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ORIGINAL RESEARCH

Is Low-Dose Ketamine or Palonosetron Effective in Prophylaxis of Post-Spinal Anaesthesia Shivering in Patients Undergoing Caesarean Section – A Randomized Controlled Trial

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ABSTRACT

Introduction: Incidence of shivering after spinal anaesthesia varies between 20-65%. Shivering causes harm to vulnerable patients.

Objectives: To evaluate whether low dose Ketamine 0.2 mg/kg or Palonosetron 0.075 mg is effective in the prevention of post-spinal anesthesia shivering following caesarean section.

Materials & Methods: In this randomized controlled parallel-arm, double-blinded trial, 105 ASA II patients undergoing caesarean sections were randomly assigned in equal numbers to one of the three groups receiving ketamine 0.2mg/kg (Group 1), palonosetron 0.075 mg (Group 2), and normal saline (Group 3) after administering spinal anesthesia. We recorded the incidence and grade of shivering, hemodynamic changes, tympanic membrane temperatures, and adverse effects

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Results: Incidence of shivering was 8 (22.85%) (Group 1), 10 (28.5%) (Group 2), and 14 (40%) (Group 3), with no statistical significance (p=0.284). There was no difference in shivering grade (p=0.401) or tympanic membrane temperature (p=0.228) across groups. No adverse effect was noted.

Conclusion: Prophylactic administration of either palonosetron 0.075 mg or ketamine 0.2 mg/kg minimises the incidence of post-spinal shivering without any adverse effect.

Keywords: Prevention, pregnancy, spinal anaesthesia, thermoregulation, shivering

INTRODUCTION

Shivering is defined as uncoordinated fasciculation of head, neck and other muscles. Though shivering is not life-threatening emergency, it increases oxygen consumption and carbon dioxide production, putting patients with low cardiorespiratory reserve at risk of decompensation due to a myocardial demand-supply mismatch. It also makes patients uncomfortable, increases surgical site pain, and disrupts electrocardiography, non-invasive blood pressure monitoring, and pulse oximetry, which can threaten safe treatment.[3]

Shivering following spinal anaesthesia occurs as both thermoregulatory response to hypothermia and non-thermoregulatory response to factors like pain, type of surgery, instillation of cold spinal drugs, and unexplained causes.

Prevention of hypothermia requires passive and active warming methods. Prewarming of patients using forced-air warmer[1] for at least 15 min and prewarming of intravenous fluids to 410°C has been shown to reduce the incidence of at least grade 1 shivering. But it precludes emergency caesarian sections and requires a separate warmer, which necessitates major infrastructural changes. A pragmatic approach would be to use pharmacological agents in addition to the intraoperative use of forced-air warmer.

Ketamine is a NMDA (N-methyl-D-aspartate) receptor antagonist, an antimuscarinic, prevents reuptake of norepinephrine, serotonin, and dopamine, and plays a role in thermoregulation at multiple levels.[3] Though placental transfer is rapid, no harm has been demonstrated to the fetus. Although a dosage of 0.25-0.5 mg/kg IV has been used effectively for anti-shivering, they cause a dose-dependent increase in side effects such as sleepiness, hallucinations, and delirium.[4] Therefore, the objective of this research is to determine whether a lower dosage of 0.2 mg/kg ketamine can effectively prevent post-spinal anesthesia shivering in pregnant population without adverse effects.

Palonosetron is a second-generation, highly selective 5HT3 antagonist with greater receptor affinity, a long half-life of 40 hours, and a better safety profile. Limited data is available regarding placental transfer, yet no harmful foetal effect is reported. The recommended dose for the prevention of postoperative nausea and vomiting is a single dose of 0.075mg. A few studies using palonosetron 0.075 mg to prevent shivering have shown conflicting results.[6,7] Therefore, this study examined whether palonosetron at the antiemetic dose of 0.075 mg has an anti-shivering effect in the pregnant population.

We hypothesized that ketamine 0.2 mg/kg or palonosetron 0.075 mg would decrease the

incidence of post-spinal shivering compared with placebo.

