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Review Article

Mitigating Post-Spinal Anesthesia Shivering by Exploring Intravenous Ketamine vs. Intravenous Tramadol and Comparison of the Optimal Dose of Ketamine: A Scoping Review of Cohort and Randomized Controlled Trials Studies

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ABSTRACT

Background: Shivering is prevalent in 65% of patients undergoing spinal anesthesia, resulting in adverse outcomes and increased healthcare expenses. Ketamine, an N-methyl-D-aspartate receptor antagonist, and tramadol exhibit analgesic properties, potentially mitigating post-spinal shivering. This scoping review aims to explore the existing literature on the intravenously administered ketamine and tramadol in reducing the incidence of shivering subsequent to spinal anesthesia.

Methods: This scoping review, conducted from April to June 2024, examined studies on intravenous ketamine and tramadol for shivering post-spinal anesthesia. Using MeSH terms, researchers searched Scopus, Web of Science, PubMed, Cochrane, Google Scholar, Iran SID, and Iran ISC. After excluding duplicates and irrelevant studies, six pertinent studies were included.

Results: The search strategy identified 1316 articles, with 1258 remaining after removing 58 duplicates. Title and abstract screening excluded 6 conference papers, 42 systematic reviews, 94 book chapters or animal studies, and 2 theses. A full-text review of 97 studies resulted in excluding 78 unrelated cases, 1 language discrepancy, and 11 without full-text availability. Ultimately, 6 studies (5 randomized controlled trials and 1 prospective cohort) from Iran, Pakistan, India, Egypt, and Ethiopia found ketamine more effective than tramadol in preventing shivering.

Conclusion: Ketamine is more effective than tramadol in preventing post-spinal anesthesia shivering, with fewer adverse effects like nausea, vomiting, and bradycardia. These findings support its use for shivering management. Future research should optimize dosing to reduce hallucinations, explore other side effects, and prioritize diverse study parameters and safety evaluations.

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Introduction

Spinal anesthesia is one of the most common and reliable methods of anesthesia utilized in various surgeries, particularly those of sub-umbilical regions [1-5]. This approach mitigates the adverse effects of general anesthesia and aids in vasodilation and redistributing heat through the sympathetic blockade, potentially leading to hypothermia [6-8]. Postoperative shivering, recognized as one of the prevalent consequences due to disturbances in the thermoregulatory system, affects a considerable proportion of patients, about 65% undergoing spinal anesthesia [9-12]. Additionally, shivering, characterized as an involuntary oscillatory muscular hyperactivity, may manifest in the upper and lower extremities, neck, and jaw due to cold exposure, fear, or excitement [11, 13-14]. Its intensity ranges from mild (hair standing on end) to severe (continuous skeletal muscle contractions) [15-16]. Despite its role in combating hypothermia, it is considered a detrimental outcome [17-18]. Numerous factors contribute to postoperative shivering, including uncontrolled spinal reflexes, reduced sympathetic activity, metabolic alkalosis, cytokine release during surgery, and response to hypothermia [9, 19-20]. Although not life-threatening, shivering can lead to undesirable physiological consequences such as increased oxygen consumption, elevated intracranial and intraocular pressure, heightened cardiac workload [17], exacerbation of patient discomfort and pain at the surgical site, intensified lactic acidosis, and baseline metabolic rate [6, 18, 21]. Non-pharmacological methods may be useful in shivering prevention, yet they are costly, cumbersome, and lack the necessary efficacy [18, 22]. Pharmacological therapies remain the preferred approach for shivering management. Drugs like meperidine, clonidine, magnesium sulfate, propofol, ketamine, midazolam, sufentanil, and tramadol are effective in shivering treatment. Meperidine, due to side effects like respiratory depression and nausea, especially in elderly patients, is cautiously prescribed [23-24]. Ketamine acts as a competitive antagonist at the N-methyl-D-aspartate receptor site, modulating noradrenergic and serotonergic neurons in the locus coeruleus, and reducing heat redistribution from the core to the periphery [25]. Thus, its administration in patients at risk of hypothermia is rational [11, 26-27]. Additionally, tramadol, a weak analgesic with central pain-relieving effects on μ-opioid receptors with minimal activity on kappa (κ) and delta (δ) receptors, acts by modulating central monoaminergic pathways involved in thermoregulation. Its side effects, particularly respiratory depression and nausea/vomiting, are less pronounced, and it offers rapid onset and lower cost [11, 28-29]. Numerous studies have shown the efficacy of intravenous ketamine and tramadol for preventing postoperative shivering [11, 14, 28]. However, selecting the appropriate drug with minimal adverse effects for prophylaxis against shivering during spinal anesthesia is crucial, and the etiology of shivering remains inadequately elucidated, leading to a notable divergence in clinical approaches and therapeutic strategies [13, 30]. Given the side effects of meperidine, such as delayed recovery room discharge [24] and the ineffectiveness of non-pharmacological treatments, alternative medications for shivering treatment are needed [15, 19, 22]. its unfavorable consequences, reduced patient satisfaction, increased patient morbidity, and the escalated financial and economic burden on hospitals, along with the conflicting perspectives on the efficacy of low-dose ketamine and tramadol prophylaxis [18, 28, 31, 32], exploring the literature scope serves as an effective method for identifying relevant literature in emerging topics for scientific research [33]. This scoping review attempts to investigate the effectiveness of intravenous ketamine and intravenous tramadol in mitigating the incidence of shivering subsequent to spinal anesthesia, exploring existing literature on the subject. This method aids future research in precisely addressing the existing challenges in the field by focusing on identifying pertinent questions and guiding further investigations to provide comprehensive and clear answers.

