REVIEW ARTICLE

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Intraoperative and Postoperative Analgesic Efficacy and Adverse Effects of Intrathecal Opioids in Patients Undergoing Cesarean Section with Spinal Anesthesia

A Qualitative and Quantitative Systematic Review of Randomized Controlled Trials

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SPINAL anesthesia is commonly used for cesarean section, and it has become a popular practice to add opioids to spinal solutions to enhance and prolong intraoperative and postoperative analgesia. Morphine and fentanyl are the opioids most often used for this purpose, but there is not a general consensus about the benefits of the various regimens, and the incidence of side effects with different opioids and doses is controversial.

Recently, a number of systematic reviews have been published in the field of pain and perioperative medicine.[1–3] The aim of a systematic review is to summarize available information from controlled clinical trials to produce evidence-based estimates of the true clinical effect of an intervention.[4–6] The purpose of this systematic review was to investigate the effect of intrathecal opioids added to spinal anesthesia on intraoperative and postoperative pain and to evaluate adverse effects in patients scheduled for cesarean section, using evidence from all relevant randomized controlled and blinded trials.

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Methods

Systematic Search and Validity Score

Reports of randomized controlled trials of opioid added to spinal anesthesia in patients undergoing cesarean section were sought systematically. Only reports that examined a single dose of opioid added to a spinal anesthetic and that included a postoperative pain outcome were considered. Only reports that compared opioid against placebo (*e.g.*, saline) or no treatment were included in the analysis.

Reports were identified using The Cochrane Library (1998, issue 2) and the MEDLINE (1966–1998) and EMBASE (1981–1998) databases without language restriction. We used different search strategies with free-text combinations, including the following key words: spinal, subarachnoidal, intrathecal, opioid, anesthesia, local anesthesia, postoperative analgesia, and cesarean section (date of final search: July 15, 1998). Reference lists of retrieved reports and review articles were searched systematically. No abstracts or unpublished observations were included. Authors were not contacted for original data.

Table 1. Summary of Randomized Controlled Studies of the Postoperative Analgesic Effects of Intrathecal Opioids in Caesarean Section

Reference	Quality Score	Number of Patients Treatment/ **Control**	Local Anesthetic	Opioid	Postoperative Pain Score Compared with Control	Postoperative Supplemental Analgesic Consumption/or Number of Patients Needing Supplemental Analgesics Compared with Control	Time to First Postoperative Analgesic Compared with Control	Comments
9	2	11/10/**12**	Bupivacaine, 9.75–11.25 mg, hyperbar	Morphine 0.1 mg 0.25 mg	 $P < 0.05$ $P < 0.05$	—	—	Pain scores reduced 3–24 h postop
10	3	17/**17**	Bupivacaine, 9.3 ± 0.2 mg, hyperbar (mean ± SEM)	Morphine 0.2 mg	—	$P < 0.05$	$P < 0.05$	Number of patients needing suppl analgesics 0–24 h postop: 6:17 *vs.* 17:17 in active *vs.* control group Suppl morphine consumption 0–24 h postop (mg): 7.2 ± 3.9 *vs.* 26.8 ± 5.6 in active *vs.* control group (mean ± SEM)
11	4	29/**21**	Bupivacaine, 9.3 ± 0.02 mg, hyperbar + 0.2 mg adr (mean ± SE)	Morphine 0.2 mg	—	$P < 0.05$	$P < 0.05$	Number of patients needing suppl analgesics 0–24 h postop: 14:29 *vs.* 21:21 in active *vs.* control group Suppl morphine consumption 0–24 h postop (mg): 11.1 ± 1.3 *vs.* 22.2 ± 2.5 in active *vs.* control group (mean ± SEM)
12	2	20/20/20/**20**	Tetracaine, 10 mg, hyperbar	Morphine 0.05 mg 0.1 mg 0.2 mg	 — — —	 $P < 0.05$ $P < 0.05$ $P < 0.05$	 NS $P < 0.05$ $P < 0.05$	Suppl analgesic consumption evaluated 0–24 h postop (indomethacin)
13	4	30/**30**	Bupivacaine, 13–14 mg, hyperbar	Morphine 0.1 mg	$P < 0.05$	$P < 0.05$	—	Pain (VAS) reduced 4 and 24 h postop Suppl morphine consumption 0–24 h postop (mg): 10 (4–32) *vs.* 29 (16–32) in active *vs.* control group (median, interquartile range)
14	5	29/**26**	Bupivacaine, 12–14 mg, hyperbar	Morphine 0.1 mg	$P < 0.05$	$P < 0.05$	$P < 0.05$	Pain (VAS) assessed from 1–24 h postop Suppl analgesic consumption evaluated 0–24 h postop (keterolac)
15	3	6/8/7/7/6/7/5/**9**	Bupivacaine, 0.75%, hyperbar	Fentanyl 2.5 μg 5 μg 6.25 μg 12.5 μg 25 μg 37.5 μg 50 μg	 — — — — — — —	 NS NS NS NS NS NS NS	 NS NS $P < 0.05$ $P < 0.05$ $P < 0.05$ $P < 0.05$ $P < 0.05$	
16	3	12/**12**	Bupivacaine, 12.5 mg, hyperbar	Fentanyl 10 μg	—	—	$P < 0.05$	
17	2	30/30/30/**30**	Bupivacaine, 15 mg, hyperbar	Fentanyl 20 μg 40 μg 60 μg	 — — —	 NS $P < 0.05$ $P < 0.05$	 $P < 0.05$ $P < 0.05$ $P < 0.05$	Suppl analgesic consumption 0–24 h postop: 2.4 ± 0.6 *vs.* 1.6 ± 0.6 *vs.* 1.2 ± 0.5 *vs.* 2.7 ± 0.7 μg/kg of fentanyl in group 20, 40, 60 μg and control, respectively (mean ± SD)
18	3	14/**14**	Lidocaine, 80 mg, hyperbar	Fentanyl 15 μg	—	NS	$P < 0.05$	
14	5	25/**26**	Bupivacaine, 12–14 mg, hyperbar	Fentanyl 25 μg	NS	NS	NS	
19	3	25/**25**	Bupivacaine, 12.5 mg, hyperbar	Fentanyl 10 μg	NS	NS	—	

