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Prophylactic Nalbuphine to Prevent Neuraxial Opioid-Induced Pruritus: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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Purpose: *Evaluate the efficacy of prophylactic nalbuphine in preventing neuraxial opioid-induced pruritus.*
Design: *Systematic review and meta-analysis.*
Methods: *Following the PRISMA statement, PubMed, CINAHL, Cochrane and EMBASE were searched for eligible studies.*
Findings: *A total of 17 trials consisting of 1,052 patients were evaluated. Compared to placebo, there is low quality of evidence that nalbuphine was effective in reducing the incidence of pruritus in all patient population (RR, 0.66; 95% CI, 0.52 to 0.83;* P = *.0004) and obstetrics (RR, 0.81; 95% CI, 0.67 to 0.98;* P = *.03). We also found moderate quality of evidence that nalbuphine lowered pruritus in non-obstetrics, the number of rescue pruritus therapy and severity of pruritus episodes. However, nalbuphine did not cause sedation and affect pain scores.*
Conclusions: *Prophylactic nalbuphine decreased the incidence and severity of pruritus without adverse effects on sedation and analgesic effect of opioids.*

Keywords: *nalbuphine, opioid-induced pruritus, neuraxial, morphine, spinal, epidural.*

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THE ADMINISTRATION OF NEURAXIAL opioids offers clinical advantages, including dense sensory blockade, enhanced and profound analgesic effects, decreased local anesthetic dose, and rapid sensory and motor recovery.[1,2] In labor and cesarean section, the addition of opioids to neuraxial anesthesia decreases pain scores, lowers the minimum effective dose (ED) of local anesthetic,[3] and enhances safety profile for both the mother and the neonate.[4] Comparable to obstetrical cases, adding neuraxial opioids in nonobstetrical surgery improves intraoperative and postoperative analgesia, reduces the time for motor regression, and shortens the length of stay in the postanesthesia care unit, which is ideal for inclusion in enhanced recovery after surgery protocols.[5]

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Intrinsic to neuraxial opioid is the occurrence of opioid-induced pruritus (OIP).[6] Thirty percent to 100% of the patients receiving neuraxial opioid experience pruritus,[7] which consequently contributes to a decrease in patient satisfaction.[8] The incidence and severity of pruritus are dependent on the type of surgery and the classification and dosage of opioids administered. In obstetrical and gynecologic cases, the rate of neuraxial OIP is between 60% and 90%.[9,10] In addition, in nonobstetric patients, the incidence of neuraxial OIP is at least 50%.[11] Although lipophilic and hydrophilic opioids have different pharmacokinetics and pharmacodynamics profiles, the incidence of pruritus is relatively similar and typically high. In fact, when seven studies were pooled comparing morphine and fentanyl, Youssef et al[12] reported no difference in the incidence of pruritus. The dose of opioid is directly proportional to the frequency of pruritus. In a meta-analysis of 11 studies, Sultan et al[13] concluded that the incidence of pruritus is considerably lower in patients receiving a low dose of intrathecal morphine (50 to 100 mcg) compared with a high dose of the same (>100 to 200 mcg).

Prevention and treatment of pruritus remain a challenge for the anesthesia provider. Previous systematic reviews on the use of nalbuphine reported efficacy in reducing OIP.[14-16] Since then, several studies estimating the effectiveness of prophylactic nalbuphine have been published with conflicting outcomes.

Nalbuphine is a mu opioid receptor antagonist and kappa opioid receptor agonist clinically used as an analgesic with minimal abuse liability.[17] The onset with intravenous (IV) administration is 2 to 3 minutes, whereas intramuscular (IM) or subcutaneous onset is less than 15 minutes with action lasting from 3 to 6 hours.[18] Although nalbuphine is used as a supplement for balanced perioperative analgesia, its utility on the prevention of neuraxial pruritus is postulated based on two proposed mechanisms. First, neuraxial opioids trigger opioid receptors located supraspinally and at the spinal cord level. In spinal and epidural anesthesia, opioids activate the mu opioid receptors in the substantia gelatinosa of the dorsal horn and trigeminal nucleus in the medulla modulating pain and enhancing some side effects such as pruritus.[19,20] Nalbuphine inhibits the side effects of opioids including pruritus. Second, studies showed that activation of the kappa opioid receptors decreased the incidence of OIP when nalbuphine is given as prophylaxis[14-16] or treatment.[21]

The purpose of this systematic review and meta-analysis was to evaluate the efficacy of prophylactic nalbuphine compared with placebo in preventing neuraxial OIP in both obstetrical/gynecologic and nonobstetrical patients.

Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement directed this review.[22] The *P*atient, *I*ntervention, *C*omparison, and *O*utcome (PICO) question guiding the extensive search of evidence was: "In patients with a neuraxial opioid, what is the effect of prophylactic nalbuphine on the incidence of neuraxial opioid-induced pruritus as compared with placebo?"

Search Strategy

Published studies of randomized controlled trials (RCTs) examining the effects of nalbuphine in preventing neuraxial OIP were searched in the MEDLINE (PubMed), Google Scholar, Cumulative Index to Nursing and Allied Health Literature, the Cochrane Review Database, EMBASE, and Scopus. Gray literature databases including clinicaltrials.gov and conference abstracts and poster presentations were explored to diminish publication bias. The medical subject heading and search terms/keywords with appropriate Boolean operators used were as follows: *nalbuphine, pruritus, itch, neuraxial, opioid-induced pruritus, intrathecal, epidural, morphine, fentanyl, sufentanil and neuraxial opioid*. The reference lists from retrieved articles were analyzed for eligible clinical trials.

Study Selection

Authors independently searched for relevant articles and examined the titles and abstracts yielded from the initial search. Articles that were not consistent with the inclusion criteria were eliminated. A discussion among the authors resolved any form of disagreement on included articles.

Full text of relevant articles was obtained, and data were extracted for analysis.

