What Epidural Opioid Results in the Best Analgesia Outcomes and Fewest Side Effects After Surgery?: A Meta-Analysis of Randomized Controlled Trials

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BACKGROUND: Epidural opioids are widely used for central neuraxial blockade and postoperative analgesia. However, differences in analgesic efficacy and side effect rates among individual opioids remain controversial.

METHODS: We conducted a random-effects meta-analysis of randomized controlled trials that compared at least 2 continuous epidural infusions for acute postoperative analgesia over at least 24 hours. Individual study data were weighted by the inverse-variance method. Visual analog scale (VAS) pain scores were the primary outcome. Secondary outcomes included opioid side effects, such as pruritus, postoperative nausea and vomiting (PONV), sedation, hypotension, and respiratory depression.

RESULTS: Nineteen of the 24 trials included compared 2 of the following opioids: morphine, fentanyl, or sufentanil. The total subjects studied were 1513. Pooled analysis by type of surgery showed no clinically significant differences in VAS pain scores at any time after surgery. There were more PONV (OR = 1.91; 95% CI, 1.14–3.18; P = 0.014) and perhaps pruritus (OR = 1.64; 95% CI, 0.98–2.76; P = 0.162) with morphine compared to fentanyl. Total opioid consumption differed only in the trials comparing morphine and fentanyl, where patients in the morphine group required 1.2 mg (of morphine equivalent) less (95% CI, 0.27–2.18). Use of analgesic adjuncts was similar for all but 2 studies.

CONCLUSIONS: Analgesic outcome, in terms of VAS pain score, was similar between the epidural opioids studied. These similarities in analgesia may reflect the common practices of concomitantly using epidural local anesthetics with the opioids and titrating infusion rates according to a patient’s pain status. With respect to side effects, the incidence of PONV and possibly pruritus was higher with morphine compared with fentanyl, despite there being similar total opioid consumption between those groups. (Anesth Analg 2014;XXX:00–00)

Epidural opioids have been widely used for facilitation of central neuraxial blockade and postoperative analgesia. Although they may be used alone in this regard, multiple studies have shown that analgesia is more effective when they are combined with local anesthetics.¹⁻³ Such mixtures minimize the risk of respiratory depression, somnolence, and pruritus associated with solitary narcotic use, while also reducing incidence of motor block, and hypotension associated with local anesthetics. Even more importantly, this multimodal approach has been shown to provide superior postoperative analgesia to that of IV patient-controlled analgesia with opioids.² Despite the effectiveness of such epidural combinations, differences in analgesic efficacy and side effect rates among opioids remain to be elucidated. This may be a function of physician preference, hospital-specific policies, or the specific opioids available on formulary. Given the unique pharmacologic properties of each opioid and studies that show different rates of accumulation in the cerebrospinal fluid, there is biologic plausibility for differences in the side effect profiles and analgesia among different opioids.⁴⁻⁷ No single large randomized controlled trial (RCT) has definitively identified the ideal opioid for a postoperative epidural infusion, either with or without local anesthetic. This ideal opioid should improve subjective postoperative analgesia while minimizing the aforementioned side effects.

As such, we conducted a meta-analysis of all RCTs comparing perioperative epidural opioid infusions. Most of these trials involved local anesthetic–opioid mixtures. Specifically, we sought to determine which opioid offers the best epidural analgesia in terms of postoperative visual analog scale (VAS) pain scores while minimizing opioid side effects after surgery.

METHODS

Ethics

The HI Reb (Hamilton Integrated REB) does not require ethics approval for systematic reviews, including network meta-analyses, because there are no data being collected from patients. We only evaluated and synthesized data that had been reported in published trials, and only used aggregate level data reported from the original trials.
Meta-Analysis: Best Epidural Opioid with Least Side Effects

**Literature Search**
Computerized searches of Ovid MEDLINE (from 1950 to November 2013), EMBASE (from 1980 to December 2013), and the Cochrane Controlled Trials Register (CCTR up to November 2013) were conducted. While identifying clinical trials, a sensitive search strategy developed by Haynes et al. was used along with free text combinations and MeSH terms (Appendix, Supplemental Digital Content 1, http://links.lww.com/AA/A931). The searches were designed to be sensitive and identify the maximum number of RCTs that compared at least 2 different perioperative epidural opioid infusions. The search was restricted to studies published or translated to the English language. Unpublished studies were not sought.