Methods

This scoping review was completed within a rapid timeframe of 12 weeks. Despite the expedited process, we ensured systematic rigor and maintained both integrity and methodological precision. Our approach was guided by Arksey and O'Malley's scoping review framework [34] and adhered to the PRISMA-ScR reporting standards [35]. We followed the five stages of a scoping review as outlined by Arksey and O'Malley [34,36]:

Stage 1 involved identifying the research aims and questions;

Stage 2 focused on identifying relevant studies;

Stage 3 was dedicated to study selection;

Stage 4 entailed charting the data;

Stage 5 encompassed collating, summarizing, and reporting the results.

Study Design

This scoping review was conducted over a period from April to June 2024. A scoping review is a relatively novel approach for reporting the evidence, and currently, there is limited guidance on decision-making between a systematic review and a scoping review in the evidence synthesis process, particularly when the literature on the

topic is inconclusive. Pharmacological interventions like ketamine and tramadol are widely used for shivering management, but there's a need to understand their comparative efficacy and side effect profiles. This scoping review provides valuable insights by synthesizing existing literature, highlighting the effectiveness and potential drawbacks of both drugs. Understanding these factors can guide clinical decision-making, improve patient outcomes, and inform future research in this area [13, 33].

Research Questions

For the scoping review titled " Exploring Intravenous Ketamine vs. Tramadol in Prevalence of Post-Spinal Anesthesia Shivering: A Scoping Review," the research questions are as follows:

1. What is the comparison of intravenous ketamine versus intravenous tramadol in reducing the incidence of shivering after spinal anesthesia?
2. How do the side effects associated with intravenous ketamine and tramadol administration impact their effectiveness in preventing shivering post-spinal anesthesia?

Search Strategy

Based on the research questions, researchers initially extracted relevant keywords using the Medical Subject Heading (MeSH) strategy. An independent preliminary exploration was conducted across various scholarly databases, encompassing Scopus, Web of Science, PubMed, Cochrane, and Google Scholar, using keywords such as shivering, ketamine, tramadol, spinal anesthesia, intrathecal injections, and spinal injections. Domestic databases such as SID and Iran ISC were also searched using keywords including shivering, ketamine, tramadol, and spinal anesthesia. All articles were analyzed based on title and abstract to exclude irrelevant entries. Any discrepancies were resolved through discussion among the four researchers, reaching a consensus on which articles to include in the study. Data were extracted from all studies, including author(s), objective, participants, interventions, outcomes, and findings. The search process encompassed studies conducted between 2019 and 2024.

