SYSTEMATIC REVIEW OPEN ACCESS

# Evaluating the Effectiveness of Nefopam Versus Tramadol in Treating Established Post-Spinal Anesthesia Shivering: A Systematic Review

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**ABSTRACT**

**Background:** Post-spinal anesthesia shivering (PSAS) was observed as a frequent and distressing complication, affecting 40–70% of patients and increasing metabolic demand. Nefopam and tramadol were two pharmacological agents for managing PSAS. Each had its distinct efficacy and side effect profiles. This study evaluated and compared the efficacy, safety, and practicality of nefopam and tramadol in the treatment of established PSAS.

**Methods:** A systematic review was conducted that adhered to PRISMA guidelines. The search took place using PubMed, ScienceDirect, and Google Scholar. Inclusion criteria focused on randomized controlled trials and observational studies published between January 2013 and April 2024. The studies were excluded if they were not based on tramadol and nefopam's therapeutic effect on PSAS. Data for the systematic review table were extracted from 16 studies evaluating sedation quality, recovery time, adverse events, and key findings. The Cochrane risk of bias tool was used for RCTs, and the Newcastle Ottawa tool was used for observational studies to assess the risk of bias. Sedation quality was assessed by a visual analog scale (VAS).

**Results:** Out of 110 initially selected studies, 16 were filtered out that aligned completely with the concept of this systematic review. Both nefopam and tramadol were shown to reduce PSAS. Tramadol demonstrated a slightly higher efficacy (90–97%) compared to nefopam (85–90%). Tramadol, due to its rapid onset (30–60 minutes) and faster recovery times, was suitable for time-sensitive cases. However, tramadol had a higher incidence of gastrointestinal side effects (nausea and vomiting: 5–11%). In contrast, nefopam, while slower in showing effect, exhibited minimal sedation and fewer side effects but occasionally caused tachycardia and hypertension.

**Discussion:** Both agents were effective for PSAS management. Tramadol was preferred for rapid control and cost-friendly settings, whereas nefopam was safer for patients who required minimal sedation or who were at risk of gastrointestinal side effects. However, there was no direct comparison of nefopam with tramadol. Future studies should focus on using standardized protocols and should provide a direct comparison of tramadol with nefopam.

**Keywords:** Shivering, Anesthesia, Nefopam, Tramadol, Patient Safety, Systematic Review

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## INTRODUCTION

Post-spinal anesthesia shivering (PSAS) was seen to be a common and distressing complication following spinal anesthesia, influencing 40% to 70% of patients [1]. PSAS was studied to be characterized by involuntary, rhythmic muscle contractions, which significantly increase metabolic oxygen demand and carbon dioxide production and hence cardiac workload [2]. What mattered more than the physical impact of shivering was that it reduced patients' comfort, interfered with devices that monitor patients, and might have caused patients to take longer to recover. Effective interventions were needed to deal with PSAS promptly and reliably because of these challenges [3]. Spinal anesthesia produced shivering that was caused, to a great extent, by the disruption of thermoregulation. It prevented the body from maintaining optimum temperature using thermoregulatory vasoconstriction, allowing redistribution of heat towards the periphery [4]. Other contributing factors were environmental exposure to low temperatures in the operating room, cold infusions of intravenous fluids, and reduced heat production during anesthesia. Physical and pharmaceutical approaches were needed to address PSAS. While prewarming fluids and warming blankets provided partial improvement, pharmacological agents remained the mainstay of treating established shivering [5].

Nefopam and tramadol were seen to be among the pharmacological options that had been widely studied and used. Nefopam is a non-opioid analgesic that has been shown to block the reuptake of serotonin, dopamine, and norepinephrine. It was considered an attractive option for postoperative patients because of its thermoregulatory properties and minimal sedation profile [6]. In contrast, tramadol is a weak μ-opioid receptor agonist that has also been shown to inhibit serotonin and norepinephrine reuptake. Its dual mechanism of action was responsible for managing pain and shivering simultaneously, making it a versatile and low-cost option in the clinical system [7].

