The Effect of Intrathecal Morphine Dose on Outcomes After Elective Cesarean Delivery: A Meta-Analysis

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BACKGROUND: The intrathecal morphine dose achieving optimal analgesia for cesarean delivery while minimizing side effects has not yet been deduced. In this meta-analysis, our objective was to determine whether low- or high-dose intrathecal morphine provides acceptable duration and intensity of analgesia with fewer side effects.

METHODS: A literature search (PubMed, EMBASE, MEDLINE, Scopus, Web of Science, and CINAHL) was performed to identify randomized controlled trials involving patients undergoing elective cesarean delivery under spinal anesthesia comparing low-dose (LD; 50–100 μg) morphine with higher dose (HD; >100–250 μg). The primary outcome was the time for first request for supplemental analgesia. The secondary outcomes included pain scores, morphine use, maternal side effects (vomiting and pruritus), and Apgar scores. Mean differences (MDs) and odds ratios (ORs) were calculated using random effects modeling with 95% confidence intervals (CIs).

RESULTS: Eleven articles met our inclusion criteria. Four hundred eighty patients were recruited in all study groups (233 patients in the HD and 247 in the LD groups). The mean time to first analgesic request was longer (MD, 4.49 hours [95% CI, 1.85–7.13]; P = 0.0008) in the HD group compared with the LD group. Pain scores (0–100 scale) at 12 hours (MD, 2.54 [95% CI, −2.55 to 7.63]; P = 0.33) as well as morphine consumption at 24 hours (MD, 1.31 mg [95% CI, −3.06 to 7.31]; P = 0.42) were not significantly different. The incidence of nausea or vomiting (OR, 0.44 [95% CI, 0.27–0.73]; P = 0.002) and pruritus (OR, 0.34 [95% CI, 0.20–0.59]; P = 0.0001) was lower in the HD group. The incidence of Apgar scores <7 at 1 minute was not different between groups (OR, 1.11 [95% CI, 0.60–20.49]; P = 0.94).

CONCLUSIONS: This meta-analysis shows that HDs of intrathecal morphine prolong analgesia after cesarean delivery compared with lower doses. The MD of 4.5 hours (95% CI, 1.9–7.1 and 99% CI, 1.0–8.2 hours) of pain relief must be balanced against the increased risk of maternal pruritus and vomiting. Results from this study can be used by clinicians to weigh the benefits and potential side effects of using HDs of intrathecal morphine for cesarean delivery. (Anesth Analg 2016;123:154–64)
respiratory depression), and neonatal outcomes (umbilical arterial and venous pH and Apgar scores at 1 and 5 minutes).

METHODS

For this meta-analysis, we sought randomized controlled trials (RCTs) in women who were not in labor undergoing elective or scheduled cesarean delivery under spinal anesthesia comparing LD (between 50 and 100 μg) to HD (>100 to 250 μg) intrathecal morphine. We conducted a literature search with no language restriction on April 29, 2014, and repeated the search on September 9, 2014. Searches were performed in PubMed (1950 to April 2014), Ovid EMBASE (1970 to April 2014), Ovid MEDLINE (1950 to April 2014), Scopus (1960 to April 2014), EBM Reviews Cochrane Central Register of Controlled Trials 2nd Quarter 2014, CINAHL (April 2014), and Web of Science (September 2015). We attempted to reduce publication bias by consulting the clinical trials registry (www.clinicaltrials.gov) on April 29, 2014. The search strategy consisted of a combination of subject headings (obstetric, cesarean, and caesarean) and keywords/key phrases (morphine and cesarean) for each of MEDLINE, EMBASE, and CINAHL, searched in specified fields (such as ti = title/ab = abstract). In the event that a database did not index articles, we conducted keyword searching in the entire record (Supplemental Digital Content 1 for detailed PubMed search criteria; other search strategies are available from the authors, http://links.lww.com/AA/B393). Reference lists of all identified studies as well as those of previous meta-analyses on similar topics were checked.

All RCTs using intrathecal morphine for cesarean delivery were considered. We only included studies comparing groups that administered ≥50 μg and ≤250 μg for elective or scheduled cesarean delivery. We excluded studies that combined different opioids (e.g., sufentanil or fentanyl) with morphine (e.g., morphine 100 μg + fentanyl 25 μg versus morphine 200 μg + fentanyl 5 μg). Studies were also excluded if they did not evaluate maternal or neonatal outcomes. The quality of studies included in the meta-analysis was reviewed by using the Cochrane Collaboration’s tool for assessing the risk of bias.11 Areas of methodologic quality assessed included concealment of allocation, random sequence generation, blinding of the assessors and participants, and accounting for all subjects. Overall quality of reporting was graded using the 5-point Jadad scale.12 At least 2 individuals extracted the study data independently using a standardized review protocol and recorded the information on a data collection sheet. Differences were resolved by reexamination of the original articles and by discussion with a third reviewer. The data were entered into a computer by 1 of the authors and checked by 2 investigators. Publication bias was assessed using the Egger test.13

The primary outcome was the duration of analgesia, defined by the authors of the meta-analysis as the time from intrathecal morphine administration until the patient’s first request for analgesia. Secondary outcomes included other measures of analgesia (pain scores and morphine use), maternal side effects (nausea, vomiting, pruritus, and respiratory depression), and neonatal outcomes (umbilical arterial and venous pH and Apgar scores at 1 and 5 minutes).

