RESEARCH

Comparison Between Ketamine and Paracetamol in The Prevention of Post-Spinal Anesthesia Shivering in Caesarean Section Procedures

Candra Ristiana✉, Himawan Sasongko, Yulia Wahyu Villyastuti

Department of Anesthesiology and Intensive Care, Faculty of Medicine, Universitas Diponegoro/ Dr. Kariadi General Hospital, Semarang, Indonesia

✉Correspondence: candraristianadr@mail.com

ABSTRACT

Background: Shivering is a common complication associated with spinal anesthesia during cesarean sections, leading to discomfort and potential cardiac ischemia. While intravenous paracetamol is known to prevent shivering, it has potential peripheral limitations and may be costly. Conversely, ketamine administration inhibits norepinephrine reuptake, potentially reducing heat redistribution and serving as a more affordable alternative.

Objective: Assessing the comparison of ketamine and paracetamol on the incidence, onset, and degree of post-spinal anaesthesia shivering in caesarean section procedures.

Methods: An experimental design was employed with a sample size of 52 patients, divided into two groups: one receiving intravenous ketamine (0.25 mg/kg) alongside intrathecal bupivacaine (15 mg), and the other receiving intravenous paracetamol (1000 mg) with intrathecal bupivacaine (15 mg). The incidence, onset, and degree of shivering were observed and recorded every 3 minutes for 90 minutes.

Results: The incidence of shivering in the ketamine group was 3 samples while in the paracetamol group there were 10 samples. The mean time of onset of shivering in the ketamine group was 55.00 minutes, and in the paracetamol group was 27.30 minutes ($p<0.05$). While the degree of shivering in the ketamine group was 1 sample of degree 1 and 2 samples of degree 2, the paracetamol group was 4 samples of degree 2, 3 samples of degree 3 and 3 samples of degree 4 ($p<0.05$).

Conclusion: Ketamine proved to be more effective in preventing shivering than paracetamol after spinal anesthesia in caesarean section procedures.

Keywords: caesarean section; ketamin, paracetamol; shivering; spinal anesthesia

INTRODUCTION

Spinal anaesthesia is a type of neuroaxial anaesthesia that is widely used for abdominal and lower limb surgical procedures such as caesarean section. 18.5 million pregnancy cases worldwide each year that undergo caesarean section, most are performed using spinal anaesthesia due to its ease of administration technique, high success rate, and low fetomaternal morbidity and mortality when compared to general anaesthesia.[1]

Shivering is one of the most common complications of spinal anesthesia during cesarean sections, with an incidence as high as 50–60%. It is primarily caused by peripheral vasodilation, which promotes rapid heat loss and redistributes body heat from the core to the periphery, leading to hypothermia and subsequent shivering.[2,3] This condition not only causes discomfort, dissatisfaction, and anxiety in patients but also has significant physiological consequences.[4] Shivering is characterized by spontaneous and repetitive involuntary contractions of skeletal muscles that can increase oxygen consumption by up to 400%, elevate carbon dioxide production, and contribute to lactic acidosis. Additionally, shivering can impair wound healing, heighten the risk of bleeding, and potentially trigger cardiac rhythm disturbances and ischemia.[3] Given these adverse effects, it is crucial to take preventive measures to manage and mitigate shivering effectively.

Non-pharmacalogical management such as the use of blankets, warm liquids, and increased operating room temperature have been used to prevent and manage perioperative shivering. However, these measures may be insufficient in cases where the patient's body temperature drops significantly. Furthermore, non-pharmacological approaches are often less effective when shivering is caused by mechanisms unrelated to body temperature regulation. In such situations, pharmacological interventions become necessary to effectively control shivering and ensure patient comfort.[3]

Ketamine is an anti-shivering agent believed to act by directly stimulating the spinal sympathetic nervous system and inhibiting norepinephrine reuptake at post-ganglionic synapses. This mechanism helps suppress the redistribution of heat from the central to the peripheral regions. While high doses of ketamine can cause side effects such as hallucinations, it offers several advantages, including a stable hemodynamic profile, widespread availability, ease of access, and affordability.[5] Sunyoto and Abubakar (2012) showed that that ketamine was more effective than pethidine in controlling shivering during cesarean sections performed under spinal anesthesia.[6] A study by Budiono (2015) demonstrated that ketamine, meperidine, and clonidine were equally effective in preventing shivering after cesarean sections performed under spinal anesthesia.[7] Similarly, research by Eydi et al. (2014) found that ketamine and pethidine were equally effective in managing post-surgical shivering following general anesthesia.[8] These findings are notable given that pethidine is widely considered the gold standard agent for perioperative shivering management.

