Systematic Review & Meta-Analysis

Efficacy of intravenous nalbuphine for managing post-anaesthesia shivering: A systematic review and meta-analysis of randomised controlled trials with trial sequential analysis

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ABSTRACT

Background and Aims: Post-anaesthesia shivering is distressing and is observed after spinal and general anaesthesia. Nalbuphine, a partial mu-opioid receptor antagonist with kappa-opioid receptor agonist properties, has been successfully used to manage post-anaesthesia shivering. **Methods:** After registering the review with the International Prospective Register of Systematic Reviews (PROSPERO), we searched PubMed/Medline, Scopus, Ovid, Cochrane Library and clinicaltrials.gov with keywords for randomised controlled trials. The risk of bias-2 (RoB-2) scale was used to assess the quality of evidence. We also used Grading of Recommendations, Assessment, Development and Evaluations (GRADE) guidelines to evaluate the strength of evidence and trial sequential analysis to validate the conclusions. **Results:** Of the 240 articles, 10 were considered eligible for review (700 patients, 350- nalbuphine, 350- control or placebo). When compared to placebo, the success rate of nalbuphine controlling shivering was significantly better (risk ratio [RR]: 2.37, 95% confidence interval [CI]:1.91, 2.94; $P = 0.04$, $I^2 = 94\%$), but comparable to the control group drugs (opioids, dexmedetomidine, ondansetron, pethidine). Compared to placebo, shivering recurrence was significantly less with nalbuphine than with placebo (RR: 0.47, 95% CI: 0.26, 0.83; $P = 0.01$, $I^2 = 61\%$), but comparable with the control group. The incidence of postoperative nausea/vomiting (PONV) was significantly less with nalbuphine when compared to the control group (RR: 0.67, 95% CI: 0.47, 0.95; $P = 0.02$, $I^2 = 37\%$), but PONV in the nalbuphine group was comparable to placebo (RR: 1.20, 95% CI: 0.68, 2.12; $P = 0.54$, $I^2 = 0\%$). Other outcomes, like the grade of shivering and hypotension, were comparable between the nalbuphine and control groups. **Conclusion:** Nalbuphine successfully controls post-anaesthesia shivering and reduces the recurrence of shivering.

Key words: Anaesthesia, dexmedetomidine, meta-analysis, nalbuphine, ondansetron, opioid, shivering, systematic review

INTRODUCTION

Shivering is common after anaesthesia and is associated with patient discomfort, nausea and vomiting, which affects the quality of recovery. Intraoperative hypothermia is one of the common causes of postoperative shivering. However, it is also possible to experience shivering in the postoperative period by normothermic patients.[1] Hypothermia

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during anaesthesia and surgery typically results from a confluence of variables, including significant heat loss during surgery, a cold-operating room atmosphere and anaesthetic-induced impairment of thermoregulatory control.[2] Postoperative shivering causes lactic acidosis, releases catecholamines, increases oxygen consumption and increases the risk of hypoxaemia.[3]

Various pharmacological treatments for shivering have been reported, including tramadol, meperidine (pethidine), ketamine, clonidine, dexmedetomidine, nefopam and ondansetron.[4-9] Opioids like tramadol and meperidine have been routinely used to control postoperative shivering. Nalbuphine is a partial mu-opioid receptor antagonist with kappa-opioid receptor agonist properties. It has been used as an anti-shivering medication to control shivering that develops perioperatively due to either neuraxial or general anaesthesia.[10,11] To date, no pooled analysis has been published in which the efficacy and safety of nalbuphine was compared to either an active control group or a placebo. This systematic review and meta-analysis aimed to assess the efficacy of intravenous (IV) nalbuphine as an intervention to treat postoperative shivering in patients undergoing various surgeries by comparing it with placebo or other anti-shivering medications.

METHODS

The study protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) (registration number: CRD42023417584, https://www.crd.york.ac.uk/prospero/). This meta-analysis follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting guidelines.[12]

Randomised controlled trials (RCTs) comparing nalbuphine to placebo or other anti-shivering medications were searched in databases including PubMed/Medline, Ovid, Cochrane Library (CENTRAL) and clinicaltrials.gov from January 2000 to July 2023 [Appendix Supplementary File 1]. The Population, Intervention, Comparator, Outcome and Setting (PICOS) criteria were followed for search as follows:[13]

Population: Adult patients (over 18 years) undergoing various surgeries under general or neuraxial anaesthesia were considered eligible for inclusion.

Intervention: The intervention was IV nalbuphine in various doses used to abort the shivering experienced by the patient in the postoperative period.

Comparator: Comparators included subjects who received no active medication or a placebo (saline). However, the subjects who received a comparative drug such as an α2-agonist or an opioid IV were considered for inclusion.

Outcomes: The primary outcome was the ability to abort postoperative shivering by the intervention. The secondary results were the time of onset of shivering and adverse effects like postoperative nausea/vomiting (PONV), sedation and hypotension.

Setting: The setting was the immediate postoperative period in the recovery room.

The studies without a control group, in which nalbuphine was administered intrathecally, editorials and case reports/series were excluded.

Methodological quality assessment

The revised Cochrane risk-of-bias tool for randomised trials (RoB-2) was used to assess the methodological quality and risk of bias of the included RCTs. The categories considered for bias assessment were bias due to randomisation, bias due to deviation from intended intervention, bias due to missing data, bias due to outcome measurement, bias due to selection of reported result and overall bias.[14]

Strength of evidence across trials

The overall methodological quality of evidence across pooled outcomes was assessed using the Grading of Recommendation, Assessment, Development and Evaluation (GRADE) guidelines. Evidence for pooled outcomes was determined based on study design, risk of bias, consistency, directness, precision and other considerations (publication bias, large effect, confounding, dose–response gradient). The certainty of evidence was defined as (1) high quality: further research will very unlikely change the confidence in the estimate of effect; (2) moderate quality: further research will very likely have an important impact on the confidence of the estimate of effect and may change the estimate; (3) low quality: further research is very likely to have an important impact on the confidence in the estimate of effect and is likely to change the estimate or (4) very low quality: there is uncertainty surrounding the estimate.[15]

Data extraction

From the publications, the reference data, populations and results were taken out and inserted into predesigned tables. Two authors (AN and UD) used a methodical procedure for data extraction. In case of any difference of opinion, it was settled by a third author (MR). The details about the participants' demographics, sample size, surgical techniques, the experimental intervention, the study design, the number of arms and the primary outcome were extracted. Dichotomous data were extracted either directly when the number of patients was mentioned or indirectly by calculating back when reported as a percentage of patients. Further, these were converted into incidence (n/N) for prespecified times. For continuous data, we computed means and standard deviations (SDs). The confidence intervals (CIs) or P values associated with the variations in means between the two groups were used to calculate SDs if they were not explicitly mentioned.