Inclusion and Exclusion Criteria

The authors evaluated the abstracts based on the following three inclusion criteria identified before the literature search: RCTs evaluating the use of nalbuphine as prophylaxis for the prevention of neuraxial OIP compared with placebo, use of nalbuphine regardless of route of administration, and English-language peer-reviewed articles. The articles obtained from the search were excluded if they involved non-neuraxial administration route of opioids, clinical trials with no placebo comparison, retrospective studies, descriptive articles, editorials, or narrative reports.

Assessment of Risk of Bias

Two authors appraised the included RCTs and assessed the methodological quality of each study using the Risk of Bias algorithm outlined in the Cochrane Handbook for Systematic Reviews of Intervention.[23] The evaluators assessed the quality of each article based on random sequence generation, allocation concealment, blinding of participants, personnel and outcome assessors, incomplete outcome data, selective reporting, and other sources of bias. Another review author resolved any discrepancies or disagreements.

Data Extraction

A piloted and standardized data extraction template was used for data collection. The following information was obtained from each trial: number of participants; American Society of Anesthesiologists physical status; the incidence of pruritus; the degree of severity of pruritus; the dose and type of opioid; the dose, route, and timing of nalbuphine administration; types of surgical procedures; types of neuraxial techniques; incidence of sedation; pain scores; and the frequency and type of rescue medications for postoperative pruritus.

Summary of Measures and Statistical Analysis

The primary outcome was the incidence of neuraxial OIP. The overall frequency of pruritus reported in each study was used to pool estimates of pruritus incidence. However, if OIP was recorded at various time points in the study, the first time point recorded after surgery was used for analysis. Data categorized as mild, moderate, and severe pruritus were considered a pruritus event. The secondary outcomes were the frequency of rescue pruritus treatment, the degree and severity of pruritus, the degree and incidence of sedation, and postoperative incisional pain scores. Visual analog and numeric rating scores were converted to a 0- to 10-point scale (0 = no pain and 10 = worst possible pain) for analysis.

For dichotomous outcomes, effect sizes were estimated by calculating the pooled risk ratio (RR) with a 95% confidence interval (CI). For continuous data, outcomes were calculated using the mean difference (MD) with a 95% CI. The random-effects model was used to pool the estimates of both dichotomous and continuous endpoints anticipating methodological and clinical heterogeneity of data. For the binary endpoint, a significant effect compared with placebo needed a 95% CI not to include 1. For continuous outcomes, a significant effect compared with placebo required a 95% CI not to include 0. In addition, a 30% reduction in the incidence of neuraxial OIP was considered a clinically relevant event.

Study authors were contacted for additional raw data if results were recorded in graphical forms. If correspondence was unsuccessful, graphical data were extracted using the previously described method.[24] When data were reported as median and range (interquartile range), the mean and SD were calculated using the algorithm proposed by Wan et al.[25] 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 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.[26] An I^2 >50% was considered substantial heterogeneity. To explore clinical and methodological heterogeneity, a priori subgroup and sensitivity analyses were designed.

Subgroup analyses investigated the incidence of neuraxial OIP in obstetrical and nonobstetrical surgery, lipophilic and hydrophilic opioids, and the neuraxial route of opioid administration. A sensitivity analysis was performed by pooling estimates of only studies with low risk of bias. If results from sensitivity analysis were unchanged, we concluded that the risk of bias did not influence the effect estimates.[26]

Publication bias was explored by visual inspection of the funnel plot for symmetrical configuration and using an Egger regression test. Asymmetrical dispersion of effect estimates suggests possible publication bias.

Authors rated the overall quality of evidence using the Grades of Recommendation, Assessment, Development, and Evaluation approach.[26] The Grades of Recommendation, Assessment, Development, and Evaluation method judges outcomes as high, moderate, low, or very low. Because all evidence included in this review were RCTs, the baseline quality of evidence was graded as high. Consequently, an outcome was downgraded by one level for serious concerns and two 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 45 articles. After a review of titles and abstracts, 18 articles were subsequently excluded. Full-text articles of the remaining studies were obtained, and a total of 17 RCTs consisting of 1,052 patients were included for review and meta-analysis.[27-43] Figure 1 shows the flow diagram of the trial selection process.

The opioids used included fentanyl, sufentanil, hydromorphone, and preservative-free morphine sulfate. The dosages of opioids varied in each study. The opioids were either administered by the epidural route or the subarachnoid space. The dosages of nalbuphine and route of administration differed in all RCTs included in this review. Nalbuphine was given before pruritus occurred and administered either IV, IM, intrathecal, or by the epidural catheter. In all the studies in this review, assessment of the presence or the absence of pruritus differed by trial.

The onset of pruritus was 1.5 to 2 hours after subarachnoid administration of morphine[27,35] and 4 hours after epidural injection of morphine.[29] The recorded peak time for pruritus in patients with fentanyl was 4 to 8 hours.[31] The characteristics of included studies are listed in Supplementary Table 1.

Primary Outcome

Figure 2 shows the forest plots of the primary outcome and the subgroup analyses.

The Incidence of Neuraxial OIP

Sixteen RCTs[27-42] comprising 1,028 patients reported the incidence of neuraxial OIP after prophylactic administration of nalbuphine. Compared with placebo, there was a statistically significant reduction of neuraxial OIP after the use of nalbuphine (RR, 0.66; 95% CI, 0.52 to 0.83; $P = .0004$). The analysis showed substantial heterogeneity ($I^2 = 83\%$). Subgroup analyses were performed to explore factors affecting heterogeneity of the estimates.

Heterogeneity could not be explained when the effect of nalbuphine was examined in subgroup analyses of studies in obstetrical patients (RR, 0.81; 95% CI, 0.67 to 0.98; $P = .03$; $I^2 = 74\%$), use of preservative-free morphine (RR, 0.65; 95% CI, 0.49 to 0.84; $P = .002$; $I^2 = 86\%$), opioid administration via the epidural (RR, 0.62; 95% CI, 0.42 to 0.93; $P = .02$; $I^2 = 87\%$) and subarachnoid routes (RR, 0.67; 95% CI, 0.50 to 0.89; $P = .005$; $I^2 = 70\%$). However, I^2 statistic was reduced when the effect of nalbuphine was evaluated in nonobstetrical patients (RR, 0.41; 95% CI, 0.27 to 0.64; $P < .0001$; $I^2 = 40\%$).