Paracetamol is a commonly used, safe medication for managing mild to moderate pain with a more favorable adverse-effect profile than opioids. Its

anti-shivering effect is believed to stem from its ability to reduce central prostaglandin synthesis, lowering the hypothalamic temperature set point and shivering threshold. Previous study by Esmat et al. (2021) found that paracetamol significantly reduced post-spinal anesthesia shivering in patients undergoing lower abdominal and limb surgeries, with higher patient satisfaction reported.[9] Similarly, Khalili et al. (2014) showed that paracetamol effectively reduced both shivering and pain after general anesthesia compared to a control group.[10] However, unlike pethidine, paracetamol is not regarded as the gold standard for shivering management but is instead used clinically as a non-opioid alternative supported by existing evidence.

Until now, there are no guidelines regarding the use of the most effective drug in preventing shivering after anaesthesia, particularly spinal anaesthesia. Recognizing this gap, the author saw the need to conduct a comparative study to identify the most effective anti-shivering agent with minimal side effects. This research focuses on comparing the effectiveness of ketamine and paracetamol in preventing shivering in patients undergoing cesarean sections with spinal anesthesia.

METHOD

This study is an experimental research with a comparative analytical test conducted on two unpaired, non-blinded groups to compare the effectiveness of ketamine versus paracetamol in preventing post-spinal anesthesia shivering during cesarean section procedures at Dr. Kariadi General Hospital, Semarang, from October to December 2023. the study included patients aged 18–45 years with ASA I–II physical status, a normal pregnancy BMI (25–29.9 kg/m²), no fetal distress, and no contraindications for spinal anesthesia. Patients also needed to consent to participate. Those with drug allergies or who declined participation were excluded. The sampling technique used was the consecutive sampling method.

Initial data collection involved medical history and records, including age, sex, weight, height, ASA status, and medical history. randomly assigned to two groups: the ketamine group (Group K), receiving intravenous ketamine at 0.25 mg/kg body weight, and the paracetamol group (Group P), receiving 1000 mg of intravenous paracetamol. Spinal anesthesia was administered at the L3-4 vertebrae in a sitting position, using 15 mg of 0.5% hyperbaric bupivacaine injected intrathecally. Patients were then positioned supine with a pillow and given 3 liters per minute of nasal oxygen during surgery. Vital signs, including blood pressure, heart rate, temperature, respiratory rate, and oxygen saturation, were recorded before and during the procedure. Shivering incidence, severity (using a standardized grading scale), and adverse effects were assessed every 3 minutes for 90 minutes by trained observers under identical perioperative conditions in both groups to minimize assessment bias. Rescue pethidine was provided for grade 3 or 4 shivering. After surgery, patients were monitored in the recovery room for blood pressure, temperature, pulse, and oxygen saturation. Data were analyzed using univariate and bivariate methods. Normally distributed data were analyzed with t-tests, while non-normally distributed data were analyzed with Mann-Whitney tests.

RESULTS

A total of 52 patients meeting the inclusion criteria were included in this study. After providing informed consent, patient data, including age, gestational age, weight, height, BMI, and initial vital signs, were recorded (Table 1). Normality testing showed that age and pre-anesthetic vital signs except temperature were normally distributed, analyzed with independent t-tests, while other parameters were analyzed with Mann-Whitney tests. No significant differences between the ketamine and paracetamol groups confirmed the groups were homogeneous and comparable.

Shivering incidence and onset were monitored for 90 minutes. In the ketamine group, shivering occurred at 45 and 60 minutes in three samples, whereas in the paracetamol group, it occurred earlier at 21, 30, and 33 minutes in 10 samples with significant differences in incidence and onset times ($p < 0.05$). (Tables 2 and 3) Rescue pethidine was administered only in the paracetamol group for patients with grade 3 or 4 shivering, occurring in 6 samples at 21, 27, and 30 minutes. Side effects, including nausea and vomiting, were observed during the procedure. No significant difference between the groups ($p > 0.05$), with nausea and vomiting occurring in 7 of 26 samples in the ketamine group and 6 of 26 in the paracetamol group (Table 4).

Hemodynamic parameters including mean arterial pressure (MAP), revealed significant differences at 30 and 33 minutes ($p < 0.05$), with the lowest MAP recorded at 21 minutes in both groups (Figure 1). Heart rate differed significantly at 12, 15, and 18 minutes ($p < 0.05$), with the paracetamol group showing elevated rates at 12 and 15 minutes but normalizing later (Figure 2). Body temperature also differed significantly at 21, 30, and 33 minutes ($p < 0.05$), with the lowest temperatures at 21 minutes in the paracetamol group (35.35°C) and 18 minutes in the ketamine group (35.96°C) (Figure 3). Respiratory rate remained within the normal range with no significant differences (Figure 4), while oxygen saturation differed significantly at several time points but stayed within normal limits for all patients (Figure 5).

Secondary outcome APGAR scores showed no significant differences between groups ($p > 0.05$). The lowest APGAR scores, though within the normal range, were observed at one minute, averaging 8.80 ± 0.49 in the paracetamol group and 9.03 ± 0.44 in the ketamine group.

