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Opioids added to local anesthetics for single-shot intrathecal anesthesia in patients undergoing minor surgery: A meta-analysis of randomized trials ☆

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ABSTRACT

Opioids are widely used as additives to local anesthetics for intrathecal anesthesia. Benefit and risk remain unclear. We systematically searched databases and bibliographies to February 2011 for full reports of randomized comparisons of any opioid added to any intrathecal local anesthetic with the local anesthetic alone in adults undergoing surgery (except cesarean section) and receiving single-shot intrathecal anesthesia without general anesthesia. We included 65 trials (3338 patients, 1932 of whom received opioids) published between 1983 and 2010. Morphine (0.05–2 mg) and fentanyl (10–50 μg) added to bupivacaine were the most frequently tested. Duration of postoperative analgesia was prolonged with morphine (weighted mean difference 503 min; 95% confidence interval [CI] 315 to 641) and fentanyl (weighted mean difference 114 min; 95% CI 60 to 168). Morphine decreased the number of patients needing opioid analgesia after surgery and decreased pain intensity to the 12th postoperative hour. Morphine increased the risk of nausea (number needed to harm [NNH] 9.9), vomiting (NNH 10), urinary retention (NNH 6.5), and pruritus (NNH 4.4). Fentanyl increased the risk of pruritus (NNH 3.3). With morphine 0.05 to 0.5 mg, the NNH for respiratory depression varied between 38 and 59 depending on the definition of respiratory depression chosen. With fentanyl 10 to 40 μg, the risk of respiratory depression was not significantly increased. For none of these effects, beneficial or harmful, was there evidence of dose-responsiveness. Consequently, minimal effective doses of intrathecal morphine and fentanyl should be sought. For intrathecal buprenorphine, diamorphine, hydromorphone, meperidine, methadone, pentazocine, sufentanil, and tramadol, there were not enough data to allow for meaningful conclusions.

1. Introduction

Since the isolation of opioid receptors in the spinal cord in 1976, intrathecal administration of opioids in patients undergoing surgery has gained wide popularity [78]. For instance, there is now strong evidence that in patients undergoing major abdominal surgery, intrathecal morphine alone significantly decreases pain intensity and opioid requirements postoperatively [57]. However, dose responsiveness of intrathecal morphine remains obscure and potentially serious adverse effects such as respiratory depression may limit the usefulness of this analgesic technique [57].

Alternatively, small doses of opioids may be added to local anesthetics for intrathecal anesthesia in patients undergoing minor surgery. For these regimens, and despite numerous studies testing a large variety of different combinations of opioids and local anesthetics, benefit and harm remain unclear. A recently published systematic review focused on adverse effects of morphine added to intrathecal local anesthetics but did not provide any quantitative estimates of analgesic efficacy [33].

We set out to systematically review analgesic efficacy and adverse effects of opioids when added to local anesthetics for intrathecal anesthesia in adult patients undergoing minor surgery.

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2. Methods

We performed this meta-analysis according to the PRISMA recommendations [52].

2.1. Inclusion and noninclusion criteria

Inclusion criteria were as follows: (1) randomized treatment allocation; (2) comparison of any opioid added to any intrathecally administered local anesthetic (experimental intervention) with the identical local anesthetic regimen but without the opioid (control intervention); (3) single-dose intrathecal anesthesia without general anesthesia; (4) adult patients (aged ⩾18 years); (5) minor surgical procedures (orthopedic, urologic, gynecologic, general surgical); and (6) trials reporting on postoperative pain outcomes and/or drug-related adverse effects.

Noninclusion criteria were as follows: (1) patients undergoing general anesthesia or having an additional epidural (combined intrathecal–epidural anesthesia), or a peripheral nerve or plexus block; (2) continuous or repeated administration of the local anesthetic; and (3) children (aged <18 years).

When further intrathecal adjuvants were used (eg, epinephrine), the data were considered only if the comparison was strictly controlled (ie, both experimental and control groups received the same regimen except for the opioid). Labor and caesarean section were not included because physiologic changes due to pregnancy may affect the effect of intrathecal local anesthetics and opioids and thus increase heterogeneity in the effects reported.

2.2. Systematic search

High-sensitivity and low-specificity searches for relevant reports were performed in MEDLINE, EMBASE, CENTRAL, BIOSIS, and CINAHL. Keywords (spinal, intrathecal, analgesia, anesthesia, opioid, random) were combined by the Boolean meanings of "and" and "or." The last electronic search was performed in February 2011. Bibliographies of retrieved articles were searched for additional references. We applied no restriction on language or year of publication. We considered only published full reports.

2.3. Study selection

Retrieved articles were reviewed for inclusion by one author (DP), and criteria for inclusion were independently checked by 2 further authors (EM, MW); queries were resolved through discussion with 2 other authors (NE, MRT).

2.4. Data collection process

One author (DP) extracted all relevant information from original reports. Two authors (MW, EM) independently checked all extracted data. Discrepancies were resolved by discussion with 2 further authors (NE, MRT).

When continuous data were not reported as means with standard deviation, we contacted the authors of the original trials and asked them to provide the necessary data. If this was unsuccessful, we computed the data whenever feasible, as previously proposed [14,40].

2.5. Data items

Extracted outcomes included all endpoints that were related to analgesic efficacy as, for instance, the duration of postoperative analgesia, 24-h morphine consumption (mg), or the number of patients requiring opioids postoperatively, and also those that were related to morphine-related adverse effects, such as nausea, vomiting, pruritus, or urinary retention.

2.6. Risk of bias in individual studies

Quality of data reporting was assessed by one author (DP) and was independently checked by 2 others (MW, EM) by using a modified 4-item, 7-point Oxford scale taking into account the method of randomization, concealment of treatment allocation, degree of blinding, and reporting of dropouts, as previously described [27]. To overcome random play of chance on estimation of treatment effects, we excluded studies with fewer than 10 participants per group [48,59].