Data synthesis and analysis

If trials were clinically homogenous in terms of demographics, intervention (the kind of block employed) and control, data pooling were performed. When sufficient numbers of adequately homogenous studies were revealed following data extraction, Review Manager software (www.cochrane.org, London, UK) was used to conduct the meta-analysis *post hoc* (version 5.4.1).[16]

For the meta-analysis, aggregate-level data were utilised. The Mantel–Haenszel technique was used to assess dichotomous variables, and the risk ratio (RR) with the associated 95% CI was determined. For units-unified continuous variables, the mean difference (MD) with the accompanying 95% CI was determined using the inverse variance approach. We evaluated the heterogeneity between studies using the I^2 statistic, which was defined as follows: 0%–40%- might not be important, 30%–60%- may represent moderate heterogeneity, 50%–90%- may represent significant heterogeneity and 75%–100%- considerable heterogeneity.[17]

The results were compared with the random- and fixed-effects models, and the reliability of the combined results was eventually analysed according to the consistency degree of the results. When $P > 0.01$ and $I^2 < 50\%$, the fixed-effects model was used, and when $P < 0.01$ and $I^2 > 50\%$, the random-effects model was used for meta-analysis. Mean difference was used to combine continuous outcomes recorded on the same scale, and the result was given as an MD with a 95% CI. RRs with 95% CI were used to report dichotomous results.[17]

Sensitivity and subgroup analysis

Subgroup analysis was performed for a few of the outcomes, like success rate and grade of shivering. Sensitivity analysis was also performed for the primary outcome after excluding the trials with a high risk of bias.

Publication bias

If more than 10 studies met the inclusion criteria, funnel plots showing effect sizes against standard errors for the outcomes were checked for asymmetry.[18] The corresponding statistical test was the Egger bias test, with $P < 0.10$ indicating asymmetry.[19]

Trial sequential analysis

Trial sequential analysis (TSA) using the TSA Module version 0.9.5.10 (Copenhagen trial unit, Denmark) was done on the results to calculate the required information size (RIS) and see if our findings were conclusive. A random-effects model with the DerSimonian–Laird (DL) method was used to create the cumulative Z curve. TSA was carried out to keep the overall risk of a type I error to 5%.[20]

When the cumulative Z curve crossed the trial sequential monitoring boundary or entered the futility area, it was possible that an adequate degree of evidence for accepting or rejecting the predicted intervention effect had been attained, and no further research was required. If the Z curve did not cross any borders and RIS was not achieved, the evidence was insufficient to form a conclusion, signalling the need for additional research.

We estimated RIS for dichotomous outcomes based on the observed proportion of patients with an outcome in the nalbuphine group (the cumulative proportion of patients with an event relative to all patients in the control/placebo group), a 30% relative risk reduction in the control/placebo group, an alpha of 5% for all our outcomes, a beta of 20% and the observed diversity as suggested by the trials in the meta-analysis.

RESULTS

Results of literature search

A total of 240 articles were identified in the initial search from the databases [Figure 1]. After removing

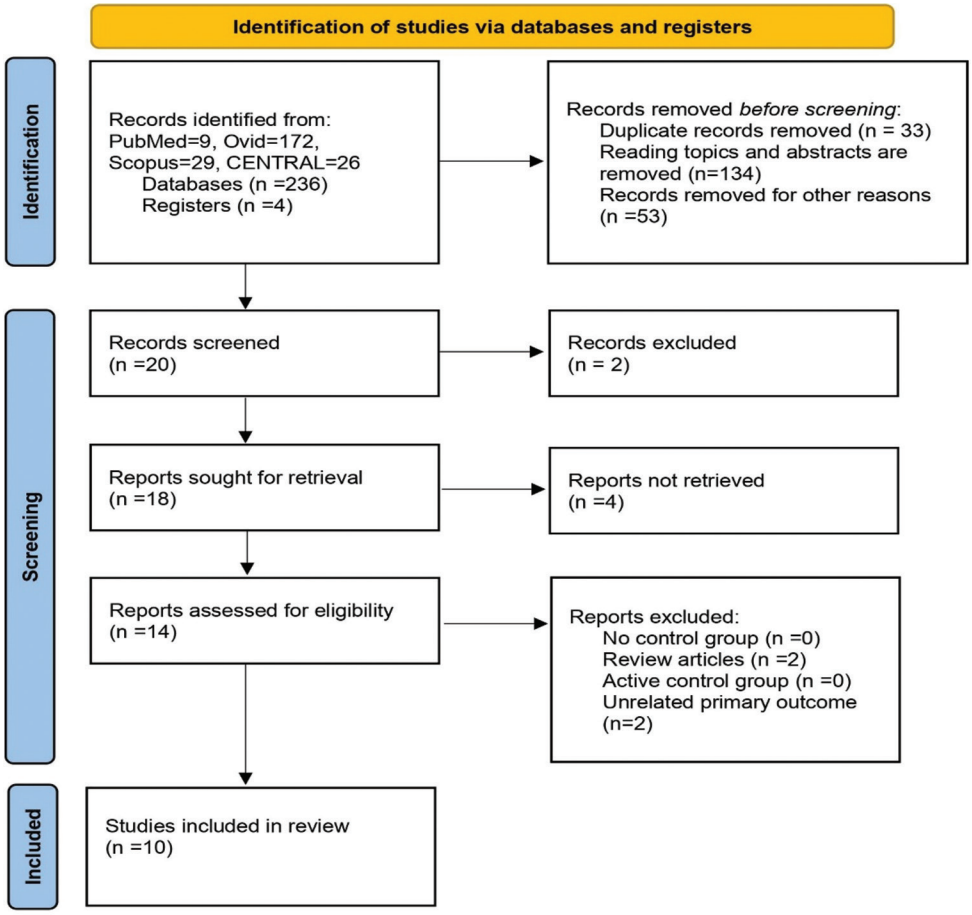

Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart

duplicates and articles that were not relevant, there were 10 eligible articles. Ten eligible RCTs published from January 2000 to May 2023 were included in the analysis.[21-30] A total of 700 patients were included in the analysis, of which 350 received IV nalbuphine and 350 received control, either a placebo or any other anti-shivering agent. All the included studies with all the relevant details have been summarised in Table 1. Patients in all RCTs were administered spinal anaesthesia, with spinal–epidural anaesthesia administered in one study.[25]

The route of administration of nalbuphine was IV in all RCTs with variable timing of administration. Out of 10 studies, in six studies, IV nalbuphine was compared to IV tramadol,[26-29] IV meperidine[22] and dexmedetomidine.[30] In the other four included RCTs, more than two groups were studied. In one study, nalbuphine was compared to tramadol, ondansetron and a placebo.[21] In two studies, nalbuphine was compared to dexmedetomidine and placebo.[23,25] In another study, nalbuphine was compared to ondansetron and a placebo.[24]