A sensitivity analysis was conducted using only those studies with low risk of bias. After removal of studies with high risk of bias one at a time, the overall effect estimates were unchanged.

Secondary Outcomes

Figure 3 summarizes the secondary outcomes.

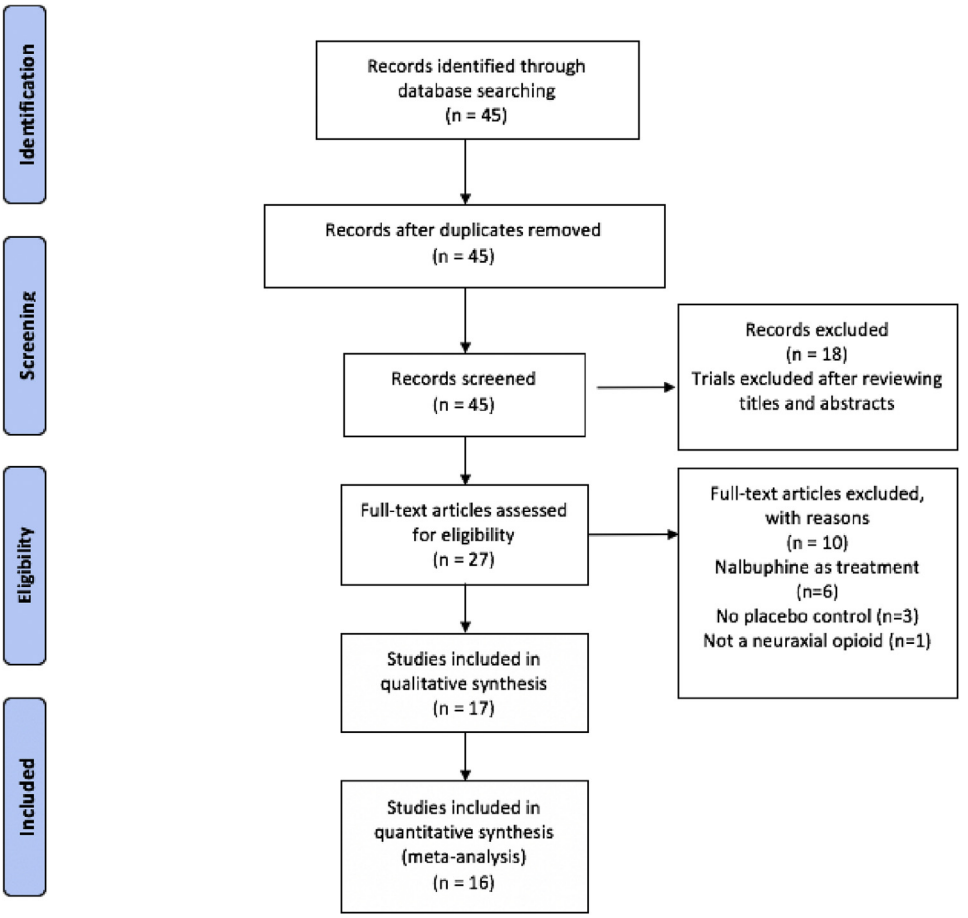

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart of literature screening and study selection. This figure is available in color online at www.jopan.org.

Frequency Rescue Pruritus Treatment

Eleven studies[27,28,32-34,35-38,42] recorded the number of patients requesting rescue antipruritic treatment. The pooled effect indicated that fewer patients (14% vs 41%) requested antipruritic rescue medication with nalbuphine group compared with placebo (RR, 0.38; 95% CI, 0.29 to 0.51; $P < .00001$).

The Incidence of Sedation

Postoperative sedation did not differ between patients treated with nalbuphine or placebo (RR, 0.73; 95% CI, 0.36 to 1.45; $P = .37$).[27,39] Using the Ramsay Sedation Scale,[44] aggregate data revealed no difference in the severity of postoperative sedation in both groups (MD, −0.13; 95% CI, −0.33 to 0.07; $P = .20$).[29,31,42]

Postoperative Incisional Pain Scores

Pooled estimates of 422 patients indicated no difference in pain scores for patients with nalbuphine compared with placebo (MD, −0.08; 95% CI, −0.21 to 0.05; $P = .24$).[29,31,33,36,38,39]

Moderate and Severe Pruritus

Five studies[27,28,31,33,35] reported on the degree of moderate pruritus. Pooled analysis revealed that fewer patients had moderate pruritus in the nalbuphine group compared with placebo (RR, 0.33; 95% CI, 0.23 to 0.46; $P < .00001$). When five studies[27,28,31,33,38] were combined, estimates revealed a difference in the number of patients with severe pruritus between nalbuphine and placebo (RR, 0.23; 95% CI, 0.07 to 0.78; $P = .02$).