Table 1. Continued

Reference	Quality Score	Number of Patients Treatment/ **Control**	Local Anesthetic	Opioid	Postoperative Pain Score Compared with Control	Postoperative Supplemental Analgesic Consumption/or Number of Patients Needing Supplemental Analgesics Compared with Control	Time to First Postoperative Analgesic Compared with Control	Comments
20	4	20/**20**	Bupivacaine, 12.5 mg, hyperbar	Fentanyl 10 μg	—	—	NS	
21	2	20/**20**	Bupivacaine, 12.5 mg, hyperbar	Fentanyl 15 μg	—	NS	$P < 0.05$	
20	4	20/20/**20**	Bupivacaine, 12.5 mg, hyperbar	Sufentanil 2.5 μg	—	$P < 0.05$	$P < 0.05$	Suppl morphine consumption 0–6 h postop (mg): 8 ± 9 *vs.* 6 ± 11 *vs.* 19 ± 12 in group 2.5 *vs.* 5 μg sufentanil *vs.* control, respectively (mean ± SD). No difference in opioid consumption from 6–24 h postop
				5 μg	—	$P < 0.05$	$P < 0.05$	
22	3	9/9/9/**10**	Bupivacaine, 10.5 mg, hyperbar	Sufentanil 10 μg	—	—	$P < 0.05$	
				15 μg	—	—	$P < 0.05$	
				20 μg	—	—	$P < 0.05$	
23	2	15/15/**15**	Bupivacaine, 22.5 mg (hyperbar)	Buprenorphine 0.03 mg	—	—	$P < 0.05$	
				0.045 mg	—	—	$P < 0.05$	

NS = no significant difference, as reported in the original study; — = no data available; suppl = supplemental.

Each report that met the inclusion criteria was read independently by three of the authors and scored using a three-item, 1–5-score quality scale.[5] Consensus was subsequently achieved. If the reports were described as randomized, one point was given, and an additional point was given if the method of randomization was described and considered adequate (computer-generated, table of random numbers, *etc.*); however, one point was deducted if randomization was inappropriate (alternate randomization, randomization according to weekday, *etc.*). If trials were described as double-blind, one point was given. An additional point was given if blinding was described and considered appropriate (blinded pharmacy-manufactured ampules, *etc.*), but one point was deducted if blinding was inappropriate. Finally, reports that described the numbers and reasons for withdrawals were given one point. By definition, studies without randomization and blinding were excluded. Thus, the minimum score of an included randomized controlled trial was 2 and the maximum score was 5.