Pain scores (evaluated at 12 and 24 hours) were converted to a unitless 0 to 100 scale, where 0 represents no pain and 100 represents worst pain imaginable to enable comparison among studies. Supplemental morphine consumption (up to 24 hours) was compared by converting opioids used postoperatively to an equivalent dose of IV morphine.14 Twenty-four-hour incidences of nausea (as defined by individual studies), vomiting and pruritus (as defined by each individual study), and severe pruritus were compared between groups. We also compared the need for antiemetic agents. Patients who required antipruritic agents were considered to have experienced severe pruritus. Maternal respiratory depression was defined as incidence of respiratory rate (RR) <10 per minute within 24 hours of intrathecal morphine administration.

When possible, data were combined and analyzed using Review Manager 5.3 (Review Manager [RevMan] Version 5.3; The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark, 2011). For dichotomous outcomes, the odds ratio (OR) and 95% confidence interval (CI) were calculated. In addition, risk difference and number needed to harm were calculated for dichotomous side effects. For continuous data, the mean difference (MD) and 95% CI were determined. The percentage of heterogeneity was assessed with the F statistic. Publication bias was assessed using Egger regression test and illustrated by a funnel plot. A P value <0.05 was considered statistically significant. All data were combined and analyzed using the DerSimonian-Laird random effects model.15 Qualitative assessment was performed for variables that had no occurrences within study groups.

RESULTS

A flow diagram outlining study selection is provided in Figure 1. Two publications were identified from reference lists of retrieved articles but neither met inclusion criteria for this meta-analysis. Excluded studies are listed in Supplemental Digital Content 2 (http://links.lww.com/AA/B393).5,16–37 We retrieved all 34 shortlisted articles that were identified from the literature search. Eleven articles met our inclusion criteria.3,9,10,38–43 Four hundred eighty patients were recruited in all study groups (247 in the LD group and 233 patients in the HD group). The included studies are summarized in Table 1, methodology pain assessment and outcomes are summarized in Table 2, and methodology of secondary outcomes is summarized in Table 3. The funnel plot for the primary outcome is shown in Figure 2. There was no evidence of publication bias, as shown by the Egger test, P value = 0.91. The risk-of-bias assessment is shown in Figure 3.

Time to First Analgesic Request

Of the 11 included studies, 7 reported data on the primary outcome. These 7 studies included 294 subjects in total (Fig; 4; 168 patients in LD group and 126 in the HD group). The MD for time to first request for additional analgesia was 4.49 hours, which is higher in the HD group (95% CI, 1.85–7.13 hours; P = 0.008; Fig. 4). The range of mean times to first analgesic request in the HD group was between 13.8 and 39.5 hours compared with 9.7 to 26.6 hours in the LD group. Moderate heterogeneity was observed for this outcome (I² = 50%). Because an inadequate description of blinding to allocation was the most serious source of bias, we performed
a sensitivity analysis comparing studies blinded to allocation to those that were not. There were 4 studies in which there was no concealment of allocation and 3 studies in which the allocation was appropriate or unclear. In both of these groups, there was significant prolongation of analgesia in the HD group compared with LD (MD = 5.9 hours; 95% CI, 0.18–11.54; P = 0.04 for unconcealed and MD = 4.4 hours; 95% CI, 1.8–7.1 hours; P = 0.0009 for the concealed studies). In this sensitivity analysis, the MD between allocation groups was not statistically different (P = 0.66).

Pain Scores and Morphine Consumption
There were no differences in pain scores (converted to 0–100 if possible; if not possible, data were not included in the analysis) at 12 and 24 hours after delivery between groups (Table 4). Pain was measured in most studies using a visual analog scale (0–10-cm). Other scales used among the studies included 0 to 5 differential verbal pain score rating and a 0 to 21 cumulative scoring system. Morphine consumption at 24 hours was similar between groups (Fig. 5).

Maternal Side Effects
The 24-hour incidences of maternal nausea or vomiting, vomiting, need for antiemetics, pruritus, and severe pruritus are outlined in Table 4. The incidence of pruritus was greater in the HD group (Fig. 6). The number needed to harm for pruritus and severe pruritus was 5.9 (95% CI, 3.4–20.0; P = 0.007), 7.0 (95% CI, 4.0–50.0; P = 0.02), respectively. Sensitivity analysis for pruritus was also performed using 4 studies in which there was no allocation concealment and 4 studies in which the allocation concealment was appropriate or unclear. In both of these groups, there was a significantly higher incidence of pruritus in the HD group compared with LD group (OR = 0.14; 95% CI, 0.04–0.44; P = 0.0008 for nonconcealed allocation and OR = 0.44; 95% CI, 0.24–0.81; P = 0.009 for the concealed studies). In this sensitivity analysis, the ORs were not statistically different (0.14 vs 0.08).