Time of administration

The time of administration was variable in the included RCTs. In six studies, nalbuphine or control was administered when the grade of shivering was 3 or 4.[21,23,25,27,29,30] In two studies, the drug was administered once shivering was noted, irrespective of the grade.[22,28] In one study, the intervention was done when the shivering grade was between 2 and 4.[26] In one study, the drug was administered before spinal anaesthesia, irrespective of shivering.[24]

Risk of bias in included studies

The risk of bias within the trials according to RoB-2 was assessed [Figure 2a]. The summary plot of the quality assessment is shown in Figure 2b. The bias from the randomisation process was low in nine studies,[21-25,27-30] and there was no information in one study.[26]

Bias due to deviations from intended interventions (allocation concealment) was low in eight studies[21,23-25,27-30] and high in two studies.[22,26] Bias arising due to missing outcome data was low in five

Table 1: Characteristics of the included studies in the meta-analysis

Authors/ year	Country	Type of study	Surgery performed	Type of anaesthesia	Number of patients	Comparator
Kyokong *et al*.[21]/2007	Thailand	Prospective, randomised, double-blind study	Caesarean section	Spinal	Nalbuphine- 70, tramadol- 71, ondansetron- 70, placebo- 69	Tramadol- 0.5 mg/kg, ondansetron- 0.1 mg/kg, placebo
Chowdhury *et al*.[22]/2007	Bangladesh	Randomised study	Caesarean section	Spinal	60 (nalbuphine- 30, pethidine- 30)	Pethidine 25 mg
Megalla *et al*.[23]/2017	Egypt	Randomised, double-blind, controlled study	Vaginal hysterectomy	Spinal	75 patients (25- nalbuphine, 25- dexmedetomidine, 25- placebo)	Dexmedetomidine- 0.5 µg/kg, saline
Liu *et al*.[24]/2019	China	Randomised, double-masked, controlled clinical trial	Caesarean section	Spinal	60 patients (nalbuphine- 20, ondansetron- 20, saline- 20)	Ondansetron 8 mg
Sun *et al*.[25]/2019	China	Double-blind, randomised, controlled study	Caesarean section	Spinal	120 (nalbuphine- 40, dexmedetomidine- 40, saline- 40)	Dexmedetomidine 0.5 µg/kg
Taneja *et al*.[26]/2019	India	Randomised study	Caesarean section	Spinal	60 (nalbuphine- 20, tramadol- 20, saline- 20)	0.25 mg/kg tramadol
Nirala *et al*.[27]/2020	India	Randomised, double-blinded, comparative study	Non-obstetric surgical procedures	Spinal	90 (nalbuphine- 45, tramadol- 45)	1 mg/kg tramadol
Thomas *et al*.[28]/2021	India	Randomised clinical trial	Lower limb orthopaedic surgeries	Spinal	60 (nalbuphine- 30, tramadol- 30)	1 mg/kg tramadol
Tudimilla *et al*.[29]/2021	India	Prospective, randomised, double-blinded study	Lower limb surgeries, percutaneous nephrolithotomy	Spinal	60 (nalbuphine- 30, tramadol- 30)	1 mg/kg tramadol
Kaur *et al*.[30]/2022	India	Randomised, prospective trial	Lower limb orthopaedic and gynaecological surgeries	Spinal	80 (nalbuphine- 40, dexmedetomidine- 40)	Dexmedetomidine 0.5 µg/kg

Authors/ year	Dose of nalbuphine used	Primary outcome	Secondary outcome	Conclusions
Kyokong *et al*.[21]/2007	0.05 mg/kg	Compare the efficacy of nalbuphine, tramadol, ondansetron and placebo for treating post-anaesthetic shivering after intrathecal morphine in caesarean delivery patients	Onset of shivering, success of controlling shivering, recurrence of shivering after treatment, adverse events (pruritus, sedation, PONV)	Tramadol and nalbuphine were superior to ondansetron in the treatment of post-anaesthetic shivering
Chowdhury *et al*.[22]/2007	5 mg	To compare the efficacy of nalbuphine with pethidine in controlling post-anaesthesia shivering	Duration of surgery, haemodynamics	Nalbuphine and pethidine in the doses used were comparable in controlling post-anaesthesia shivering
Megalla *et al*.[23]/2017	0.07 mg/kg	To clinically compare the ability of either drug to control post-spinal shivering effectively	To compare haemodynamics, complications, side effects and cost-effectiveness	Dexmedetomidine was found to be better than nalbuphine for treatment of post-spinal shivering due to its shorter response time, lower recurrence rate and associated sedation, but nalbuphine provided haemodynamic stability and is cost-effective
Liu *et al*.[24]/2019	0.08 mg/kg	To compare the incidence of maternal shivering during the period from intrathecal drug injection to delivery	To compare the incidence and severity of maternal shivering (30, 60 and 120 min of spinal anaesthesia), neonatal Apgar scores (1 and 5 min after delivery), the pH and base excess from umbilical artery blood gas analysis, haemodynamics and sedation scores	Nalbuphine prevented post-spinal anaesthesia shivering in parturients undergoing urgent caesarean delivery, but caused transient dizziness, while ondansetron 8 mg had no significant effect
Sun *et al*.[25]/2019	0.07 mg/kg	To compare the time to cessation of shivering between two groups	Success rate, recurrence rate, adverse events, haemodynamics	Nalbuphine has a significantly better effect in reducing shivering with lesser adverse reactions compared to dexmedetomidine

Contd...

Table 1: Contd...

Authors/ year	Dose of nalbuphine used	Primary outcome	Secondary outcome	Conclusions
Taneja *et al*.[26]/2019	0.28 mg/kg	To compare the effectiveness of the anti-shivering action of tramadol and nalbuphine after spinal anaesthesia	Recurrence rate, success rate	Both nalbuphine and tramadol provide similar rapid and potent anti-shivering effects
Nirala *et al*.[27]/2020	0.06 mg/kg	To compare the efficacy of nalbuphine and tramadol for the treatment of post-anaesthetic shivering following subarachnoid block	Onset of shivering, recurrence, adverse events	The time taken for cessation of shivering is significantly less with nalbuphine compared to tramadol
Thomas *et al*.[28]/2021	0.1 mg/kg nalbuphine	To compare the efficacy of nalbuphine and tramadol in treating post-spinal shivering	To evaluate the haemodynamic profile and side effects of these drugs	Nalbuphine has greater efficacy than tramadol in controlling post-spinal anaesthesia shivering, with minimal side effects
Tudimilla *et al*.[29]/2021	0.05 mg/kg	To compare the efficacy of haemodynamic changes due to nalbuphine and tramadol, when used for the control of post-spinal anaesthesia shivering	To compare the complications and adverse effects associated with the drugs	Both drugs are effective in treating patients with post-spinal anaesthesia shivering
Kaur *et al*.[30]/2022	0.08 mg/kg	To compare the efficacy of both the drugs in terms of response time	To compare recurrence, time of shivering, adverse events	Dexmedetomidine is a better alternative than nalbuphine for the treatment of post-spinal shivering with quicker response time and side effects comparable to nalbuphine