**Study Selection**
Inclusion for data abstraction was determined by reviewing each study abstract identified by the search. All abstracts were read by 2 authors, and agreement was reached by consensus to either include or exclude a study. Full articles were obtained so that reference lists could be reviewed to further identify additionally relevant studies. The reviewers were not blinded to the authors’ names, affiliated institutions, or the journal of publication for any of the studies.

**Population**
Studies were included if they enrolled male or female participants of any age undergoing either elective or emergency surgery. Studies involving epidural analgesia in parturients during labor were excluded for many potential confounding factors, including differences between labor and postoperative pain, variability in epidural insertion site, and time use during labor.

**Intervention**
Studies must have compared at least 2 different continuous epidural opioid infusions ceteris paribus for at least 24 hours postoperatively. Studies were limited to opioids used in common practice, which include morphine, fentanyl, hydromorphone, oxycodone, or sufentanil. In most cases, opioids were combined with local anesthetics. Studies were excluded if comparisons involved only varying concentrations of the same opioid or various types of local anesthetics.

**Outcomes**
Analgesia in terms of VAS pain scores measured for at least 24 hours was the primary outcome. Secondary outcomes included opioid side effects, such as nausea/vomiting, pruritus, and respiratory depression. No a priori definition was set for the latter, although in the majority of studies it was defined as administration of naloxone.

**Study Design**
Only RCTs were included in our review, regardless of the quality of assessment or results. Crossover trials were not included due to the potential for inadequate washout period between compared opioids.

**Study Evaluation**
Each study included in the analysis was assessed independently by each author, and any discrepancies were resolved by consensus. The assessment was performed using a modified version of the 5-point methodological quality scale designed by Jadad et al. To receive full points, a study had to meet the following criteria: be randomized; be double-blind; include appropriate follow-up for 24 hours at a minimum; use suitable techniques to create the randomization sequence; and describe an acceptable blinding method. To satisfy the follow-up criteria of the modified Jadad scale, withdrawals/dropouts must be described or all study participants accounted for in the results. Funnel plots were constructed of the primary outcome to evaluate for publication bias.

**Data Extraction**
The methodological data were extracted and later verified. The extracted methodological data included the type of surgery and detail of the anesthetics. Medications used at induction, maintenance, and emergence were recorded. Descriptions of the epidural included the level of insertion, initiation of the epidural within the delivery of anesthesia, and time course for epidural administration. Additionally, the number and baseline characteristics of subjects in each treatment group were recorded. Numerical data were extracted and also verified. These data included VAS pain scores at rest (primary outcome) and incidence of opioid-related side effects (secondary outcomes). Pain scores could not be extracted from the study by Coppe and Willaert because poor graphical quality precluded differentiation of the treatment arms. Numerous attempts to contact the authors were unsuccessful, and only partial data (concerning opioid side effects) were included.

**Statistical Analysis**
The reporting of this review was done in accordance with the PRISMA guideline. The selection process for articles is summarized using a flow diagram. Due to interstudy variability in the timing of pain assessment, pain scores were grouped in 6- to 8-hour intervals where necessary. In cases where the standard deviation (SD) was not reported, it was derived from range or interquartile range. When studies reported multiple infusion rates for the same opioid, data for the most equipotent dose (the one most similar to the comparison opioid in the trial) were retained for analysis. Categorical outcomes (e.g., none, mild, and severe) were converted into binary data by summing the number of patients who experienced the outcome, regardless of severity.

Due to the known dose dependency of opioid analgesia and side effects, we conducted subgroup analyses to explore (1) whether equipotent infusion rates were used within individual studies and (2) whether comparable doses of the same opioid were used among studies. Equipotency was determined by comparing the relative average rates of infusion within a study to epidural equianalgesic tables. Total opioid consumption was also analyzed for studies that administered opioids via equianalgesic infusions and a non-fixed amount of opioid.

Under each predefined clinical outcome, the eligible studies with available data were pooled using the random-effects model, which incorporated statistical heterogeneity. The weight of each individual study was calculated using
the inverse-variance method. The overall pooled estimates were reported as weighted mean difference and odds ratio with the associated confidence intervals for continuous and dichotomous outcomes, respectively. The statistical heterogeneity was quantified as the $I^2$ statistic, which measures the between-study variance as a percentage of total variance. The $Q$ test was used to test heterogeneity. The criteria used to define statistical significance were set at $\alpha = 0.01$ for continuous data (because there were multiple comparisons over time) and $\alpha = 0.05$ for dichotomous data. The overall pooled estimates and individual studies included were graphically presented using forest plots. Bias was assessed through funnel plots and Egger’s regression. Stata 12.0 (StataCorp, College Station, TX) was used to conduct the meta-analyses and assessment of bias.