2.7. Analyses

As in previous similar analyses, there was an arbitrary pre hoc decision that meta-analysis was considered worthwhile when data from at least 5 trials or at least 100 patients could be combined [26].

To test for dose responsiveness, we plotted odds ratios (OR) (for binary outcomes) or mean differences (for continuous outcomes) with corresponding 95% confidence intervals (CI) for each trial according to increasing doses of the opioid. For dose-response trials, each dose was plotted separately. Dose responsiveness was then explored graphically. If the graphical display suggested dose responsiveness (ie, the point estimates changed consistently with increasing doses) and heterogeneity between trials was statistically significant ($P < 0.1$), we intended to use metaregression to assess whether an increase in dose was associated with an increase in treatment effect.

If there was no graphical support of dose responsiveness, the data were pooled. For continuous outcomes from dose-response studies, we selected the dose that was closest to the most commonly tested dose of all trials of that meta-analysis. This was done to avoid double counting the patients in the control group and to avoid unnecessary heterogeneity. We computed weighted mean differences (WMD) with 95% CI and performed formal heterogeneity testing. When the data were homogenous ($P \geqslant 0.1$), we used a fixed effect model to combine data. When the data were heterogeneous, we searched for other sources of heterogeneity. When none could be identified, we combined the data by using a random effects model. For binary outcomes, experimental groups from dose-response studies were combined. We calculated Peto OR with 95% CI. To estimate the clinical relevance of beneficial or harmful effects, we additionally computed numbers needed to treat/harm (NNT/NNH) with 95% CI by using weighted averages of experimental and control event rates. NNT/NNH were computed only when the results were statistically significant.

Analyses were performed by the RevMan computer program, version 5.0.25 (Cochrane Centre, Cochrane Collaboration, Copenhagen, Denmark); Microsoft Excel version 11.3. for Mac; Maple 9.5 (University of Geneva, Geneva, Switzerland); and Stata 11, version 11 (StataCorp, College Station, TX).

3. Results

3.1. Trial selection

We retrieved 331 potentially relevant titles (Fig. 1). Through title screening, we excluded 240 inadequate studies. Through abstract screening, we excluded a further 26 studies. Sixty-five randomized controlled trials met the inclusion criteria [1–9,11–13,15–21,23–25,28–31,34–39,41–47,49–51,54–56,58,60–66,68–77,79,80]. Two

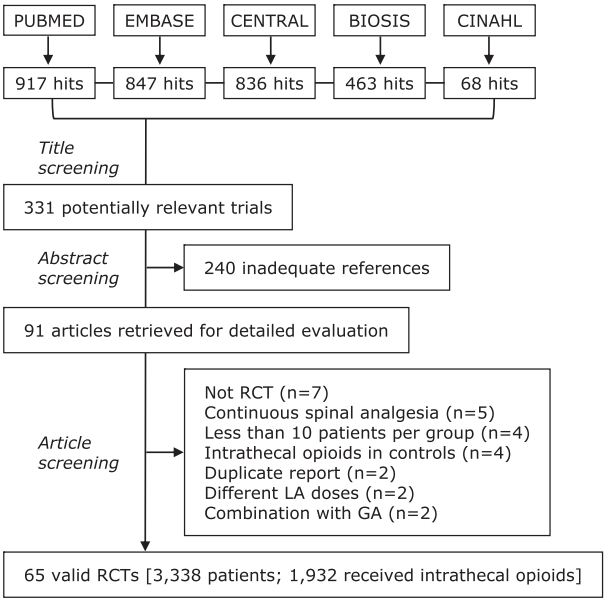

Fig. 1. Flow chart. RCT: randomized controlled trial; LA: local anesthetic; GA: general anesthesia.

studies were published twice; we considered the first published report of each cluster [34,49] and excluded the duplicate [32,53].

3.2. Trial characteristics

Included trials were published between 1983 and 2010 and included 3338 patients, of whom 1932 received an opioid added to an intrathecal local anesthetic (Table 1; Supplemental Data 1). Almost half of the trials included patients undergoing orthopedic surgery. Other frequently performed surgeries were urologic or gynecologic.

Forty-four trials tested 1 dose of an opioid, and 17 tested more than 1 dose (12 tested 2 doses, 3 tested 3 doses, and 2 tested 4 and 5 doses, respectively). Four trials tested 2 different opioids.

Opioids tested were morphine (31 trials), fentanyl (19), sufentanil (5), diamorphine and buprenorphine (3 each), tramadol (2), and meperidine, pentazocine, methadone, and hydromorphone (1 each). Local anesthetics were bupivacaine (47 trials), tetracaine (7), lidocaine (6), and mepivacaine, amethocaine, procaine, and ropivacaine (1 each). Two trials used epinephrine as an additional intrathecal adjuvant in both active and control groups.

The median quality score was 3 (range 1 to 7). Forty-eight studies (74%) used a double-blind design; the procedure of randomization was adequately described in 24 (59%), but concealment of treatment allocation was described in only 10 (15%).

We contacted the corresponding authors of 25 trials to obtain additional information; and were eventually able to include additional data from 6 trials [2,34,35,39,47,61].

Only for morphine or fentanyl added to bupivacaine were there enough valid data to warrant meta-analysis according to our pre hoc decision. Morphine trials tested doses between 0.05 and 1 mg, except one that tested 2 mg [63]. Fentanyl trials tested doses between 10 and 50 μg. Doses of bupivacaine ranged from 5 to 20 mg.

3.3. Synthesis of results

3.3.1. Duration of postoperative analgesia

Duration of postoperative analgesia was defined as time from the end of surgery until first analgesic request.