METHODOLOGY

This parallel-arm, double-blind, randomized controlled trial was conducted between March 2022 and Jan 2023 at Chettinad Hospital and Research Institute. Sample size was calculated using the Clinicalc sample size calculator with expected proportions of shivering p1 and p2 as 0.70 and 0.36 in the saline and ketamine groups, respectively, as reported by Seyam et al., at a 95% confidence interval and 80% power; the sample size was calculated to be 34 in each group, which was rounded to 35 per group.[8]

After institutional ethics committee approval (IHEC-I/0346/21) and CTRI registration (CTRI/2022/01/039225), we enrolled eligible, consenting ASA grade 2 patients aged 18 to 40 years who presented for elective/emergency cesarean section. Patients with coagulopathy, allergy to study drugs, sepsis, stenotic valve, and infection at the lumbar region were excluded.

Recruited patients were randomly allocated to one of three groups comprising thirty-five patients each: Group 1– Ketamine 0.2 mg/kg, Group 2 – Palonosetron 0.075 mg, Group 3 – Normal Saline. Randomization was done using computer-generated numbers. Allocation concealment was done through opaque sealed envelopes.

Baseline vital parameters were recorded in the preoperative ward. On shifting the patient to the operation theatre, an 18-gauge IV cannula was inserted, co-loading was started, and standard monitors such as noninvasive blood pressure, electrocardiogram, and pulse oximetry were applied and measured every 5 minutes. The tympanic membrane temperature was recorded every ten minutes. Baseline theatre temperature was measured and maintained between 24 - 27°C. Patients were warmed using a forced-air warmer.

Intrathecal injection of 2-2.2ml of 0.5% hyperbaric bupivacaine with 0.2ml (60 mcg) of buprenorphine was administered using a 26G Quincke needle. Sensory block was assessed with a pinprick. Sensory block level of T6 and bromage score of 3 were considered adequate. The anesthetist not involved in the anesthesia care prepared the allotted study drug in a syringe according to the code in the opaque sealed envelope. It was given as a slow IV bolus soon after spinal anaesthesia. The time of administering the drug is taken as time 0. The caring anaesthetist assessed and graded shivering every five minutes according to the scale developed by Crossley and Mahajan.[10] Grade 1 is peripheral vasoconstriction or piloerection, but no obvious shivering; grade 2 is muscular activity in only one muscle group; grade 3 is muscular activity in more than one muscle group but not generalized; grade 4 is shivering involving the whole body. Grade 3/4 shivering that persisted was treated with rescue drugs, pethidine 25 mg. Sedation score was measured using Ramsay sedation score. Adverse effects such as hallucinations were noted.

Data entry was done using Microsoft Excel 2016, and statistical analysis was done using SPSS version 26. Continuous data such as age, weight, height, and BMI between the three groups were reported as mean and standard deviation and analyzed using ANOVA. Categorical data, such as incidence of shivering and maximum grade of shivering in the three groups, were reported as frequencies and analyzed using the chi-square test. Haemodynamic variables

like heart rate, systolic, diastolic, and mean arterial pressure and intraoperative tympanic membrane temperature were analyzed using repeated measures ANOVA both within groups and between groups. P-value less than 0.05 was considered significant.