Despite the demonstrable effectiveness of these options, the debate was still there that which one of nefopam or tramadol was the most appropriate choice to treat PSAS. The minimal sedative and cardiovascular side effects of nefopam made it useful, but questions had been raised about its slow onset and limited availability in some settings [8]. While tramadol had a rapid onset and robust efficacy, the latter was offset by a greater incidence of gastrointestinal side effects (nausea and vomiting). It was therefore crucial to evaluate these agents in comparison so that further clinical decisions could be guided in areas with different patient populations and varying resource constraints [9].

Healthcare systems have become more focused on interventions that are effective, safe, and cost-friendly. Tramadol was an inexpensive and widely available drug, which made it an attractive option in resource-limited areas. However, nefopam's distinct safety profile characterized it as a useful alternative for patients with contraindications to opioids or those who were at increased risk of adverse events. Understanding the nuances that characterized the agents' performance could help guide more tailored treatment strategies that incorporate both patient's gain and economic considerations [10].

The objective of this systematic review was to perform an overall evaluation of the efficacy of nefopam compared to tramadol for the treatment of established PSAS. This review aimed to synthesize findings from various studies to shed light on the comparative efficacy, safety, and practicality of these two pharmacological options. The intent was to give clinicians evidence, to direct them to the most suitable agent for the treatment of PSAS, ensuring optimized therapy and enhanced patient experience.

## METHODS

To ensure a comprehensive and transparent reporting of findings, PRISMA guidelines were adhered to for this systematic review. The articles on the clinical effectiveness of nefopam vs tramadol to treat established post-spinal anesthesia shivering were searched through three databases i.e., PubMed, Science Direct, and Google Scholar. English language studies that were published between January 2013 and April 2024 were considered. Non-English articles were excluded because of translation limits. The search strategy was designed to ensure to retrieval relevant articles using Boolean operators and combinations of defined keywords. The keywords used to retrieve relevant articles were: "Nefopam AND Shivering/drug therapy", "Tramadol AND Shivering/drug therapy", and "Shivering/therapy AND Postoperative Complications".

Studies were included if they focused on patients with post-spinal anaesthesia shivering. Only randomized controlled trials (RCTs), observational studies, and cohort studies were selected. Studies were excluded if shivering outcomes were not reported, if there was insufficient data, or if the procedures involved non-spinal anaesthesia procedures.

Of 106 articles initially screened, 96 were reviewed, and 40 met the eligibility criteria. Two independent reviewers performed the screening and data extraction process. The disagreements among reviewers were resolved by the third reviewer through discussion or consultation. No missing data was found. Data extraction involved the following variables: study details, sedation time, intervention specifics, key outcomes, and limitations. Assumptions were made for the sake of comparison among heterogeneous

data measures and categorization of unspecified randomized as "unclear risk" in bias assessments.

The studies included were assessed with the Cochrane Risk of Bias tool for randomized control trials and the Newcastle-Ottawa scale for observational studies. Descriptive statistics, and where appropriate, mean differences, and odds ratios, were calculated statistically. Since the studies were so heterogeneous the findings were synthesized narratively by the following Synthesis without a meta-analysis framework. No subgroup or sensitivity analyses were performed during the study.

In narrative synthesis, the studies were categorized based on efficacy, sedation quality, recovery time, and adverse events. The results showed that both nefopam and tramadol significantly reduced post-spinal anesthesia shivering, whereas tramadol showed greater efficacy (90–97% vs. 85–90%) and faster onset (30–60 min) than nefopam. However, tramadol had more gastrointestinal side effects (5–11% nausea/vomiting) while nefopam had fewer. However, the conclusion was made that the choice of agent should be guided by the clinical context and condition of patients.

16 studies were finally selected and summarized in tables. The efficacy of nefopam and tramadol for the treatment of shivering after spinal anaesthesia was reviewed and the safety profiles and optimal dosing regimens for future research were identified.

