta^2 = 0.63$) identified several factors associated with longer shivering duration, including vomiting requiring treatment (p = 0.034), blanket use in the OR (p = 0.004), and rescue medication use with meperidine (p = 0.007) or other agents (p = 0.012). However, these findings should be interpreted cautiously, given the zero-inflated distribution of the outcome variable.

Shivering in the post-anesthesia recovery room occurred in 22% of patients (n = 22). Comparison of the two treatment groups showed a clinically meaningful but statistically borderline reduction in recovery-room shivering among patients who received ketamine. Shivering occurred in 30% of patients in Group B (15 of 50) compared with 14% in Group A (7 of 50). Fisher's exact test demonstrated a trend, although non-significant, favoring ketamine (two-tailed p = 0.090). The odds ratio suggested 62% lower odds of recovery-room shivering in Group A (OR = 0.38; 95% CI 0.14–1.04). A multivariable logistic regression model showed a statistically significant overall model fit ($\chi^2 = 82.7$, $p < 0.001$; Nagelkerke $R^2 = 0.864$).

Of the patients studied in the recovery room, 78% experienced no shivering (Grade 0), while 9% and 13% demonstrated mild (Grade 1) and moderate (Grade 2) shivering, respectively. No patients experienced Grade 3 (severe) or Grade 4 shivering. There was a lower shivering severity among patients who received ketamine. Mann–Whitney U analysis demonstrated a borderline non-significant trend in grade distribution (U = 1048.5, Z = –1.922, p = 0.055).

The mean rank was higher in Group B (54.53) compared with Group A (46.47), with a small effect size (r = –0.192). An ordinal regression model demonstrated significant overall model fit ($\chi^2 = 69.1$, df = 22, $p < 0.001$), and the treatment group remained one of the variables contributing meaningfully to the model's predictive performance, consistently favoring reduced shivering grades with ketamine.

In the PACU, among those who experienced shivering, the duration was significantly longer in Group B. The median (IQR) shivering duration in Group B was 0.00 (14.00) minutes compared to 0.00 (0.00) minutes in Group A (due to the high volume of shivering-free patients). The Mann-Whitney U test demonstrated a statistically significant difference between groups (U = 1011.5, Z = -2.310; exact p = 0.018), with Group B showing higher mean ranks (55.27 vs. 45.73), indicating a moderate effect size (r = -0.231).

Sensory block duration was 120.00 (IQR 13.00) minutes in Group B and 110.00 (IQR 20.00) minutes in Group A. Due to non-normal distribution (Shapiro-Wilk $p < 0.001$), the Mann-Whitney U test was used, showing a statistically marginally significant difference (U = 974.5, Z = -1.97, p = 0.049, r = -0.197) (Table 4).

As shown in (Table 4), motor block duration was comparable between groups. The median (IQR) motor block duration was 210.00 (40.00) minutes in Group B and 210.00 (40.00) minutes in Group A. The Mann-Whitney U test demonstrated no statistically significant difference (U = 1160.0, Z = -0.606, p = 0.545, r = -0.061). The negligible effect size indicates that there is no clinically meaningful difference between the groups, confirming that intrathecal ketamine does not prolong motor block recovery.

The median time to first analgesic request was significantly longer in Group A [145.00 minutes (IQR = 11)] compared to Group B [125.00 minutes (IQR = 11)]. The Mann-Whitney U test revealed a statistically significant difference (U = 373.000, Z = -6.096, $p < 0.001$, effect size r = -0.61), indicating that the addition of 0.1 mg/kg intrathecal ketamine significantly prolonged the duration of postoperative analgesia by approximately 20 minutes with a large effect size (Table 5).

Table 4- Spinal Anesthesia Block Characteristics

Variable	Bupivacaine (n=50)	Ketamine + Bupivacaine (n=50)	P value	Effect Size
Sensory block duration (min) - Median (IQR)	120.00 (13.00)	110.00 (20.00)	0.049[b]	r = -0.197
Motor block duration (min) - Median (IQR)	210.00 (40.00)	210.00 (40.00)	0.545[b]	r = -0.061

[b] Mann-Whitney U test. r = effect size correlation coefficient. Effect size interpretation: negligible (|r| < 0.10), small (0.10–0.29), medium (0.30–0.49), large (≥ 0.50). IQR = Interquartile Range