**A Priori Hypothesis for Sources of Heterogeneity**

Before analyzing the results, potential sources of heterogeneity among studies were identified, and hypotheses were formulated to explain this heterogeneity. Much of the possible heterogeneity from RCTs comparing opioids was thought to depend on dose dependency of opioid analgesia and side effects. First, inconsistent use of analgesic adjucnts (nonsteroidal anti-inflammatory drugs or local anesthetics) among studies may result in an opioid-sparing effect, which may decrease rates of side effects and give rise to synergistic or additive benefits. Second, deviation from equianalgesic dosing within a study may inflate the number of side effects in patients receiving inappropriately large amounts of opioid or increase pain in those receiving too little. Third, it is important to consider the infusion rates of the same opioid between each study, which in some cases varied by approximately 10-fold. Higher rates of infusion may lead to better analgesia and a higher incidence of side effects.

In addition to factors related to opioid dosage, additional anesthetic and surgical factors should be considered. Intraoperative factors include administration of any antipruritic or antiemetic medication. Furthermore, certain anesthetic drugs are associated with particular side effects, such as nitrous oxide and postoperative nausea and vomiting (PONV). In addition, administration of opioids intraoperatively may raise the risk of side effects in 1 group if it is unevenly distributed. With respect to the type of surgery, certain procedures are more invasive than others and thus may give rise to more postoperative pain, leading to increased opioid consumption and systemic side effects. Additionally, thoracic surgery has relatively higher rates of postoperative respiratory complications compared with other types of operations. With respect to data reporting, continuous versus dichotomous outcome measures may give rise to differences in side effect profiles among patients, due to the higher sensitivity of a continuous scale to detect a difference.

With regard to pediatric studies, the measurement of pain in pediatric patients relies on assessing cues, such as crying or facial expression. These third-person methods may differ in sensitivity from the standard VAS administered to adult patients. Furthermore, pediatric patients as a group are heterogeneous and experience different rates of side effects based on age. Thus, for these reasons, pediatric studies were analyzed separately.

**RESULTS**

**Literature Search**

The initial search retrieved 8219 articles. After title review, 113 studies were retained for abstract and/or full-text review (Fig. 1). Ultimately, 24 of these studies met the inclusion criteria (Table 1).11,21-43

**Study Description**

Nineteen studies obtained a Jadad quality score of 3/5 or higher. The most common methodological shortcomings were failure to fully describe the randomization or blinding technique.

Abdominal, orthopedic, and cesarean delivery with non-laboring epidural accounted for 10, 7, and 2 of the 24 studies, respectively. Five trials included a mix of abdominal or thoracic surgery. Of the 24 studies, 2 included pediatric patients.

Sufficient data were available to analyze the following secondary outcomes: nausea and vomiting (24/24), pruritus (22/24), respiratory depression (19/24), sedation (17/24), and hypotension (9/24).

Most studies described confirmation of epidural catheter placement (18/24) at a spinal level appropriate for the specific operations reported (16/24) (Table 1). In addition, the majority of trials made a binary comparison between two different opioids, except the pediatric study by Goodarzi that compared morphine, fentanyl, and hydromorphone (Table 1).41

**Primary Outcome: VAS Pain Scores**

Pain scores were compared for at least the first 24 hours among various intervals of time, if pain was assessed during that interval. For trials comparing morphine to fentanyl, pooled analysis revealed significant heterogeneity at the 0 to 6, 13 to 18, 19 to 24, and 48-hour time intervals. Given the overall small number of studies, this heterogeneity appeared to be primarily driven by certain individual studies that showed significant pain reduction in favor of either opioid (Fig. 2). Subgroup analysis by type of surgery significantly reduced the amount of heterogeneity at these time points (Fig. 3). Care was taken not to pool studies in this subgroup analysis unless there were at least 3 studies comparing the same type of surgery at that time interval, in order to avoid presenting a misleading pooled estimate.

There was no significant difference between pain scores for fentanyl versus sufentanil (Fig. 4). The significant heterogeneity at the 19- to 24-hour time interval was likely driven by the single discordant study that favored sufentanil. Subgroup analysis was not feasible given the small number of studies.