## RESULTS

Sixteen studies were included in this systematic review which compared the effectiveness of nefopam with tramadol against the treatment of post-spinal anesthesia shivering. The flow diagram is shown in Figure 1, through which the selection of studies is performed. Most of the studies were taken from Google Scholar (70%) from PubMed, while others were from ScienceDirect and PubMed. The included studies contained 9 RCTs, 5 cohort studies, and 2 prospective studies to provide a sound data set.

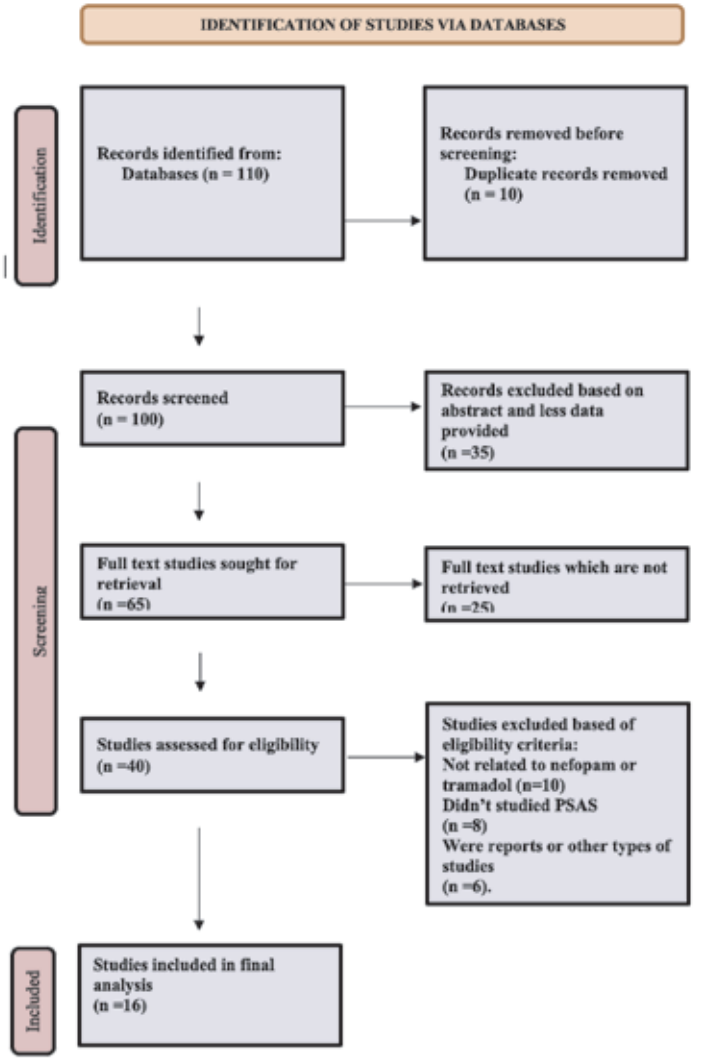


**Figure 1: PRISMA Flow Diagram Demonstrating Filtering of Studies According to Inclusion and Exclusion Criteria. 16 Studies Were Selected for Systematic Review**

To reduce shivering, nefopam and tramadol both were significantly efficient but tramadol on average was more efficient (90-97% versus 85-90%). Being rapid in onset of action (typically 30-60 minutes), tramadol was the drug of choice for time-sensitive cases. Unlike nefopam, which had a slower onset, it was beneficial for patients who required less sedation and clearer cognitive function. Patients returned to normal activities much quicker after use of tramadol (less than an hour) than on nefopam (more than 24 hours).

Some studies seemed to be relevant but excluded due to the difference in methodologies. Gaballah and Abdullah (2020) examined oral tramadol but lacked comparability with other drugs, while Amsalu et al. (2022) focused on shivering management in general without the use of the review's specified drugs. Similarly, some other studies didn't provide data that could be compared.

Sedation quality was measured by using visual analog scales (VAS) and other commonly used sedation scales in the postoperative setting. Data from these scales revealed that tramadol produced mild to moderate sedation in some patients and nefopam caused minimal sedation in most patients, making it suitable for patients who require minimal cognitive impairment. These findings were observed in all the studies cited in this review.