Sensitivity analysis for nausea and vomiting was also performed using 3 studies in which there was no allocation concealment and 4 in which the allocation concealment was appropriate or unclear. The incidence of nausea and vomiting was higher in the HD group compared with the LD group in both allocation groups (OR = 0.61; 95% CI, 0.32–1.14; P = 0.12 for concealed studies and OR = 0.26; 95% CI, 0.12–0.60; P = 0.001 for the nonconcealed studies). The ORs were not different between concealed and nonconcealed studies (0.61 vs 0.26; P = 0.12).

Eight studies investigated the incidence of maternal respiratory depression in the 24 hours after intrathecal morphine administration. Three studies defined respiratory depression as RR <10/min, 1 study as RR <8/min, and 1 study as RR <10/min or oxygen saturation (Spo2) <93%. Three studies did not provide parameters for their definition of respiratory depression. None of the studies reported any patients experiencing respiratory depression in any of the morphine groups. One study explored the difference between LD and HD morphine groups on respiratory depression by using the ventilatory responses to progressive hypercapnia using a modified Read rebreathing technique (involving extrapolating carbon dioxide response curves with a computer-controlled data acquisition system). Ventilatory responses to carbon dioxide 2.5 to 3 hours after injection of morphine were not different from those in the placebo group, indicating that intrathecal morphine did not cause depression of the ventilatory variables in this time frame.

Neonatal Outcome
Three studies investigated neonatal outcome at delivery. All 3 reported data on neonatal Apgar scores at 1 and 5 minutes, with 1 study also reporting additional data on...
### Table 1. Details of Studies Included in Meta-Analysis

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Country</th>
<th>Jadad score</th>
<th>Allocation of concealment</th>
<th>Local anesthetic dose</th>
<th>Morphine doses</th>
<th>Fluids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abboud et al.39</td>
<td>United States</td>
<td>2/5</td>
<td>Unclear. No concealment method described.</td>
<td>9.75–11.25 mg hyperbaric bupivacaine</td>
<td>2 groups (0.1 and 0.25 mg)</td>
<td>10 0.1 11 0.2</td>
</tr>
<tr>
<td>Cohen et al.40</td>
<td>United States</td>
<td>4/5</td>
<td>Sealed, consecutively numbered envelopes. Uncertain whether created offsite or opaque.</td>
<td>12 mg hyperbaric bupivacaine</td>
<td>2 groups (0.1 and 0.2 mg)</td>
<td>12 0.1 11 0.2</td>
</tr>
<tr>
<td>Girgin et al.10</td>
<td>Turkey</td>
<td>4/5</td>
<td>Sealed envelopes. Uncertain whether created offsite/ opaque/ sequentially numbered.</td>
<td>7.5 mg hyperbaric bupivacaine</td>
<td>4 groups (0.1, 0.2, 0.3, 0.4 mg)</td>
<td>18 0.1 19 0.1</td>
</tr>
<tr>
<td>Jiang et al.41</td>
<td>Taiwan</td>
<td>3/5</td>
<td>Unclear. No concealment method described.</td>
<td>10 mg hyperbaric bupivacaine</td>
<td>5 groups (0.025, 0.05, 0.075, 0.125 mg)</td>
<td>33 0.05 35 0.075</td>
</tr>
<tr>
<td>Milner et al.42</td>
<td>United Kingdom</td>
<td>5/5</td>
<td>Computer-generated list. No concealment method described.</td>
<td>12.5 mg hyperbaric bupivacaine</td>
<td>2 groups (0.1 and 0.2 mg)</td>
<td>25 0.1 25 0.2</td>
</tr>
<tr>
<td>Palmer et al.3</td>
<td>United States</td>
<td>5/5</td>
<td>Computer-generated list. No concealment method described.</td>
<td>12.75 mg hyperbaric bupivacaine</td>
<td>8 groups (0.025, 0.05, 0.075, 0.1, 0.125 mg)</td>
<td>36 0.05 36 0.075</td>
</tr>
<tr>
<td>Sarvela et al.38</td>
<td>Finland</td>
<td>5/5</td>
<td>Computer-generated list. No concealment method described.</td>
<td>CSE: IT 8–9 mg plain bupivacaine. 15 μg fentanyl; epidural: 3 mL of 2% lidocaine after 90 min</td>
<td>2 groups (0.1 and 0.2 mg)</td>
<td>49 0.1 47 0.2</td>
</tr>
<tr>
<td>Sharma et al.43</td>
<td>Nepal</td>
<td>1/5</td>
<td>Unclear. No concealment method described.</td>
<td>12.5 mg hyperbaric tetracaine</td>
<td>3 groups (0.05, 0.1, 0.15 mg)</td>
<td>40 0.05 40 0.1</td>
</tr>
<tr>
<td>Uchijima et al.44</td>
<td>Japan</td>
<td>3/5</td>
<td>Unclear. No concealment method described.</td>
<td>10 mg hyperbaric tetracaine</td>
<td>2 groups (0.1 and 0.2 mg)</td>
<td>30 0.1 30 0.2</td>
</tr>
<tr>
<td>Unlugenc et al.44</td>
<td>Turkey</td>
<td>5/5</td>
<td>Pharmacy dispensed study drugs according to computer-generated list</td>
<td>9–13.5 mg plain hyperbaric bupivacaine</td>
<td>2 groups (0.1 and 0.25 mg)</td>
<td>30 0.1 26 0.25</td>
</tr>
<tr>
<td>Yang et al.45</td>
<td>Canada</td>
<td>3/5</td>
<td>Unclear. No concealment method described.</td>
<td>9–13.5 mg plain hyperbaric bupivacaine</td>
<td>2 groups (0.1 and 0.25 mg)</td>
<td>30 0.1 26 0.25</td>
</tr>
</tbody>
</table>

All studies used spinal anesthesia unless stated otherwise. Doses provided where specified.