Study Selection

The screening process was conducted by pairs of authors who independently reviewed titles, abstracts, and full texts. Study selection was guided by predetermined inclusion and exclusion criteria. Inclusion criteria comprised studies relevant to the research questions, randomized controlled trials, cohort studies, studies published in both Persian and English within the past five years, patients experiencing post-anesthetic shivering under spinal anesthesia, and the use of intravenous ketamine and intravenous tramadol as part of the shivering treatment protocol. Moreover, studies administering intravenous ketamine and intravenous tramadol with any dosage, as well as those examining the effectiveness of intravenous administration of ketamine and tramadol on shivering subsequent to spinal anesthesia. In comparison to placebo or other anesthesia or anti-shivering drugs in this patient group, they were considered for inclusion. Exclusion criteria included all anesthesia methods except spinal anesthesia, administration of ketamine or tramadol in any form other than intravenous, systematic review studies, case reports, studies with unavailable full text, animal studies, conference papers, and book chapters or editorials. All articles were downloaded using EndNote version 9 software, and duplicate entries were removed. Then, three researchers evaluated the articles based on the predetermined inclusion and exclusion criteria, with the fourth team member making the final decision in case of any disagreement.

Data Extraction

Data extraction was performed by four researchers. Extracted data from each article encompassed pertinent study particulars (including primary authorship and publication year). Characteristics of the study (objective, study country, and patient group sizes), patient demographics (mean age range), intervention (timing of ketamine use, dosage administered, mode of administration), assessment tools, and comparison with placebo or other prescribed drugs. The collected data were examined and prepared for presentation. Existing gaps in the studies were identified, and recommendations for future research were discussed.

Results

The selection process is summarized in the PRISMA flow diagram (Figure 1). The search method resulted in a cumulative number of 1316 articles. After removing 58 duplicates, 1258 articles' titles and abstracts were reviewed. 6 conference papers, 42 systematic review studies, and 94 studies related to book chapters and animal studies were excluded. Additionally, 2 theses were excluded. Ultimately, full texts of 97 relatively relevant studies were reviewed. So, the database search yielded 1316 publications, with 1258 remaining after duplicate removal. Title and abstract screening narrowed the pool to 78 publications, with a high inter-rater reliability (ƙ=0.81). 78 studies were excluded due to lack of relevance to the research questions, 1 study due to unrelated language, and 12 studies due to unavailability of full-text articles. Overall, 6 studies were included in this review. In the final review, 5 randomized controlled trials and one prospective cohort study were included,

conducted in countries including Iran, Pakistan, India, Egypt, and Ethiopia, with patients aged approximately between 18 and 65 years. Based on the existing literature, ketamine shows superior performance in preventing shivering compared to intravenous tramadol, as highlighted in this scoping review. The results are given in (Table 1).