Both agents reduced opioid consumption by 25–30%, with nefopam demonstrating a more favorable profile against side effects, particularly nausea and vomiting. Tramadol, while efficient, was associated with higher rates of nausea and vomiting (5–11%), which were, however, manageable by prophylaxis. Gastrointestinal disturbances were fewer with nefopam, but tachycardia and hypertension were occasional, particularly at higher dosage rates.

**Table 1:Systematic Review Table Showing Agents Selected for Study and Their Key Findings**

| Author & year, Reference (Location) | Sample Size (Agent Studied) | Sedation Quality | Recovery Time | Adverse Events | Key Findings |
|---|---|---|---|---|---|
| Basman et al., 2024 (UAE, Multiple hospitals)[11] | 150, Tramadol | Stable maternal vitals | Within 1–2 days | Minimal: nausea (5%), vomiting (3%) | Tramadol reduced post-spinal anesthesia shivering incidence and severity without neonatal impact. |
| Ayad et al., 2022 (Iraq)[12] | 60, Nefopam | Mild sedation | Less than 2 days | Minimal: nausea (2%), vomiting (2%) | Nefopam effectively reduced postoperative shivering with a 95% response rate. |
| Jatuporn et al., 2020 (Thailand)[13] | 96, Nefopam | Mild sedation in some cases | Within 2 days | Minimal: tachycardia (4%), nausea/vomiting (5–10%) | Adding nefopam to opioids did not significantly improve analgesic efficacy after spine surgery. |
| Shoyemi et al., 2024 (Nigeria)[14] | 68, Nefopam, Tramadol | Mild sedation | The recovery time of both was 1 hour 6 minutes (p=0.16) | Nausea in the Tramadol group (11.8%), none in the Nefopam group | Nefopam was significantly more effective in preventing shivering during spinal anesthesia than tramadol. |
| Eman M. Abd El Azeem et al., 2023 (Egypt)[15] | 86, Tramadol | Standardized protocols and triple-blinded randomization. | Uniform postoperative monitoring. | Lower nausea in the intrathecal tramadol group, vomiting, and hypotension. | Intrathecal tramadol significantly reduced shivering (intraoperative: 4.6% vs. 18.6%; postoperative: 7% vs. 21%) with fewer adverse effects. |
| Chalermkitpanit et al., 2022 (Thailand)[16] | 100, (49 nefopam, 45 saline) | Nefopam had no sedative effects; a standardized anesthesia protocol was used. | ~4 days | Nausea, dizziness, drowsiness | Nefopam did not significantly reduce opioid use, postoperative pain, or enhance recovery outcomes in minimally invasive spine surgery. |
| Chalermkitpanit et al., 2023 (Thailand)[17] | 100, Nefopam | Standard anesthesia protocol | Length of stay (LOS): 4.3 ± 1.0 days (Nefopam) | Nausea/vomiting or dizziness | Nefopam reduced LOS and early postoperative pain but did not affect morphine use. |
| Hwisa et al., 2024 (Libya)[18] | 60, Tramadol IV | Room temperature IV fluids | Shivering duration: 20.3 ± 9.6 min (Tramadol) | Nausea/vomiting | Tramadol significantly reduced shivering duration compared to blankets. |
| Baloch et al., 2021 (Qatar)[19] | 120, Tramadol | Standardized anesthetic and IV fluid temp | Shivering resolved in ≤15 min for Tramadol vs. persisted in Control | Minimal adverse effects; no dose-dependent differences | Both Tramadol doses controlled shivering effectively with low side effect profiles. |
| Lee et al., 2021 (Korea)[20] | 135, Nefopam (alone, combo) | No sedation comparison | 1 day | Postoperative nausea and vomiting | Nefopam alone showed limited efficacy compared to fentanyl. |

