Use of Nalbuphine for Treatment of Neuraxial Opioid-Induced Pruritus: A Systematic Review and Meta-Analysis

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Opioid-induced pruritus is prevalent after neuraxial administration of opioid. A number of preventive measures have been reported; however, only a few studies evaluated treatment strategies for established pruritus. The pharmacokinetics and pharmacodynamic profiles of nalbuphine make this drug ideal for the treatment of established pruritus. The primary outcome of this systematic review and meta-analysis was the incidence of pruritus after neuraxial opioid administration. Secondary outcomes were the incidence of sedation and postoperative nausea and vomiting. Pooled estimates were reported by calculating the risk ratio (RR) with 95% confidence interval (CI). Five trials consisting of 494 patients were included for analysis. There was a low quality of evidence that nalbuphine was effective in reducing the incidence of pruritus compared with active control (RR, 0.59; 95% CI, 0.38 to 0.93; P = .02). Conversely, there was no difference between the incidence of sedation (RR, 1.06; 95% CI, 0.42 to 2.71; P = .90) and postoperative nausea and vomiting (RR, 1.58, 95% CI, 0.75 to 3.31; P = .23). Although large studies are needed to decrease heterogeneity across studies, the current review showed that nalbuphine appears to reduce the incidence of opioid-induced pruritus.

Keywords: Epidural, morphine, nalbuphine, opioid-induced pruritus, spinal.

The addition of opioids in a neuraxial blockade contributes to a number of clinical advantages, including enhanced analgesic effects, profound sensory blockade, and rapid sensory and motor recovery.1,2 However, the addition of opioid in spinal or epidural anesthesia causes adverse side effects such as pruritus, which is troublesome to many patients and is a factor of low patient satisfaction scores. Neuraxial opioid-induced pruritus (OIP) is a common side effect, with a prevalence rate ranging between 50% and 100% despite prophylactic measures.3,4 Some pharmacologic agents including ondansetron, naloxone, diclofenac, propofol, droperidol, and gabapentin have been studied for the prevention and treatment of OIP.3 Nalbuphine is one of the agents that has been studied, and results from clinical trials demonstrated that prophylactic nalbuphine might reduce the incidence of pruritus. Yet, studies evaluating pharmacologic treatments of pruritus have been scarce and report conflicting results.

The efficacy of nalbuphine has been postulated based on its pharmacologic profiles. Nalbuphine is a μ-receptor antagonist and a κ-receptor agonist.3,5-7 The activation of the κ opioid receptors accounts for its utility as a treatment agent for pruritus. Although some clinical studies have reported on the use of nalbuphine prophylactically, only a few studies have evaluated the effect of nalbuphine as a treatment of established pruritus. The results of these studies are clinically relevant and add to the treatment regimen of pruritus.

The objective of this systematic review and meta-analysis was to evaluate the efficacy of nalbuphine in treating OIP after the administration of a neuraxial opioid.

Methods
This systematic review with meta-analysis was conducted following the guidelines set by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.8 The clinical PICO (Patient, Intervention, Comparison, and Outcome) question that guided the search of the literature was, In patients with a neuraxial opioid, how does nalbuphine affect the incidence of neuraxial OIP?

• Search Strategy and Study Selection. The following key terms were used to search for evidence with appropriate Boolean mechanics: nalbuphine, epidural, spinal, opioid-induced pruritus, and neuraxial. The electronic databases searched were MEDLINE (PubMed), Google Scholar, Cumulative Index to Nursing and Allied Health Literature, the Cochrane Review Database, Embase, and Scopus. Gray literature databases including www.clinicaltrials.gov, conference abstracts, and poster presentations were explored to reduce reporting bias. Additional
studies were retrieved using the ancestry approach. The last search for evidence was performed on June 7, 2018.

The titles and abstracts of relevant results were evaluated using predetermined inclusion criteria. A discussion among the authors resolved any disagreement on included articles. The full text of each relevant article was obtained, and data were extracted for analysis.

- **Inclusion and Exclusion Criteria.** The authors evaluated the abstracts based on the following 3 inclusion criteria identified before the literature search: randomized controlled trials (RCTs) evaluating the use of nalbuphine as a treatment of established neuraxial OIP compared with active control, use of nalbuphine regardless of route of administration, and English-language peer-reviewed articles. The studies were excluded if they involved non-neuraxial administration route of opioids, retrospective studies, descriptive articles, editorials, or case reports.