RESULTS

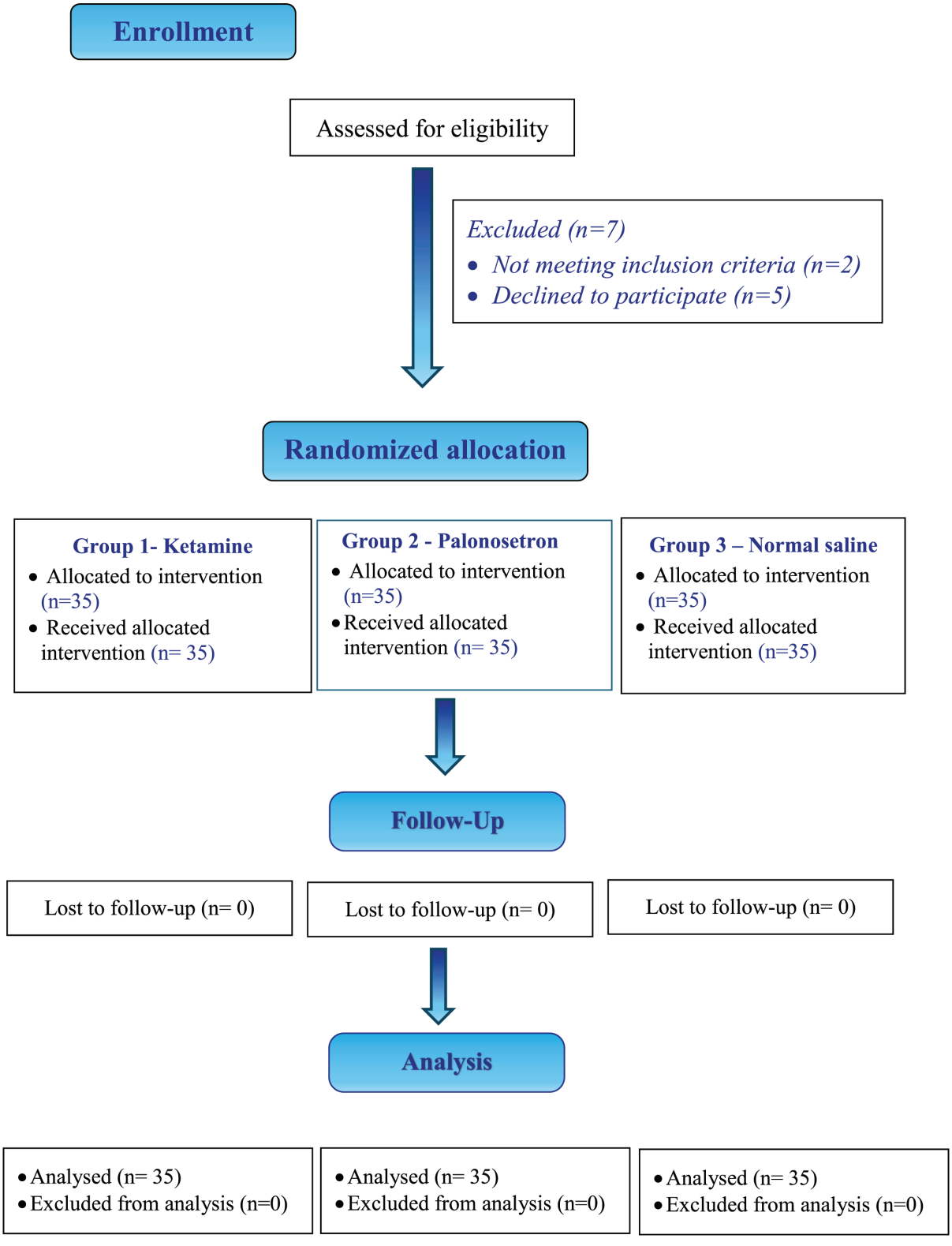


Figure 1: CONSORT Flow Diagram.

The demographic characteristics, ASA physical status, and repeat surgery status were comparable among the three groups (Table 1). The mean age of patients was 26.3±4.1, 27±3.3, and 26.7±3.9 years in the three groups, respectively.

Shivering was present in 8 patients (22.9%) in the ketamine group, 10 patients (28.6%) in the palonosetron group, and 14 patients (40%) in the normal saline group. There was no significant difference between the three groups (p=0.284) (Table 2). The Kruskal-Wallis test showed no significant statistical difference in the highest shivering score among the three groups. (Test statistic 1.829, degrees of freedom 2, p=0.401). Severe shivering (grade 3/4) was seen in 5 (14.3%) patients in the ketamine group, 3 (8.6%) patients in the palonosetron group, and 5 (14.3%) patients in the saline group (Table 2). Rescue drug pethidine 25 mg IV was administered to five patients each in groups 1 and 3 and three patients in group 2.