Data Extraction and Analysis

Information about patients, type and dose of local anesthetic, and opioid used for spinal anesthesia and analgesia, study end points, adverse effects, and observation periods were taken from each report.

When possible, retrieved data were analyzed quantitatively. We used a metaanalysis to calculate the weighted number needed to treat (NNT) or number needed to harm (NNH) with 95% confidence intervals (CIs), counting the dichotomous outcome for all the individuals across all included studies, *i.e.*, a fixed-effects model. NNT refers to the number of patients needed to treat to yield one successful outcome. NNH refers to the number of patients needed to treat to harm one individual.[4,7,8] A significant difference between NNT or NNH was assumed when CIs did not overlap. This is a conservative criterion because it involves the comparison of an improbable extreme for one estimate with an equally improbable extreme for the other.[2] When one bound of the CI was ∞, this indicated that the CI included no benefit or harm of the intrathecal opioid over placebo/control. Data from control patients in studies investigating more than one opioid or dose (more than one treatment arm) were included in more than one analysis, but control data were not counted more than once for the combined analysis. NNT was calculated for number of patients not needing supplemental intraoperative analgesics.

Data on postoperative pain scores and supplemental analgesics were insufficient to perform a quantitative analysis and were evaluated qualitatively. In this analysis, effectiveness was defined as a significant difference (as

reported in the original trials) between the active and the control groups in three different measures of analgesic efficacy: postoperative pain intensity (visual analog score or similar pain scores), time to first administration of postoperative analgesic, or total consumption of postoperative analgesic.

Four different side effects were extracted in dichotomous form (presence or absence of side effect) and evaluated quantitatively with calculation of NNH: pruritus, nausea, vomiting, and respiratory depression (defined as respiratory rate < 10 breaths/min).

Evidence for a dose response was assumed when CIs between NNT or NNH of two doses or dose ranges did not overlap (see above).[2] In addition, the dose–response relationship between pruritus, nausea and vomiting, and intrathecal morphine, fentanyl, or sufentanil was evaluated by means of univariate logistic regression.

Results

Fifteen reports fulfilled the inclusion criteria.[9–23] In these reports, 535 patients were given four different opioids (morphine, fentanyl, sufentanil, buprenorphine) in 32 treatment arms and 23 different doses (table 1); 281 patients served as controls. In one study, fentanyl doses were weight normalized.[17] For the quantitative analysis, these doses were recalculated to total dose based on the demographic data provided in the report.[17] Two studies compared two different opioids.[14,20] Three different local anesthetics were used for spinal anesthesia: bupivacaine (13 studies), lidocaine (one study), and tetracaine (one study; table 1).

Studies by the following investigators were excluded from the final analysis: Pan *et al.*[24] (single-blinded), Chu *et al.*[25] (no information about blinding), and Cooper *et al.*[26] (administration of epidural fentanyl intraoperatively in a fraction of patients).

Analgesic Efficacy

Postoperative Pain Scores. Only four studies with a total of six treatment arms evaluated postoperative pain scores beyond the time to first administration of supplemental analgesic (table 1).[9,13,14,19]

Abboud *et al.*[9] reported prolonged postoperative pain relief of $\geq 50\%$ as measured with visual analog score with morphine 0.1 mg and 0.25 mg compared with control. Morphine (0.1 mg) decreased pain scores for 24 h postoperatively in two other studies.[13,14] Fentanyl (10 μg and 25 μg) had no effect on pain scores during 24 h postoperatively in the studies by Olofsson *et al.*[19] and Sibilla *et al.*,[14] respectively.

Time to First Administration of Supplemental Analgesic Postoperatively. Data on time to first administration of supplemental analgesic postoperatively could be extracted from 12 studies (table 1).[10–12,14–18,20–23] The criteria for this outcome was clearly specified in 10 studies: time from subarachnoid administration of opioid to patient request for analgesia was the criterion in eight studies,[10–12,14,16–18,23] and time to visual analog score $>$ 3 or 4 was the criterion in two studies.[20,22] In two other studies,[15,21] no distinct criteria could be derived from the reports.