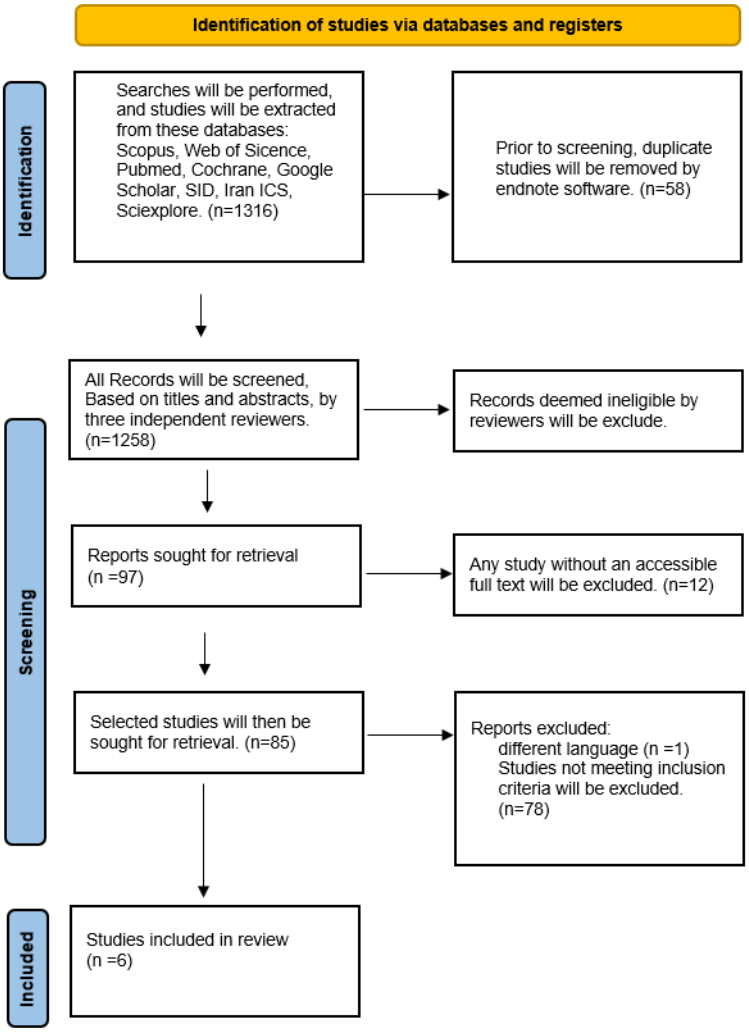

Figure 1- Diagram of study screening and selection

Table 1- Summary of studies comparing effects of the intravenous ketamine and tramadol on the incidence of shivering after spinal anesthesia

Num	1	2	3	4	5	6
Year/ Author	2023- FARAZ A, et al [31].	2021 -A. Jouryabi, et al [27].	2022- A. Gemechu, et al [28].	2023- ABDUL WAHEED, et al [37]	2020- S. H. Seyam, et al. [14].	2022- KHAN, T., et al. [10].
Country	Pakistan	Iran	Ethiopia	Pakistan	Egypt	India
Title	Comparing the effects of low doses of ketamine and tramadol in preventing shivering after spinal anesthesia in	Comparing the Effects of Low Dose of Ketamine, Tramadol, and Ondansetron in Prevention of Post Spinal Anesthesia	The effect of ketamine versus tramadol on prophylactic post-spinal shivering in those patients undergoing	The Effect of Ketamine Versus Tramadol on Prophylactic Post-Spinal Shivering in Those Patients Undergoing	Prevention of Post-Spinal Anesthesia Shivering: Low Dose Ketamine vs Tramadol	Comparative Analysis of intravenous Dexmedetomidine, Ketamine, and Tramadol for mitigating shivering subsequent to spinal anesthesia