Thirteen trials (16 comparisons) tested morphine 0.05 to 2 mg added to bupivacaine compared with bupivacaine alone and reported on the duration of postoperative analgesia [3,4,21,30,34,37,38,43,46,61,63,69,75] (Fig. 2). In controls, the median of all mean durations of analgesia was 283 min (range 153 to 618 min). Data were heterogenous (P for heterogeneity <0.001); however, there was no graphical evidence of dose responsiveness. Intrathecal morphine significantly increased duration of analgesia (WMD 503 min, 95% CI 315 to 641).

Eight trials (12 comparisons) tested fentanyl 10 to 50 μg added to bupivacaine [28,31,44,51,63,66,70,76] (Fig. 3). In controls, the median of the mean durations of analgesia was 192 min (range 126 to 527 min). Data were heterogeneous (P for heterogeneity <0.001); however, there was no graphical evidence of dose responsiveness. Fentanyl significantly increased duration of analgesia (WMD 114 min, 95% CI 60 to 168).

3.3.2. Cumulative 24-h morphine consumption

Postoperative morphine consumption was quantified with a patient-controlled analgesia device in 5 trials, and through adding up doses from intravenous and intramuscular injections in one trial each.

Seven trials (9 comparisons) tested morphine 0.05 to 1 mg added to bupivacaine and reported on cumulative 24-h morphine consumption [4,30,38,41,56,61,74] (Supplemental Data 2). In controls, the median of the mean 24-h cumulative morphine consumption was 23 mg (range 4 to 47 mg). Data were heterogeneous (P for heterogeneity <0.001); however, there was no graphical evidence of dose responsiveness. Intrathecal morphine significantly reduced morphine consumption (WMD −12 mg, 95% CI −18 to −5).

There were not enough relevant data on the effect of intrathecal fentanyl on cumulative 24-h morphine consumption to warrant meta-analysis.

3.3.3. Postoperative pain intensity

In trials that tested morphine 0.05 to 1 mg added to intrathecal bupivacaine, pain intensity was reported at 2, 4, 6, 8, 12, and 24 h after surgery (Fig. 4). Data were heterogeneous (P for heterogeneity <0.01) at all time points in all comparisons, but there was no graphical evidence of dose responsiveness. Intrathecal morphine significantly decreased pain intensity up to 12 h; WMD point estimates varied from −0.9 (at 8 h) to −1.9 (at 4 h). At 24 h, there was no evidence of a beneficial effect of intrathecal morphine on pain intensity (WMD −0.3, 95% CI −1.2 to 0.7) (Supplemental Data 3).

There were not enough relevant data on the effect of intrathecal fentanyl on pain intensity up to 24 h to warrant meta-analysis.

3.3.4. Number of patients requiring opioids postoperatively

Six trials (9 comparisons) tested morphine 0.05 to 0.5 mg added to bupivacaine and reported the number of patients requiring an opioid for rescue analgesia postoperatively [34,38,39,42,46,61] (Supplemental Data 4). The proportion of controls requiring opioids ranged from 0% to 100% (median, 73%). The data were homogeneous (P for heterogeneity = 0.86) suggesting no dose responsiveness. Intrathecal morphine significantly decreased that proportion (OR 0.05, 95% CI 0.02 to 0.14; NNT 2.9, 95% CI 1.5 to 25).

There were not enough relevant data on the effect of intrathecal fentanyl on the number of patients requiring opioids postoperatively to warrant meta-analysis.

3.3.5. Sensitivity analyses

In an attempt to identify sources of heterogeneity, we tested the impact of type of surgery or doses of bupivacaine on duration of postoperative analgesia, pain intensity, incidence of patients who required opioids postoperatively, or cumulative 24-h morphine

consumption. In none of these sensitivity analyses could the degree of heterogeneity be reduced.

3.3.6. Dose responsiveness in individual trials

Four trials tested individually for dose responsiveness with morphine added to intrathecal bupivacaine [35,42,43,61].

Kamath et al. compared morphine 0.1 and 0.2 mg, and placebo, added to intrathecal bupivacaine in 20 patients per group [43]. They reported on a significant mean increase in duration of postoperative analgesia of 588 min by doubling the morphine dose from 0.1 mg to 0.2 mg [43]. There was no dose–effect relationship for any other endpoint.

Gehling et al. compared morphine 0.1 and 0.2 mg, and placebo, added to intrathecal bupivacaine in 60 patients per group [35]. They reported on a significant increase in the percentage of patients who did not require an opioid at 24 h postoperatively by doubling the morphine dose from 0.1 mg to 0.2 mg. They also reported on a significant, dose-dependent, increase in the intensity of pruritus compared with placebo [35]. There was no dose–effect relationship for any other endpoint.

Murphy et al. compared morphine 0.05, 0.1, and 0.2 mg and placebo added to intrathecal bupivacaine in 15 patients per group [61]. They reported on a statistically significant mean increase in the duration of postoperative analgesia of 271 min by doubling the morphine dose from 0.05 mg to 0.1 mg, and on a nonsignificant mean increase of 50 min by further doubling the dose to 0.2 mg. They also reported on a significant decrease in morphine consumption (on average, −4.7 mg per 24 h) when the dose of intrathecal morphine dose was doubled from 0.05 mg to 0.1 mg. However, a further doubling of the dose to 0.2 mg did not result in a significant reduction of morphine consumption. Finally, they were unable to find any difference between the active groups in the number of patients requiring morphine for postoperative rescue analgesia [61].

Kalso compared morphine 0.2 and 0.4 mg and placebo added to intrathecal bupivacaine in 10 patients per group [42]. This study reported on a significant reduction in the number of patients requiring morphine when the dose of morphine was increased from 0.2 mg to 0.4 mg [42]. There was no dose–effect relationship with any other endpoint.