The median time to first administration of analgesic with local anesthetic alone (control) was 2 h (range, 1–4 h) in 10 studies with bupivacaine, and 1 h and 8 h in two studies with lidocaine and tetracaine, respectively (fig. 1).

Morphine was evaluated in four studies[10–12,14] with a total of six treatment arms and three doses (table 1). Morphine at doses of 0.1 mg and 0.2 mg increased the time to first administration of analgesic in all five comparisons, whereas a 0.05-mg dose had no significant effect on this outcome in one study. In one study, administration of 0.05 mg, 0.1 mg, and 0.2 mg morphine showed no clear dose–response relationship.[12] Figure 1 shows time to first postoperative analgesic for the different studies and treatment arms. Median time to first analgesic with the various effective doses of morphine was 27 h (range, 11–29 h).

Fentanyl was evaluated in seven studies[14–18,20,21] with a total of 15 treatment arms and 12 doses (table 1). In the study by Hunt *et al.*,[15] seven doses of fentanyl, from 2.5 μg to 50 μg, were examined, but only data with 6.25 μg are reported. Except for four comparisons with 2.5 μg, 5 μg, 10 μg, and 25 μg fentanyl, respectively,[14,15,20] all comparisons with doses of fentanyl $>$ 6.25 μg increased time to first administration of analgesic. In one study, administration of 20 μg, 40 μg, and 60 μg fentanyl yielded evidence of a dose–response relationship.[17] Median time to first analgesic with the various effective doses of fentanyl was 4 h (range, 2–13 h; fig. 1).

Finally, two doses of buprenorphine were evaluated in one study,[23] and five doses of sufentanil were evaluated in two studies[20,22] (table 1). Both drugs increased time to first administration of analgesic with all doses (fig. 1). The increase with the various doses of sufentanil showed no evidence of a dose–response relationship.[20,22]

Consumption of Postoperative Supplemental Analgesics. Data on consumption of postoperative supplemental analgesics could be extracted from 11 studies