CSL = compound sodium lactate or Hartmann solution; CSE = combined spinal-epidural; IT = intrathecal.
Table 2. Methodology Pain Assessment and Outcomes

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Intraoperative analgesics</th>
<th>Postoperative analgesics</th>
<th>Reported need for rescue analgesia?</th>
<th>Pain assessment and definition of duration of analgesia (where applicable)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abboud et al.</td>
<td>SC morphine 8 mg prn</td>
<td>IV meperidine 12.5-25 mg every 30 min prn (maximum 50 mg/h)</td>
<td>Yes</td>
<td>VAS (0–100) 3, 6, 12, 16, and 24 h and pain relief of ≥50% as measured on VAS (0–100). Not stated as to whether pain assessments at rest or movement.</td>
</tr>
<tr>
<td>Cohen et al.</td>
<td>IV fentanyl 50–100 μg if in pain</td>
<td>IV morphine PCA: 2 mg every 10 min lockout IV diclofenac if needed</td>
<td>Yes</td>
<td>VAS (0–10) before spinal, 15-min after delivery, 2, 8, 14, and 20 h and time of meperidine request. Not stated as to whether pain assessments at rest or movement.</td>
</tr>
<tr>
<td>Girgin et al.</td>
<td>IV Morphine PCA: 2 mg every 10 min lockout IV diclofenac if needed</td>
<td></td>
<td>Yes</td>
<td>VAS (0–10) 4 hourly for 24 h, number of analgesia requests and time to first morphine PCA dose. Not stated as to whether pain assessments at rest or movement.</td>
</tr>
<tr>
<td>Jiang et al.</td>
<td>Droperidol 1.25 mg, diazepam 5 mg. No opioids</td>
<td></td>
<td>No</td>
<td>Differential pain VRS (0–5) every 1 h for 6 h, then every 2 h for 18 h, then 4 h till 72 h, and time interval from spinal when pain score &gt;2/5. VRS used to assess pain takes into consideration if pain at rest/deep breathing/movement.</td>
</tr>
<tr>
<td>Milner et al.</td>
<td>Morphine: If &lt;12 h postoperative administered IV, if &gt;12 h postoperative administered IM. Diclofenac 100 mg PR at end of surgery, then 18 hourly, acetaminophen 325 and 32.5 mg dextropropoxyphene 6 hourly prn</td>
<td></td>
<td>Yes</td>
<td>VAS (0–100) 4, 8, 12, and 24 h, nature of first analgesia and time to first analgesia. Not stated as to whether pain assessments at rest or movement.</td>
</tr>
<tr>
<td>Palmer et al.</td>
<td>IV fentanyl 10–20 μg increments if in pain (for analysis: fentanyl 10 μg = morphine 1 mg IV)</td>
<td>Morphine bolus in PACU (up to 30 mg), morphine PCA thereafter</td>
<td>Yes</td>
<td>Total morphine milligram required: intraoperative (IV fentanyl conversion) intraoperative + morphine in PACU + morphine via PCA use. No pain assessment conducted.</td>
</tr>
<tr>
<td>Sarvela et al.</td>
<td>IV ketoprofen 100 mg to all patients, fentanyl 50 μg prn for pain</td>
<td>PO/PR ketoprofen 8 hourly, IM oxycodone 0.1 mg/kg prn if VAS &gt;3</td>
<td>Yes</td>
<td>VAS (0–10) intraoperatively, 3 hourly for 24 h. Pain assessed at rest during deep breathing.</td>
</tr>
<tr>
<td>Sharma et al.</td>
<td>IM diclofenac 75 mg to all patients</td>
<td></td>
<td>No</td>
<td>Hours not requiring analgesia postblock (described as &lt;12 h/12 h). Pain assessment method not described.</td>
</tr>
<tr>
<td>Uchiyama et al.</td>
<td>PR 25 mg indomethacin</td>
<td></td>
<td>Yes</td>
<td>Number of supplemental requests in 48 h and time to first analgesia request. Pain assessment method not described.</td>
</tr>
<tr>
<td>Unlugenc et al.</td>
<td>Epidural top-up, if VRS &gt;3/10 (excluded from study)</td>
<td>Epidural top-up if VRS &gt;3/10, IM diclofenac 150 mg/24 h</td>
<td>No</td>
<td>VRS (0–10) at 5 min prespinal; postspinal at 5, 10, 15 20, 25, 30, and every 15 min and time to first analgesia. Pain assessments conducted at rest.</td>
</tr>
<tr>
<td>Yang et al.</td>
<td>PR indomethacin 100 mg at end of surgery, then PO naproxen 500 mg every 12 h, acetaminophen (325–650 mg) prn, and nalbuphine and dextromethorphan prn</td>
<td></td>
<td>Yes</td>
<td>VAS (0–10) before spinal, PACU, 2, 4, 8, and 24 h, additional analgesia and time to first analgesia (no raw data). Not stated as to whether pain assessments at rest or movement.</td>
</tr>
</tbody>
</table>

All studies used spinal anesthesia unless stated otherwise. Doses provided where specified.