| | | | | | |
|---|---|---|---|---|---|
| Rana et al., 2024 (Pakistan)[21] | 100, Tramadol | Tramadol avoids sedation | 60 minutes | Nausea, vomiting, dizziness | Tramadol was more effective in reducing shivering. |
| Kim et al., 2013 (Korea)[22] | 65, Nefopam | Nefopam does not induce sedation | ~60 minutes | Nefopam caused injection pain (15.6%) | Nefopam was effective in shivering prevention with stable vitals. |
| Raksakietisak et al., 2022 (Thailand)[23] | 50, Nefopam | No sedation reported | 24 hours | Hypertension was observed with nefopam | Nefopam did not significantly reduce morphine consumption or pain. |
| Nirala et al., 2020 (India)[24] | 90, Tramadol | Tramadol causes less sedation than nalbuphine | 30 minutes | Tramadol caused more nausea and vomiting | Tramadol effectively reduced post-spinal anesthesia shivering. |
| Gemechu et al., 2022 (Ethiopia)[25] | 516, Tramadol | Tramadol avoided excessive sedation | 60 minutes | Higher nausea and vomiting in the tramadol group | Tramadol significantly reduced shivering. |
| Acharya et al., 2023 (Nepal)[26] | 106, Oral tramadol | Mild sedation in 17.9% of patients | 1 hour (initial monitoring) | No nausea, vomiting, or significant adverse events | Oral tramadol effectively prevented post-anesthetic shivering. |

**Table 2: Nefopam Vs Tramadol Efficacy**

| Parameter | Nefopam | Tramadol |
|---|---|---|
| **Mechanism of Action** | Non-opioid analgesic: inhibits reuptake of serotonin, norepinephrine, and dopamine. | Weak μ-opioid receptor agonist inhibits serotonin and norepinephrine reuptake. |
| **Primary Use** | Postoperative pain and shivering prevention. | Post-spinal anesthesia shivering and mild to moderate pain. |
| **Efficacy in Shivering** | Effective in preventing shivering but not significantly better than comparators like tramadol or opioids in some studies. | More effective than several agents (e.g., nefopam, ketamine, saline) in reducing shivering incidence and severity. |
| **Sedation Quality** | Minimal sedation was reported in most studies. | Mild to moderate sedation in some patients; causes less sedation than nalbuphine. |
| **Recovery Time** | Typically, within 24 hours to 2 days. | Recovery time is typically faster, ranging from 30 minutes to 1 hour. |
| **Adverse Events** | Nausea, vomiting, tachycardia, and hypertension (less frequent). | Nausea, vomiting, dizziness; higher incidence of gastrointestinal effects. |
| **Onset of Action** | Slower onset compared to opioids; effectiveness enhanced with combinations. | Rapid onset of action in shivering prevention; oral and IV forms are both effective. |
| **Formulations** | Intravenous (IV). | Oral, intravenous (IV), and intrathecal options are available. |
| **Cost and Availability** | Relatively more expensive and less widely available. | Cost-effective and widely available, including in low-resource settings. |
| **Shivering Reduction Rates** | Approximately 90–95% effectiveness, depending on the study. | Consistently high effectiveness, ~90–97%, depending on dose and method of administration. |

As there was high heterogeneity in the included studies regarding design, outcome measures, and reporting format, a meta-analysis was not feasible. The findings were instead synthesized narratively. **Table 1** presents key characteristics and findings of individual studies, and **Table 2** shows the summary of the comparison between nefopam and tramadol regarding activity, safety, and onset of action.

**Table 3: Risk of Bias Assessment using Cochrane Risk of Bias Tool for RCTs**

| Study | Sequence Generation – Selection Bias | Allocation Sequence Concealment – Selection Bias | Blinding of Participants and Personnel – Performance Bias | Blinding of Outcome Assessment – Detection Bias | Incomplete Outcome Data | Selective Outcome Reporting | Other Bias |
|---|---|---|---|---|---|---|---|
| Jatuporn et al., 2020 (Thailand) | + | ± | + | ± | ± | + | ± |
| Shoyemi et al., 2024 (Nigeria) | + | + | + | + | + | + | + |
| Eman M. Abd El Azeem et al., 2023 (Egypt) | + | + | + | + | + | + | + |
| Chalermkitpanit et al., 2022 (Thailand) | + | ± | ± | + | + | + | ± |
| Chalermkitpanit et al., 2023 (Thailand) | + | ± | + | ± | ± | + | ± |
| Hwisa et al., 2024 (Libya) | + | ± | ± | + | + | + | ± |
| Lee et al., 2021 (Korea) | + | ± | ± | + | + | + | ± |
| Raksakietisak et al., 2022 (Thailand) | + | ± | ± | + | + | + | ± |
| Nirala et al., 2020 (India) | + | + | + | + | + | + | + |