Table 1: Comparison of demographic data of the three groups

	Group - 1 Ketamine	Group - 2 Palonosetron	Group - 3 Normal saline	*p*-value
Age (yrs.) (mean±SD)	26.34±4.137	27.00±3.343	26.74±3.967	0.787
Weight (kg) (mean±SD)	71.17±9.676	72.97±9.080	74.71± 9.177	0.286
Height (meters) (mean±SD)	1.605±0.0729	1.631±0.0782	1.627±0.0761	0.309
BMI (kg/m^2) (mean±SD)	27.17±4.141	26.97±3.519	27.91±3.935	0.577
Previous LSCS (n; %)	21 (60%)	21 (60%)	19 (54.3%)	0.855
ASA status 2 (n; %)	35 (100%)	35 (100%)	35 (100%)	> 0.05

Calculated using one-way ANOVA; SD-Standard Deviation

Table 2: Comparison of grades of shivering

Grade of shivering	Group - 1 (Ketamine 0.2mg/kg)	Group - 2 (Palonosetron 0.075mg)	Group - 3 (Normal Saline)	*p*-value
Grade 0	26	25	22	Kruskal-Wallis Test statistic 1.827, degrees of freedom 2, p=0.401
Grade 1	0	4	3	
Grade 2	4	3	5	

(Continued)

Grade of shivering	Group - 1 (Ketamine 0.2mg/kg)	Group - 2 (Palonosetron 0.075mg)	Group - 3 (Normal Saline)	*p*-value
Grade 3	3	3	4	
Grade 4	2	0	1	
Shivering present (n; %)	8 (22.9%)	10 (28.6%)	14(40%)	Chi-square test Pearson Chi square is 2.517, degrees of freedom 2, p=0.284

A repeated-measures ANOVA showed a significant difference in intraoperative tympanic membrane temperature over time (p=0.01). However, the temperature change was less than 0.5°C and was not clinically significant. There was no significant difference in the temperature over time between the three groups (F statistic 1.498, p=.0.228) (Figure 2).

Though there was a significant difference in the trend in diastolic, systolic, and mean blood pressure over time (F statistic is 28.212; degrees of freedom are 2.9; p<0.001), there was no significant difference in the hemodynamic data between the three groups (p>0.05) (Figure 3). Perioperative saturation using pulseoximetry was between 98-100% in all patients. The modified Ramsay sedation score was less than 2 in all patients. None had a score higher than 3. No adverse effects of hallucination were noted in any of the groups.