Two trials tested for dose responsiveness with intrathecal fentanyl added to intrathecal bupivacaine [18,70]. Contreras Dominguez et al. compared 15 μg with 25 μg and placebo in 25 patients per group. They were unable to find any significant difference in any reported endpoint between the active groups. Seewal et al. compared fentanyl in 4 dosages (10 μg, 20 μg, 30 μg, and 40 μg) and placebo in 12 patients per group. They were unable to find any significant difference in the duration of analgesia or any other endpoint between the active groups.

3.3.7. Respiratory depression

Fourteen trials (19 comparisons) tested morphine 0.05 to 0.5 mg added to bupivacaine and reported on presence or absence of postoperative respiratory depression [4,6,34,35,37,38,41–43,46,56,61,75,79]. Respiratory depression was defined as respiratory rates <8, <9, <10, or <12 min^{-1}, or as $PaCO_2$ >6 kPa or different ranges of SpO_2, or as the need for naloxone treatment. One trial reported on 4 different definitions of respiratory depression, SpO_2 90–94%, SpO_2 85–90%, SpO_2 <85%, and respiratory rate <12 min^{-1} [61]. We discarded 2 of these endpoints; with SpO_2 <85%, none of the patients was reported to have respiratory depression, with SpO_2 90–94%, 23 of 45 patients (51%) were reported to have respiratory depression. We performed 2 sensitivity analyses using the 2 remaining endpoints from that trial (Table 2).

When the endpoint "SpO_2 85–90%" was considered [61], a total of 3 of 290 (1.0%) patients receiving bupivacaine alone and 15 of 410 (3.7%) receiving bupivacaine with morphine had respiratory depression (OR 3.49, 95% CI 1.25 to 9.73, NNH 38). When the endpoint "respiratory rate <12 min^{-1}" was considered [61], a total 5 of 290 (1.7%) patients receiving bupivacaine alone and 14 of 410 (3.4%) receiving bupivacaine with morphine had respiratory depression (OR 2.09, 95% CI 0.77 to 5.68, NNH 59) (Supplemental Data 5).

Seven trials (7 comparisons) tested fentanyl 10 to 40 μg added to bupivacaine and reported on presence or absence of respiratory depression [18,31,44,47,66,70,76] (Table 2). None of 180 patients receiving bupivacaine alone and 1 of 245 (0.4%) receiving bupivacaine with fentanyl had respiratory depression. That difference was not statistically significant. The single case of respiratory depression was reported in 1 of 27 patients who had received fentanyl 25 μg [66].

3.3.8. Pruritus

Seventeen trials (21 comparisons) tested morphine 0.05 to 1 mg added to bupivacaine and reported on the incidence of postoperative pruritus [4,21,30,34,37–39,41–43,46,56,61,69,74,75,79] (Table 2; Supplemental Data 6). The average incidence of pruritus with bupivacaine alone was 4.4%. The data were homogeneous ($P = 0.450$). Intrathecal morphine significantly increased that incidence to 29.2% (OR 6.92, 95% CI 4.51 to 10.6, NNH 4).

Thirteen trials (17 comparisons) tested fentanyl 10 to 40 μg added to bupivacaine and reported on the incidence of postoperative pruritus [7–9,18,28,31,39,44,47,66,70,73,76] (Table 2; Supplemental Data 7). The average incidence of pruritus with bupivacaine alone was 0%. The data were homogeneous ($P = 0.999$). With intrathecal fentanyl, the risk was 27.3%, a difference that was significant (OR 10.8, 95% CI 7.09 to 16.5, NNH 3.3).

3.3.9. Nausea

Ten trials (10 comparisons) tested morphine 0.05 to 1 mg added to bupivacaine and reported on the incidence of postoperative nausea [4,30,34,38,39,41,56,69,74,79] (Table 2; Supplemental Data 8). The average incidence of nausea with bupivacaine alone was 29.3%. The data were homogeneous ($P = 0.10$). Intrathecal morphine significantly increased the risk of nausea to 39.4% (OR 1.66, 95% CI 1.05 to 2.64, NNH 9.8).

Six trials (6 comparisons) tested fentanyl 20 or 25 μg added to bupivacaine and reported on the incidence of postoperative nausea [7,39,47,66,73,76] (Table 2; Supplemental Data 9). The average incidence of nausea with bupivacaine alone was 4.1% only. The data were homogeneous ($P = 0.517$). With intrathecal fentanyl, the incidence was 6.1%; this difference was not significantly different (OR 1.52, 95% CI 0.53 to 4.33).

3.3.10. Vomiting

Thirteen trials (13 comparisons) tested morphine 0.05 to 1 mg added to bupivacaine and reported on the incidence of postoperative vomiting [3,4,21,30,34,37–39,41,46,56,69,74] (Table 2; Supplemental Data 10). The average incidence of vomiting with bupivacaine alone was 16.6%. The data were homogeneous ($P = 0.568$). Intrathecal morphine significantly increased that risk to 26.2% (OR 1.88, 95% CI 1.20 to 2.94, NNH 10).

There were not enough relevant data on the effect of intrathecal fentanyl on postoperative vomiting to warrant meta-analysis.

3.3.11. Urinary retention

Urinary retention was always defined as the need for bladder catheterization. Seven trials (8 comparisons) tested morphine 0.05 to 0.5 mg added to bupivacaine and reported on the incidence of postoperative urinary retention [6,34,39,41,42,56,69] (Table 2; Supplemental Data 11). The average incidence of bladder catheterization with bupivacaine alone was 16.5%. The data were homogeneous ($P = 0.77$). Intrathecal morphine significantly increased that risk to 31.9% (OR 3.90, 95% CI 1.94 to 7.86, NNH 6.5).

Table 1
Analyzed randomized controlled trials.