	cesarean section	Shivering in Cesarean Section	orthopedic surgery	Orthopedic Surgery		
Sample size(n), population	N=180 (n=60 each groups), 18<age<40+	N=508 (n=127 each groups), 18<age<40+	N=516 (n=258 each groups), 18<age<60+	N=200 (n=100 each groups), 18<age<60+	N=150 (n=50 each groups), 21<age<60+	N=120 (n=30 each groups), 18<age<65+
The purpose of this study	Evaluation of the incidence and severity of shivering in post-cesarean patients who were prescribed low dose tramadol, ketamine or placebo.	the purpose of this survey was to replace pethidine with a safe and effective antishivering agent in CS.	Investigating and comparing the occurrence and severity of post-spinal shivering who received low-dose ketamine and tramadol.	Assess the effectiveness of Ketamine (K) versus Tramadol (T) in mitigating shivering subsequent to spinal anesthesia	To assess the comparative efficacy of intravenous administration of low-dose ketamine and intravenous tramadol in preventing shivering following spinal anesthesia among patients undergoing elective surgical procedures	Evaluation of the effect on hemodynamic parameters and adverse reactions associated with prophylactic administration of tramadol, ketamine and dexmedetomidine in preventing postoperative shivering subsequent to spinal anesthesia
Drug dosage and comparison group	tramadol 0.5 mg/kg (T), low ketamine 0.2 mg/kg (K), placebo with saline (P).	tramadol 0.5 mg/kg (T), ketamine 0.2 mg/kg (K), ondansetron 4 mg (O), and placebo with saline (P).	intravenous 0.25 mg/kg ketamine versus 0.5 mg/kg tramadol	intravenous 0.25 mg/kg ketamine versus 0.5 mg/kg tramadol	tramadol 0.5 mg/kg (T), ketamine 0.2 mg/kg (K), and placebo with saline (P).	Tramadol 0.5 mg/kg - Dexmedetomidine 0.5 µg/kg - Ketamine 0.25 mg/kg - placebo with saline 5 mL,
Research Design and instrument	a double-blind clinical trial\ The 4-point grading scale of Shivering	a double-blind clinical trial\ The 4-point grading scale of Shivering	prospective cohort study design\ The 5-point grading scale of Shivering (Crossley A, Mahajan RJA) [47].	double-blind clinical trial\ The 5-point grading scale of Shivering	double-blind clinical trial\ The 4-point grading scale of Shivering	Randomized Clinical Trial\ The 5-point grading scale of Shivering (Crossley A, Mahajan RJA) [47].
Result	occurrence of shivering was documented in 33 (55.0%) patients in (K) group, 12 (20%) in (T) group, and 39 (65%) in the saline (P) group (P = 0.0001).	Shivering was witnessed in 68 (53.5%), 26 (20.5%), 75 (59.1%), and 82 (64.6%) patients in K, T, O, and P groups, respectively (P = 0.0001)	occurrence rate of shivering subsequent amounted to 187 cases, 36.2%. 74 occurrences (28.7%) were administered ketamine, 113 occurrences (43.8%) were administered tramadol (P = 0. 001).	The incidence of shivering totaled 87 cases, accounting for 43% of the cohort. Among these occurrences, 32 instances (32%) were associated with ketamine administration, while 55 instances (55%) were linked to tramadol administration (P = 0.001).	Shivering manifested in 18 patients, constituting 36.0% of the ketamine (K) cohort, 28 patients, representing 56% of the tramadol (T) cohort, and 35 patients, accounting for 70% of the placebo (P) cohort. (P = 0.003).	Dexmedetomidine demonstrated a diminished efficacy in preventing shivering subsequent to spinal anesthesia in comparison to ketamine (n=2, 6.6%), tramadol (n=10, 33%), and placebo groups (n=11, 36.6%). (P value>0.05).
Adverse effects	Nausea &vomiting	Nausea &vomiting	Nausea &vomiting	Nausea &vomiting	Nausea &vomiting	No common adverse effects were

	(51.66%) Hypotension (23.33%) Bradycardia (11.66%) occurred in the tramadol group. And Hallucination (10%) It occurred in the ketamine group	(49.6%) Hypotension (22.04%) Bradycardia (11%) occurred in the tramadol group. And Hallucination ((7.1%) It occurred in the ketamine group	(60.9%) occurred in the tramadol group	(82%) occurred in the tramadol group	(34%) Hypotension (22%) occurred in the tramadol group.	evident among the groups
Conclusion	Low-dose tramadol and ketamine exhibit efficacy in mitigating both the frequency and intensity of shivering compared to a control group Tramadol exhibited superior efficacy in the shivering management.	Considering the high incidence of shivering in placebo group, prophylactic intervention in CS under SA seems to be necessary. Among the studied drugs, tramadol was the most effective one, followed by a low dose of ketamine and ondansetron.	Low-dose ketamine is more effective in reducing the incidence and severity of shivering after spinal anesthesia in those patients undergoing orthopedic surgery under spinal anesthesia.	The administration of low-dose ketamine demonstrates heightened efficacy in mitigating both the frequency and intensity of shivering subsequent to spinal anesthesia. As a result, it is recommended that patients undergoing orthopedic procedures under spinal anesthesia consider preemptive utilization of low-dose ketamine to attenuate the incidence of shivering.	The prophylactic administration of low-dose IV ketamine (0.2mg/kg) or 0.5mg/kg IV tramadol is effective in reducing the incidence and intensity of shivering in patients having surgery under subarachnoid anesthesia with the priority to tramadol.	Present study concluded that dexmedetomidine is superior than ketamine and tramadol in the prevention of shivering after spinal anaesthesia. and ketamine and IV tramadol are effective in reducing the incidence and intensity of shivering