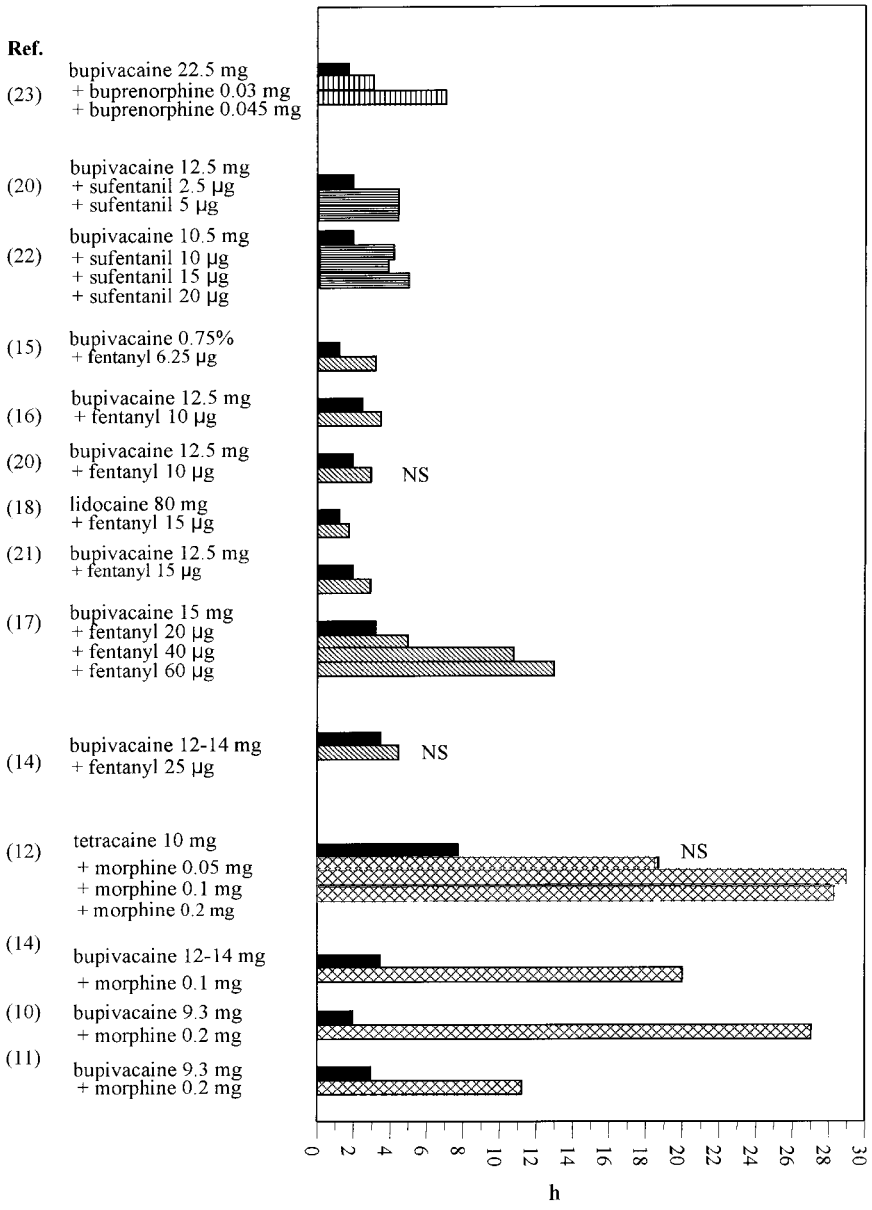

Fig. 1 Time to first administration (hours) of postoperative supplemental analgesics in patients receiving spinal anesthesia with local anesthetic alone (*solid bars*) or local anesthetic combined with buprenorphine, sufentanil, fentanyl, or morphine in varying doses (*various bars*). NS = no statistically significant difference from control.

(table 1).[10–15,17–21] Morphine was evaluated in five studies[10–14] with a total of seven treatment arms and three doses. Morphine at doses of 0.05 mg, 0.1 mg, and 0.2 mg decreased consumption of postoperative supplemental analgesic from 0 to 24 h postoperatively in all comparisons.[10–14]

Fentanyl was evaluated in six studies[14,15,17–19,21] with a total of 14 treatment arms and 12 doses. Except for one study in which 40 μg and 60 μg fentanyl decreased consumption of supplemental analgesic from 0 to 24 h postoperatively,[17] no effect of intrathecal fentanyl was demonstrated on this outcome.

Sufentanil was evaluated in one study.[20] Sufentanil at doses of 2.5 μg and 5 μg decreased consumption of postoperative supplemental analgesics from 0 to 6 h but not from 6 to 24 h postoperatively. No data are available on buprenorphine.

Number of Patients Not Needing Supplemental Analgesics Intraoperatively. Data could be extracted from 13 studies; 485 patients received opioid, and 254

Table 2. Adverse Effects (Pruritus, Nausea, Vomiting) with Intrathecal Opioids Compared with Control

Event/Opioid	Number of Studies/ Treatment Arms	Number of Patients, Treatment/ Control	Response with Treatment (%) (95% CI)	Response with Control (%) (95% CI)	NNH (95% CI)
Pruritus					
Morphine 0.05–0.25 mg	6/9	182/126	51 (44–59)	12 (7–19)	2.6 (2.1–3.3)
Fentanyl 2.5–60 μg	3/11	166/65	49 (41–57)	3 (0–13)	2.2 (1.8–2.7)
Sufentanil 2.5–20 μg	2/5	67/10	84 (73–92)	10 (0–45)	1.4 (1.1–1.9)
Buprenorphine 0.03–0.045 mg	1/2	30/15	10 (2–27)	0 (0–22)	10.0 (4.8–∞)
All drugs and doses	11/27	445/190	52 (48–57)	9 (5–14)	2.3 (2.0–2.7)
Nausea					
Morphine 0.05–0.25 mg	5/8	152/96	21 (15–28)	5 (2–12)	6.3 (4.2–12.5)
Fentanyl 2.5–60 μg	4/12	186/85	14 (9–20)	9 (4–18)	21.9 (8.0–∞)
Sufentanil 2.5–20 μg	1/3	27/10	33 (17–54)	10 (0–45)	4.3 (2.0–∞)
Buprenorphine 0.03–0.045 mg	1/2	30/15	30 (15–49)	7 (0–32)	4.3 (2.3–38.0)
All drugs and doses	11/25	395/180	19 (15–23)	9 (5–14)	9.7 (6.2–21.5)
Vomiting					
Morphine 0.05–0.25 mg	6/9	182/126	19 (13–25)	9 (4–15)	10.1 (5.7–41.0)
Fentanyl 2.5–60 μg	2/4	119/56	6 (2–12)	4 (0–12)	43.3 (11.4–∞)
Sufentanil 2.5–20 μg	—	—	—	—	—
Buprenorphine 0.03–0.045 mg	1/2	30/15	23 (10–42)	7 (0–32)	6.0 (2.7–∞)
All drugs and doses	8/15	331/171	15 (11–19)	8 (4–13)	14.5 (8.1–70.9)