Table 5- Secondary Outcomes

Outcome	Bupivacaine 12.5 mg (n=50)	Ketamine 0.1 mg/kg + Bupivacaine 12.5 mg (n=50)	P value	Effect Size
Time to first analgesic request (min) - Median (IQR)	125.00 (11.00)	145.00 (11.00)	<0.001[b]	r = -0.61
Patient Satisfaction - Median (IQR)	4.00 (1.00)	5.00 (1.00)	0.098[b]	r = -0.17
Nausea requiring treatment	17 (34.0%)	14 (28.0%)	0.666 [a]	φ = 0.065
Vomiting requiring treatment	4 (8.0%)	5 (10.0%)	1.000 [a]	φ = 0.035

Data are presented as median (IQR) or n (%). [a] Fisher's Exact Test for categorical variables. [b] Mann-Whitney U test. r = correlation coefficient. φ = phi coefficient for 2×2 contingency tables. Effect size interpretation: negligible (|r| < 0.10), small (0.10–0.29), medium (0.30–0.49), large (≥ 0.50). IQR = Interquartile Range. Patient satisfaction measured on a 5-point Likert scale (1 = very dissatisfied, 5 = very satisfied)

The incidence of postoperative nausea and vomiting (PONV) was comparable between the two study groups. Nausea requiring treatment occurred in 17 patients (34.0%) in Group B compared to 14 patients (28.0%) in Group A. Fisher's Exact Test revealed no statistically significant difference ($p = 0.666$; $\varphi = 0.065$). Similarly, vomiting requiring treatment was reported in 4 patients (8.0%) in Group B and 5 patients (10.0%) in Group A, with no significant difference (Fisher's Exact Test, $p = 1.000$; $\varphi = 0.035$). The negligible effect sizes ($\varphi < 0.10$) indicate that the addition of low-dose intrathecal ketamine to bupivacaine does not increase the risk of PONV (Table 5).

Overall, 94% of participants reported being satisfied or very satisfied with spinal anesthesia. The distribution of satisfaction levels differed descriptively between groups, with the ketamine group showing a higher proportion of "Very Satisfied" responses (56.0% vs 42.0%) and fewer "Neutral" responses (2.0% vs 10.0%). However, this difference did not reach statistical significance (Fisher's Exact Test, $p = 0.138$; Cramer's $V = 0.20$). The Mann-Whitney U test confirmed no significant difference in satisfaction rankings between groups ($U = 1034.5$, $Z = -1.670$, $p = 0.098$, $r = -0.17$).

Ordinal logistic regression revealed that the overall model significantly predicted satisfaction levels ($\chi^2 = 45.33$, $df = 20$, $p < 0.001$; Nagelkerke $R^2 = 0.44$). The treatment group was not a significant predictor of satisfaction ($B = 0.429$, $p = 0.401$). Significant predictors of higher satisfaction included older age ($B = 0.097$, $p = 0.046$, OR = 1.10 per year) and use of warm intravenous fluids ($p = 0.014$). Vomiting requiring treatment was significantly associated with lower satisfaction ($B = -3.093$, $p = 0.005$, OR = 0.045) (Table 5). There were no new neurological deficits observed in patients during or in the two months after the surgery.

Discussion

Ketamine, as an NMDA receptor antagonist and a non-opioid adjuvant, provides a compelling clinical approach for improving the safety and efficacy profile of spinal anesthesia in elective cesarean section patients. Our findings demonstrate a clinically and statistically significant reduction in intraoperative shivering with the addition of intrathecal ketamine. The incidence of operating room shivering was reduced from 40% in the bupivacaine-only group to 10% in the ketamine-bupivacaine group, representing that for every 3-4 patients treated with intrathecal ketamine, one additional case of intraoperative shivering is prevented, with a 75% relative risk reduction (RR = 0.25; 95% CI: 0.10–0.61; $p = 0.001$). The effect size ($\varphi = 0.346$) indicates a medium-to-large clinical effect. These results align with or exceed the efficacy reported for other intrathecal adjuvants such as pethidine, where meta-analyses have documented shivering reductions of approximately 87% [16].

The two treatment groups demonstrated excellent baseline comparability, strengthening the internal validity of our findings. Age, height, weight, and BMI showed no significant differences (all $p > 0.05$, negligible effect sizes). Comorbidity distribution was balanced: hypertension was present in 12% versus 18% ($p = 0.577$), and gestational diabetes in 20% of both groups ($p = 1.000$). Obstetric history, including parity (median 1 previous delivery in both groups), was similarly distributed ($p = 0.754$). Logistic regression confirmed that parity did not predict postoperative shivering in our cohort, although one prospective study has reported 44% lower odds of shivering per previous delivery [5].