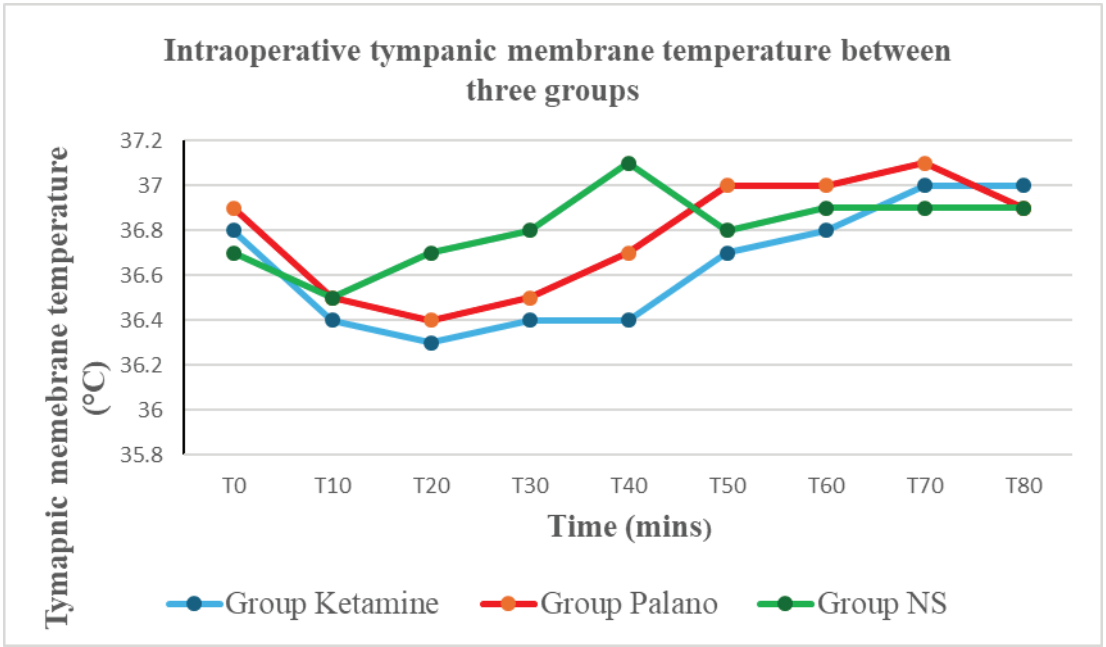


Figure 2: Trends in intraoperative tympanic membrane temperature.

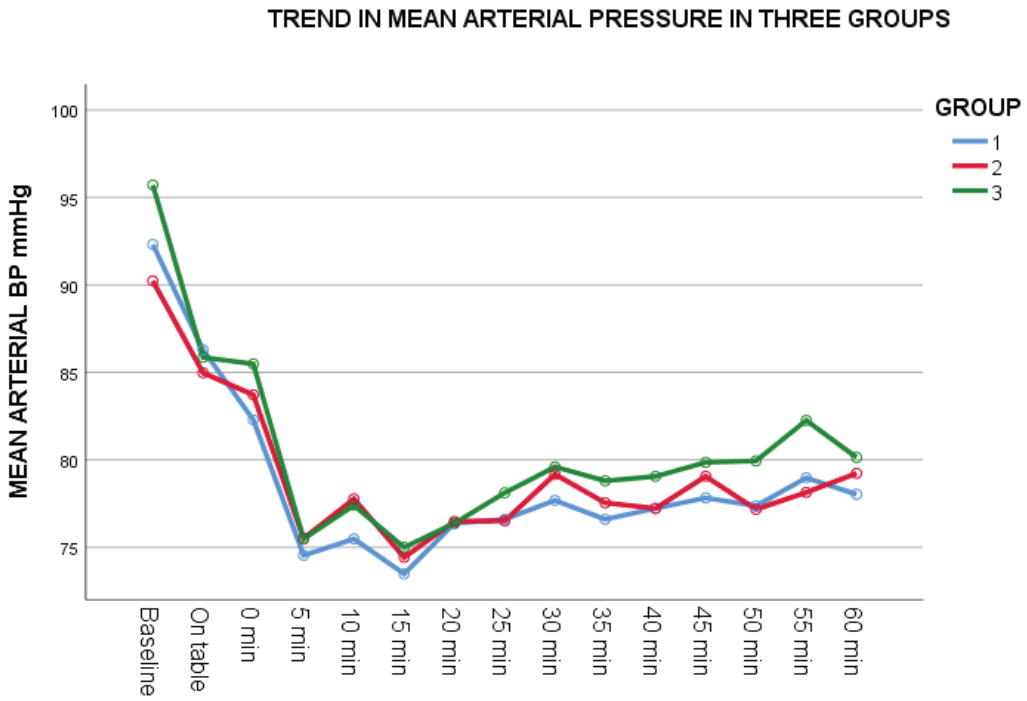


Figure 3: Trends in mean arterial pressure.

DISCUSSION

In this study, shivering occurred in 22.85% of the low-dose ketamine group and 28.5% of the palonosetron group (p=0.28). The incidence of shivering in the placebo group in our study is 40%, within the range reported in the literature (21% to 62.5%)[11,12]. Tympanic membrane temperature did not change clinically or statistically significantly.

Among 5HT3 antagonists, ondansetron at 8 mg has been proven to reduce the incidence of shivering, as shown by the meta-analysis by He et al. (relative risk [RR]: 0.33 vs placebo, 95% confidence interval [CI]: 0.19–0.58, p=0.0001).[13] Though Browning et al. found it ineffective in cesarean patients[14], many later studies have shown ondansetron to be effective.[6,7] When palonosetron was introduced because of its advantages of greater affinity for receptor and longer half-life, it was studied by Jo et al. in general anaesthesia in gynecological laparoscopic patients in 2013 which did not find palonosetron useful 26.6% vs 33.3%[6], contrary to the study by Sharma et al (2021) in caesarian section patients under spinal with incidence of shivering in palonosetron vs ondansetron group 9.5% vs 23.8% p=0.07.[7] As they did not perform active warming, unlike our study, the palonosetron effect may have been amplified, supporting our findings.