PONV=Postoperative nausea vomiting

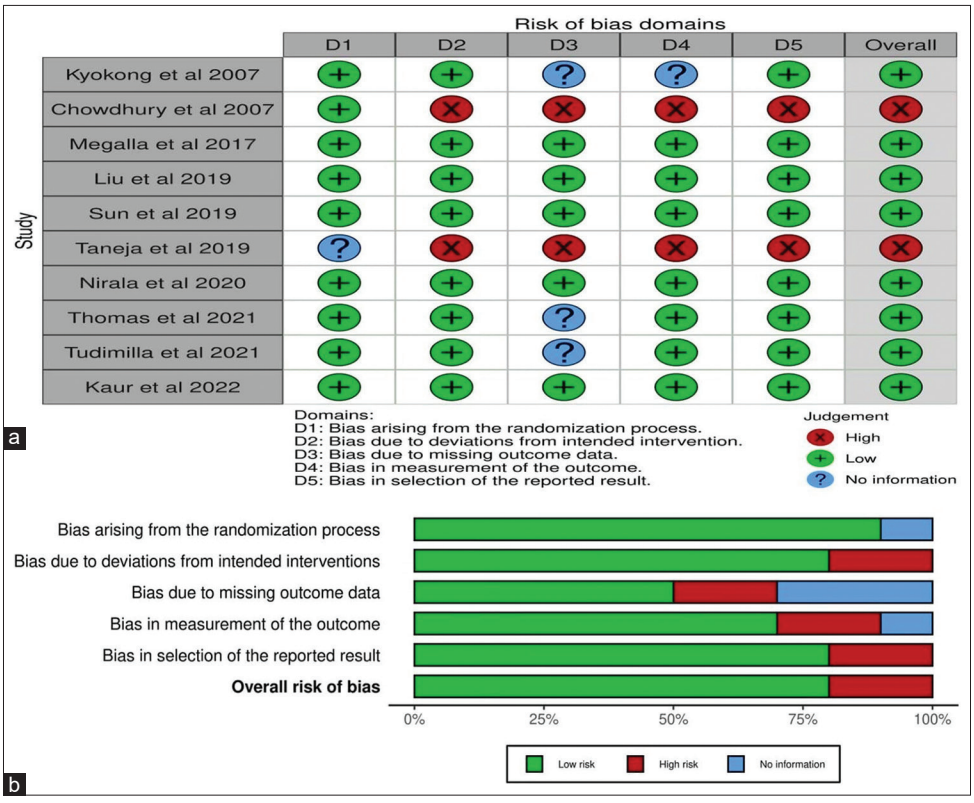

Figure 2: Bias assessment. (a) Traffic light plot. (b) Summary plot

studies,[23-25,27,30] high in two studies[22,26] and there was no information in three studies.[21,28,29] Bias in the measurement of outcome was low in seven studies,[23-25,27-30] high in two studies[22,26] and there was no information in one study.[21] Bias arising due to the selection of reported results was low in all studies,[21,23-25,27-30] except for two studies in which the bias was high.[22,26] The overall bias was low.

Quality of evidence

Using the GRADE system, the 11 outcomes were assessed for the quality of evidence [Table 2]. The quality of evidence was moderate for the following outcomes: the success of treating shivering: nalbuphine versus control and placebo, the timing of shivering: nalbuphine versus control, shivering grade: nalbuphine versus dexmedetomidine, recurrence of shivering: nalbuphine versus control and placebo, PONV: nalbuphine versus control and placebo, and incidence of hypotension: nalbuphine versus control. The quality of evidence was low for shivering grade: nalbuphine versus tramadol and placebo.

Primary outcome meta-analysis

Meta-analysis of success rate

Five studies reported success rates between two groups (179 patients in the nalbuphine group and 179 patients in the control group).[21,23,25,26,28] Meta-analysis revealed a comparable success rate between nalbuphine and control, that is, with active medication (RR: 0.97, 95% CI: 0.91, 1.04; $P = 0.46$, $I^2 = 0\%$) (GRADE = moderate) [Figure 3a].

Four studies reported success rates between the nalbuphine group (155 patients) and placebo (154 patients).[21,23,25,26] Meta-analysis revealed a statistically significant success rate in the nalbuphine group when compared to placebo (RR: 2.37, 95% CI: 1.91, 2.94; $P = 0.04$, $I^2 = 94\%$) (GRADE = moderate) [Figure 3b]. For the primary outcome of the success of shivering with nalbuphine versus placebo, TSA revealed that the accrued information size ($n = 309$) reached 99% of the estimated RIS ($n = 311$). The cumulative Z score crossed the trial sequential monitoring and conventional boundary. Therefore, TSA of the pooled meta-analysis showed firm evidence for the anticipated intervention effect [Figure 4].

Meta-analysis of the grade of shivering

Three studies reported the grade of shivering between the nalbuphine group and the tramadol group as control (95 patients in the nalbuphine group and 95 patients in the tramadol group).[26-28] Meta-analysis revealed that the grade of shivering between the nalbuphine and control (tramadol) groups was comparable (RR: 0.98, 95% CI: 0.81, 1.20; $P = 0.88$, $I^2 = 0\%$) (GRADE = low) [Figure 3c].

Four studies reported a grade of shivering between the nalbuphine (125 patients) and the dexmedetomidine (125 patients) groups.[23-25,30] Meta-analysis revealed a comparable grade of shivering between the nalbuphine and dexmedetomidine groups (RR: 0.95, 95% CI: 0.81, 1.12; $P = 0.58$, $I^2 = 84\%$) (GRADE = moderate) [Figure 3d].

Five studies reported the grade of shivering in the nalbuphine and placebo groups (135 patients in the