Table 1. Patient characteristics

Characteristics	Ketamine Group (n=26)	Paracetamol Group (n=26)	p-value
Patient age (years)	30.81 ± 3.86	31.27 ± 3.43	0.651§
Gestational age (weeks)	38.50 ± 0.86	38.00 ± 1.20	0.151‡
Body weight (kg)	71.57 ± 5.70	71.19 ± 5.32	0.885‡
Height (m)	1.57 ± 0.88	1.55 ± 0.70	0.709‡
Body mass index (BMI) (kg/m²)	29.01 ± 3.86	29.21 ± 3.74	0.560‡
TTV Pre-anestesi			
Systolic Blood Pressure (SBP, mmHg)	126.11 ± 13.7	123.84 ± 9.80	0.494§
Diastolic Blood Pressure (DBP, mmHg)	65.27 ± 6.93	61.53 ± 7.03	0.060§
Mean Arterial Pressure (MAP, mmHg)	85.50 ± 8.46	82.30 ± 6.61	0.130§
Heart Rate (beats/min)	77.11 ± 12.1	74.96 ± 10.1	0.490§
Temperature (°C)	36.73 ± 0.45	36.88 ± 0.32	0.163‡

Note: §, Independent t-test; ‡ Mann-Whitney U test

Table 2. Test of difference in the incidence of shivering in the two groups

Group	Shivering		No Shivering		
	n	%	n	%	p-value
Ketamine	3	11.53	23	88.47	0.025*
Paracetamol	10	38.46	16	61.54	

Note: *Significant ($p < 0.05$)

Table 3. Test of difference on the time to onset of shivering in the two groups

Groups	N	Mean ± SD	Median (min-max)	Normality	p-value
Ketamine	3	55.00 ± 8.67	60 (45 – 60)	0.000	0.009‡*
Paracetamol	10	27.30 ± 5.56	30 (21 – 33)	0.004	

Table 4. Test of difference of side effects (nausea and vomiting) in two groups

Group	Side Effects				p-value
	Yes		No		
	N	%	n	%	
Ketamine	7	53.8	19	48.7	1.000^
Paracetamol	6	46.2	20	51.3	

Note: ^, Chi-Square test; *Significant ($p < 0.05$)