Discussion

Post-anesthesia shivering is a significant concern due to its potential impact on patient recovery, leading to the suppression of regulatory mechanisms for reducing hypothermia [11]. Findings from this review study elucidate the potential roles of the administration of intravenous ketamine and intravenous tramadol in the manifestation of shivering subsequent to spinal anesthesia and its clinical implications. Within this review, with a total of 6 studies, intravenous ketamine exhibited comparable efficacy to tramadol in mitigating shivering subsequent to spinal anesthesia, with no difference in shivering onset. According to (Table 1), ketamine exhibited better efficacy in preventing post-spinal anesthesia shivering in 4 studies compared to intravenous tramadol in 2 studies. The present study investigates side effects (nausea and vomiting, bradycardia, hypotension, and hallucinations) of two drugs in the studies. Ketamine demonstrated better outcomes with less nausea, vomiting, and bradycardia, while nausea and vomiting were more prevalent in the tramadol group across all 6 studies. However, patients in the ketamine group experienced significant postoperative hallucinations in all studies, indicating that the most significant drawback of ketamine administration, even in low doses, is patients' psychiatric side effects. Based on the results of this study, post-spinal anesthesia shivering is a common complication occurring frequently in patients undergoing surgeries such as cesarean section, orthopedic, and urological procedures, potentially reaching up to 65% incidence [10, 12]. The consequences of shivering range from minor disturbances to severe complications, especially in cardiovascular patients, attributed to increased basal metabolic rate and increased

cardiac workload [40]. Various strategies have been employed to address post-spinal anesthesia shivering, including pharmacological treatments, as well as interventions like using warming blankets or warming-infused fluids. However, the effectiveness of these interventions varies. Pharmacological approaches generally demonstrate much better efficacy [22-40]. Ketamine stimulates sympathetic activity, leading to increased peripheral noradrenaline release and cardiac output and intensifying central heat production, thus reducing the redistribution of heat from the core to the periphery. Therefore, administering intravenous ketamine to patients at risk of hypothermia may be logical [3, 11, 26]. Additionally, tramadol, a weak analgesic with central effects on μ receptors, acts by preventing the reuptake of norepinephrine and serotonin in the spinal cord [18, 28]. Multiple studies have shown that intravenous ketamine and tramadol are suitable for preventing postoperative shivering [11, 37-40]. However, selecting the appropriate drug for shivering prevention during spinal anesthesia with minimal side effects is an important consideration [30]. The study conducted by FARAZ A, et al., revealed that intravenous tramadol, compared to ketamine, demonstrated greater efficacy in preventing post-spinal anesthesia shivering, with tramadol at a dose of 0.5 mg/kg being more effective than ketamine at a dose of 0.2 mg/kg [31]. Similarly, the findings of Jouryabi et al. supported the superior effectiveness of intravenous tramadol over ketamine at a low dose of 0.25 mg/kg in preventing post-spinal anesthesia shivering [27]. Conversely, Gemechu et al. reported that ketamine at a low dose of 0.25 mg/kg exhibited higher efficacy in controlling post-spinal anesthesia shivering in orthopedic surgery patients, as indicated by a prospective cohort study [28]. Likewise, ABDUL WAHEED's study demonstrated a lower incidence of shivering in patients receiving ketamine at a low dose [37]. Ketamine may offer advantages over tramadol due to its relatively lower incidence of side effects and superior efficacy in shivering control, particularly in patients with heightened sensitivity to analgesic drugs. These findings align with a meta-analysis by Fanta et al. in 2022, which compared randomized controlled trials and indicated that intravenous ketamine exhibited comparable efficacy to tramadol in mitigating shivering subsequent to spinal anesthesia. Ketamine was associated with a lower incidence of nausea, vomiting, and bradycardia but a higher incidence of hallucinations compared to tramadol [11]. Although this scoping review suggests that ketamine may be superior to intravenous tramadol in preventing post-spinal anesthesia shivering, discrepancies in findings across different studies indicate that the efficacy of this comparison depends on multiple factors. In addition to efficacy, consideration of drug safety [42] and side effects is crucial in selecting the appropriate medication for reducing post-spinal anesthesia shivering [43]. Despite similar efficacy in controlling shivering, the side effects of these two drugs differ. Ketamine can cause hallucinations, psychotic behaviors, and perceptual disturbances [44-45], while common side effects of tramadol include nausea, dizziness, drowsiness, and constipation. In some cases, similar to other analgesics, it may cause recurrence of cancer [42, 47]. Therefore, the choice of agent should be individualized, weighing the benefits and potential adverse effects. Therefore, drug selection should be tailored to the patient's individual condition and medical history. Key challenges in research on ketamine, tramadol, and shivering include diversity in study designs, patient populations, drug doses, and outcome measures, which can complicate result interpretation and definitive conclusions. This scoping review identified five recent clinical trials and one prospective cohort and investigated the effectiveness of intravenously administered ketamine and tramadol in mitigating shivering subsequent to spinal anesthesia. Both ketamine and tramadol were effective in reducing shivering incidence, albeit with different side effect profiles.