- **Data Extraction.** A pilot-studied and standardized data extraction template was used to tabulate the results of each study. The following information was obtained from each trial: the total number of participants; ASA physical status classification; the incidence of neuraxial OIP after treatment; the dose and type of opioid used; the dose, route, and timing of nalbuphine administration; types of surgical procedures; types of neuraxial techniques; incidence of sedation as defined by the trial's authors; the rate of postoperative nausea and vomiting (PONV); and other adverse effects.

- **Assessment of Risk of Bias.** Two authors appraised the included RCTs and assessed the methodologic quality of each study according to the Risk of Bias algorithm outlined in the *Cochrane Handbook for Systematic Reviews of Intervention.* The evaluators assessed the quality of the study or report based on random sequence generation; allocation concealment; blinding of participants, personnel, and outcomes assessors; incomplete outcomes

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Figure 1. PRISMA Flowchart of Literature Screening and Study Selection
Abbreviation: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.
data; selective reporting; and other sources of bias. Two independent authors rated the study as “high risk,” “low risk,” or “unclear risk,” and each evaluator was instructed to identify the reasons for each rating. Another review author resolved any discrepancies or disagreements in the appraisal of the quality of the studies.

• Summary of Measures and Statistical Analysis. The primary outcome was the incidence of neuraxial OIP. The overall number of patients with pruritus after treatment (defined by the trial’s authors) with nalbuphine and the other active control medications reported in each study was used to pool estimates of pruritus incidence. To minimize observational bias due to different methods used to determine the presence and absence of pruritus, we considered data classified as mild, moderate, and severe pruritus to be pruritus events. The secondary outcomes were the incidence of sedation and the rate of PONV.

The incidence of neuraxial OIP, sedation, and PONV was estimated by calculating the pooled risk ratio (RR) with 95% confidence interval (CI). The random-effects model was used to pool the estimates anticipating methodologic and clinical heterogeneity of data. For the binary endpoint, a significant effect compared with placebo needed a 95% CI not to include one.

If any data were not explicitly reported, study authors were contacted for additional raw data. In RCTs with multiarm groups, data were processed individually. Moreover, in studies when opioids were administered initially in the subarachnoid space and followed by an epidural infusion, the opioid used in the latter section of the anesthesia technique was counted as the type of anesthetic and dosage of opioid used for that RCT. Trials with data not suitable for meta-analysis were described qualitatively in the review.

Heterogeneity was assessed using $I^2$ statistics. As described in the Cochrane Handbook for Systematic Reviews of Intervention, the following model was used in determining heterogeneity: an $I^2$ statistic of 0% to 40% indicated low heterogeneity; 30% to 60%, moderate heterogeneity; 50% to 90%, substantial heterogeneity; and 75% to 100%, considerable heterogeneity. For exploration of clinical and methodologic heterogeneity, a priori subgroup and sensitivity analyses were designed. Subgroup analyses investigated the incidence of neuraxial OIP in obstetric and nonobstetric surgery, lipophilic and hydrophilic opioids, and the epidural and subarachnoid routes of opioid administration. A sensitivity analysis was performed by removing studies with a high risk of bias one study at a time. If results from sensitivity analysis were unchanged, we concluded that the risk of bias did not influence the effect estimates.

The overall quality of evidence was rated using the Grading of Recommendation, Assessment, Development and Evaluation (GRADE) approach. The GRADE method categorizes outcomes as “high,” “moderate,” “low,” or “very low.” Because all evidence included in this review was from RCTs, the baseline quality of evidence was graded as “high.” Consequently, an outcome was downgraded by 1 level for serious concerns and 2 levels for very serious concerns about the risk of bias assessment, inconsistency, imprecision, indirectness, and high probability of publication bias.

Results
The initial search yielded 58 RCTs. After a comprehensive review of the titles and abstracts, 5 studies were included in the review and meta-analysis. The flowchart in Figure 1 details the search of the review.

The opioids used either intrathecally or via the epidural space were preservative-free morphine and fentanyl. Different opioid dosages were administered. The dose of nalbuphine differed, and the route of administration varied after confirming the presence of pruritus using a self-invented Likert scale assessment tool. Propofol, naloxone, ondansetron, chlorpheniramine, and diphenhydramine were the active controls examined in all studies. Table 1 summarizes the characteristics of the included studies.