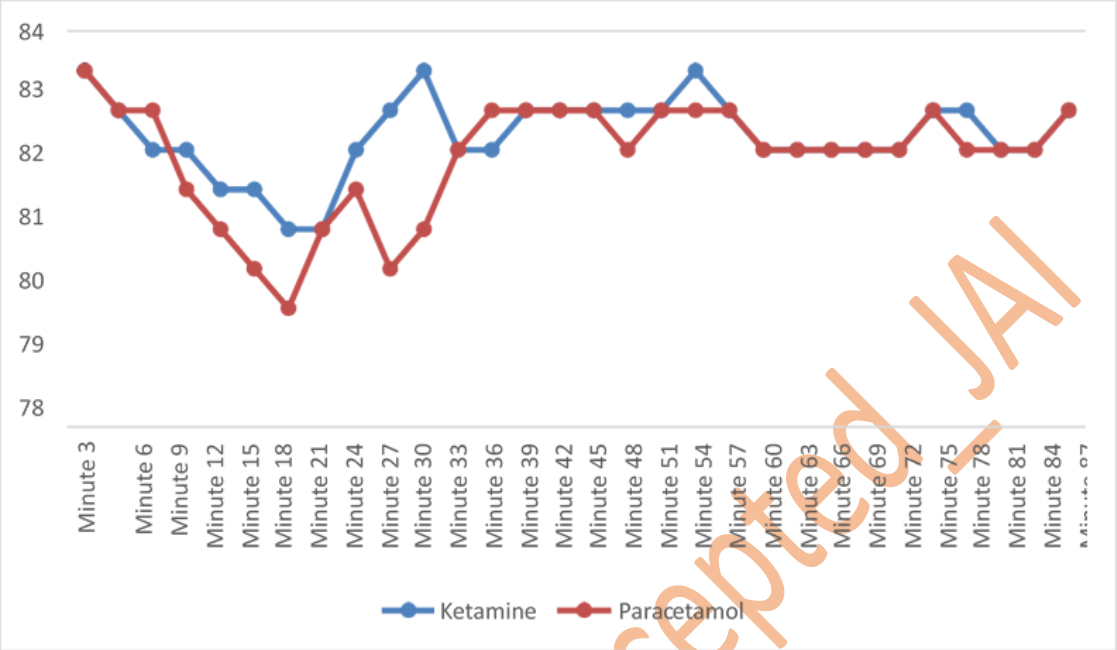

Figure 1. MAP graphic in the two groups

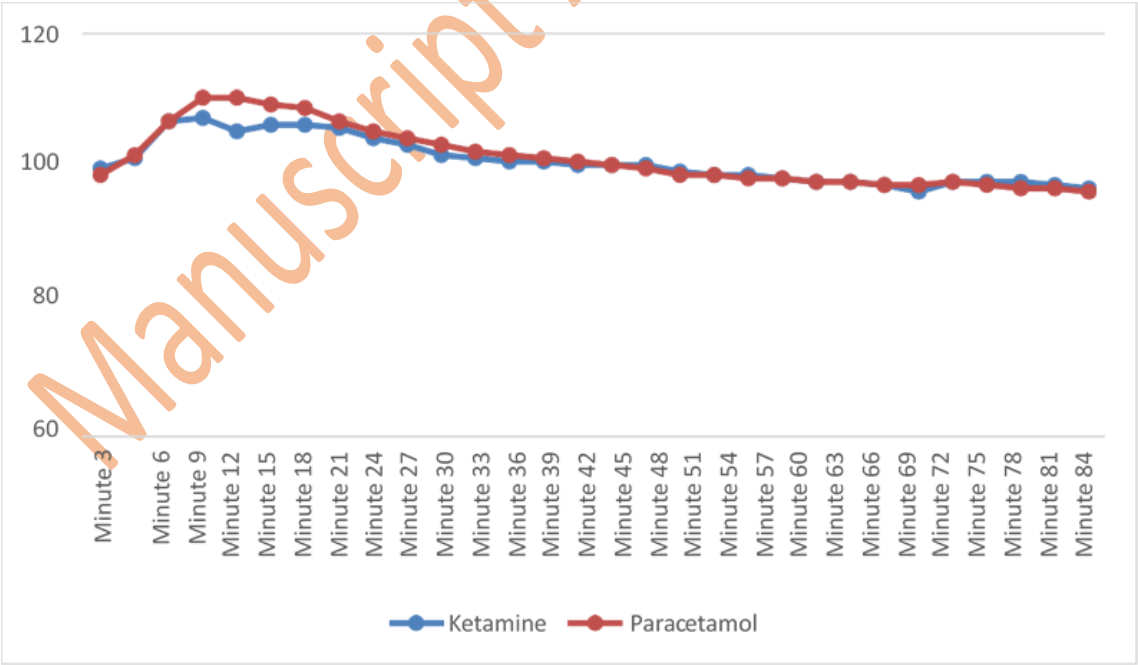

Figure 2. Heart rate graphic in the two groups

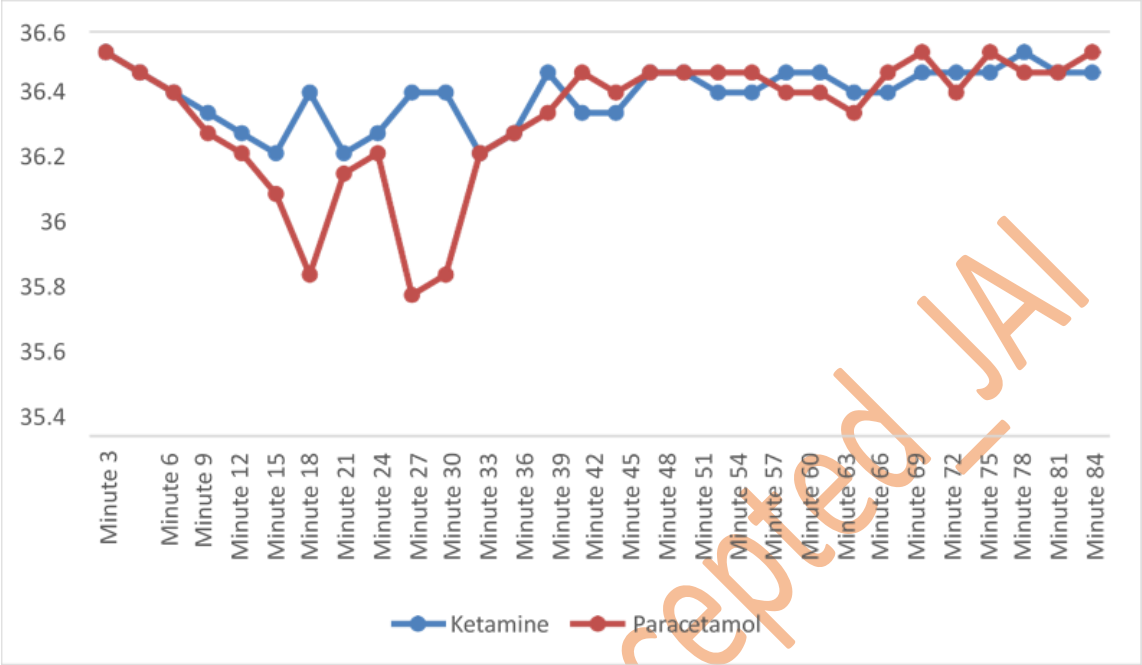

Figure 3. Body temperature graphic in the two groups

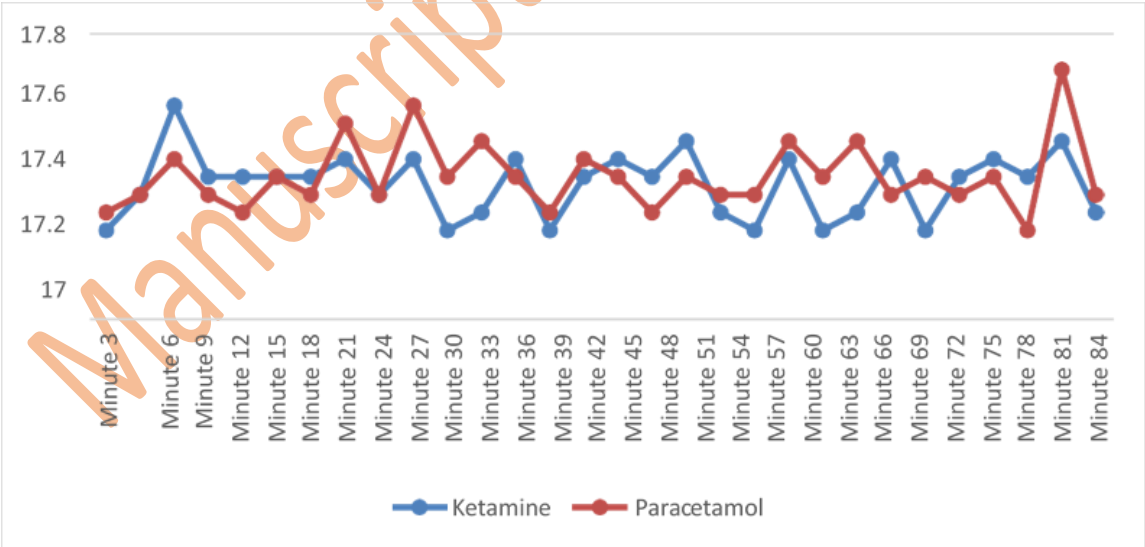

Figure 4. Respiratory rate graphic in the two groups

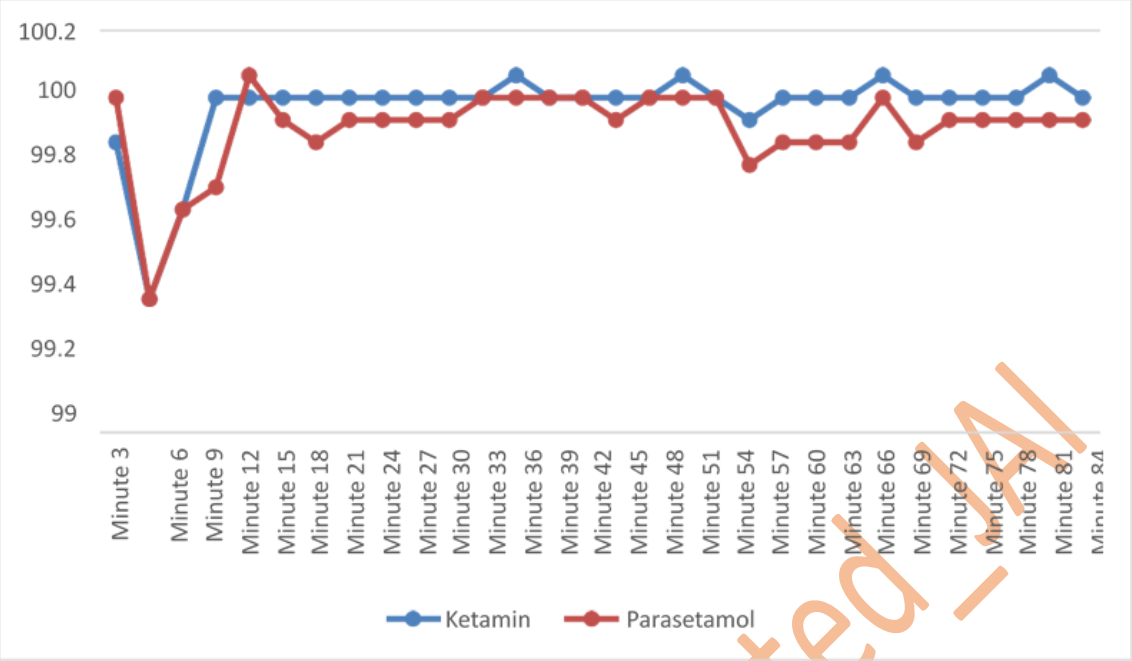

Figure 5. Oxygen saturation graphic in the two groups

DISCUSSION

This study revealed a significant difference in the incidence of shivering between the ketamine and paracetamol groups ($p < 0.05$). The percentage of shivering was 11.5% in the ketamine group and 38.5% in the paracetamol group. Both percentages were lower than the global incidence of shivering reported in previous studies, which was 52.5%. Shivering in the paracetamol group coincided with fluctuations in hemodynamic status, particularly lower body temperatures at specific time points compared to other intervals. This finding aligns with research by Sadeh et al. (2020) and Shakya et al. (2010), which noted that shivering often occurs during decreases in mean arterial pressure, pulse rate, and body temperature, even when the temperature remains within normal limits.[11,12] These hemodynamic changes may result from spinal anesthesia agents, as observed by Helmi (2010), who noted that mean arterial pressure and pulse rate were generally lower within the first 20 minutes after administration of hyperbaric bupivacaine.[13]

In the ketamine group, shivering occurred later, at 45 and 60 minutes, likely due to ketamine's ability to stabilize blood pressure, pulse rate, and systemic vascular resistance, as well as to prevent heat redistribution and temperature drops during the early postoperative period. The hemodynamic stabilization effect of ketamine peaks approximately two minutes after injection and lasts for 15–20 minutes, although individual responses may vary.[14] These findings suggest that ketamine is more effective in preventing shivering than paracetamol.