Other comparisons involving morphine versus either sufentanil or oxycodone did not reveal any differences (data not shown). There were also no differences detected by the single adult study comparing morphine to hydromorphone and 2 pediatric studies that compared the same opioids.41-43

**Secondary Outcomes**

**Postoperative Nausea and Vomiting**

There was a higher incidence of PONV in patients receiving morphine compared with fentanyl (OR = 1.91; 95% CI,
Table 1. Description of Included Studies

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1.14–3.18; Fig. 5). The absolute risk reduction for this result was 10.46%, which corresponds to a number needed-to-treat (NNT) of 9.6 patients (95% CI, 5.9–26.2). No other differences in PONV for other opioids were detected in pooled (Fig. 5) and subgroup analyses.

**Pruritus**
Patients receiving morphine experienced more pruritus than those receiving fentanyl, although the data were not statistically significant (OR = 1.64; 95% CI, 0.98–2.76; Fig. 6). Two studies in this group were not pooled. First, we excluded the data from Tsui et al.31 because an anti-pruritic was randomly administered to all study subjects. Second, the study by Vallejo et al.29 was the only trial to report pruritus on a continuous scale, and no difference between the groups was detected. With respect to other opioids and subgroup analyses (data not shown), no further differences were detected.

**Respiratory Depression, Hypotension, and Sedation**
Regardless of the opioids being compared, the incidence of respiratory depression and hypotension was low across most trials, with 0 to 2 patients generally experiencing the outcome in each group. In addition, the number of patients experiencing sedation was generally similar between groups in the same trial but varied markedly among trials. For example, 1 trial reported sedation in 98 of all 105 patients35 and another reported sedation in 2 of 64 patients.27 The only exception to this is the study by Chrubasik et al., where 0 and 9 of 20 patients receiving morphine and fentanyl were sedated, respectively.25 Given the similarity in respiratory depression, hypotension, and sedation among studies, it is unsurprising that pooled and subgroup analyses did not reveal any significant differences in these outcomes (data not shown).

**Total Opioid Consumption**
Total opioid consumption was only compared for studies that used equipotent infusion rates and was standardized per 24 hours. As a caveat, not all studies reported the SD associated with the infusion rate, and in some cases it had to be estimated. There was slightly lower opioid consumption in the morphine group compared with trials comparing morphine versus fentanyl (1.22 mg of morphine equivalent; 95% CI, 0.27–2.18; P = 0.012; Fig. 7). There were no differences in opioid consumption in studies comparing fentanyl to sufentanil and insufficient data to perform this analysis for the other groups.

**Pediatric Studies**
Cho et al.42 showed a higher incidence of pruritus in the sufentanil group compared with the fentanyl group (P = 0.026). Goodarzi43 showed a higher incidence of pruritus, urinary retention, and respiratory depression in the morphine group compared with both fentanyl and hydromorphone.

**Individual Studies**
The single study that compared morphine versus hydromorphone found a higher incidence of pruritus in those receiving morphine in the first 24 hours postoperatively.

### Table 1. Continued

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<td>ND</td>
<td>Yes</td>
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</table>

ND = not described or could not be determined.

*Dosing for morphine versus fentanyl was equipotent but not for hydromorphone.*
Meta-Analysis: Best Epidural Opioid with Least Side Effects

(44.4% vs 11.5%, respectively; P < 0.01) with no other differences detected.31

**Adjuncts to Analgesia**

Dyer et al.23 reported significantly higher use of supplementary IV morphine in the epidural sufentanil group compared with the epidural morphine group. In addition, despite detecting no difference in VAS pain scores, the pediatric study by Cho et al.42 showed that patients in the fentanyl group required more rescue analgesia than those receiving sufentanil (6/32 subjects compared with 0/32 subjects; P = 0.012). Otherwise, the use of analgesic adjuncts was similar in the rest of the studies.

**Assessment of Publication Bias**

Funnel plots were constructed for the analyses presented in Figures 2 to 6 (Supplemental Digital Content 2, http://links.lww.com/AA/A932). Egger’s regression was nonsignificant (P > 0.05) for all these analyses, and all the plots were symmetric with the exception of that corresponding to Figure 3. The symmetry in these plots suggests that there was no publication bias in this review. This asymmetry in the plot for the studies in Figure 3 may have been due to the small number of studies included in that analysis, given the nonsignificant Egger’s regression.