Reference		Surgery	Local anesthetic	Dose (mg)	Opioid	Dose (mg)	No. of analyzed patients		Quality score[a]
First author	Year						Opioid	Control	
Abuzaid [1]	1993	GEN, VASC, URO	Bupivacaine	20	Diamorphine	1	30	30	1/0/2/0
Alhashemi [2]	2003	URO	Bupivacaine	15	Tramadol	25	32	32	2/0/2/0
Almeida [3]	2003	GYN	Bupivacaine	15	Morphine	0.1	12	12	1/0/2/0
Altunkaya [4]	2005	ORTH	Bupivacaine	15	Morphine	0.3	15	15	1/0/1/0
Alves [5]	1999	URO, GYN	Bupivacaine	17.5	Sufentanil	0.01	15	15	1/0/2/0
Amanor-Boadu [6]	1992	GEN	Bupivacaine	15	Morphine	0.5	18	14	1/0/0/0
Atallah [7]	2003	URO	Bupivacaine	5	Fentanyl	0.02	40	40	2/1/2/0
Atallah [8]	2006	URO	Bupivacaine	7.5	Fentanyl	0.01	53	52	2/0/2/2
Ben-David [9]	1997	ORTH	Bupivacaine	5	Fentanyl	0.01	25	25	2/1/2/0
Biswas [11]	2002	GEN	Lidocaine	75	Fentanyl	0.025	20	20	2/0/2/0
Boucher [12]	2001	GEN, ORTH, URO	Procaine	100	Fentanyl	0.02	26	26	1/0/2/1
Capogna [13]	1988	URO	Bupivacaine	30	Buprenorphine	0.03/0.045	60	30	1/0/1/0
Chakraborty [15]	2008	GYN	Bupivacaine	15	Tramadol	20	25	25	1/0/2/0
Chawla [16]	1989	GEN, URO, ORTH	Bupivacaine	20	Pentazocine	1/2/3/4/5	50	10	1/0/2/0
Chilvers [17]	1997	GYN	Lidocaine	20	Fentanyl	0.01/0.025	42	21	2/1/2/2
Contreras Dominguez [18]	2007	ORTH	Bupivacaine	12.5	Fentanyl	0.01/0.025	50	25	1/0/2/0
Contreras-Dominguez [19]	2008	ORTH	Bupivacaine	12.5	Sufentanil	0.0025/0.005	50	25	1/0/2/0
Cunningham [20]	1983	URO	Amethocaine	13	Morphine	1	12	12	1/0/2/0
Demiraran [21]	2008	ORTH	Bupivacaine	6	Morphine	0.16	30	30	2/0/2/1
Donadoni [23]	1987	URO	Lidocaine	75	Sufentanil	0.01	19	19	1/0/2/1
Drakeford [24]	1991	ORTH	Tetracaine	n/a	Morphine, hydromorphone	0.05, 0.15	40	20	1/0/2/0
Eichler [25]	2004	ORTH	Mepivacaine	80	Morphine	0.1	20	20	2/0/2/1
Fernandez-Galinski [28]	1996	ORTH	Bupivacaine	15.5	Fentanyl	0.025	19	21	1/0/2/0
Fernández-Liesa [29]	2000	ORTH	Bupivacaine	15	Methadone	4	15	15	1/0/2/0
Fogarty [30]	1993	ORTH	Bupivacaine	13.75	Morphine	1	30	30	1/0/2/0
Garg [31]	2010	GYN	Bupivacaine	15	Fentanyl	0.025	60	60	2/0/2/1
Gehling [34]	2003	ORTH	Bupivacaine	15	Morphine	0.1	15	15	2/0/2/0
Gehling [33]	2009	ORTH	Bupivacaine	15	Morphine	0.1/0.2	122	66	2/1/2/1
Goyagi [36]	1995	GYN	Tetracaine	12	Morphine	0.2	13	12	1/0/0/0
Grace [38]	1994	ORTH	Bupivacaine	13.75	Morphine	0.5	30	30	1/0/2/0
Grace [37]	1995	ORTH	Bupivacaine	13.75	Morphine	0.5	30	30	2/1/2/0
Gürkan [39]	2004	ORTH	Bupivacaine	6	Morphine, fentanyl	0.05, 0.025	40	20	2/1/2/0
Johnson [41]	1992	ORTH	Bupivacaine	20	Morphine	0.3	10	10	1/0/1/1
Kalso [42]	1983	ORTH	Bupivacaine	15	Morphine	0.2/0.4	30	20	1/0/1/0
Kamath [43]	2009	ORTH, URO	Bupivacaine	15	Morphine	0.1/0.2	40	20	1/0/1/0
Khan [44]	2006	URO	Bupivacaine	15	Fentanyl, buprenorphine	0.01, 0.03	40	20	2/1/2/1
Kirson [45]	1989	URO	Lidocaine	75	Morphine	0.1/0.2	20	10	1/0/1/0
Klamt [46]	1997	GYN	Bupivacaine	20	Morphine	0.1	12	12	1/0/1/1
Kuusniemi [47]	2000	ORTH	Bupivacaine	10	Fentanyl	0.025	20	20	2/0/2/0
Lanz [49]	1984	ORTH	Tetracaine	20	Morphine	0.5	23	19	1/0/2/0
Lauretti [51]	1998	GYN	Bupivacaine	15	Fentanyl	0.025	10	10	2/0/2/0
Lauretti [50]	1998	ORTH	Bupivacaine	15	Sufentanil	0.01	15	12	2/0/2/1
Martin [54]	1999	GYN	Lidocaine	45	Fentanyl	0.01	38	40	1/0/2/0
Matsuda [55]	2001	ORTH	Tetracaine	10	Morphine	0.1	25	25	1/0/0/0
Mendieta Sánchez [56]	1999	ORTH	Bupivacaine	15	Morphine	0.1	15	15	1/0/2/0
Milligan [58]	1993	ORTH	Bupivacaine	13.75	Diamorphine	0.75/1	30	30	1/0/0/0
Mora [60]	1985	URO	Prilocaine	100	Morphine	0.5/1	30	15	1/0/0/0
Murphy [61]	2003	ORTH	Bupivacaine	15	Morphine	0.05/0.1/0.2	45	15	1/0/2/1
Murto [62]	1999	URO	Lidocaine	75	Meperidine	12.3/23.2	27	13	2/0/2/1
Özmen [63]	2000	GEN	Bupivacaine	10	Morphine, fentanyl	2, 0.05	55	15	1/0/0/0
Rathmell [64]	2003	ORTH	Tetracaine	10	Morphine	0.1/0.2/0.3	40	20	1/0/2/1
Reay [65]	1989	ORTH	Bupivacaine	22.5	Diamorphine	0.25/0.5	40	20	1/0/2/0
Roussel [66]	1999	ORTH	Bupivacaine	12	Fentanyl	0.025	27	23	2/1/2/0