Ketamine, a competitive N-methyl-D-aspartate (NMDA) receptor antagonist and opioid agonist, has thermoregulatory effects. It is commonly used for short-term procedural sedation and rapid sequence intubation and is considered safe for a wide range of ages.[5,15] Previous studies suggest ketamine prevents shivering through non-shivering thermogenesis, likely mediated by its effects on the hypothalamus and the

beta-adrenergic effects of norepinephrine.[12] Despite its benefits, no consensus exists on its suitability for shivering prevention, emphasizing the need for evidence-based guidelines to optimize its use. This study aligns with a meta-analysis by Zhou et al. (2019), which showed ketamine was more effective than placebo in reducing shivering. When compared to tramadol, ketamine was still more effective, albeit without a significant difference between the two.[5] Shakya et al. (2010) also reported that ketamine at a dose of 0.25 mg/kg body weight minimized side effects and was more effective than ondansetron, with a shivering incidence 4.33 times higher in the ondansetron group compared to the ketamine group.[12]

Paracetamol, a mild to moderate analgesic with antipyretic effects, primarily acts by inhibiting prostaglandin synthesis, which lowers the hypothalamic set point temperature. Kinjo et al. (2020) suggested that paracetamol prevents shivering by suppressing the rise in the core temperature set point rather than reducing the shivering threshold. Its onset of action is rapid (15–20 minutes), and its effect lasts about four hours. Unlike