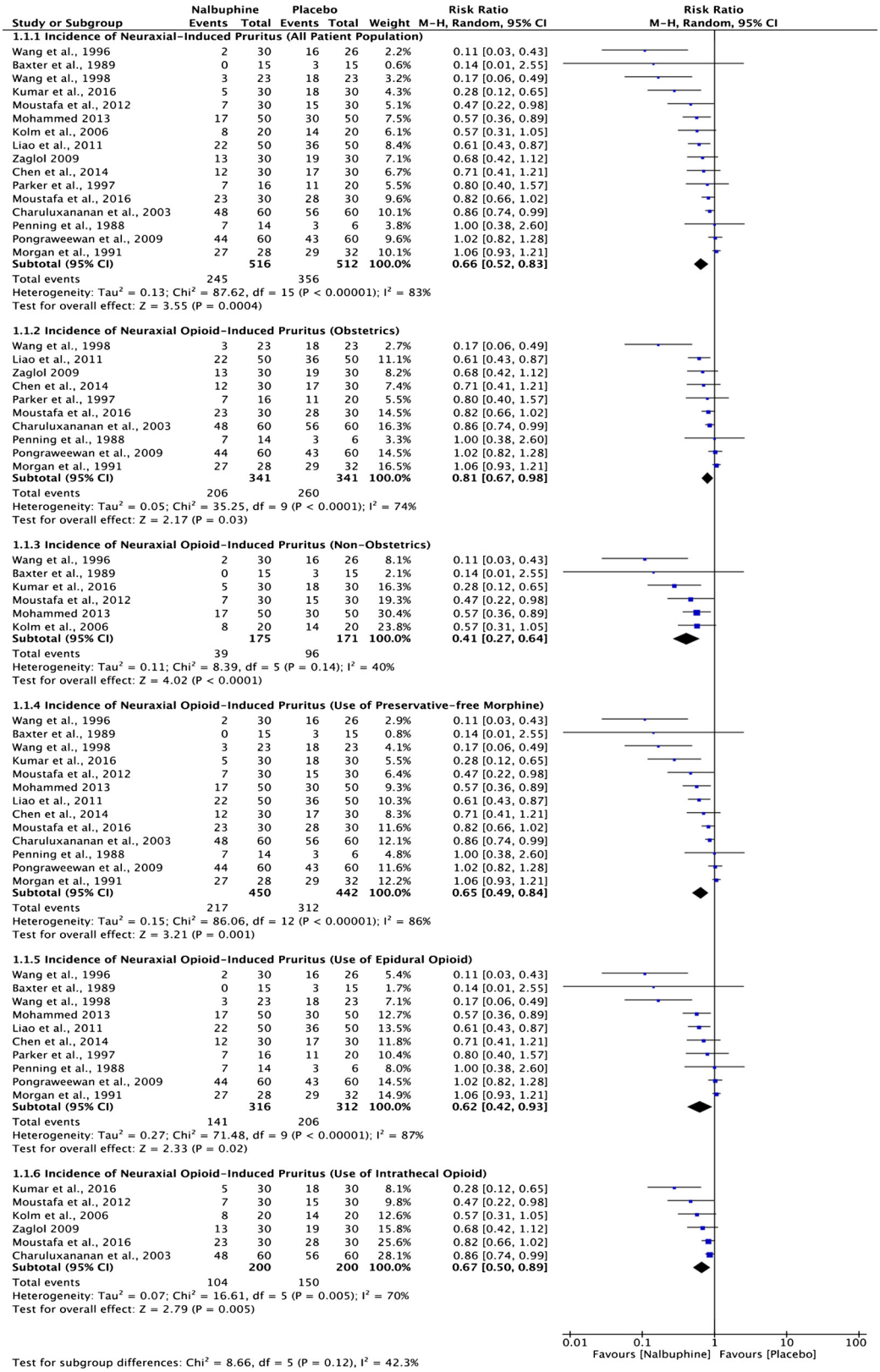

Figure 2. Forest plot of the incidence of neuraxial opioid-induced pruritus comparing prophylactic nalbuphine and placebo. CI, confidence interval; M-H, Mantel-Haenszel; Random, random-effects model. This figure is available in color online at www.jopan.org.

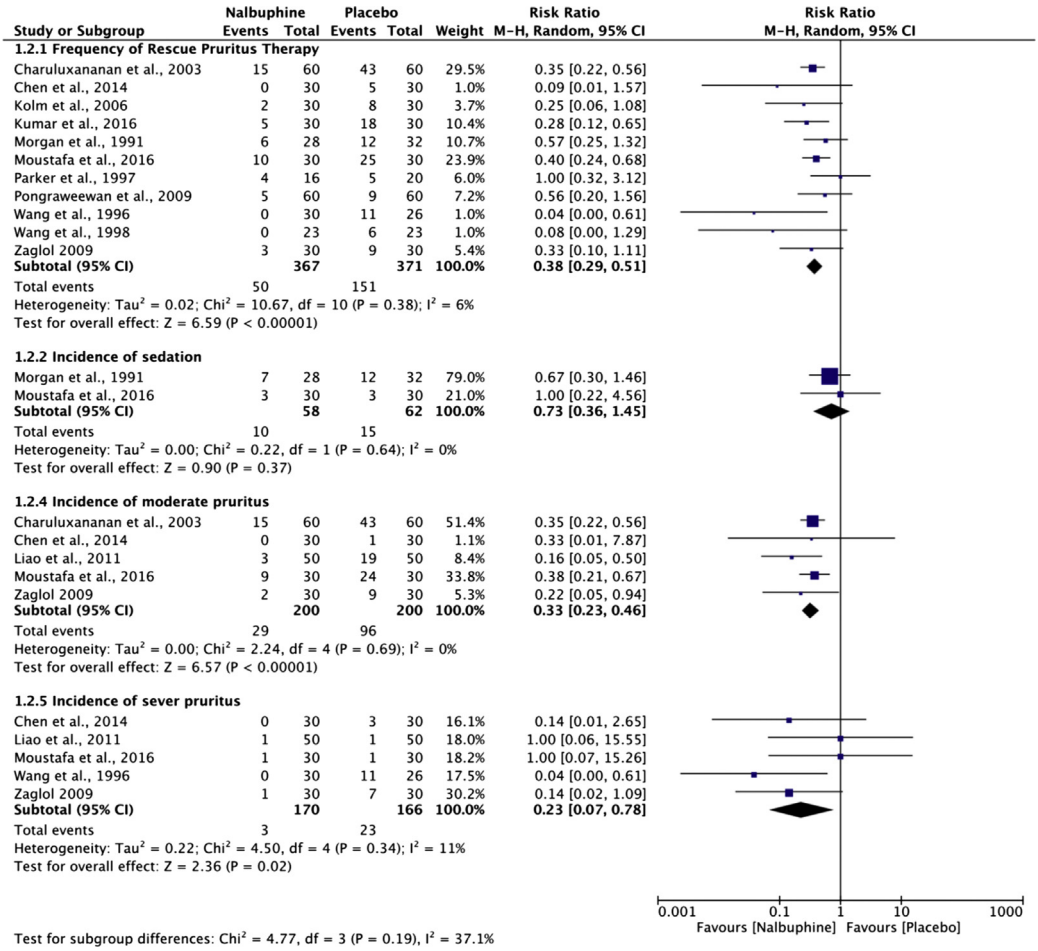

Figure 3. Forest plot of the frequency of rescue pruritus therapy, incidence of sedation, and incidence of moderate and severe pruritus comparing prophylactic nalbuphine and placebo. CI, confidence interval; M-H, Mantel-Haenszel; Random, random-effects model. This figure is available in color online at www.jopan.org.