Sakai [68]	2003	URO	Tetracaine	10	Morphine	0.1/0.2	28	14	2/0/1/0
Schaer [69]	1992	ORTH	Bupivacaine	n/a	Morphine	0.06–0.08	15	15	1/0/0/0
Seewal [70]	2007	GEN	Bupivacaine	11	Fentanyl	0.01/0.02/0.03/0.04	48	12	2/1/2/0
Sen [71]	1992	ORTH	Bupivacaine	10	Buprenorphine	0.3	30	30	1/0/0/0
Singh [72]	1994	ORTH, URO	Tetracaine	12	Fentanyl	0.01	10	10	1/0/2/1
Singh [73]	1995	ORTH, URO	Bupivacaine	13.5	Fentanyl	0.025	21	22	1/0/0/0
Sites [74]	2003	ORTH	Bupivacaine	15	Morphine	0.25	20	21	2/0/2/0
Tan [75]	1999	ORTH	Bupivacaine	15	Morphine	0.3	20	20	1/0/2/1
Techanivate [76]	2004	GEN	Bupivacaine	20	Fentanyl	0.02	20	20	2/1/2/0
Wang [77]	2008	GEN	Bupivacaine	15	Sufentanil	0.0025/0.005/0.0075	45	15	1/0/1/0
Yamashita [79]	2009	ORTH	Bupivacaine	14	Morphine	0.05	10	10	2/0/2/0
Yegin [80]	2005	URO	Ropivacaine	18	Fentanyl	0.025	15	16	1/0/2/0

GEN = general surgery; GYN = gynecologic surgery; ORTH = orthopedic surgery; URO = urologic surgery; n/a = dose not reported. Detailed information of included trials is freely accessible on the author's Web site at http://www.hcuge.ch/anesthesia/data.htm.

[a] Quality score: randomization (0–2 points); concealment of treatment allocation (0–1); blinding (0–2); description of withdrawals (0–2).

Five trials tested fentanyl 20 to 50 μg added to bupivacaine and reported on the incidence of postoperative urinary retention [18,39,66,70,76] (Table 2; Supplemental Data 12). The average incidence of bladder catheterization with bupivacaine alone was 6% only. With intrathecal fentanyl the risk was 6.7%, a difference that was not significant (OR 1.15, 95% CI 0.35 to 3.72).

3.3.12. Further opioids

Data on buprenorphine [13,44,71], diamorphine [1,58,65], hydromorphone [24], meperidine [62], methadone [29], pentazocine [16], sufentanil [5,19,23,50,77], or tramadol [2,15] added to intrathecal local anesthetics were reported in less than 5 trials and less than 100 patients each and were therefore not further analyzed.

3.3.13. Further efficacy endpoints

Further endpoints were reported, for instance, "time to onset of sensory block," "time to maximal level of sensory block," "duration of sensory block," "time to onset of motor block," and "duration of motor block." Because opioids are not expected to have any impact on one of these endpoints, these data were not further analyzed.

4. Discussion

4.1. Main results

Several results emerge from this meta-analysis. Firstly, when morphine is added to intrathecal bupivacaine, the duration of postoperative analgesia is prolonged by more than 8 h compared with bupivacaine alone. With fentanyl, prolongation of postoperative analgesia is about 2 h. Second, morphine, but not fentanyl, added to intrathecal bupivacaine reduces cumulative 24-h opioid consumption and the number of patients requiring morphine as a rescue analgesic, and decreases pain intensity up to 12 h postoperatively. Third, morphine added to intrathecal bupivacaine increases the risk of postoperative nausea, vomiting, pruritus and urinary retention; for fentanyl, there was evidence for an increased risk of pruritus only. Fourth, there is some evidence that with morphine added to intrathecal bupivacaine, the risk of postoperative respiratory depression is increased; it seems that there is less risk with fentanyl. Fifth, for all of these effects, either beneficial or harmful, we were unable to demonstrate dose responsiveness. And finally, there is not enough evidence for buprenorphine, diamorphine, hydromorphone, meperidine, methadone, pentazocine, sufentanil, or tramadol, as adjuvants to intrathecal local anesthetics for surgery, to draw meaningful conclusions.