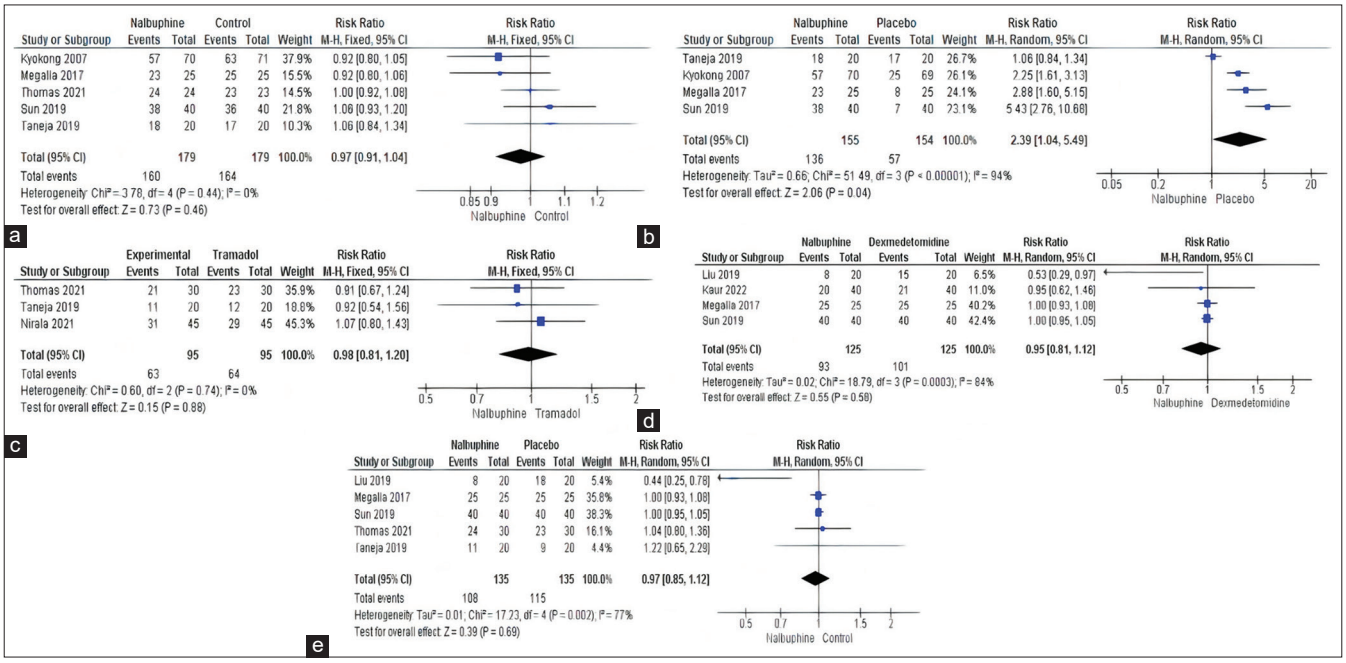

Figure 3: (a) Forest plot comparing the success of treating shivering between nalbuphine and the control group. (b) Forest plot comparing the success of treating shivering between nalbuphine and placebo. (c) Forest plot comparing the grades of shivering between nalbuphine and tramadol. (d) Forest plot comparing the grades of shivering between nalbuphine and dexmedetomidine. (e) Forest plot comparing the grades of shivering between nalbuphine and placebo

Table 2: GRADE strength of evidence

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Nalbuphine	Control or placebo	Relative (95% CI)	Absolute (95% CI)		
Success of treating shivering: nalbuphine versus control												
5	Randomised trials	Not serious	Not serious	Serious	Not serious	None	160/170 (94.1%)	164/170 (96.5%)	RR 0.97 (0.91-1.04)	29 fewer per 1000 (from 87 fewer to 39 more)	⊕⊕⊕◯ Moderate	CRITICAL
Success of treating shivering: nalbuphine versus placebo												
4	Randomised trials	Not serious	Not serious	Serious	Not serious	None	136/155 (87.7%)	57/154 (37.0%)	RR 2.39 (1.04-5.49)	514 more per 1000 (from 15 more to 1000 more)	⊕⊕⊕◯ Moderate	CRITICAL
Shivering grade: nalbuphine versus tramadol												
3	Randomised trials	Serious	Not serious	Not serious	Not serious	Publication bias strongly suspected	63/95 (66.3%)	64/95 (67.4%)	RR 0.98 (0.81-1.20)	13 fewer per 1000 (from 128 fewer to 135 more)	⊕⊕◯◯ Low	CRITICAL
Shivering grade: nalbuphine versus dexmedetomidine												
4	Randomised trials	Not serious	Not serious	Not serious	Not serious	Publication bias strongly suspected	93/125 (74.4%)	101/125 (80.8%)	RR 0.95 (0.81-1.12)	40 fewer per 1000 (from 154 fewer to 97 more)	⊕⊕⊕◯ Moderate	CRITICAL
Shivering grade: nalbuphine versus placebo												
5	Randomised trials	Serious	Not serious	Not serious	Not serious	Publication bias strongly suspected	108/135 (80.0%)	115/135 (85.2%)	RR 0.97 (0.85-1.12)	26 fewer per 1000 (from 128 fewer to 102 more)	⊕⊕◯◯ Low	CRITICAL
Recurrence of shivering: nalbuphine versus control												
6	Randomised trials	Serious	Not serious	Not serious	Not serious	None	24/175 (13.7%)	22/184 (12.0%)	RR 1.15 (0.69-1.94)	18 more per 1000 (from 37 fewer to 112 more)	⊕⊕⊕◯ Moderate	CRITICAL
Recurrence of shivering: nalbuphine versus placebo												
3	Randomised trials	Not serious	Not serious	Not serious	Not serious	Publication bias strongly suspected	16/120 (13.3%)	19/73 (26.0%)	RR 0.47 (0.26-0.83)	138 fewer per 1000 (from 193 fewer to 44 fewer)	⊕⊕⊕◯ Moderate	CRITICAL
Timing of shivering: nalbuphine versus control												
6	Randomised trials	Not serious	Not serious	Not serious	Very serious	None	250	249	-	MD 0.31 lower (1.34 lower to 0.72 higher)	⊕⊕◯◯ Low	CRITICAL
PONV: nalbuphine versus control												
4	Randomised trials	Not serious	Not serious	Not serious	Not serious	Publication bias strongly suspected	32/175 (18.3%)	48/176 (27.3%)	RR 0.67 (0.47-0.95)	90 fewer per 1000 (from 145 fewer to 14 fewer)	⊕⊕⊕◯ Moderate	CRITICAL
PONV: nalbuphine versus placebo												
3	Randomised trials	Not serious	Not serious	Not serious	Not serious	Publication bias strongly suspected	18/130 (13.8%)	15/129 (11.6%)	RR 1.20 (0.68-2.12)	23 more per 1000 (from 37 fewer to 130 more)	⊕⊕⊕◯ Moderate	CRITICAL
Incidence of hypotension: nalbuphine versus control												
4	Randomised trials	Not serious	Not serious	Not serious	Not serious	Publication bias strongly suspected	7/129 (5.4%)	11/129 (8.5%)	RR 0.65 (0.27-1.58)	30 fewer per 1000 (from 62 fewer to 49 more)	⊕⊕⊕◯ Moderate	CRITICAL

CI=Confidence interval, GRADE=Grading of Recommendations, Assessment, Development, and Evaluations, MD=Mean difference, RR=Risk ratio