IM = intramuscular; PACU = postanesthetic care unit; PCA = patient-controlled analgesia; PO = oral; PR = per rectum; prn = as required; SC = subcutaneous; VAS = visual analog scale; VRS = verbal reporting scale.
### Table 3. Assessment Method and Measurement Times of Maternal Side Effects

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Nausea assessment and time points measured</th>
<th>Vomiting assessment and time points measured</th>
<th>Reported need for antiemetics? (yes/no)</th>
<th>Pruritus assessment and time points measured</th>
<th>Reported need for antipruritics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abboud et al.39</td>
<td>No assessment method described. Incidence in 24 h measured.</td>
<td>No assessment method described. Incidence in 24 h measured.</td>
<td>No</td>
<td>No assessment method described. Incidence in 24 h measured.</td>
<td>Yes</td>
</tr>
<tr>
<td>Cohen et al.40</td>
<td>Severity assessed using VAS (0-10) before spinal, 15-min postspinal, and 2, 8, 14, and 20 h postspinal.</td>
<td>Severity assessed using VAS (0-10) before spinal, 15-min postspinal, and 2, 8, 14, and 20 h postspinal.</td>
<td>No: measured but not reported Yes*</td>
<td>No: measured but not reported No: measured but not reported</td>
<td>No</td>
</tr>
<tr>
<td>Girgin et al.10</td>
<td>Severity assessed using VRS (0-3). Measured intraoperatively, then 4 hourly for 24 h.</td>
<td>Severity assessed using VRS (0-3). Measured intraoperatively, then 4 hourly for 24 h.</td>
<td>Yes*</td>
<td>Severity assessed using VRS (0-3). Measured intraoperatively, then 4 hourly for 24 h. Yes*</td>
<td>No</td>
</tr>
<tr>
<td>Jiang et al.46</td>
<td>No assessment method described. Presence 1 hourly for 6 h, 2 hourly for 18 h, and 4 hourly for 72 h.</td>
<td>No assessment method described. Presence 1 hourly for 6 h, 2 hourly for 18 h, and 4 hourly for 72 h.</td>
<td>No</td>
<td>No assessment method described. Presence 1 hourly for 6 h, 2 hourly for 18 h, and 4 hourly for 72 h. No</td>
<td>No</td>
</tr>
<tr>
<td>Milner et al.42</td>
<td>Severity assessed using 5-point scale. Incidence 24 h measured.</td>
<td>Severity assessed using 5-point scale. Incidence 24 h measured.</td>
<td>No</td>
<td>Severity assessed using 5-point scale but reported incidence in 24 h No</td>
<td>No</td>
</tr>
<tr>
<td>Palmer et al.3</td>
<td>Severity assessed using 3-point scale. Measured intraoperatively and then 4 hourly for 24 h.</td>
<td>Severity assessed using 5-point scale. Measured intraoperatively and then 4 hourly for 24 h.</td>
<td>Yes*</td>
<td>Severity assessed using 5-point scale. Measured intraoperatively and then 4 hourly for 24 h. Yes*</td>
<td>Yes*</td>
</tr>
<tr>
<td>Sarvela et al.38</td>
<td>Severity assessed using 3-point scale. Measured 3 hourly for 24 h.</td>
<td>Severity assessed using 3-point scale. Measured 3 hourly for 24 h.</td>
<td>Yes</td>
<td>Severity assessed using 3-point scale. Measured 3 hourly for 24 h. Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Sharma et al.43</td>
<td>No definition provided. Incidence 2 hourly for 24 h measured.</td>
<td>No definition provided. Incidence 2 hourly for 24 h measured.</td>
<td>No</td>
<td>No definition provided. Incidence 2 hourly for 24 h measured. No</td>
<td>No</td>
</tr>
<tr>
<td>Uchiyama et al.2</td>
<td>Severity assessed using 4-point scale. Scale incorporated both nausea and vomiting. Measured for 48 h, time intervals not stated.</td>
<td>Severity assessed using 4-point scale. Scale incorporated both nausea and vomiting. Measured for 48 h, time intervals not stated.</td>
<td>No</td>
<td>Severity assessed using 4-point scale. Measured for 48 h, time intervals not stated. No</td>
<td>No</td>
</tr>
<tr>
<td>Unlugenc et al.44</td>
<td>Definition not provided. Incidence measured and reported, but time frame not stated.</td>
<td>Definition not provided. Incidence measured and reported, but time frame not stated.</td>
<td>No</td>
<td>Definition not provided. Incidence measured and reported, but time frame not stated. No</td>
<td>No</td>
</tr>
<tr>
<td>Yang et al.45</td>
<td>Severity assessed using 5-point scale. Scale incorporated both nausea and vomiting. Assessments made before spinal, PACU, 2, 4, 8, and 24 h.</td>
<td>Severity assessed using 5-point scale. Scale incorporated both nausea and vomiting. Assessments made before spinal, PACU, 2, 4, 8, and 24 h.</td>
<td>Yes</td>
<td>Severity assessed using VAS (0-10) before spinal, PACU, 2, 4, 8, and 24 h. Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

VAS = visual analog scale; VRS = verbal rating scale; PACU = postanesthesia care unit.