4.2. Lack of dose responsiveness

Perhaps the most disturbing result was the lack of evidence of dose responsiveness for any endpoint. This does not necessarily mean that there was none. Meta-analysis with data from independent trials is not a particularly sensitive tool to identify a dose-response relationship if there is one. The same dilemma has been shown in a similar setting before [26]. It cannot be excluded that dose responsiveness was hidden by confounding factors (eg, type of surgery, concomitant usage of nonopioid analgesics). Six trials tested individually for dose responsiveness, 4 with intrathecal morphine and 2 with fentanyl [18,33,42,43,61,70]. Four of those testing morphine (dose range 0.05 to 0.4 mg) reported on some outcomes that suggested dose responsiveness. The 2 trials that tested dose responsiveness with fentanyl (dose range 10 to 40 μg) were unable to show any. Thus, there is a lack of evidence for dose responsiveness that is based on data from a large number of meta-analytically combined data from randomized trials and conflicting evidence concerning dose responsiveness from a small

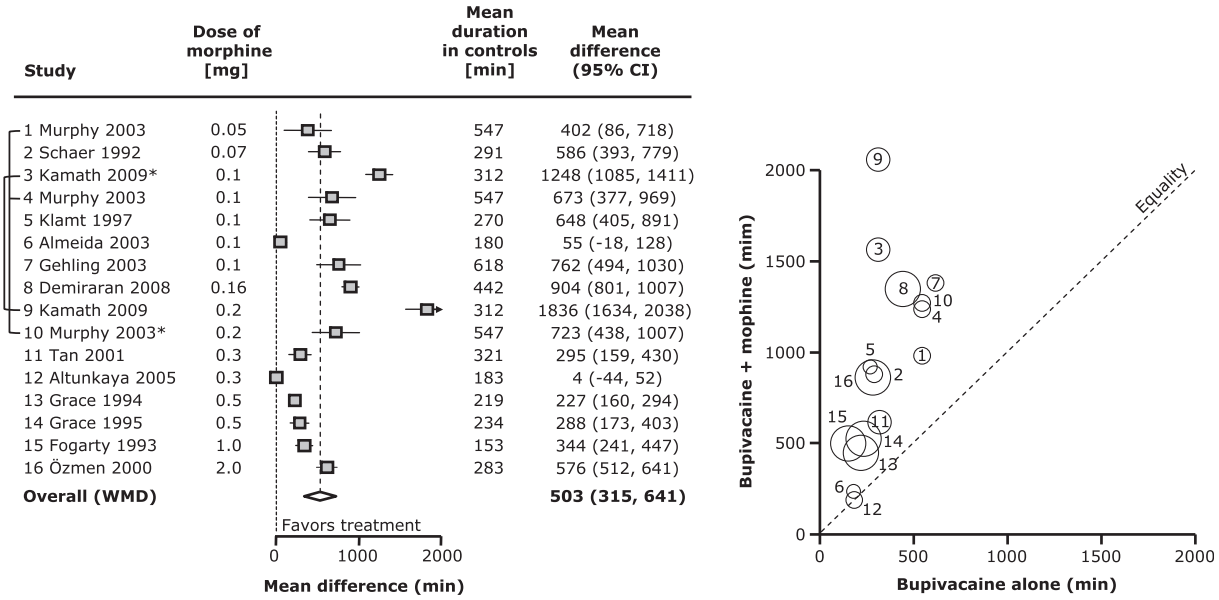

Fig. 2. Duration of postoperative analgesia with intrathecal morphine. Comparisons are shown according to increasing doses of intrathecal morphine. For trials that tested multiple morphine doses, each comparison is shown. On the event rate scatter, each symbol represents one comparison; diameters of symbols represent number of patients in each comparison. *Comparisons from multiple dose trials that were selected for meta-analysis. CI = Confidence interval. WMD = Weighted mean difference.

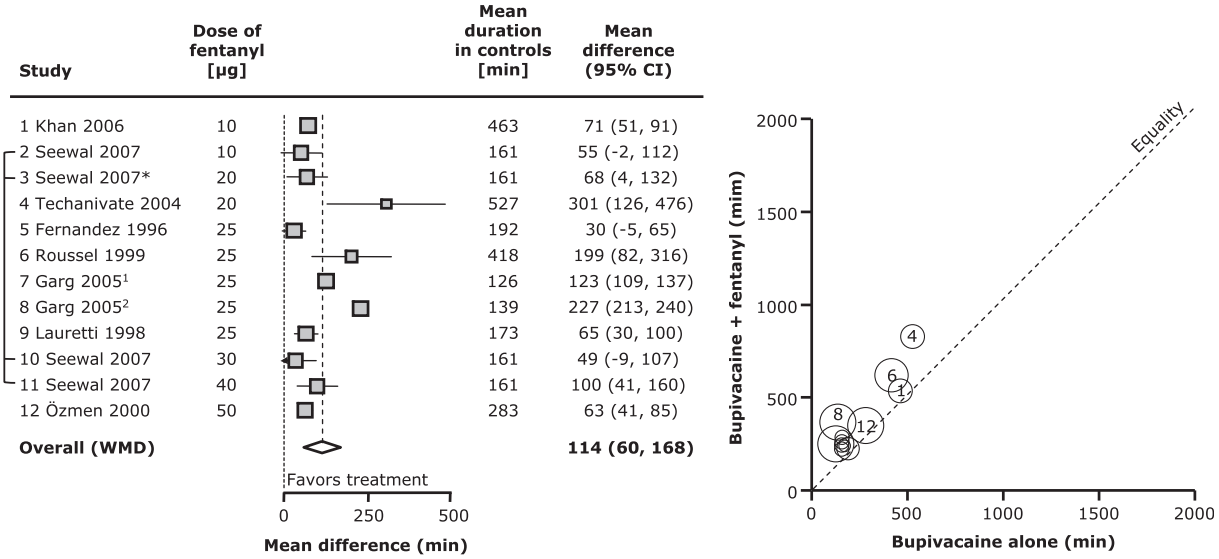

Fig. 3. Duration of postoperative analgesia with intrathecal fentanyl. Comparisons are shown according to increasing doses of intrathecal fentanyl. For trials that tested multiple fentanyl doses, each comparison is shown. On the event rate scatter, each symbol represents one comparison; diameters of symbols represent number of patients in each comparison. *Comparison from multiple dose trial that was selected for meta-analysis. CI = Confidence interval. WMD = Weighted mean difference. Garg 2005[1] = Excluding patients with nitroglycerine patch; Garg 2005[2] = Including patients with nitroglycerine patch.