NNH = number-needed-to-harm; ∞ = infinity (absence of a statistically significant difference); CI = confidence interval. The "All drugs and doses" number of studies may not be equal to the sum of studies with the various opioids because some studies evaluated more than one opioid.

patients served as controls.[10–21,22] Ten of 28 comparisons showed significant reduced need for intraoperative analgesic with intrathecal opioid over control. Pooled results from all opioids and doses showed that the number of patients not needing supplemental analgesics intraoperatively was 464 of 485 (96%) with treatment and 192 of 254 (76%) with control. The median NNT for not needing any supplemental analgesics intraoperatively was 4.9 (range, 3.9–6.9), with no significant differences between the various opioids. Combined analysis of data from 0.1 mg *versus* 0.2 mg morphine, and 15–35 μg *versus* 40–60 μg fentanyl showed no significant differences between the two doses/dose ranges, *i.e.*, no evidence for a dose–response relationship.

Adverse Effects

Pruritus, nausea, vomiting, and respiratory depression were reported in 11,[9–15,17,20,22,23] 11,[9–15,17,21–23] 8,[9–14,17,23] and 12 studies,[9–15,17,20–23] respectively (table 2). Observation periods for side effects were 0–24 h postoperatively in 9 studies[9–11,13–15,17,20,21] and until first narcotic administration,[22] 0–12 h,[23] and 0–48 h[12] postoperatively in three other studies, respectively. Data from all studies, irrespective of observation periods, are pooled in the quantitative analysis. NNH for the different adverse effects and opioids is shown in table 2. Pooled NNH for all opioids and doses indicated that both pruritus and nausea and vomiting occurred significantly more often with intrathecal opioids than with control. When analyzed separately, however, only morphine increased all three adverse effects, whereas fentanyl and sufentanil increased pruritus, but not nausea and vomiting, compared with control. The number of patients needed to treat with 0.05–0.25 mg morphine to harm one individual was 2.6 (95% CI, 2.1–3.3) for pruritus, 6.3 (95% CI, 4.2–12.5) for nausea, and 10.1 (95% CI, 5.7–41.0) for vomiting, respectively. NNH for pruritus with 2.5–60 μg fentanyl and 2.5–20 μg sufentanil was 2.2 (95% CI, 1.8–2.7) and 1.4 (95% CI, 1.1–1.9), respectively, and was not significantly different from NNH with morphine (table 2). Data for buprenorphine and sufentanil are based on few studies and should be interpreted with caution. Combined analysis of data from 0.1 mg *versus* 0.2 mg morphine and 15–35 μg *versus* 40–60 μg fentanyl showed no significant differences between doses, except for pruritus with fentanyl, with an NNH of 3.3 (95% CI, 2.3–5.4) *versus* 1.5 (95% CI, 1.3–1.9) with the low- and high-dose ranges, respectively. A trend toward re-

Table 3. Dose-related Adverse Effects (Pruritus, Nausea, Vomiting) with Intrathecal Morphine 0.1 mg and 0.2 mg Compared with Control