*"+" indicates a low risk of bias (adequate methodology), "±" indicates an unclear risk of bias (some concerns), and "-" (if needed) indicates a high risk of bias (serious concerns).*

**Table 4: Risk of Bias Assessment using Newcastle Ottawa for Remaining Studies**

| Study | Selection (max ★★★★) | Comparability (max ★★) | Outcome (max ★★★) | Total (max ★★★★★★★★★) |
|---|---|---|---|---|
| Basman et al., 2024 (UAE) | ★★★★ | ★★ | ★★★ | ★★★★★★★★★ |
| Ayad et al., 2022 (Iraq) | ★★★★ | ★ | ★★ | ★★★★★★ |
| Baloch et al., 2021 (Qatar) | ★★★★ | ★ | ★★ | ★★★★★★ |
| Rana et al., 2024 (Pakistan) | ★★★★ | ★★ | ★★★ | ★★★★★★★★★ |
| Kim et al., 2013 (Korea) | ★★★ | ★ | ★★ | ★★★★★★ |
| Gemechu et al., 2022 (Ethiopia) | ★★★★ | ★ | ★★★ | ★★★★★★★ |
| Acharya et al., 2023 (Nepal) | ★★★★ | ★ | ★★★ | ★★★★★★★ |

Quality and risk of bias were assessed for included studies using the Cochrane Risk of Bias tool for RCTs and the Newcastle-Ottawa Scale for observational studies. All studies had low to moderate risk of bias, but few had limitations regarding unclear randomization and incomplete outcome data. The risk of bias is presented in **Tables 3** and **4**. The number of studies included in the review was not sufficient to assess publication bias properly using statistical methods such as funnel plots.

## DISCUSSION

Nefopam and tramadol were assessed for their effectiveness in treating PSAS in this systematic review. Key differences in onset of action, recovery time, and adverse event profiles were seen for both agents. But both agents showed efficacy. Across multiple studies tramadol had a rapid onset and consistently high efficacy for reducing shivering incidences and severity by 90% to 97%. In contrast, the tolerability profile of nefopam was more favorable, especially in minimizing gastrointestinal side effects, though slightly less effective for reducing shivering in some cases.

The studies included in this review provided strong evidence from many clinical settings, thereby increasing the generalizability of findings. A large sample size with over 500 patients supported tramadol's efficacy, as mentioned in one study. Though smaller in scale, nefopam studies provided good ideas regarding safety and applicability, especially for patients with contraindications to opioids[25].

As study designs were heterogeneous therefore direct comparison was not the best option. Variations in dosing regimens, outcome measurements, and patient populations made it difficult to draw definitive conclusions. Moreover, there was a lack of standardization in many studies to measure shivering severity, recovery times, and adverse events, hence, more uniform methodologies are needed in future studies.

Tramadol's rapid onset and high efficacy were particularly well suited for the scenarios where immediate shivering control was required[26, 27]. Two studies highlighted its ability to resolve shivering within less than 30–60 minutes. Unlike nefopam, which took 24 hours or more to achieve full recovery in some patients, this might limit its usage in acute settings, but did not diminish its effectiveness in wider perioperative care [28].

The distinct mode of action of nefopam (non-opioid, acting by serotonin, norepinephrine, and dopamine reuptake inhibition) and tramadol (weak opioid agonist with similar reuptake inhibition effects) was self-explanatory for their diverse effects on shivering prevention and adverse events[29]. Nefopam's slower onset might seem like a limitation, but its consistent efficacy and milder side effects made it a suitable choice in patients who needed less urgent interventions. In longer recovery settings, nefopam reduced shivering severity effectively without significant sedation, making it a versatile option, as pointed out by one study [30].