*Not reported quantitatively; Palmer et al. report grouped nausea and vomiting and pruritus interventions.
umbilical cord blood gases. The incidence of Apgar scores <7 at 1 minute was not significantly different between groups (OR, 1.11; 95% CI, 0.06–20.49;  P = 0.94). There were no incidences of Apgar scores <7 at 5 minutes in any of the 3 studies that assessed this outcome. The one study investigating umbilical cord blood gases reported no neonates with umbilical artery pH of <7.2 with the administration of either 0.1 or 0.25 mg intrathecal morphine.39

**DISCUSSION**

The primary finding of this study is that the mean time to requirement of supplemental analgesia with HD (>100–250 μg) intrathecal morphine is approximately 4.5 hours longer than with LD (50–100 μg). Although this is the best estimate of treatment effect, the CI around this value warrants discussion. Based on the calculated 95% CI, the duration of analgesia is prolonged by between 1.9 and
7.1 hours. This interval may be too conservative because of the small number of studies, heterogeneity among studies, and the possibility that the data in each study are not normally distributed. The more conservative 99% CI yields an increase in duration of analgesia between 1.0 and 8.2 hours for HD compared with LD intrathecal morphine. Factors that may have been responsible for the heterogeneity include the use of different protocols for the administration of adjuvant analgesic agents and other factors that may cause variations among study participants (e.g., geography, ethnicity).

Use of multimodal analgesic therapy has been shown to improve analgesia and decrease opioid requirements after cesarean delivery. The studies in this meta-analysis used a variety of nonsteroidal antiinflammatory drugs (NSAIDs) (indomethacin, ketoprofen, diclofenac, and naproxen) administered via different routes and in various regimens including intraoperative use only, perioperative and regular postoperative use, regular postoperative use only, and as required postoperative use. Furthermore, various different definitions were used among the studies for duration of analgesia, including time until pain score reached a certain level (>2/5 or visual analog scale pain score <50/100), time to first meperidine request, time to first analgesic request, and time to first patient-controlled analgesia dose administration. Pain score assessment in many of the studies also did not state the site of pain scores or whether taken at rest or on movement.

Dahl et al. in 1999 observed a prolonged time to first postoperative analgesia with the use of intrathecal morphine compared with placebo/control; however, they did not analyze a dose response. Their reported median time to

Table 4. Summary of Maternal Secondary Outcomes

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>No. studies</th>
<th>No. patients (low dose, high dose)</th>
<th>MD/OR</th>
<th>MD/OR (95% CI)</th>
<th>P</th>
<th>P</th>
<th>NNT/NNH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain scores at 12 h</td>
<td>2</td>
<td>74, 72</td>
<td>MD</td>
<td>2.54 (−2.55 to 7.63)</td>
<td>0.33</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td>Pain scores at 24 h</td>
<td>1</td>
<td>18, 19</td>
<td>MD</td>
<td>1.00 (−2.50 to 4.50)</td>
<td>0.58</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Pruritus</td>
<td>8</td>
<td>228, 192</td>
<td>OR</td>
<td>0.34 (0.20 to 0.59)</td>
<td>0.0001</td>
<td>0</td>
<td>5.9</td>
</tr>
<tr>
<td>Severe pruritus</td>
<td>5</td>
<td>156, 131</td>
<td>OR</td>
<td>0.32 (0.16 to 0.61)</td>
<td>0.0006</td>
<td>0</td>
<td>7.0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>7</td>
<td>180, 138</td>
<td>OR</td>
<td>0.38 (0.19 to 0.75)</td>
<td>0.0005</td>
<td>0.03</td>
<td>7.7</td>
</tr>
<tr>
<td>Nausea or vomiting</td>
<td>7</td>
<td>196, 174</td>
<td>OR</td>
<td>0.44 (0.27 to 0.73)</td>
<td>0.002</td>
<td>0</td>
<td>8.3</td>
</tr>
<tr>
<td>Antiemetics</td>
<td>2</td>
<td>79, 75</td>
<td>OR</td>
<td>0.69 (0.32 to 1.45)</td>
<td>0.33</td>
<td>0</td>
<td>NA</td>
</tr>
</tbody>
</table>

CI = confidence interval; MD = weighted mean difference; NA = not applicable; NNT = numbers needed to treat; OR = odds ratio.

Figure 5. Forest plot for morphine consumption at 24 hours. Mean difference is represented in milligrams.