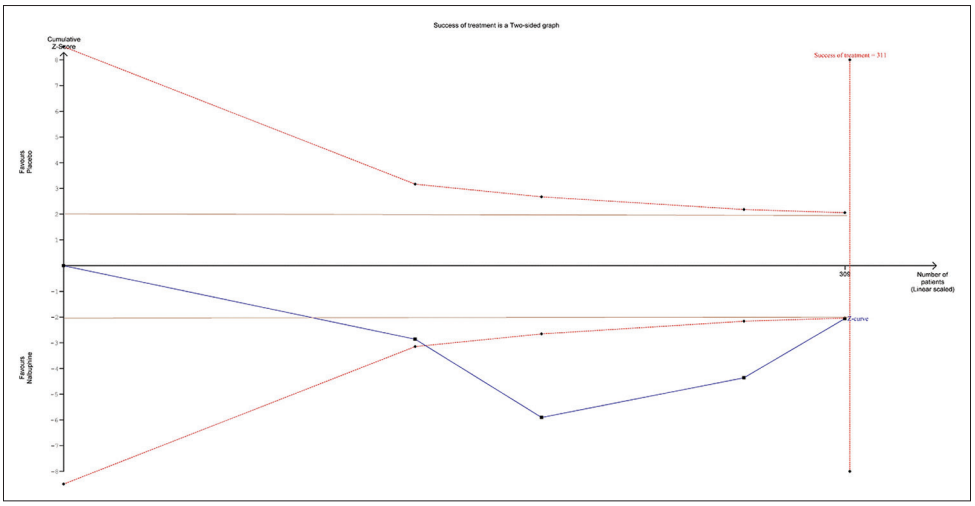

Figure 4: Trial sequential analysis for the effect of nalbuphine in controlling post-anaesthesia shivering. The lower half favours nalbuphine, and the upper half favours placebo. The horizontal brown line: conventional threshold for statistical significance at an Z-value of 1.96 (corresponds to $P = 0.05$). The curved red line: trial sequential boundaries. Blue line: cumulative Z-curve (each square is a trial). The blue line (cumulative Z-score line) crosses the brown lines, that is, conventional boundaries, suggesting nalbuphine's superiority over placebo. The curved red lines (above and below) have crossed the red vertical line, which indicates that the required information size (RIS) has reached

nalbuphine group and 135 patients in the placebo group).[23-26,28] Meta-analysis revealed a comparable grade of shivering in the nalbuphine and placebo groups (RR: 0.97, 95% CI: 0.85, 1.12; $P = 0.69$, $I^2 = 77\%$) (GRADE = low) [Figure 3e].

Meta-analysis of recurrence of shivering after the intervention

Six studies reported a recurrence of shivering after medication use (175 patients in the nalbuphine group and 184 patients in the control group).[21,23,25,26,28,30] Meta-analysis revealed a comparable incidence of recurrence of shivering between the nalbuphine and the control groups (RR: 1.15, 95% CI: 0.69, 1.94; $P = 0.59$, $I^2 = 12\%$) (GRADE = moderate) [Figure 5a].

Three studies reported a recurrence of shivering after the use of medication between the nalbuphine group (120 patients) and placebo (73 patients).[21,23,25] Meta-analysis revealed significantly lesser incidence of recurrence of shivering in the nalbuphine group when compared to placebo (RR: 0.47, 95% CI: 0.26, 0.83; $P = 0.01$, $I^2 = 61\%$) (GRADE = moderate) [Figure 5b]. TSA revealed that the accrued information size ($n = 193$) reached 23% of the estimated RIS ($n = 810$), much below RIS. The cumulative Z score curve did not cross the conventional boundary or trial sequential monitoring boundary [Appendix Supplementary File 2].

Meta-analysis of the time of shivering

Six studies reported the time of shivering after spinal anaesthesia between the nalbuphine group (250 patients) and the control (249 patients).[21,23,25,27,29,30] Meta-analysis revealed comparable time of shivering between the nalbuphine and control groups (MD: −0.31, 95% CI: −1.34, 0.72; $P = 0.56$, $I^2 = 0\%$) (GRADE = moderate) [Figure 5c].

Meta-analysis of PONV

Four studies reported the incidence of PONV between the nalbuphine group (175 patients) and the control group (176 patients).[21,23-25] Meta-analysis revealed significantly lesser PONV in the nalbuphine group when compared to the control group (RR: 0.67, 95% CI: 0.47, 0.95; $P = 0.02$, $I^2 = 37\%$) (GRADE = moderate) [Figure 6a]. TSA revealed that the accrued information size ($n = 351$) reached 25% of the estimated RIS ($n = 1385$), much below RIS. The cumulative Z score curve did not cross the conventional boundary or trial sequential monitoring boundary [Supplementary File 3].

Three studies reported the incidence of PONV between two groups (130 patients in the nalbuphine group and 129 patients in the placebo group).[21,24,25] Meta-analysis revealed a comparable incidence of PONV in the nalbuphine and placebo groups (RR: 1.20, 95% CI: 0.68, 2.12; $P = 0.54$, $I^2 = 0\%$) (GRADE = moderate) [Figure 6b].

The study by Kyokong *et al*.[21] had two more control groups (ondansetron and tramadol), the study by Liu *et al*.[24] had another control group (ondansetron) and the study by Sun *et al*.[25] had dexmedetomidine as another control group. In the study by Nirala *et al*.,[27]