• Primary Outcome: Incidence of Neuraxial Opioid-Induced Pruritus. The primary endpoint of the current meta-analysis is presented in Figure 2. Five studies consisting of 494 patients were evaluated for the efficacy of nalbuphine to treat neuraxial pruritus (see Figure 2).
<table>
<thead>
<tr>
<th>Source</th>
<th>No./ASA class/procedure type</th>
<th>Opioids</th>
<th>Study group</th>
<th>Outcome measure</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cruz-Ferretti et al., 11 2014</td>
<td>28 ASA classes 1-2 Non-OB surgery</td>
<td>Morphine, 100 µg, subarachnoid or via epidural space or both</td>
<td>Intervention: Nalbuphine, 4 mg IV</td>
<td>No significant difference in incidence of pruritus in nalbuphine and ondansetron. More patients complained of pruritus in first 12 h vs 2 and 6 h after administration of opioid.</td>
<td>Allocation concealment was not clear. No assessment tool used to assess presence or absence of pruritus.</td>
</tr>
<tr>
<td>Mohd Salleh et al., 12 2012</td>
<td>200 ASA classes 1-2 C-section</td>
<td>Combination of morphine, 200 µg, and 25 µg of fentanyl subarachnoid</td>
<td>Intervention: Nalbuphine, 4 mg IV; repeated every 8 h for 24 h only.</td>
<td>Lesser number of patients complained of pruritus 6, 8, 12 and 24 h after opioid administration in patients treated with nalbuphine vs chlorpheniramine.</td>
<td>Did not evaluate other outcomes. Assessment tool to grade severity of pruritus: 0 = no pruritus to 3 = severe pruritus.</td>
</tr>
<tr>
<td>Charuluxananan et al., 13 2001</td>
<td>181 ASA classes 1-2 C-section</td>
<td>Morphine, 200 µg, subarachnoid</td>
<td>Intervention: Nalbuphine, 2 mL of 3 mg IV</td>
<td>There were few patients treated with nalbuphine who had pruritus vs propofol (P &lt; .001). More patients had recurrence of pruritus in nalbuphine group than propofol group.</td>
<td>Decreased pain scores were observed in nalbuphine group. Pruuritus assessment tool used following scale: 1 = no pruritus; 2 = mild pruritus, treatment not requested; 3 = moderate pruritus, treatment requested; and 4 = severe pruritus. Only patients with a pruritus score of ≥ 3 received treatment medications. Overall pruritus incidence was 62%.</td>
</tr>
<tr>
<td>Alhashemi et al., 14 1997</td>
<td>45 ASA classes 1-2 C-section</td>
<td>Morphine, predetermined doses of 5 mg, 10 mg, and 10 mg IV</td>
<td>Intervention: Nalbuphine, predetermined doses of 25 mg, 50 mg, and 50 mg</td>
<td>Successful treatment with nalbuphine is higher than in patients treated with diphenhydramine (P &lt; .01).</td>
<td>Similar frequency of sedation in both groups. Pruuritus assessed using VAS (0 = no pruritus and 10 = severe pruritus). Patients with pruritus who requested treatment were included in the study. Overall incidence of pruritus was 90%.</td>
</tr>
<tr>
<td>Cohen et al., 15 1992</td>
<td>40 ASA classes 1-2 C-section</td>
<td>Morphine, 5 mg, epidural given immediately after delivery</td>
<td>Intervention: Nalbuphine, 5 mg, IV Two additional doses given if pruritus persisted; doses were administered at no less than 30-min interval</td>
<td>No difference in terms of efficacy between nalbuphine and naloxone in treating pruritus (P = .1).</td>
<td>Sedation higher in nalbuphine (P &lt; .05). Pain scores higher in naloxone (P &lt; .01). Assessment of pruritus (0 = none and 3 = severe pruritus). Patients with pruritus who requested treatment were included in the study. Overall incidence of pruritus was 45%.</td>
</tr>
</tbody>
</table>

Table 1. Summary of Evidence Sources Examining Use of Nalbuphine for Treatment of Neuraxial Opioid-induced Pruritus

Abbreviations: C-section, cesarean delivery; IV, intravenous; OB, obstetric; PONV, postoperative nausea and vomiting; VAS, visual analog score.

aNo standardized assessment tool was used to evaluate presence and absence of pruritus.

#α set at .05
Pooled estimates of the rate of pruritus were significantly lower in the nalbuphine group compared with active control (RR, 0.59; 95% CI, 0.38 to 0.93; P = .02). An I² statistic of 62% suggested substantial heterogeneity. A priori tests were performed to elucidate the causes of substantial heterogeneity and variations across all studies.