Figure 6. Forest plot for incidence of pruritus.
first analgesic requirement after cesarean delivery was 27 hours (range, 11–29) with various doses of intrathecal morphine (50–200 μg) with or without other intrathecal opioids (sufentanil, fentanyl, and buprenorphine). Our results demonstrate that duration of analgesia after cesarean delivery is dependent on the intrathecal dose of morphine. A systematic review of various epidural morphine doses after cesarean delivery reported median time until first request for analgesia as 19.0 hours (range, 5.4–29.2 hours); and duration of analgesia was longer with larger epidural morphine doses (8.9 hours with 2 mg vs 26.8 hours with 6 mg). However, the largest RCT to date exploring the effect of epidural morphine on analgesic duration demonstrated no significant difference between 1.5 and 3 mg. This study by Singh et al. included a multimodal regimen with scheduled NSAIDs for both arms of the trial. This result suggests that multimodal analgesic regimens may mitigate analgesic differences between LDs and HDs of intrathecal morphine. Multimodal analgesia was used in 6 studies (4 studies using NSAIDs and acetaminophen) and 2 studies using NSAIDs (42,45).

Of the 11 studies in our review, 9 studies considered 100 μg morphine as LD. Three of the studies included in this meta-analysis had >1 group in the LD group. These groups were combined and compared with the HD group. Only 1 of these studies reported duration of analgesia. In this study, the authors showed a significant dose response over the range of doses (0–125 μg) although the dose response for side effects such as pruritus and vomiting was not apparent. Palmer et al. studied a wider range of doses (100–500 μg) but did not report the duration of action. They noted an increase in IV patient-controlled morphine use in women who received lower doses but concluded this was not a linear relationship. Unfortunately, there are not enough patients in our studies to conduct a meta-regression based on individual doses. Nor would a sensitivity analysis based on dose produce significant results when examining the primary outcome or side effects because of lack of power.

Neuraxial compared with parenteral opioids have been found to consistently decrease pain and opioid requirement after cesarean delivery. With the increase in analgesic duration demonstrated with HD morphine, we expected differences in pain scores and morphine consumption between groups. However, we found no differences in pain scores at 12 and 24 hours or morphine consumption at 24 hours between the HD and LD intrathecal morphine groups. Based on a longer duration of action with HDs of intrathecal morphine, we would expect greater differences in analgesic effects over the 24- to 48-hour period after surgery. Pain scores and morphine usage were, however, only consistently recorded until 24 hours within the included studies, and therefore, greater breakthrough pain and analgesia doses beyond this period of time may have been missed through the design of studies.

The results of studies exploring intrathecal morphine doses and pain or analgesic use after cesarean delivery are inconsistent. For assessment of analgesic efficacy, the isolated statistical analysis of pain score or morphine consumption as surrogate markers for pain not only loses statistical efficiency but may also incur increased false-positive findings because of multiple testing. It is possible that some women used an increased amount of opioids to reduce pain to acceptable levels, and others may have tolerated higher pain scores to avoid opioids and their related side effects. Tools are available to measure this interaction; however, integrated outcomes evaluating this were not possible in this study because we did not have access to individual patient data. Other possible explanations for the disparity demonstrated among studies include regional differences in pain scales and opioid use, small sample size, postpartum maternal avoidance of opioids despite presence of pain to minimize breastfeeding-related neonatal drug exposure, and the standard 24-hour study assessment methodology used in many studies is likely to miss the peak in postoperative pain that occurs 36 to 48 hours after neuraxial morphine administration for cesarean delivery.

Although the association between the use of neuraxial morphine and increased maternal side effects (pruritus, nausea, and vomiting) is well described, the dose-response relationship is less consistently shown in studies. This meta-analysis demonstrates significant differences in pruritus between the HD and LD intrathecal morphine groups. Significant differences were also demonstrated after sensitivity analyses for both studies with and without adequate concealment of allocation group for the outcomes of duration of analgesia and pruritus. Our results are consistent with the findings from Dahl et al. who describe increased pruritus with higher intrathecal morphine doses. Palmer et al. found no differences in nausea or vomiting with increasing dose of intrathecal morphine (25–500 μg). In contrast, our meta-analysis did find an increase in nausea or vomiting. Increased nausea or vomiting is consistent with previously reported increased antiemetic use (52% vs 24%) with 200 μg compared with 100 μg intrathecal morphine for cesarean delivery. This meta-analysis confirms that larger intrathecal morphine doses are associated with increased maternal opioid-related pruritus and nausea or vomiting, which should be considered when selecting the optimal dose of intrathecal morphine. The “better studies” did not show the statistical difference, probably because there were too few studies, but the possibility of bias in the “poorer studies” cannot be excluded. Sensitivity analysis for the outcome of nausea and vomiting did not demonstrate statistical significance in the studies with adequate concealment, which may have been attributable to the presence of too few studies for this analysis. Furthermore, the possibility of bias in the studies without concealment cannot be excluded.