Ketamine's anti-shivering efficacy likely stems from its antagonism of central and spinal NMDA receptors, which play a central role in thermoregulatory integration and central sensitization [9,11]. Compared to other anti-shivering adjuvants, ketamine offers several advantages, such as lower pruritus, respiratory depression, nausea, bradycardia, and hypotension risks. Studies of oral, intravenous, or intrathecal drugs showed beneficial results. Tramadol and nefopam demonstrate that both agents can achieve 85-97% shivering suppression, with tramadol slightly stronger and nefopam showing more stable hemodynamics but occasionally causing tachycardia [14,17]. Intrathecal dexmedetomidine consistently shows significant shivering reduction, though with mild hypotension and sedation risks [18]. Butorphanol and nalbuphine regimens have proven efficacy, but adverse event profiles skew toward opioid-

specific effects, making them less ideal in certain populations [19]. Several other drugs are also used to control post-spinal shivering with various results [20–24]. Non-pharmacological strategies such as active warming and fluid tempering reliably decrease lower-grade shivering and may raise core temperature by 0.5°C but lose impact in higher-risk or older populations, with pharmacological counterparts trending superior for moderate to severe episodes [3,25]. Compared to other anti-shivering adjuvants, ketamine offers several advantages, such as pruritus, respiratory depression, nausea, bradycardia, and hypotension risks that can be seen with the above drugs.

The ketamine group also saw a significant reduction, both in terms of severity and duration of shivering episodes. The Mann-Whitney U test showed significantly shorter shivering duration in ketamine group ($U = 913.5$, $Z = -3.149$, $p = 0.001$; $r = -0.315$), where the control group had both higher incidence and longer episode duration (mean rank 57.23 vs 43.77). Grade distribution analysis showed that 90% of ketamine-treated patients experienced no shivering (Grade 0) compared to only 60% in the control group, with no severe (Grade 3-4) shivering events in the ketamine arm. These findings align with recent dexmedetomidine studies for shivering treatment in general anesthesia; however, dexmedetomidine is often associated with bradycardia and hypotension risk [26].

In the post-anesthesia recovery room, shivering occurred in 30% of Group B patients compared to 14% in Group A, suggesting a 62% reduction in odds (OR = 0.38; 95% CI: 0.14–1.04). While this difference showed a trend toward significance (Fisher's exact $p = 0.090$), the medium effect size ($\varphi = 0.193$) indicates clinical relevance despite non-statistical significance. The duration of recovery room shivering was significantly shorter in the ketamine group ($p = 0.021$; $r = -0.231$).

A noteworthy secondary finding was the significant prolongation of postoperative analgesia with intrathecal ketamine. The median time to first analgesic request was extended by 20 minutes in the ketamine-bupivacaine group (145 minutes vs. 125 minutes, $p < 0.001$). The large effect size ($r = 0.61$) underscores both statistical and clinical significance. This finding corroborates ketamine's established role as an analgesic adjuvant through NMDA receptor antagonism, which modulates central sensitization and wind-up phenomena [27–29]. Importantly, this analgesic benefit was achieved without the adverse effects commonly associated with intrathecal opioids, such as pruritus, respiratory depression, or delayed gastric emptying. Analysis of spinal anesthesia block characteristics revealed nuanced differences between groups. Sensory block duration was slightly shorter in the ketamine group (median 110 vs. 120 minutes, $p = 0.049$; $r = -0.197$), representing a small effect size. These findings contrast with some previous reports suggesting prolonged sensory blockade with intrathecal ketamine [30]. However, motor block duration remained equivalent between groups (median 210 minutes in both; $p = 0.545$; $r = -0.061$, negligible effect). This dissociation is clinically advantageous, as it suggests ketamine's anti-shivering and analgesic effects are independent of prolonged motor blockade, thereby facilitating earlier mobilization- a key component of enhanced recovery after cesarean protocols. These findings for motor function were supported by past studies of both ketamine and dexmedetomidine as adjuvants [18,31]. Although others reported a significantly longer duration of motor block [30,32], our findings reinforce the idea that ketamine may exert a favorable effect on analgesia quality without prolonging neural block duration unnecessarily. Intrathecal ketamine did not increase the incidence of postoperative nausea and vomiting (PONV), with rates of 30% nausea and 8% vomiting, compared to 36% and 12% in the bupivacaine-only group, an important distinction versus intrathecal tramadol, which can yield gastrointestinal side effects of about 9% [33]. Neither group displayed clinically significant hemodynamic instability or psychotomimetic events, mitigating key concerns relevant to the introduction of systemic ketamine or strong opioid adjuvants [34-35]. This result was the same as other studies [12,30,36]. The favorable safety profile of ketamine is substantiated by several large clinical series and meta-analyses, positioning it effectively, but with no opioid-related adverse effects [37]. Previous neurotoxicity studies using the intrathecal route have demonstrated spinal cord lesions after ketamine in several animal models but these preservatives seem to be a major culprit for the apparent toxicity [38–40]. Other studies involved the administration of intrathecal ketamine without symptoms of side effects although six other studies indicated some type of adverse reaction. Postmortem case report in which intrathecal infusion of preservative-free ketamine or a mixture of ketamine, clonidine, morphine and bupivacaine secondary to isolated lymphocytic vasculitis of spinal cord/leptomeninges without neurologic deficit [41]. In our study, ketamine with a preservative was used, but the dose used in our study was much lower than in other studies, and several previous studies in Iran have not reported any side effects [12,32]. Maternal satisfaction remained high (94%), with no differences attributable to treatment group, echoing satisfaction data from literature regarding spinal anesthesia with dexmedetomidine or low-dose opioid adjuncts, indicating the acceptability of ketamine in obstetric contexts [42-43]. Mechanistically, ketamine likely works through spinal NMDA inhibition, preventing excessive central sensitization and perhaps blunting distribution hypothermia [9], which is reflected in the odds ratio and Cohen's effect sizes both intraoperatively and in the recovery room. These effects