Dose, Morphine	Number of Studies	Number of Patients, Treatment/Control	Response with Treatment (%) (95% CI)	Response with Control (%) (95% CI)	NNH (95% CI)
Pruritus					
0.1 mg	4	85/88	53 (42–64)	10 (5–19)	2.3 (1.8–3.3)
0.2 mg	3	66/58	53 (40–65)	9 (3–19)	2.3 (1.7–3.3)
Nausea					
0.1 mg	3	55/58	16 (8–29)	5 (1–14)	9.9 (4.4–∞)
0.2 mg	3	66/58	35 (24–48)	7 (2–17)	3.6 (2.4–6.8)
Vomiting					
0.1 mg	4	85/88	21 (13–31)	9 (4–17)	8.3 (4.4–65.4)
0.2 mg	3	66/58	20 (11–31)	5 (1–14)	6.9 (3.9–29.8)

duced NNH with higher doses was demonstrated with most opioids (tables 3 and 4). With univariate logistic regression analysis, the relative risk of postoperative pruritus increased with increasing doses of morphine ($P < 0.00001$), fentanyl ($P < 0.002$), and sufentanil ($P < 0.002$). Likewise, logistic regression analysis showed that increasing the dose of morphine increased the relative risk of postoperative nausea ($P < 0.00001$) and vomiting ($P < 0.006$).

Data on respiratory depression were reported in 12 studies, with 485 patients receiving opioids and 250 patients serving as controls. The criterion for respiratory depression was respiratory rate < 10 breaths/min in all studies except two,[12,21] with respiratory rate < 8 breaths/min. Respiratory depression was only noted in one study[13] in which one patient receiving 0.1 mg morphine had an episode of respiratory rate < 10 breaths/min. Consequently, pooled NNH for respiratory depression with intrathecal opioids (all opioids and doses) was high (476; 95%CI, 164–∞) and not significantly different from control.

Discussion

The main finding of this systematic review was that intrathecal morphine prolonged time to first postoperative analgesic administration and created a clinically relevant reduction in postoperative pain, whereas fentanyl and sufentanil were not effective to any clinically significant extent.

Only one randomized, placebo-controlled study has made direct comparisons between intrathecal morphine and lipid-soluble opioids in patients undergoing cesarean section.[14] In this study, the quality of postoperative analgesia with 25 μg fentanyl was inferior to that with 0.1 mg morphine and not different from placebo. The incidence of pruritus, but not nausea and vomiting, was less with fentanyl compared with morphine.[14] It may be difficult to make useful direct comparisons between single doses of morphine and fentanyl in postoperative pain because of differences in pharmacokinetic profiles. Nevertheless, the present metaanalysis confirms that 10–25 μg fentanyl, as studied by Sibilla *et al.*[14] and other investigators,[15,16,18–21]

Table 4. Dose-related Adverse Effects (Pruritus, Nausea, Vomiting) with Intrathecal Fentanyl 15–35 μg and 40–60 μg Compared with Control

Dose, Fentanyl	Number of Studies	Number of Patients, Treatment/Control	Response with Treatment (%) (95% CI)	Response with Placebo (%) (95% CI)	NNH (95% CI)
Pruritus					
15–35 μg	3	65/65	34 (23–47)	3 (0–11)	3.3 (2.3–5.4)
40–60 μg	3	65/39	68 (55–79)	3 (0–13)	1.5 (1.3–1.9)
Nausea					
15–35 μg	4	85/85	9 (4–18)	9 (4–18)	∞
40–60 μg	3	65/39	6 (2–15)	5 (1–17)	97.5 (9.9–∞)
Vomiting					
15–35 μg	2	59/56	7 (2–16)	4 (0–12)	31.2 (8.9–∞)
40–60 μg	2	60/30	5 (1–14)	3 (0–17)	60.0 (9.9–∞)

NNH = number-needed-to-harm; ∞ = infinity (absence of a statistically significant difference); CI = confidence interval.

does not provide meaningful postoperative analgesia. However, the analysis does not confirm that intrathecal morphine is more likely to cause pruritus than the lipid-soluble opioids. Thus, another finding of our review was that the incidence of pruritus is very high, but similar, with morphine, fentanyl, and sufentanil. However, nausea and vomiting occurred less frequently with the lipophilic opioids than with morphine.