Four RCTs involving 466 patients who underwent cesarean delivery demonstrated that nalbuphine was more effective compared with active control in treating pruritus (RR, 0.51; 95% CI, 0.32 to 0.81; P = .004; I² = 60%). Only one RCT was done in a nonobstetric setting, consisting of 28 patients. This study demonstrated no difference in success rate in nalbuphine vs ondansetron.

When aggregate data from 4 studies using preservative-free morphine were combined, nalbuphine was not effective in treating pruritus (RR, 0.53; 95% CI, 0.28 to 1.01; P = .05; I² = 62%). Only one RCT used fentanyl, and therefore no meta-analysis was conducted.

Three studies administered opioid in the subarachnoid space. Pooled estimates showed that patients treated with nalbuphine had fewer episodes of pruritus compared with active control (RR, 0.50; 95% CI, 0.34 to 0.90; P = .02, I² = 62%). Only a single trial administered opioid via the epidural space, and 1 study did not clearly identify the number of subjects who received opioids in the subarachnoid or epidural space.

Secondary Outcomes. Figures 3 and 4 illustrate the forest plot of the secondary outcomes, which are the incidence of sedation and PONV. Two studies reported the incidence of sedation as defined by the trial’s authors (see Figure 3). The use of nalbuphine did not affect the number of patients who were considered sedated (RR, 1.06; 95% CI, 0.42 to 2.71; P = .90; I² = 54%).

Aggregate data from 3 RCTs demonstrated no difference in the incidence of PONV (RR, 1.58; 95% CI, 0.75 to 3.31; P = .23; I² = 38%; see Figure 4).

Risk of Bias. All studies were rated as low risk of random sequence generation. Two clinical trials reported adequate allocation concealment. Blinding of participants and study assessors were sufficient in 4 trials. The risks of bias of included studies are shown in Figure 5.

Quality of Findings. The quality of findings table was generated using GRADEpro software (Table 2). In this review, we drew our conclusions regarding the overall efficacy of nalbuphine on the treatment of established neuraxial OIP based on 5 studies consisting of 494 patients. We downgraded the evidence of the incidence of pruritus to low quality because of potential publication bias, the existence of clinical and methodologic heterogeneity, and imprecision. However, we found the quality of evidence for the frequency of sedation and PONV was moderate because of the small effect size.

Discussion
Several significant findings emerged from this meta-analysis. The administration of nalbuphine to treat established pruritus after neuraxial opioid was effective at a statistically significant level compared with active control. We found that the number of patients successfully treated with nalbuphine was higher compared with intravenous (IV) chlorpheniramine (47% vs 38%), diphenhydramine (83% vs 57%), propofol (92% vs 57%), and naloxone (80% vs 40%). Successful treatment of established pruritus required different nalbuphine doses
and treatment protocols. Alhashemi et al.\textsuperscript{14} administered 3 dosing regimens of IV nalbuphine, with subsequent doses given 30 minutes after the first dose if pruritus persisted. The first dosing regimen was 5 mg intravenously followed by a 10-mg IV dose if itchiness persisted. If the second dose of nalbuphine was ineffective, the patient received a third IV dose of 10 mg.\textsuperscript{14} One study used nalbuphine at 5 mg throughout the entire study, and 2 additional treatments using the same dose were administered 30 minutes after the first dose if pruritus symptoms continued.\textsuperscript{15} Three studies administered 3 mg\textsuperscript{13} or 4 mg\textsuperscript{12,13} of nalbuphine at 8-hour intervals if symptoms persisted. The variability in the doses and the frequency of nalbuphine make it challenging to make recommendations on an effective nalbuphine dose for the treatment of established pruritus.

The incidence of sedation was similar between nalbuphine and the active control groups. Although this outcome was based on only 2 RCTs\textsuperscript{13,14} combined, the finding is congruent with the reports in the previous review suggesting no increase in sedation with low-dose (4-mg) nalbuphine.\textsuperscript{16,17} However, this result should be cautiously interpreted because the studies did not describe how sedation was measured, which could introduce bias in the results.

The effect of nalbuphine on PONV was not statistically significant. In this review, we found no difference in PONV between use of nalbuphine and active control. Our finding is not similar to previous reports demonstrating an increased incidence of PONV.\textsuperscript{18} Our findings, although coming from only 3 RCTs, are promising because decreased PONV would improve patient satisfaction after opioid administration.