opioids, paracetamol does not cause sedation, respiratory depression, constipation, or vomiting. Wahdan et al. (2023) found no significant difference between paracetamol and ondansetron in shivering prevention, whereas other studies reported ketamine as more effective than ondansetron. This could explain why shivering occurs earlier in patients receiving paracetamol compared to ketamine.[16,17] Another hypothesis is that the peak hypothermic effect of paracetamol occurs around 120 minutes after administration. Since paracetamol was given at the start of the surgery in this study, its hypothermic effects may have coincided with those induced by the operating room environment and spinal anesthesia, contributing to the higher incidence of shivering.[18]

Nausea and vomiting were observed in both groups during surgery. Although the ketamine group had a slightly higher incidence, the difference was not statistically significant ($p > 0.05$). These side effects were likely triggered by changes in hemodynamic status, the administration of rescue pethidine, and ketamine's known effects. Among the paracetamol group, six patients who experienced nausea and vomiting had also received rescue pethidine. In the ketamine group, three cases were linked to rescue pethidine, while four were attributed to ketamine's effects. This finding is consistent with Zhou et al. (2019), which reported nausea and vomiting in ketamine and placebo groups at similar rates.[5] Ketamine is associated with potential side effects such as emergence reactions, including hallucinations, nightmares, delirium, agitation, and mood changes.[5,19] These effects are linked to glutamatergic signaling and are dose-dependent. However, no hallucinations were reported in this study, likely due to the low dose of 0.25 mg/kg body weight.