Our study reported a 25.7% incidence of shivering in the ketamine group. Lema et al. showed an incidence of shivering in LSCS as 41.5% compared to placebo group 70.1% p-0.028.[9] They also used ketamine 0.2 mg/kg. A higher incidence despite prophylactic use of ketamine could be because they did not use the forced-air warmer. In our study, the ketamine group showed grade 3/4 shivering in 14.3% of patients, similar to that in the saline group. The higher proportion of grade 3/4 shivering in the ketamine group may be because 0.2mg/kg was less effective at preventing severe shivering.

However, Watson et al. contradict this, finding lower grade 3 shivering with ketamine 0.5mg/kg than with control (10% vs 54%, p=0.001). Whether the low dose explains this needs verification in larger studies. Yet Lakhe et al. reported higher odds of shivering with placebo compared to ketamine at 0.25mg/kg (OR 11.76, 10% vs 56.7%, p=0.000),[16] as concurred by Fenta et al. in his meta-analysis[17], but both reported higher relative risk of hallucination with ketamine compared to tramadol. Even Zhou et al. reported the odds of hallucinations of 0.25mg/kg of ketamine as OR 0.08 (95% CI: 0.03 to 0.18) versus 0.5 mg/kg.[18] Our study showed 0.2 mg/kg ketamine to be effective without any report of hallucinations.

Our findings concur with Lema et al., who reported shivering in 41.5% vs 70.1% in the ketamine 0.2mg/kg versus the saline groups, respectively, p=0.028.[9] Higher incidence was likely driven by the use of drapes only and no forced warm air, unlike our study. Jouryabi et al. also did not show a statistically significant lower incidence of shivering (53.5% vs 64.6%) in the ketamine 0.2 mg/kg vs saline group, which is also not clinically significant.[19]

In light of the above studies, our study results are significant but require a larger sample size to confirm them statistically.

CONCLUSION

The present study supports the preventive effect of ketamine 0.2 mg/kg or palonosetron 0.075 mg/ kg administered intravenously soon after spinal anaesthesia, in minimising post-spinal anaesthesia shivering. Ketamine at the low dose used has the added advantage of avoiding adverse effects like hallucinations. Larger studies are needed to establish statistical significance, as we also used active warming methods.

LIMITATIONS

The small sample size limited the study's power to detect statistically significant improvement in shivering episodes in the treatment groups.

As shivering is commonly attributed to hypothermia, continuous monitoring of both core and skin temperature would have provided more information on distributive heat loss during shivering. We had two subsets of patients for cesarean section, emergency and elective, and their anxiety and pain levels would have been different, which we did not assess preoperatively, and this could have led to an interaction effect.

Further studies with a larger sample size with assessment of preoperative anxiety levels and different doses of ketamine are needed to establish the true effectiveness and the minimum required dose.

AUTHORS' CONTRIBUTIONS

Conceptualization and design: COD, MSRS

Literature search: COD, MSRS, PSR

Data collection: COD, MSRS

Data analysis: MSRS

Manuscript drafting and critical revision: COD, MSRS, PSR

Proofreading and approval of the manuscript: COD, MSRS, PSR

FUNDING

No external funding was received to prepare the manuscript.

DECLARATION OF CONFLICTS OF INTEREST

There are no conflicts of interest to declare.

ETHICAL CLEARANCE

Approved by the Institutional Ethics Committee of Chettinad Hospital and Research Institute, Kelambakkam, Tamil Nadu, India (No: IHEC-I/0346/21); Approval date: December 1, 2021.

The study was registered with the Clinical Trials Registry – India.

(CTRI No: CTRI/2022/01/039225)

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