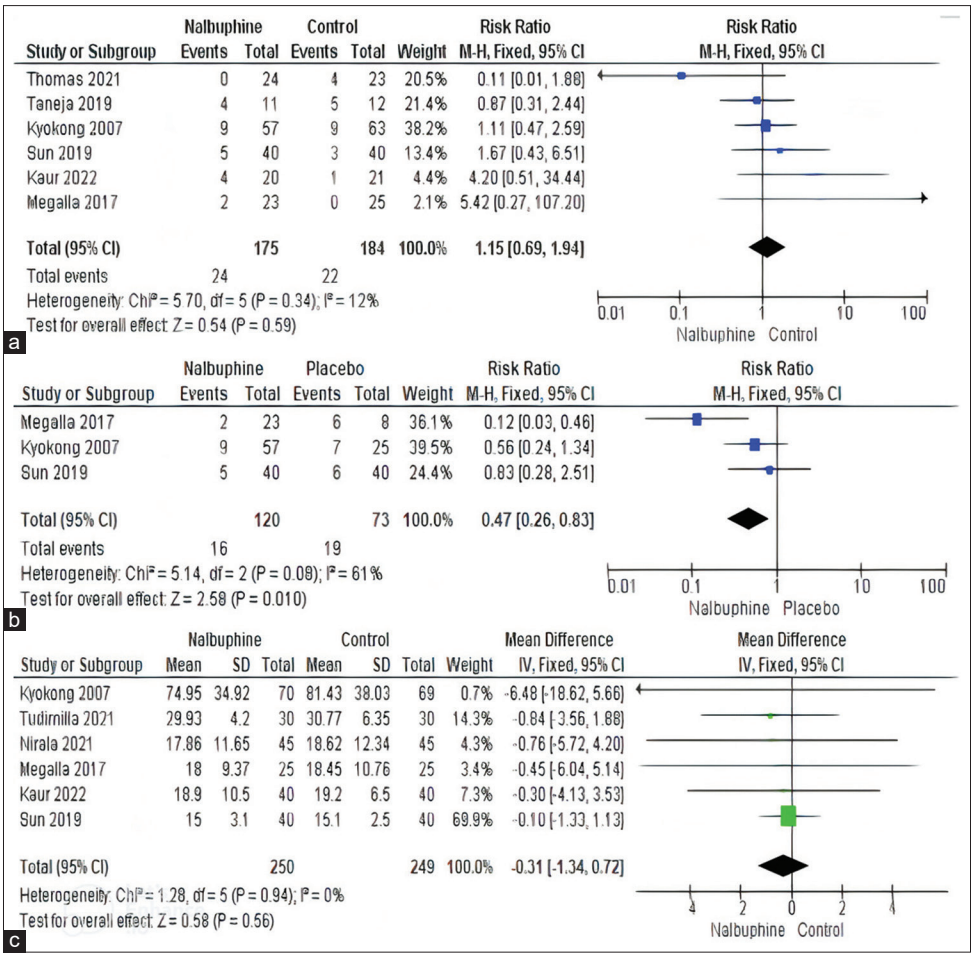

Figure 5: (a) Forest plot comparing recurrence of shivering between nalbuphine and control group. (b) Forest plot comparing recurrence of shivering between nalbuphine and placebo. (c) Forest plot comparing the timing of shivering between nalbuphine and the control group

the control was tramadol; in the other studies, the control was a placebo. This could explain why the control group had more PONV (when tramadol was used) than nalbuphine. However, as the control groups were inconsistent, a subgroup analysis for PONV still needed to be done.

Meta-analysis of hypotension

Four studies reported the incidence of hypotension between two groups (129 patients in the nalbuphine group and 129 patients in the control group).[23,25,28,30] Meta-analysis revealed comparable hypotension between nalbuphine and control groups (RR: 0.65, 95% CI: 0.27, 1.58; P = 0.34, I^2 = 35%) (GRADE = moderate) [Figure 6c].

Sensitivity analysis

The sensitivity analysis was performed by removing the studies which could lead to heterogeneity.[21,26] The results of sensitivity analysis were similar to those based on primary analysis.

Subgroup analysis

For outcomes like success rate of intervention, recurrence, grade of intervention and PONV, a subgroup analysis was done [Figures 3c, d, 5a, 6a].

Other outcomes

Two studies reported sedation or dizziness as absolute numbers and percentages: 1/70 (tramadol), 1/70 (nalbuphine), 4/71 (ondansetron), 1/69 (placebo),[21] and 5/25 (nalbuphine), 0/20 (ondansetron), 4/20 (placebo).[24] Sedation scores were reported by two studies as mean (SD): Nirala[27] (at zero, 1, 2, 3, 4, 5, 6 h) and in Tudimilla *et al*.[29] (nalbuphine: 2.3 (0.70); tramadol: 1.1 (0.3); P = 0.06). However, as the number of studies was less than three, a pooled analysis was not performed for the two outcomes.

DISCUSSION

Summary of results

This systematic review and meta-analysis revealed that IV nalbuphine, when used either prophylactically

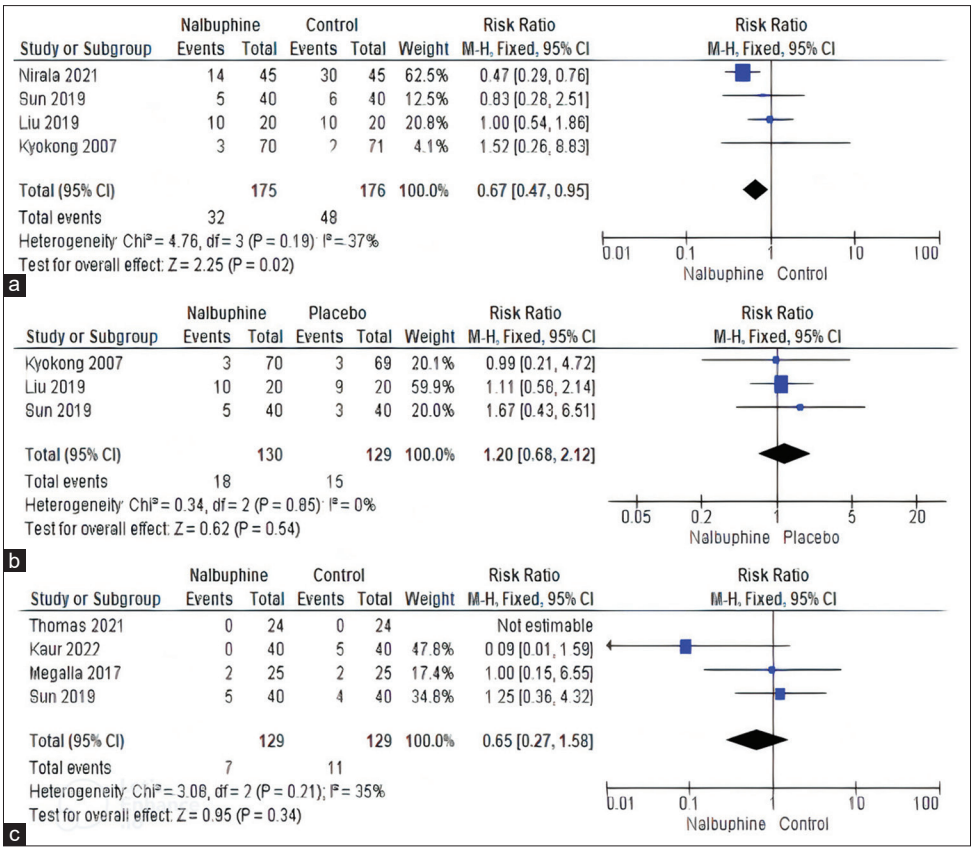

Figure 6: (a) Forest plot comparing postoperative nausea and vomiting (PONV) between nalbuphine and the control group. (b) Forest plot comparing PONV between nalbuphine and the placebo group. (c) Forest plot comparing the incidence of hypotension between nalbuphine and the control group

before or after induction of anaesthesia, is significantly better than a placebo, but is comparable in terms of safety and efficacy with a control group comprising other medications like tramadol, meperidine, ondansetron and dexmedetomidine. TSA of primary outcome attested that the studies reached RIS and demonstrated strong evidence of the therapeutic effect, which was the success rate of controlling shivering. The incidence of recurrence of shivering was significantly lesser when compared to placebo, but comparable with other medications. The incidence of PONV was significantly lesser in the nalbuphine group than the control group but was comparable to placebo.

Pharmacological interventions are required postoperatively to control shivering. The medications act by resetting the shivering threshold to a lower level, reducing or stopping shivering.[31-33] Several medications have been used in different doses for managing shivering experienced perioperatively. Opioids like tramadol and meperidine have been very effective in controlling shivering compared to placebo.[34-36] However, a study that compared 0.5 mg/kg meperidine to 1 mg/kg tramadol found tramadol superior to meperidine.[34] Eydi *et al*.[37] compared 0.2 mg/kg ketamine and 0.5 mg/kg pethidine in patients undergoing ear, nose throat (ENT) surgeries and found both drugs at the doses used to be equally effective.