Risk of Bias and Publication Bias

All studies were rated as low risks of random sequence generation. Five clinical trials reported adequate allocation concealment.[27-29,31,35] Blinding of participants and study assessors were sufficient in 13 trials.[27-29,31,32,35-41,43] The risks of bias of included studies are shown in Figure 4. By visual inspection, the funnel plot was asymmetrical, suggesting potential publication bias. Egger test showed visual asymmetry (RR = −3.583; $P < .001$) (Figure 5).

We also performed a power analysis of our primary outcome using the methodology described by Valentine et al.[45] For all studies included in this meta-analysis, the sample size had 80% power to detect 30% difference in the incidence of neuraxial OIP.

Quality of Findings

The summary of findings was generated using GRADEPro software (The Cochrane Collaboration; Supplementary Table 2). In this review, we drew our conclusions regarding the overall efficacy of prophylactic nalbuphine on the prevention of neuraxial OIP based on 16 studies consisting of 1,028 patients. We downgraded the evidence to low quality because of a potential publication bias and existence of clinical and methodological heterogeneity. However, we found the quality of evidence for the frequency of rescue antipruritic

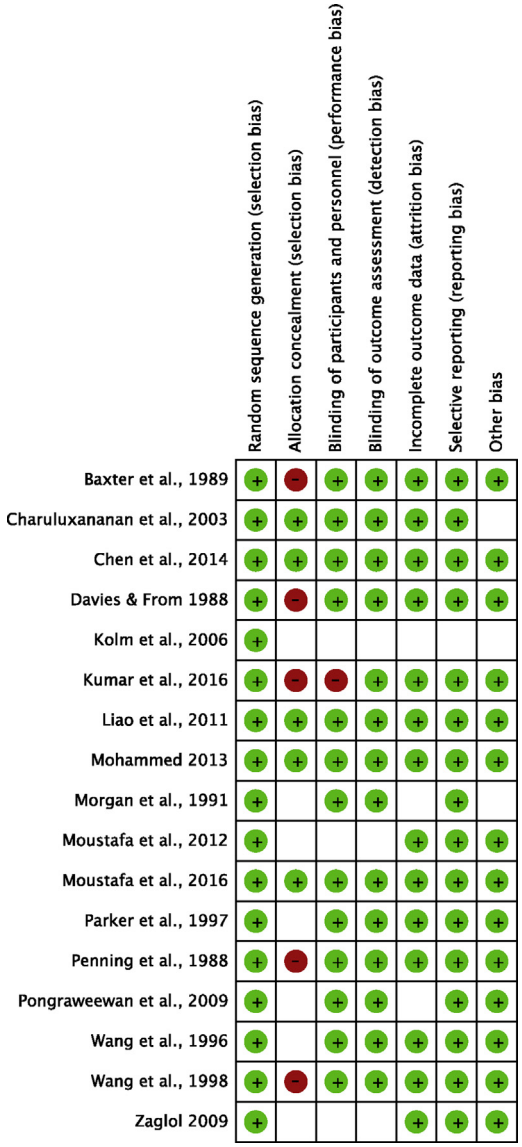

Figure 4. Risk of bias summary: review authors' judgments about each risk of bias item for each included study. Green = low risk of bias; white = unclear risk of bias; and red = high risk of bias. This figure is available in color online at www.jopan.org.

treatment, the incidence of sedation, and the incidence of OIP in nonobstetrical subjects moderate, which was primarily because of publication bias.

Discussion

The most important finding of the current review was the positive effect of prophylactic nalbuphine in decreasing the overall incidence of neuraxial

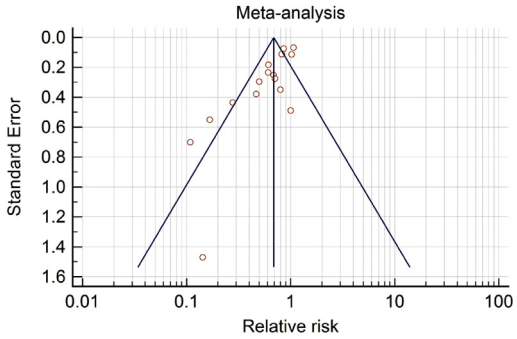

Figure 5. Funnel plot of studies examining the effects of prophylactic nalbuphine on the incidence of neuraxial opioid-induced pruritus. This figure is available in color online at www.jopan.org.

OIP in all patient populations, including obstetrical and nonobstetrical patients who received opioid administered by the epidural space or the subarachnoid space. With the lower rate of moderate and severe pruritus episodes in the nalbuphine group, the number of patients seeking rescue antipruritic medication was also lower compared with the placebo group.

In this current review, the overall incidence of neuraxial OIP was 47% for those patients with prophylactic nalbuphine and 70% in the placebo group. Incidence of pruritus with neuraxial fentanyl was relatively similar to those with preservative-free morphine. This finding was comparable with the meta-analysis reported by Youssef et al.[12] In addition, our investigation suggested that the onset of pruritus differed between opioid administered by the epidural space and the subarachnoid space. The difference in the onset of pruritus can be attributed to a faster peak concentration of morphine if given in the cerebrospinal fluid and a delay for up to 4 hours in the peak opioid concentration when administered in the epidural space.[7,46]

Prophylactic nalbuphine was effective in preventing neuraxial OIP for both patients receiving preservative-free morphine and fentanyl. Of the 13 RCTs evaluating the antipruritic efficacy of nalbuphine in patients with preservative-free morphine, seven studies[29-31,35,36,38,42] reported a reduction in risk between 14% and 89%. Also, one RCT[33] in patients with fentanyl concluded a risk reduction of neuraxial OIP of 32% and a 50% risk reduction when sufentanil was used.[34] The

decreased incidence of neuraxial OIP in this current investigation was similar to a previous RCT examining the effects of nalbuphine for OIP. In a study of intrathecal morphine, Somrat et al[21] reported the efficacy of nalbuphine when they evaluated 90 patients scheduled for a cesarean section using three different doses of nalbuphine. The authors concluded that nalbuphine reduced and mitigated morphine-induced pruritus without other side effects.