Postoperative pain scores were not estimated because of inadequate data to pool. However, Charuluxananan and colleagues\textsuperscript{13} reported no clinically significant decrease of pain score between their nalbuphine and propofol groups. As in the study by Cohen et al.,\textsuperscript{15} pain scores before and after treatment of nalbuphine remained the same.\textsuperscript{13} These outcomes were incongruent with previous RCTs and case reports demonstrating a reversal in pain control with the use of nalbuphine.\textsuperscript{19,21} In some reports, investigators recorded an increase in pain intensity with nalbuphine.

There are limitations to this review. We acknowledge that sample sizes and effect sizes of the studies included in this meta-analysis are small; hence, we recommend that extrapolation of the results should be guided following their limitations. In this review, we included studies comparing nalbuphine with a variety of active control agents. Although pooling the data from these studies yielded a statistically significant outcome, a clinically significant implication is limited because of the absence of head-to-head comparison with either a standard pharmacologic treatment of established pruritus or consistent active control. The pooled estimates showed substantial variation across studies in which none of the a priori subgroup analyses explained the presence of heterogeneity. In addition, with the different dosages used in included studies, we could not determine the most effective dose for pruritus treatment. Furthermore, publication bias was not explored by visual inspection of the funnel plot for symmetrical configuration and by using an Egger regression test because of the small number of studies included in the review, because this may introduce inaccurate findings.\textsuperscript{22,23}

Because of a small to moderate effect size and the overall quality of the evidence (GRADE), we recommend future large, randomized, double-blind studies comparing nalbuphine with placebo and active control. Estimating the effects of nalbuphine compared with placebo tests the real efficacy of nalbuphine. In all studies included in the review, assessment of the presence and absence of pruritus was quantified using different metrics, from asking the patient to using a Likert scale. This inconsistency may have created variations across studies, as evidenced by high $I^2$ statistics. We did not include a subgroup analysis of the instruments used to assess pruritus because of the number of studies included. Use of a universal method of assessing pruritus may minimize heterogeneity. Our rec-
ommendation is to use the numeric rating scale, similar to the pain scale with 2 opposing anchors. An ordinal assessment of the pruritus score obtained from a numeric rating scale will provide a more reliable assessment tool of the incidence and severity of pruritus and a clinically significant difference.24

Conclusion

Nalbuphine was successfully used to treat patients with neuraxial OIP. The addition of nalbuphine as part of the anesthesia plan in patients receiving neuraxial opioid may reduce the incidence of OIP and improve patient satisfaction. However, because of the small sample sizes and the substantial heterogeneity of results, we caution the extrapolation of the outcomes to clinical practice until large randomized studies are conducted.

Table 2. Summary of Findings: Key Outcomes of Nalbuphine on Treatment of Neuraxial Opioid-Induced Pruritus

<table>
<thead>
<tr>
<th>Outcome/No. of participants (studies)</th>
<th>Relative effect (95% CI)</th>
<th>Anticipated absolute effects, % (95% CI)</th>
<th>Certainty</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence of neuraxial opioid-induced pruritus N = 404 (5 RCTs)</td>
<td>RR = 0.59 (0.38-0.93)</td>
<td>54.7</td>
<td>32.3</td>
<td>-22.4</td>
</tr>
<tr>
<td>Incidence of sedation N = 226 (2 RCTs)</td>
<td>RR = 1.06 (0.42-2.71)</td>
<td>27.0</td>
<td>28.6</td>
<td>1.6</td>
</tr>
<tr>
<td>Incidence of postoperative nausea and vomiting N = 266 (3 RCTs)</td>
<td>RR = 1.58 (0.75-3.31)</td>
<td>12.2</td>
<td>19.3</td>
<td>7.1</td>
</tr>
</tbody>
</table>

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Author’s Correction
Dosing
In the April 2019 issue the authors correct the midazolam dosing in the figure on page 148 and again in the first line of page 150, by changing the dosing of midazolam instead of the printed “0.3 mg/kg” to read “0.03 mg/kg IV midazolam” and “midazolam dose of 0.03 mg/kg intravenously” respectively. The correct dosing of 0.03 mg/kg midazolam is previously mentioned in the article on page 147 under the “Midazolam” heading. See Collins S, Schedler P, Veasey B, Kristofy A, McDowell M. Prevention and treatment of laryngospasm in the pediatric patient: a literature review. AANA Journal. 87(2), 145-151. The online version of the article has been corrected.