Hemodynamic monitoring included mean arterial pressure (MAP), heart rate (HR), respiratory rate (RR), body temperature, and oxygen saturation. Both groups maintained values within normal ranges, though significant differences were observed at specific time points. The ketamine group showed greater stability in MAP, HR, and body temperature compared to the more fluctuating values in the paracetamol group. These results are consistent with Liebe et al. (2017), which demonstrated that sub-anesthetic doses of ketamine

stabilized cardiovascular responses, increasing MAP by an average of 13 mmHg for up to 60 minutes.[20] Similarly, studies by Shakya et al. (2010) and Pratama et al. (2020) noted ketamine's ability to minimize changes in blood pressure and heart rate due to its indirect effects on the sympathetic nervous system and vasoconstrictive properties.[12,19] In terms of temperature regulation, the ketamine group maintained more stable body temperatures, with significant differences at 21, 30, and 33 minutes compared to the paracetamol group. These findings align with Shakya et al. (2010), which reported less temperature decline in ketamine-treated patients, likely due to its vasoconstrictive effects and central modulation of thermoregulation.[12]

No significant differences in neonatal outcomes were observed between the two groups ($p > 0.05$). The mean APGAR scores were above 8.5 at one minute and above 9 at five and ten minutes, with no infants requiring resuscitation or experiencing complications. These findings align with Behdad et al. (2013), which reported no adverse neonatal outcomes following ketamine use and highlighted ketamine's safety during spinal anesthesia for cesarean sections. Ketamine's ability to maintain maternal blood pressure and uterine blood flow may improve uterine perfusion, benefiting neonatal outcomes.[15,18,21]

This study had several limitations. Shivering was monitored for only 90 minutes after spinal anesthesia, whereas other studies indicate shivering may persist for up to 10 hours post-procedure. Additionally, the assessment of shivering was subjective, with no objective measurement tools used, potentially introducing variability in evaluations.

CONCLUSION

This study found that ketamine (0.25 mg/kg body weight) was more effective than paracetamol (1000 mg) in preventing post-spinal anesthesia shivering during cesarean sections. Longer monitoring of shivering is advised, as some studies suggest shivering may persist up to 10 hours post-procedure. Further research comparing the incidence, onset, and severity of shivering between ketamine and paracetamol under general anesthesia is also recommended.

REFERENCES

1. Zhang YW, Zhang J, Hu JQ, Wen CL, Dai SY, Yang DF, et al. Neuraxial adjuvants for prevention of perioperative shivering during cesarean section: A network meta-analysis following the PRISMA guidelines. World J Clin Cases. 2019 Aug 26;7(16):2287–301. doi:10.12998/wjcc.v7.i16.2287 PubMed PMID: 31531322; PubMed Central PMCID: PMC6718794.
2. Ferede YA, Aytolign HA, Mersha AT. "The magnitude and associated factors of intraoperative shivering after cesarean section delivery under Spinal anesthesia": A cross sectional study. Ann Med Surg (Lond). 2021 Dec;72:103022. doi:10.1016/j.amsu.2021.103022 PubMed PMID: 34820120; PubMed Central PMCID: PMC8599996.
3. Amsalu H, Zemedkun A, Regasa T, Adamu Y. Evidence-Based Guideline on Prevention and Management of Shivering After Spinal Anesthesia in Resource-Limited Settings: Review Article. IJGM. 2022 Sep 5;15:6985–98. doi:10.2147/IJGM.S370439

4. Lopez MB. Postanaesthetic shivering – from pathophysiology to prevention. Rom J Anaesth Intensive Care. 2018 Apr;25(1):73–81. doi:10.21454/rjaic.7518.251.xum PubMed PMID: 29756066; PubMed Central PMCID: PMC5931188.
5. Zhou Y, Mannan A, Han Y, Liu H, Guan HL, Gao X, et al. Efficacy and safety of prophylactic use of ketamine for prevention of postanesthetic shivering: a systematic review and meta analysis. BMC Anesthesiology. 2019 Dec 30;19(1):245. doi:10.1186/s12871-019-0910-8
6. Sunyoto AE. Perbandingan Respon Rate Ketamin 0,25 mg/KgBB IV dengan Pethidin 25 mg IV untuk Mengatasi Shivering pada Seksio Sesaria dengan Anestesi Spinal [Internet]. Universitas Gadjah Mada; 2012 [cited 2024 Dec 4]. Available from: https://etd.repository.ugm.ac.id/penelitian/detail/54725
7. Budiono U. Meperidin, Ketamin dan Klonidin Efektif Untuk Terapi Menggigil pada Sectio Secaria dengan Anestesi Spinal. JAI (Jurnal Anestesiologi Indonesia). 2015 Jul 1;7(2):120–32. doi:10.14710/jai.v7i2.9825
8. Eydi M, Golzari SE, Aghamohammadi D, Kolahdouzan K, Safari S, Ostadi Z. Postoperative Management of Shivering: A Comparison of Pethidine vs. Ketamine. Anesth Pain Med. 2014 Mar 14;4(2):e15499. doi:10.5812/aapm.15499 PubMed PMID: 24829883; PubMed Central PMCID: PMC4013503.
9. Esmat IM, Mohamed MM, Abdelaal WA, El-Hariri HM, Ashoor TM. Postspinal anesthesia shivering in lower abdominal and lower limb surgeries: a randomized controlled comparison between paracetamol and dexamethasone. BMC Anesthesiol. 2021 Oct 30;21(1):262. doi:10.1186/s12871-021-01483-7 PubMed PMID: 34717535; PubMed Central PMCID: PMC8556952.
10. Khalili G, Sajedi P, Alinaghian A. The effect of intravenous infusion of paracetamol before anesthesia induction on the core and peripheral temperature changes and post-operative shivering in patients undergoing general anesthesia. Adv Biomed Res. 2014;3:89. doi:10.4103/2277-9175.128468 PubMed PMID: 24761397; PubMed Central PMCID: PMC3988594.
11. Samimi Sadeh S, Hashemi E, Aminnejad R, Bastanhagh E. The Impact of Optimal Dose of Ketamine on Shivering Following Elective Abdominal Hysterectomy: A Randomised Comparative Study. Anesth Pain Med. 2020 Oct 20;10(5):e106220. doi:10.5812/aapm.106220 PubMed PMID: 34150566; PubMed Central PMCID: PMC8207838.
12. Shakya B, Chaturvedi A, Sah BP. Prophylactic Low Dose Ketamine and Ondansetron for Prevention of Shivering During Spinal Anaesthesia. J Anaesthesiol Clin Pharmacol. 2010;26(4):465–9. PubMed PMID: 21547171; PubMed Central PMCID: PMC3087257.