The rate of rescue antipruritic supplementation was lower in nalbuphine compared with placebo. This outcome was expected as the number of patients with moderate and severe episodes of pruritus was also reduced in the nalbuphine group. In most of the studies, moderate and severe pruritus were mostly localized in the face, neck, back, and trunk.[27,28,35]

In this review, our finding showed that sedation did not differ between nalbuphine and placebo, which was contrary to the data of previous reviews reporting significant sedation and dizziness with the use of nalbuphine.[14-16] An earlier review[16] reported no increase in sedation with low-dose nalbuphine (2.5 to 5.0 mg) IV compared with 10 mg; however, in our review, we recorded no difference in sedation in 10 mg of nalbuphine IM.[29,31] The probable explanation for this inconsistency is the route of nalbuphine administration.

Incisional pain scores between nalbuphine and placebo groups were similar, which was inconsistent with former reports[47-49] describing a reversal of analgesia with nalbuphine. In their case report, Blaise et al[47] recognized that increases in heart rate, blood pressure, and pain scores were associated with the reversal of respiratory depression with nalbuphine. Two other RCTs documented that increased pain scores and consumption of additional opioids were related to nalbuphine use.[48,49] Because our pooled pain score estimates did not differ between groups, nalbuphine, in this setting, did not negatively affect analgesia.

There was substantial variation across all studies as evidenced by the high I^2 statistics. However, subgroup analysis on nonobstetrical patients was identified as the possible clinical and methodological explanation that could lower heterogeneity.

Limitations

There were limitations to the review. First, we did not determine the minimum ED (ED_{50}) of nalbuphine because there were no dose-finding studies included in this review. However, there were sufficient RCTs that were pooled to determine a reduction in pruritus risk. At 4 mg of nalbuphine IV, our data indicated that fewer patients treated with nalbuphine suffered from pruritus (70%) compared with those in the placebo group (86%) providing a reduction in pruritus risk of 26%.[27,33,35] Similarly, at 10 mg of nalbuphine IM, those treated with nalbuphine had better pruritus control.

Second, we cannot make recommendations as to whether nalbuphine is more efficacious than other antipruritic agents because only two studies comparing nalbuphine with ondansetron were eligible for meta-analysis. When these trials evaluated 4 mg of nalbuphine compared with 4 mg of ondansetron, the incidence of neuraxial OIP did not differ between the drugs.[27,35] Similarly, there was no difference in the incidence of neuraxial OIP when 4 mg of nalbuphine was compared with 8 mg of ondansetron.[33,35] Thus, a head-to-head comparison between nalbuphine and other antipruritic agents was impractical because to this date, there is no gold standard of preventive antipruritic medication for comparison.[50]

Third, there was no acceptable assessment tool determining the presence and absence of pruritus. The assessment methods in most studies were self-invented and nonvalidated. A more precise assessment tool would be a scale that is simple, universal, reliable, and validated to measure current pruritus intensity. The possible solution is to modify the numeric rating scale (NRS) used for pain assessment. The 11-point scale can be anchored by two verbal descriptions of extremity of symptoms (0 = no pruritus and 10 = worst pruritus imaginable). Like the NRS for pain assessment, the scale could be administered by clinicians or self-administered by the patient. A reduction in NRS of 3 points, like in pain assessment, manifests alleviation of pruritus symptoms and represents a clinically significant difference.[51]

Fourth, it is intuitive that administration of a higher dose of opioids yields a higher rate of pruritus. However, we did not compare the incidence of pruritus in low- and high-dose opioids because

no studies included in our review examined two different opioid dosages. In fact, the variability of the dosages and routes of administration made it difficult to combine data.

Future Research

This review features areas where future studies are needed. Despite the efficacy of nalbuphine in preventing the incidence of neuraxial OIP, the incidence rate is still high and warrants more studies to elucidate other possible mechanisms of neuraxial pruritus. Finding the ED with acceptable risks of adverse effects of nalbuphine, whether given IV, IM, subcutaneous, spinal, or via the epidural route, requires more dose-finding studies that will include the minimum ED in 50% (ED_{50}) and 95% (ED_{95}) of patients. Determining the ED_{50} and ED_{95} of nalbuphine would provide clinicians a choice depending on the patient population. Meanwhile, because of the medium effect size of the studies in this review, we recommend future large-scale randomized controlled and double-blind trials using standardized outcomes and a validated pruritus assessment tool to minimize heterogeneity.

Conclusion

In this systematic review and meta-analysis, the incidence rate of pruritus is at least 50%. Some pharmacologic agents have been evaluated to prevent pruritus. Despite these interventions, the incidence is still considerably high. Having an additional antipruritic agent to prevent this common complication after neuraxial opioid administration is a promising development. Although large studies are needed to reduce heterogeneity and determine the optimal dose, this current review shows that the administration of prophylactic nalbuphine decreases the incidence and severity of pruritus and the number of rescue pruritus treatments in patients receiving opioids without negative effects on sedation and compromising the analgesic effect of neuraxial opioids.

Supplementary Data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.jopan.2018.06.098.

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Appendices

Appendix A can be found at https://doi.org/10.1016/j.jopan.2018.06.098.