**DISCUSSION**

**Summary of Key Findings**

This novel meta-analysis identified 24 RCTs that compared various continuous infusions of epidural opioids for postoperative analgesia and side effects. Most trials (19/24) compared the clinically relevant opioids morphine, fentanyl, and sufentanil. Overall, there were no

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**Figure 2.** Visual analog scale (VAS) pain scores for trials comparing morphine to fentanyl grouped by time. SD = standard deviation; CI = confidence interval.
clinically significant differences in analgesia. There was an increased rate of PONV (OR = 1.91; 95% CI, 1.14–3.18; and NNT 9.6; 95% CI, 5.9–26.2) and pruritus (OR = 1.64; 95% CI, 0.98–2.76) among patients receiving morphine versus fentanyl. There were no other differences in opioid side effects detected, including respiratory depression, which had a low event rate. Limitations of our analysis included the heterogeneity in surgical populations, differences in outcome reporting among studies, and overall paucity of trials.

### Analgesia

It was challenging to combine the data for analgesia in a manner that is both clinically meaningful and not misleading. For instance, a pooled analysis ignoring the type of surgery would have been better powered but at the cost of equating the bony pain of orthopedics to the laboring pain of a parturient.\(^9,45\) Furthermore, by virtue of their interaction with different parts of the body, certain surgical procedures give rise to higher rates of side effects, such as the increased risk of respiratory complications after thoracotomy.\(^18\) With this rationale in mind, we opted to pool only data involving the same type of surgery and at least 3 trials for adequate power.

Very few individual studies\(^24,25\) reported statistically significant differences in analgesia that met the 20-mm VAS threshold suggested by Farrar et al.\(^46,47\) for clinically meaningful pain reduction. These isolated findings did not persist when studies were pooled overall and in subgroup analysis by type of surgery. Importantly, the use of analgesic adjuncts was similar between groups (for all but 2 trials),\(^23,42\) as was overall total opioid consumption.

Several factors may account for this lack of difference in analgesia. First, all studies reported epidural titration...
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according to the patients’ VAS pain scores using either a bolus or increase in infusion rate of the study solution (by patient-controlled analgesia or staff administration) or analgesic adjunct pro re nata. Although the standard of care, such protocols were problematic when interpreting pain scores because they minimize any difference between the opioids being compared. As an alternative to pain scores, time to first rescue analgesia and total opioid consumption can be considered.48,49 Unfortunately, none of the studies reported the former. With respect to the latter, the small magnitude of the reduced morphine consumption (1.2 mg of morphine equivalent; 95% CI, 0.27–2.18) from the morphine versus fentanyl analysis would not be considered clinically relevant.

Opioid Side Effects

With respect to secondary outcomes, our meta-analysis revealed more similarities than differences among the side effect profiles of opioids being compared. Notably, morphine resulted in more PONV (OR = 1.91; 95% CI, 1.14–3.18) and perhaps pruritus (OR = 1.64; 95% CI, 0.98–2.76) relative to fentanyl. The NNT for the former is <10 patients, which is arguably clinically significant in settings where epidural analgesia is performed in high volume.

The general lack of differences in secondary outcomes is unsurprising given both the dose-dependent nature of opioid side effects and the similarities in total opioid consumption across all studies.13 Nonetheless, morphine still gave rise to more PONV and pruritus than fentanyl, although the latter was not statistically significant. This higher rate of side effects may reflect morphine’s propensity for cephalad migration due to its higher hydrophilicity relative to fentanyl.5 Furthermore, although both fentanyl and morphine can give rise to pruritus directly via opioid receptor stimulation, morphine and its derivatives have an additional mechanism of doing so via inducing histamine release.45

Similarly, the lack of difference in analgesic properties or side effects between sufentanil and fentanyl may be accounted for by their closely shared lipophilic nature, which permits similar penetration of the blood–brain barrier and onset of central nervous system effects (effect-site equilibration time of 6.2 minutes for

<table>
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<tr>
<th>Study</th>
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<th>VAS scores (95% CI)</th>
<th>% Fentanyl</th>
<th>% Sufentanil</th>
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<td>Wilhelm, 1984</td>
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<tr>
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Figure 4. Visual analog scale (VAS) pain scores for trials comparing fentanyl to sufentanil grouped by time. CI = confidence interval.
sufentanil versus 6.8 minutes for fentanyl).\textsuperscript{50} In contrast, better powered analyses (in other clinical contexts) have found differences in analgesia and side effects between sufentanil and fentanyl that were not observed herein.\textsuperscript{51} Biologic plausibility for such a difference is suggested by animal studies that show sufentanil has a much larger spinal volume of distribution compared with fentanyl, which instead preferentially distributes to the epidural space and fat.\textsuperscript{52}