Nallam *et al*.[38] demonstrated that prophylactic 8 mg IV ondansetron, when administered in parturients undergoing caesarean section under spinal anaesthesia, was effective in preventing or reducing the incidence of shivering compared to placebo. Entezari *et al*.[39] compared the anti-shivering efficacy of 4 mg ondansetron to 0.4 mg/kg of meperidine in females undergoing gynaecological surgeries under general anaesthesia. They found that both drugs were equally effective compared to placebo. In a study in which authors compared 25 mg meperidine, 0.1 mg/kg dexamethasone, to normal saline in patients undergoing surgeries under general anaesthesia, both dexamethasone and pethidine in the doses mentioned above were effective compared to placebo.[40] Lamontagne *et al*.[41] demonstrated that a single dose of 30 μg dexmedetomidine could control shivering in parturients undergoing caesarean section under

spinal anaesthesia compared to saline. In a systematic review by Wang *et al*.,[42] the authors compared the anti-shivering properties of dexmedetomidine and tramadol. They found dexmedetomidine to be superior in terms of early onset, lesser recurrence and fewer adverse events.

Nalbuphine is an opioid used IV for managing postoperative pain in adults and children effectively.[43,44] Besides being a partial mu-opioid receptor antagonist, nalbuphine is a kappa-opioid receptor agonist.[45-47] Several studies have investigated the anti-shivering properties of nalbuphine in the postoperative period.[48,49] This review concluded that nalbuphine is not superior but is comparable to other anti-shivering drugs in controlling shivering after central neuraxial block. Adverse events like PONV and hypotension are also comparable. There is insufficient evidence to advocate nalbuphine as an anti-shivering agent over other medications.

Our review has several limitations. The reporting of shivering was inconsistent and did not follow a single grading system. Secondly, the timing of administration was not uniform in all the studies. The comparators were not uniform in all the studies. The dose of nalbuphine used was also not consistent throughout the various studies. Adverse events like dizziness, PONV, hypotension and bradycardia were not consistently reported in all the included studies. Outcomes like length of stay in recovery and cost of treatment were not compared. Postoperative shivering is very uncomfortable, and patients expect immediate relief from such an uncomfortable experience. However, none of the studies reported patient satisfaction after the medications were used. In all studies, the medication was administered before the induction of anaesthesia, except in the study by Liu *et al*.[24] Some studies had a small sample size, which could overestimate the findings when included in the analysis. However, all the studies included in this analysis were RCTs with an overall low bias, which is the strength of this review. In all the studies, the consistency of shivering being investigated after spinal anaesthesia only was also noted. However, the results of this study should be interpreted with caution due to the clinical heterogeneity of the studies, variable doses investigated, variable comparators and different types of surgeries in which studies were conducted. Further studies are necessary to determine the time of administration and dosing of nalbuphine for various kinds of surgery.

CONCLUSIONS

Nalbuphine successfully controls postoperative shivering due to spinal anaesthesia with minimal adverse effects, reduces the recurrence of shivering, is significantly more efficient than a placebo and is comparable to other medications (tramadol, dexmedetomidine, ondansetron, pethidine).

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Nil.

Conflicts of interest

There are no conflicts of interest.

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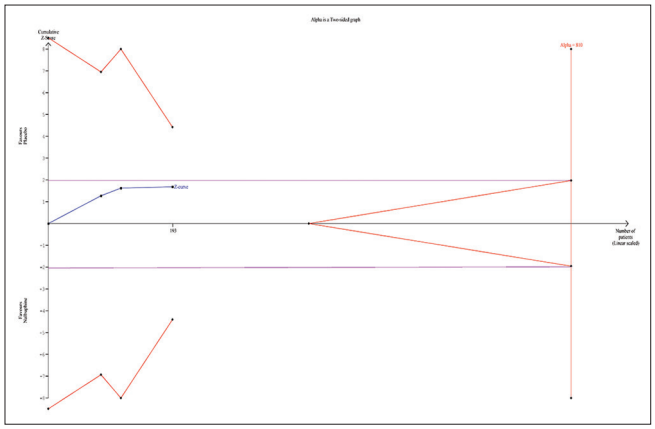
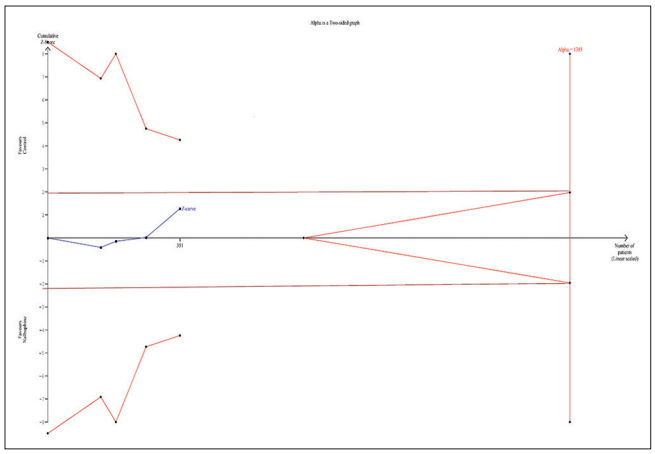
APPENDIX

Supplementary files:

Appendix Supplementary File 1: Details of database search	
Database	**Search details**
PubMed	(“nalbuphine”[MeSH Terms] OR “nalbuphine”[All Fields] OR “nalbuphin”[All Fields]) AND (“shiverers”[All Fields] OR “shivering”[MeSH Terms] OR “shivering”[All Fields] OR “shiver”[All Fields] OR “shivered”[All Fields] OR “shiverer”[All Fields] OR “shiverings”[All Fields] OR “shivers”[All Fields]) AND (“postoperative period”[MeSH Terms] OR (“postoperative”[All Fields] AND “period”[All Fields]) OR “postoperative period”[All Fields] OR “postop”[All Fields] OR “postoperative”[All Fields] OR “postoperatively”[All Fields] OR “postoperatives”[All Fields])
Ovid	(Nalbuphine AND Shivering And postoperative). mp. [mp=tx, bt, ti, ab, ct, sh, hw, tn, ot, dm, mf, dv, kf, fx, dq, nm, ox, px, rx, an, ui, ds, on, sy, ux, mx, pt]
Scopus	TITLE-ABS -KEY (Nalbuphine AND Shivering AND Postoperative)
CENTRAL	“Nalbuphine “AND “Shivering” AND “Postoperative” in Title Abstract
	Keyword



Appendix Supplementary File 2: Trial sequential analysis for the effect of nalbuphine in controlling post-anaesthesia shivering



Appendix Supplementary File 3: Trial sequential analysis comparing postoperative nausea vomiting between nalbuphine and placebo