Appendix B. PubMed Example Literature Search Strategy

Search	Keywords	Yields
1	("nalbuphine"[MeSH Terms] AND "pruritus"[All Fields])	42
2	("nalbuphine"[MeSH Terms] AND "itch"[All Fields])	44
3	("nalbuphine"[MeSH Terms] AND "neuraxial"[All Fields])	2
4	("nalbuphine"[MeSH Terms] AND "neuraxial opioid induced pruritus"[All Fields])	2
5	("nalbuphine"[MeSH Terms] AND "opioid induced pruritus"[All Fields]) AND “intrathecal” "[All Fields])	11
6	("nalbuphine"[MeSH Terms] AND "morphine-induced pruritus"[All Fields])	6
7	("nalbuphine"[MeSH Terms] AND "morphine-induced pruritus"[All Fields]) AND “epidural” "[All Fields])	6
8	("nalbuphine"[MeSH Terms] AND "fentanyl-induced pruritus"[All Fields])	4
9	("nalbuphine"[MeSH Terms] AND "fentanyl-induced pruritus"[All Fields]) AND “epidural” "[All Fields])	0
10	("nalbuphine"[MeSH Terms] AND "fentanyl-induced pruritus"[All Fields]) AND “intrathecal” "[All Fields])	0
11	("nalbuphine"[MeSH Terms] AND "morphine-induced pruritus"[All Fields]) AND “intrathecal” "[All Fields])	5

Supplementary Table 1. Summary of the Characteristics of RCTs Evaluating the Efficacy of Prophylactic Nalbuphine Compared With Placebo on the Incidence of Neuraxial OIP

Studies Country	Sample Size/ASA Class/Surgical Cases	Neuraxial Technique/ Anesthetics Administered	Neuraxial Opioid/Dose/ Route	Nalbuphine Dose/Route/ Timing	Neuraxial OIP	
					Evaluation Method	Rescue Criteria and Treatment
Moustafa et al, 2016[27] Egypt	240 ASA I-II Cesarean section	Spinal Hyperbaric bupivacaine 0.5% 2.2 mL	Morphine 200 mcg Subarachnoid	4 mg IV Immediately after delivery	*4-point scale* 1 = no pruritus 2 = mild pruritus, treatment not requested 3 = moderate pruritus, treatment requested 4 = severe pruritus, treatment requested	Pruritus scare ≥3 Naloxone 10-20 mcg IV
Kumar et al, 2016[42] India	120 ASA I-II Lower abdominal and lower limb surgery	Spinal Hyperbarci bupivacaine 0.5%	Morphine 100 mcg Subarachnoid	0.5-1.0 mg Subarachnoid During spinal induction	*3-point scale*[*] 0 = no pruritus 1 = mild to moderate facial pruritus that may or may not require treatment 2 = severe facial pruritus requiring treatment 3 = pruritus involving extra facial region requiring treatment	Rescue treatment criteria not described Ondansetron 4 mg IV

(Continued)

Supplementary Table 1. Continued

Studies Country	Sample Size/ASA Class/Surgical Cases	Neuraxial Technique/ Anesthetics Administered	Neuraxial Opioid/Dose/ Route	Nalbuphine Dose/Route/ Timing	Neuraxial OIP	
					Evaluation Method	Rescue Criteria and Treatment
Chen et al, 2014[28] Taiwan	90 ASA II Cesarean section	Spinal Lidocaine 2% 12-15 mL with epinephrine 5 mcg/mL + fentanyl 100 mcg	Morphine 0.06 mg/mL 10 mL Epidural	5-10 mcg/kg/h Epidural After delivery	Patients were asked about desire to scratch	If requested by patient, naloxone 0.1 mg IV
Mohammed, 2013[29] Egypt	51 ASA I-II Lower abdominal surgeries	Epidural Bupivacaine 0.5% 15 mL	Morphine 1.5 mg Epidural	10 mg IM After skin closure	*4-point scale* 1 = no pruritus 2 = mild pruritus, restricted to one area 3 = moderate pruritus, affecting large area 4 = severe pruritus, extensive area disturbing patient	Rescue treatment criteria not described No rescue treatment
Moustafa et al, 2012[30] Egypt	60 ASA I-II Total knee arthroplasty	Spinal Hyperbaric bupivacaine 0.5%	Morphine 200 mcg Subarachnoid	1 mg Subarachnoid During SAB injection	Did not indicate assessment method	Rescue treatment criteria not described Dexamethasone 8 mg IV
Liao et al, 2011[31] Taiwan	150 ASA I-II Cesarean section	Epidural Lidocaine 2% 400 mg, 1-2 mL fentanyl with epinephrine 1:200,000	Morphine 1.5 mg Epidural	10 mg/mL IM After surgery	*4-point scale* 1 = no pruritus 2 = mild pruritus, restricted to one area 3 = moderate pruritus, affecting large area	Rescue treatment criteria not described No rescue treatment

					4 = severe pruritus, extensive area disturbing patient	
Pongraweewan et al, 2009[32] Thailand	182 ASA I-II Cesarean section	Epidural Lidocaine 2% with epinephrine 1:200,000	Morphine 4 mg Epidural	5 and 10 mg Epidural After cord clamping	Visual analog score (0-10)	Patient request Chlorpheniramine 10 mg IV
Zaglol, 2009[33] Egypt	90 ASA I-II Cesarean section	Spinal Hyperbaric 0.5% 10 mg	Fentanyl 25 mcg Spinal	4 mg IV Before spinal induction	*4-point scale* 1 = no pruritus 2 = mild pruritus 3 = moderate pruritus 4 = severe pruritus	If requested by patient, diphenhydramine 12.5 mg IV
Kolm et al, 2006[34] Brazil	100 ASA I-II Nonobstetric procedures	Spinal Hyperbaric bupivacaine 15 mg	Sufentanil 10 mcg Spinal	10 mg IV After sensory block	*5-point scale* 0 = absent 1 = mild, not requiring scratching 2 = moderate, occasional scratching 3 = severe, constant need for scratching 4 = refractory to naloxone	Rescue treatment criteria not described Naloxone IV
Charuluxananan et al, 2003[35] Thailand	240 ASA I-II Cesarean section	Spinal Hyperbaric bupivacaine 2.2 mL	Morphine 200 mcg Spinal	4 mg IV Immediately after delivery	*4-point scale* 1 = no pruritus 2 = mild pruritus, treatment not requested 3 = moderate pruritus, treatment requested	Treatments of pruritus when pruritus score is ≥3 Propofol 20 mg initially, then naloxone 0.1-0.2 mg IV if unsuccessful

(Continued)