A meta-analysis on intrathecal opioids (in combination with local anesthetics) found similar results to the study presented herein, with higher rates of PONV with intrathecal morphine compared with fentanyl, which instead preferentially distributes to the epidural space and fat.\textsuperscript{52}

A meta-analysis on intrathecal opioids (in combination with local anesthetics) found similar results to the study presented herein, with higher rates of PONV with intrathecal morphine compared with fentanyl, which instead preferentially distributes to the epidural space and fat.\textsuperscript{52}

**Limitations**

There are several limitations to our analysis. Article assessors were not blinded, and we did not include non-English language studies. Only one study published in Italian\textsuperscript{53} that compared morphine to sufentanil was excluded for this reason. Unfortunately, only the abstract for this trial is accessible.\textsuperscript{53} Although analgesia was found to be equivalent, the incidence of pruritus and PONV was an unspecified amount higher with morphine (\(P < 0.0001\)).\textsuperscript{53}

Without a proper full-text appraisal of this study, it is difficult to ascertain how our results would be affected. We also specified a priori that we would exclude cross-over trials due to the potential for inadequate washout of longer-acting opioids, but no trials had to be excluded for this reason.

We considered epidural anesthesia-specific quality factors such as surgery-appropriate level of epidural catheter insertion and confirmation of epidural placement. With regard to the former, “catheter-congruent” epidural anesthesia (relative to the surgical incision level) results in decreased side effects and patient morbidity.\textsuperscript{54} Although only two-thirds of studies described catheter-congruence, the one-third that did not were mainly concentrated in single studies and had minimal impact on our pooled analyses.
With respect to the latter, the majority of studies did confirm placement, and it is hoped that the standard of care was followed in cases where it was left undescribed.

There was a paucity of trials comparing certain opioids and much variability in the surgical populations and outcome reporting among trials. Therefore, some of our analyses (particularly those related to analgesia) were relatively underpowered because data could not be pooled in full. In addition, our subgroup analyses relied on reported equianalgesic ratios for epidural opioids, which some authors argue are widely variable. Thus, the results of any dependent analyses may differ if repeated using a different set. Furthermore, in contrast to the 10 trials comparing morphine to fentanyl, there was a relative dearth of data comparing other opioids and thus less power to detect any differences. Last, due to differences in the timing of pain assessment across studies, we grouped pain scores by time. These bands of time created difficulty with detecting differences in analgesia at finer time points. The comparison of the same subjects across many time points also may have introduced an inherent autocorrelation in the results, obscuring any differences in analgesia.

**CONCLUSIONS**

In summary, this meta-analysis did not demonstrate any convincing or clinically meaningful differences in analgesia or total opioid consumption among the opioids studied. It is reasonable to conclude that fentanyl gives rise to less PONV and perhaps pruritus compared with morphine. As most trials focused on morphine versus fentanyl and fentanyl versus sufentanil, further studies are required to elucidate any differences in analgesia and side effect profiles between other opioids.

**Figure 6.** Odds ratios of postoperative pruritus. CI = confidence interval.
DISCLOSURES

All authors are members of the McMaster Epidural Research Group.

Name: Nayer Youssef, MD.
Contribution: This author was responsible for identifying the clinical question and performing the literature search.
Attestation: Nayer Youssef approved the final manuscript and attests to the integrity of the original data and the analysis reported in this manuscript.

Name: David Orlov, MD.
Contribution: This author was responsible for identifying the clinical question and performing the literature search.
Attestation: David Orlov approved the final manuscript.

Name: Tristan Alie, MSc, MD.
Contribution: This author was responsible for extracting methodological data and identifying the approach for data extraction from graphical sources.
Attestation: Tristan Alie approved the final manuscript.

Name: Matthew Chong, BHSc.
Contribution: This author was responsible for extracting numerical data, performing the data analysis, and interpreting the results.
Attestation: Matthew Chong approved the final manuscript.

Name: Ji Cheng, MSc, PhD.
Contribution: This author analyzed the data and reviewed drafts of manuscript.
Attestation: Ji Cheng approved the final manuscript.

Name: Lehana Thabane, PhD.
Contribution: This author supervised the analysis and reviewed drafts of manuscript.
Attestation: Lehana Thabane approved the final manuscript.

Name: James Paul, MD, MSc, FRCPC.
Contribution: This author is the principal investigator and supervised the completion of the project. James Paul will act as the archival author.
Attestation: James Paul approved the final manuscript.

This manuscript was handled by: Spencer S. Liu, MD.

REFERENCES

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