Neonatal outcomes were not significantly different between groups. It should, however, be noted that none of the studies included in this meta-analysis were powered to demonstrate differences in the neonatal outcomes assessed. Similarly, none of the studies had sufficient power to detect maternal respiratory depression. This analysis shows that duration of analgesia of intrathecal morphine can be prolonged by increasing the dose, at the potential expense of increasing maternal side effects. This information can be used to help decide the correct choice of intrathecal morphine dose for women undergoing cesarean delivery. In particular, patients who are at high risk for severe postoperative pain may benefit from an increased dose of intrathecal morphine, and women.
reporting sensitivity to opioids and their related side effects may benefit from lower doses.\textsuperscript{50} There are several limitations to this study. Studies included in the analysis for the primary outcome of time until first request for analgesia may be at risk of selection bias because concealment of allocation was not described. Sensitivity analysis considering allocation concealment to address the study quality did not, however, change the overall result for the primary outcome. Whether time to first request for supplemental analgesia correlates well with duration of analgesia was not evaluated in this study. Also, the variety of NSAID administration methods and varied use among studies may be a confounding factor in this analysis. Multimodal analgesic regimens may mitigate analgesic differences between LDs and HDs of intrathecal morphine. LD morphine may, for example, provide acceptable analgesia if combined with NSAIDs and/or acetaminophen but inadequate analgesia without NSAIDs and/or acetaminophen. This may also alter the duration of analgesia (i.e., small difference with NSAIDs and larger difference without NSAIDs). There was significant clinical heterogeneity in the local anesthetic drug dose and baricity across studies. In addition, the intraoperative and postoperative rescue analgesic drugs and the mode of analgesic administration varied among studies, resulting in heterogeneity for the primary outcome. The method of primary outcome measurement also varied among studies (Table 1). This meta-analysis included 5 studies from Asia, 4 from North America, 4 from Europe, and 1 from South America. The wide geographical study population may have increased heterogeneity; however, this geographic variation does increase generalizability of the results and could also be considered a strength of this study. We included studies using \( \geq 50 \) \( \mu \)g morphine dose because smaller intrathecal morphine doses are rarely used or studied and may have limited efficacy.\textsuperscript{3} We used 100 \( \mu \)g as the cutoff for HD and LD to reflect common clinical practice and to be consistent with most studies that defined 100 \( \mu \)g as an LD intrathecal morphine. We excluded studies that used doses of intrathecal morphine >250 \( \mu \)g because these doses are not commonly used in clinical practice and may be associated with respiratory depression.\textsuperscript{4}

We did not evaluate the probability distribution of the duration of pain relief; therefore, the lower 99\% confidence limit of 1.0 hours should be considered as the amount of extra duration of analgesia at minimum achieved with the higher intrathecal morphine dose. We calculated the 95\% CI for the ORs and weighted MDs; however, we acknowledge that the use of 99\% confidence limits provides more robust coverage.\textsuperscript{21} Although this meta-analysis focused on pain, analgesic, and side effect outcomes, we appreciate that good measures for evaluating patient satisfaction are lacking. The optimal balance between analgesia and side effects may be best reflected by a global satisfaction measure. Dose selection should preferably account for patients’ preferences for pain relief and maternal desire to limit potential side effects. Further studies are needed to elucidate optimal dose selection that leads to greatest patient satisfaction.

In summary, this meta-analysis demonstrates that HDs of intrathecal morphine prolong analgesia after cesarean delivery. The additional MD of 4.5 hours of pain relief (may be as low as additional 1.0 hours and as much as 8.2 hours) must be balanced against the increased risk of maternal pruritus and nausea or vomiting. The trade-off between improved analgesia and increased side effects should be appreciated by both care providers and women undergoing cesarean delivery. Results from this study can be used by clinicians to aid decision making regarding drug selection and to inform patients of the benefits and potential side effects of using larger doses of intrathecal morphine for cesarean delivery.

**DISCLOSURES**

**Name:** Pervez Sultan, MBChB, FRCA.

**Contribution:** This author helped design the study, conduct the study, and write the manuscript.

**Attestation:** Pervez Sultan has seen the original study data, reviewed the analysis of the data, approved the final manuscript, and is the author responsible for archiving the study files.

**Name:** Stephen H. Halpern, MD.

**Contribution:** This author helped design the study, conduct the study, analyze the data, and write the manuscript.

**Attestation:** Stephen Halpern has seen the original study data, reviewed the analysis of the data, approved the final manuscript, and is the author responsible for archiving the study files.

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**Contribution:** This author helped design the study, analyze the data, and write the manuscript.

**Attestation:** Ellile Pushpanathan has seen the original study data, reviewed the analysis of the data, approved the final manuscript, and is the author responsible for archiving the study files.

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**Contribution:** This author helped design the study, analyze the data, and write the manuscript.

**Attestation:** Selina Patel has seen the original study data, reviewed the analysis of the data, approved the final manuscript, and is the author responsible for archiving the study files.

**Name:** Brendan Carvalho, MBBC, FRCA.

**Contribution:** This author helped design the study, conduct the study, and write the manuscript.

**Attestation:** Brendan Carvalho has seen the original study data, reviewed the analysis of the data, approved the final manuscript, and is the author responsible for archiving the study files.

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**REFERENCES**


42. Milner AR, Bogod DG, Harwood RJ. Intrathecal administration of morphine for elective Caesarean section. A comparison between 0.1 mg and 0.2 mg. Anesthesia 1996;51:871–3.


45. Yang T, Breen TW, Archer D, Fick G. Comparison of 0.25 mg and 0.1 mg intrathecal morphine for analgesia after Cesarean section. Can J Anaesth 1999;46:856–60.