Supplementary Table 1. Continued

Studies Country	Sample Size/ASA Class/Surgical Cases	Neuraxial Technique/ Anesthetics Administered	Neuraxial Opioid/Dose/ Route	Nalbuphine Dose/Route/ Timing	Neuraxial OIP	
					Evaluation Method	Rescue Criteria and Treatment
					4 = severe pruritus, treatment requested	
Wang et al, 1998[36] Taiwan	68 ASA I-II Total hysterectomy	CSE Hyperbaric bupivacaine 0.5% 0.25 mg/kg with intermittent bolus of low dose of hyperbaric bupivacaine 0.5%	Morphine 3 mg Epidural	60 mcg/kg/h continuous IV infusion At the end of surgery	*3-point scale* 0 = none 1 = pruritus, no treatment requested 3 = pruritus with treatment requested	Pruritus score of 3 Diphenhydramine 20 mg IM
Parker et al, 1997[37] USA	78 ASA I-II Cesarean section	Epidural Bupivacaine 0.5%	Hydromorphone 0.075 mg/mL Epidural	Three dosages all via epidural catheter 0.02 mg/mL 0.04 mg/mL 0.08 mg/mL On arrival in PACU	*Visual analog score* (0 = no itching, 100 = severe itching)	Rescue treatment criteria not described Diphenhydramine IV
Wang et al, 1996[38] China	56 ASA I-II Radical hemorrho-idectomy	Epidural Hyperbarci bupivacaine 0.5%	Morphine 4 mg Epidural	15 mcg/kg/min continuous IV infusion After surgery	*3-point scale* 0 = none 1 = pruritus, no treatment requested 2 = pruritus with treatment requested	Pruritus score of 2 Naloxone 40 mcg IV
Morgan et al, 1991[39] Canada	60 ASA I-II Cesarean section	Epidural Lidocaine 2% 3 mL and intermittent lidocaine 2% with epinephrine 1:200,000	Morphine 5 mg Epidural	20 mg IV At skin closure	*6-point scale* 0 = no pruritus 5 = unbearable pruritus	Rescue treatment criteria not described Diphenhydramine 50 mg IM or PO

Baxter et al, 1989[41] Canada	63 ASA I-III Thoracotomy	Epidural Used in conjunction with GETA	Morphine 0.15 mg/kg Epidural	50-200 mcg/kg bolus followed by infusion for 24 h Epidural After surgery	*5-point scale* 1 = none 2 = mild 3 = moderate 4 = moderately severe 5 = severe	Rescue treatment criteria not described No rescue treatment
Penning et al, 1988[40] USA	20 ASA I Total abdominal hysterectomy	Epidural Used in conjunction with GETA	Morphine 0.1 mg/kg Epidural	0.1 mg/kg IV After surgery	Asking the question "Do you itch?"	Rescue treatment criteria not described No rescue treatment
Davies & From, 1988[43] USA	24 No ASA classification Extracorporeal shockwave lithotripsy	Epidural sedation	Fentanyl 100 mcg Epidural	10 mg Subcutaneous After surgery	0-10 cm visual analog scale	Rescue treatment criteria not described No rescue treatment

RCTs, randomized controlled trials; OIP, opioid-induced pruritus; ASA, American Society of Anesthesiologists; IV, intravenous; SAB, subacromial bursa; IM, intramuscular; CSE, combined epidural-spinal; PACU, postanesthesia care unit; PO, per orem; GETA, general-endotracheal anesthesia.

*This scale was classified as a 3-point scale by the authors.

Supplementary Table 2. Summary of Findings: Key Outcomes Comparing Prophylactic Nalbuphine With Placebo on the Attenuation of Neuraxial OIP

Prophylactic Nalbuphine Compared With Placebo in Neuraxial OIP

Patient or Population: Neuraxial OIP
Setting: Perioperative Setting
Intervention: Prophylactic Nalbuphine
Comparison: Placebo

Outcome No. of Participants (Studies)	Relative Effect (95% CI)	Anticipated Absolute Effects (95% CI)			Certainty	What Happens
		Without Prophylactic Nalbuphine	With Prophylactic Nalbuphine*	Difference		
Incidence of neuraxial OIP No. of participants: 1,028 (16 RCTs)	RR, 0.66 (0.52-0.83)	69.5	45.9% (36.2-57.7)	23.6% fewer (33.4 fewer to 11.8 fewer)	⊕⊕ Low*,†,‡	Unexplained heterogeneity across studies warrants additional trials to determine the effects of nalbuphine on neuraxial OIP. Publication bias potentially exists
Incidence of neuraxial OIP in obstetrical patients No. of participants: 662 (10 RCTs)	RR, 0.81 (0.67-0.98)	81.0	65.6% (54.3-79.4)	15.4% fewer (26.7 fewer to 1.6 fewer)	⊕⊕ Low*,†,‡	Unexplained heterogeneity across studies warrants additional trials to determine the effects of nalbuphine on neuraxial OIP. Publication bias potentially exists
Incidence of neuraxial OIP in nonobstetrical patients No. of participants (6 RCTs)	RR, 0.41 (0.27-0.64)	56.1	23.0% (15.2-35.9)	33.1% fewer (41 fewer to 20.2 fewer)	⊕⊕⊕ Moderate†,‡	Not affected by heterogeneity. Publication bias potentially exists
Number of rescue antipruritus treatment	RR, 0.38 (0.29-0.51)	40.7	15.5% (11.8-20.8)	25.2% fewer (28.9 fewer to 19.9 fewer)	⊕⊕⊕ Moderate†,‡	Not affected by heterogeneity.

No. of participants: 738 (11 RCTs)						Publication bias potentially exists
Incidence of sedation No. of participants: 120 (2 RCTs)	RR, 0.73 (0.36-1.45)	24.2	17.7% (8.7-35.1)	6.5% fewer (15.5 fewer to 10.9 more)	⊕⊕⊕ Moderate[†,‡]	Not affected by heterogeneity. Publication bias potentially exists

OIP, opioid-induced pruritus; 95% CI, 95% confidence interval; RCTs, randomized controlled trials; RR, risk ratio.

Grades of Recommendation, Assessment, Development, and Evaluation Working Group grades of evidence:

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

*The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

*Substantial heterogeneity.

†Small sample size.

‡Risk of publication bias.