It may be speculated whether larger doses of fentanyl produce clinically significant postoperative analgesia. The evidence from the available controlled clinical trials is controversial. Two studies have investigated dose response with intrathecal fentanyl on postoperative analgesic effectiveness. In one study, no further increase in duration of analgesia nor decrease in 24-h opioid requirements was observed when the dose of intrathecal fentanyl was increased to > 6.25 μg.[15] However, the results from this study should be interpreted with care because each study group included very few patients (table 1), with a major risk of committing a type II error. In another study,[17] time to request of postoperative analgesic increased and total analgesia consumption decreased in a dose-dependent manner when intrathecal fentanyl was applied in doses of 20 μg, 40 μg, and 60 μg. Thus, time to first postoperative analgesic request increased from 3 h with control to 11 h and 13 h with 40 μg and 60 μg fentanyl, respectively. Pruritus, but not nausea and vomiting, increased with increasing doses of fentanyl.[17] The latter study indicates that 40–60 μg fentanyl may indeed produce meaningful postoperative analgesia with relatively few adverse effects.

A major end point in a number of the retrieved reports was the effect of intrathecal opioids on intraoperative analgesia.[14,16,18–21] Our quantitative analysis demonstrated that only 24% (95% CI, 9–30%) of patients in the control groups required supplemental analgesics intraoperatively. This means that a substantial number of patients given intrathecal opioids for intraoperative analgesia will be exposed to unnecessary adverse effects. Based on the present data, it is hardly justified to recommend intrathecal opioids if the only purpose is to improve intraoperative analgesia.

The most important clinical question that emerges from the present review is whether the postoperative pain relief benefit of intrathecal morphine is worth the side effects. Unfortunately, it was not possible to describe the impact of intrathecal morphine on postoperative pain in the same quantitative fashion as on adverse effects. This was not because of a lack of raw data *per se*, but rather because of the fact that the various original articles were dissimilar with respect to their outcome parameters. Furthermore, no clear dose–response relationship relating to analgesic efficacy was observed in two studies that investigated more than one dose of morphine.[9,12] However, univariate logistic regression analysis showed that the relative risk of postoperative pruritus, nausea, and vomiting increased with increasing doses of morphine.

It seems relatively clear from the qualitative analysis that 0.1 mg intrathecal morphine results in at least 11 h of effective analgesia and a significant reduction in postoperative analgesic requirements. The question thus remain whether such benefits are worth pruritus, nausea, and vomiting in a significant number of patients? The estimated incidences of these adverse effects may be considered very high. However, it should be recognized that our analysis may overestimate the clinical significance of the various adverse effects, because these were evaluated by presence or absence and not by severity.

Delayed respiratory depression is the most feared side effect of intrathecal opioids, and its true incidence is not known. In a prospective study of 856 patients given 0.2 mg intrathecal morphine for cesarean section, 8 had respiratory depression, as defined by a respiratory rate of < 8 breaths/min or an oxygen saturation of $< 85\%$.[27] Respiratory depression was observed in only 1 of 485 patients in the present review. However, the calculated NNH for respiratory depression (476; 95% CI, 164–∞) does not contribute much to our knowledge of respiratory depression after intrathecal opioids.

Variation in Occurrence of Events and Quality of Reports

It is well recognized that the incidence of events in a comparison group can vary widely between studies.[4] Very low or very high event rates may influence the overall estimate of efficacy or harm.[28] In the qualitative analysis of time to first postoperative analgesic, event rates varied widely in the control group. In contrast, the average control event rates of adverse effects (table 2) were all within a narrow range. Consequently, comparisons between the various opioids and doses were not substantially confounded by event rates far from the average.

The randomized controlled studies considered in the present review had median quality scores of 3 (range, 2–5). It has been shown that the results of a metaanalysis are influenced by the quality of the primary studies included. Trials of poor quality tend to exaggerate the overall estimate of treatment effect and may lead to

incorrect inferences.[29] Consequently, trials with a score of < 2 were not included in this review.

Conclusion

There is evidence that intrathecal morphine produced a clinically relevant reduction in postoperative pain and analgesic consumption; however, there is only evidence for a small effect with fentanyl and sufentanil. Logistic regression analysis showed that the relative risk of both postoperative pruritus and nausea/vomiting increased in a dose-dependent manner with morphine. Based on the current evidence, we recommend 0.1 mg morphine as the drug and dose of choice. However, for every 100 women receiving 0.1 mg intrathecal morphine added to a spinal anesthetic, 43 patients will experience pruritus, 10 will experience nausea, and 12 will experience vomiting postoperatively, all of whom would not have experienced these adverse effects without treatment.

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