In 5% to 11% of cases, the adverse event profile of tramadol primarily consisted of gastrointestinal disturbances, such as nausea and vomiting. However, these effects were dose-dependent, and they could be prevented by prophylactic antiemetics. On the other hand, a more favorable profile was seen for nefopam, which had fewer gastrointestinal side effects, but some cases of tachycardia and hypertension were reported. One study's finding indicated that nefopam was suitable for use in patients who had a risk of either gastrointestinal complications or opioid-related sedation[31].

In the perioperative settings, recovery time and sedation profiles were important factors that affected patient turnover and satisfaction. Tramadol helped accelerate recovery, and it was generally reported that most patients resumed normal activity within 30 to 60 minutes of taking Tramadol [32]. Its preference in resource-constrained or high turnover environments aligned with its ability to rapidly resolve symptoms. On the other hand, it might take nefopam up to 24h or more for recovery, which could be too long for instantaneous recovery in demanding situations. In addition, nefopam's minimal sedative effect made nefopam quite useful to patients who should remain alert or prevent respiratory depression. This was the quality that made nefopam the preferred agent, in settings where cognitive clarity was most important [33].

Choosing between nefopam and tramadol should be based on patient-specific factors such as comorbid illnesses, risk of adverse events, and resource availability. Tramadol was an affordable and accessible medication in resource-limited settings. However, Nefopam was costlier and had advantages in patients with contraindications to opioids or increased sensitivity to gastrointestinal effects. These findings were consistent with the general healthcare goals of providing cost-effective, patient-focused care [34].

Economic analyses of these agents demonstrated the necessity of weighing upfront costs with long-term consequences [35]. While tramadol was cheaper, it was also more likely to cause higher rates of nausea and vomiting, which might require more treatments. On the other hand, nefopam's higher cost was justified in patients where the reduced side effects resulted in short hospital stays or fewer interventions[36].

When the rapidly increasing emphasis on precision medicine was considered, it became critical to develop management strategies for shivering tailored to the individual patient profile[37]. Agent selection must be guided by risk factors such as age, comorbidities and prior adverse reactions. Furthermore, patient preferences concerning sedation and recovery time should be integrated into clinical decisions to maximize adherence with treatment plans and increase satisfaction in patients[38].

There was a need for more future studies that should compare nefopam and tramadol head-to-head, by employing standardized dosing regimens and outcome measures. Further studies to confirm findings and to address existing gaps in evidence should be randomized controlled trials with larger sample sizes. Moreover, combination therapies or novel agents might further improve the management of PSAS[39,40].

Stratification of patients based on risk factors such as comorbidities or severity of shivering should also be investigated to identify optimal agent selection.

Longitudinal studies evaluating long-term outcomes such as quality of life and cost-effectiveness would be of significant value to clinical practitioners and policymakers. Furthermore, advances in pharmacogenomics could pinpoint patient-specific determinants of response to nefopam and tramadol. These insights, when integrated into clinical practice, would promote more effective and personalized PSAS management strategies.

## CONCLUSION

Based on this systematic review, nefopam and tramadol appeared to be effective for established PSAS. Nefopam was a slightly safer option for patients who needed minimal sedation and a reduction in gastrointestinal side effects as compared to tramadol, which had other advantages like rapid shivering control and cost effectiveness. Optimal perioperative care and choices of agents should be tailored according to individual patient needs and clinical context, with optimal outcomes. Future studies should integrate standardized protocols with a direct comparison of tramadol and nefopam for more definitive results.

## LIST ABBREVIATIONS

**PSAS:** Post-Spinal Anesthesia Shivering
**RCT:** Randomized Controlled Trial
**PRISMA:** Preferred Reporting Items for Systematic Reviews and Meta-Analyses
**VAS:** Visual Analog Scale
**IV:** Intravenous
**LOS:** Length of Stay


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None


## CONFLICT OF INTEREST

None

## AUTHORS' CONTRIBUTIONS

All authors contributed equally as per ICMJE.

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