remain significant after adjusting for age, BMI, comorbidity, and parity. Block characteristics, by contrast, show only small differences, indicating that ketamine's anti-shivering impact is independent of block duration. Because the ketamine used in this trial contained a preservative, it is important to address the potential neurotoxicity associated with preserved intrathecal preparations. Animal studies consistently show that neurotoxic changes attributed to intrathecal ketamine are primarily related to preservatives rather than ketamine itself. Malinovsky et al. [38] demonstrated in rabbits that preservative-containing ketamine caused neuronal and meningeal alterations, whereas preservative-free formulations produced no structural injury. Similar dose- and frequency-dependent pathological changes were reported in swine by Errando et al. [39]. Conversely, Borgbjerg et al. [40] showed that repeated injections of preservative-free ketamine did not cause histopathologic damage, reinforcing the role of preservatives as the main driver of toxicity. Human evidence remains limited but generally reassuring; Stotz et al. [41] described only mild lymphocytic vasculitis after long-term intrathecal infusion of preserved ketamine, with no clinical neurological deficits. Importantly, several clinical studies have safely used preserved intrathecal ketamine at the same 0.1 mg/kg dose as our protocol. Khezri et al. [12,32] administered preserved ketamine 0.1 mg/kg with bupivacaine in parturients undergoing cesarean section and reported improved analgesia without sensory, motor, or sphincter dysfunction during follow-up—findings that align with our results. In our study, preserved ketamine was administered as a single low intrathecal dose (0.1 mg/kg), far below the repeated or high-dose exposures associated with toxicity in animal models. No neurological complications were observed intraoperatively or during the two-month follow-up period. While current evidence supports the short-term safety of low-dose preserved intrathecal ketamine, a theoretical risk remains; therefore, future studies should use preservative-free formulations and include longer-term neurological monitoring. Several limitations warrant consideration. The single-center design may constrain the generalizability of the findings to broader populations and diverse clinical settings. The sample size of 100 participants may be insufficient to detect differences in infrequent adverse events, which limits the precision of safety estimates. Another limitation of our study is that temperature monitoring could not be applied to the parturients. However, all active warming measures were standardized prospectively and applied identically to both groups. Intravenous fluids were consistently pre-warmed to 37°C, and the operating room was maintained at a stable 22-24°C throughout all procedures. The short duration of follow-up (only two months) prevents any meaningful assessment of long-term neurological outcomes. Although a preserved ketamine formulation was used, it was administered at low doses with an established safety profile; nonetheless, its use introduces a potential source of bias. The zero-inflated distribution of shivering outcomes required reliance on non-parametric analytical methods and restricted the ability to perform robust multivariable modeling. In addition, sparse data patterns, with up to 75 percent of cells showing zero frequencies in some models, necessitate cautious interpretation of the resulting regression coefficients.

Conclusion

Intrathecal ketamine (0.1 mg/kg) combined with bupivacaine significantly reduces the incidence and severity of post-spinal shivering during cesarean section compared to bupivacaine alone, with an 83% relative risk reduction in operating room shivering (NNT ≈ 3). Secondary benefits include prolonged postoperative analgesia without increased adverse effects or motor block duration. The intervention demonstrates a favorable safety profile with no neurological complications observed during the 2-month follow-up. These findings support consideration of low-dose intrathecal ketamine as an effective non-opioid adjuvant for shivering prevention in obstetric spinal anesthesia, pending confirmation in larger multicenter trials with extended follow-up.

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