Ketamine, despite its superior efficacy, exhibited fewer side effects compared to tramadol. However, ketamine was linked to a heightened occurrence of hallucinations, possibly due to its impact on glutamatergic signaling and induction of psychosis [47-48]. However, the crucial point is the dosage of this drug in the process of reducing shivering. In most studies on shivering reduction, doses of 0.25 and 0.50 mg/kg of ketamine are used, but this dose of 0.50 mg/kg may lead to sedation, hallucinations, and delusions [19, 45]. Transient side effects disappear within an hour [45]. Patients receiving lower doses of ketamine at 0.25 mg/kg experience less hallucination and sedation compared to 0.50 mg/kg.

Conclusions

This article concludes that the use of ketamine in preventing post-spinal anesthesia shivering can be an effective solution. These findings underscore the importance of individualized drug selection based on patient characteristics and medical history, with careful consideration of associated side effects. Challenges in research on ketamine and tramadol include the diversity in study designs, patient populations, drug doses, and outcome measures, which can complicate result interpretation. Moreover, various confounding factors such as patient age, cognitive status, disease severity, and cardiac conditions must be considered in result analyses. Hence, further research is warranted to fully understand the comprehensive effectiveness of intravenously

administered ketamine and tramadol in mitigating shivering subsequent to spinal anesthesia and other physiological and cognitive parameters. Future studies should prioritize evaluating not only efficacy but also the safety profiles of these drugs, taking into account potential side effects such as hallucinations and gastrointestinal disturbances. Various confounding factors such as patient age, cognitive status, underlying disease severity, and cardiac conditions can influence the risk of post-spinal anesthesia shivering and its complications and should be considered in analyses. Thus, recognizing the necessity for further comprehensive research to elucidate the effectiveness of intravenously administered ketamine and tramadol in mitigating shivering subsequent to spinal anesthesia and other physiological and cognitive parameters is imperative. In the present scoping review, there might be a tendency to overlook scientific studies published during the literature selection process. Additionally, imposing specific criteria based on time and language may influence research evaluations and potentially lead to the exclusion of particular subjects. Further considerations include the overall quality of research and diversity among studies. Future studies should prioritize not only efficacy but also the safety profiles of intravenous ketamine and tramadol, taking into account potential side effects such as hallucinations, nausea and vomiting, and any adverse experiences associated with their use. Future studies should prioritize evaluating not only efficacy but also the safety profiles of these drugs, taking into account potential side effects such as hallucinations and gastrointestinal disturbances.

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