13. Helmi M. Perbandingan onset dan durasi bupivakain 0,5 persen isobarik 20 mg dan bupivakain 0,5 persen hiperbarik 20 mg pada subarachnoid block [Internet]. Universitas Gadjah Mada; 2010 [cited 2024 Feb 11]. Available from: https://etd.repository.ugm.ac.id/home/detail_pencarian/46185
14. Thangavelu R, George SK, Kandasamy R. Prophylactic low dose ketamine infusion for prevention of shivering during spinal anesthesia: A randomized double blind clinical trial. J Anaesthesiol Clin Pharmacol. 2020;36(4):506–10. doi:10.4103/joacp.JOACP_201_19 PubMed PMID: 33840932; PubMed Central PMCID: PMC8022048.
15. Rosenbaum SB, Gupta V, Patel P, Palacios JL. Ketamine. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 [cited 2024 Jan 19]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK470357/ PubMed PMID: 29262083.
16. Kinjo T, Tadokoro T, Tokushige A, Zamami T, Taira S, Ikehara Y, et al. Effects of Perioperative Administration of Acetaminophen on Postoperative Shivering: A Randomized, Triple-Blind, Placebo-Controlled Trial. Anesth Analg. 2020 Apr;130(4):983–90. doi:10.1213/ANE.0000000000004306 PubMed PMID: 31274602.
17. Wahdan AS, Loza GE, Alshehri HO, Shedid AF, Salama AK, Wahdan WS, et al. Paracetamol Versus Ondansetron for Prevention of Postoperative Shivering in Liposuction Surgeries Under Combined General Epidural Anaesthesia: A Randomized Controlled Trial. Turk J Anaesthesiol Reanim. 2023 Jun 16;51(3):199–206. doi:10.4274/TJAR.2022.22927 PubMed PMID: 37455437; PubMed Central PMCID: PMC10339746.
18. Mohta M, Mounika TB, Tyagi A. Effect of timing of intraoperative administration of paracetamol on postoperative shivering: A randomised double-blind controlled trial. Indian J Anaesth. 2023 Dec;67(12):1071–6. doi:10.4103/ija.ija_720_23 PubMed PMID: 38343687; PubMed Central PMCID: PMC10858702.
19. Pratama A, Pradian E, Erlangga ME. Perbandingan Efek Fentanil dengan Ketamin terhadap Skor Pemulihan Pascaanestesi Umum Diukur dengan QoR-40 serta Perubahan Tekanan Darah dan Nadi pada Operasi Odontektomi. Jurnal Anestesi Perioperatif. 2020 Dec 30;8(3):3. doi:10.15851/jap.v8n3.2096

20. Liebe T, Li S, Lord A, Colic L, Krause AL, Batra A, et al. Factors Influencing the Cardiovascular Response to Subanesthetic Ketamine: A Randomized, Placebo-Controlled Trial. Int J Neuropsychopharmacol. 2017 Jun 30;20(11):909–18. doi:10.1093/ijnp/pyx055 PubMed PMID: 29099972; PubMed Central PMCID: PMC5737852.

21. Behdad S, Hajiesmaeili MR, Abbasi HR, Ayatollahi V, Khadiv Z, Sedaghat A. Analgesic Effects of Intravenous Ketamine during Spinal Anesthesia in Pregnant Women Undergone Caesarean Section; A Randomized Clinical Trial. Anesth Pain Med. 2013 Sep;3(2):230–3. doi:10.5812/aapm.7034 PubMed PMID: 24282773; PubMed Central PMCID: PMC3833040.