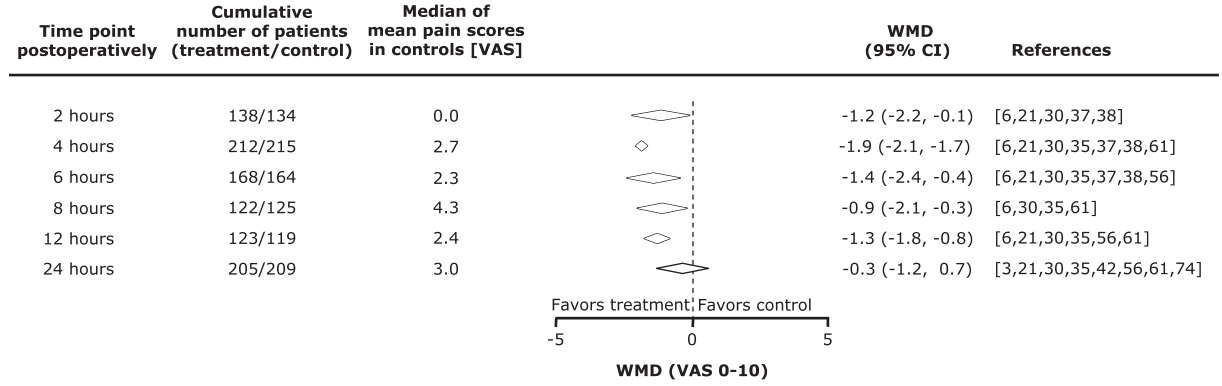

Fig. 4. Pain intensity (VAS 0-10) at 2, 4, 6, 8, 12 and 24 hours postoperatively in trials comparing intrathecal bupivacaine+morphine with bupivacaine alone. Diamonds are pooled estimates with 95% confidence intervals. VAS = Visual analogue scale. WMD = Weighted mean difference. CI = Confidence interval.

Table 2
Opioid-related adverse reactions.

Endpoint	No. of patients with:		OR (95% CI)	NNH (95% CI)	References
	Opioid	No opioid			
Respiratory depression					
Morphine[a]	15/410 (3.7%)	3/290 (1.0%)	3.49 (1.25 to 9.73)	38 (21 to 215)	[4,6,34,35,37,38,41–43,46,56,61,75,79]
Morphine[b]	14/410 (3.4%)	5/290 (1.7%)	2.09 (0.77 to 5.68)	59	[4,6,34,35,37,38,41–43,46,56,61,75,79]
Fentanyl	1/245 (0.4%)	0/180 (0.0%)	6.37 (0.12 to 325)	245	[18,31,44,47,66,70,76]
Pruritus					
Morphine	95/325 (29.2%)	14/326 (4.4%)	6.92 (4.51 to 10.6)	4.0 (3 to 5)	[4,21,30,34,37–39,41–43,46,56,61,69,74,75,79]
Fentanyl	99/362 (27.3%)	0/360 (0.0%)	13.2 (8.45 to 20.7)	3.3 (3 to 4)	[7–9,18,28,31,39,44,47,66,70,73,76]
Nausea					
Morphine	71/180 (39.4%)	53/181 (29.3%)	1.66 (1.05 to 2.64)	9.8 (5 to 138)	[4,30,34,38,39,41,56,69,74,79]
Fentanyl	9/148 (6.1%)	6/145 (4.1%)	1.52 (0.53 to 4.33)	51	[7,39,47,66,73,76]
Vomiting					
Morphine	66/252 (26.2%)	42/253 (16.6%)	1.88 (1.20 to 2.94)	10 (6 to 40)	[3,4,21,30,34,37–39,41,46,56,69,74]
Fentanyl[c]	—	—	—	—	—
Urinary retention					
Morphine	37/116 (31.9%)	18/109 (16.5%)	3.90 (1.94 to 7.86)	6.5 (4 to 23)	[6,34,39,41,42,56,69]
Fentanyl	7/104 (6.7%)	6/100 (6.0%)	1.15 (0.35 to 3.72)	105	[18,39,66,70,76]

OR = odds ratio, CI = confidence interval, NNH = number needed to harm. NNHs were calculated as numbers needed to treat (a 95% CI was computed around the NNH point estimate only when the result was statistically significant). Definitions of respiratory depression included various respiratory rates (<8, <9, <10, or <12/min), need for naloxone, $Paco_2$ >6 kPa, or various ranges of Spo_2.

[a] From Murphy et al. [61], the definition "Spo_2 85–90%" was selected.

[b] From Murphy et al. [61], the definition "respiratory rate <12/min" was selected.

[c] Data from only 2 trials with a total of 80 patients.

number of trials with a limited number of patients per group. This clearly highlights the need for further research in this area.

4.3. Indirect comparisons

Only for morphine and fentanyl, the quality and quantity of available data allowed for combining data from independent trials. It has been suggested that the degree of liposolubility of an intrathecal opioid may have an impact on its effect [10]. We would expect, for instance, that a hydrophilic opioid (morphine) prolonged postoperative analgesia more than does a lipophilic opioid (fentanyl). Because only 2 trials compared these 2 opioids head to head [39,63], we had to rely on indirect comparisons to estimate their relative efficacy and harm. In all relevant trials, the local anesthetic was bupivacaine, thus minimizing unnecessary heterogeneity. However, the frequency or magnitude of outcomes in controls (patients who received bupivacaine alone) were not always comparable in trials testing morphine compared to those testing fentanyl, suggesting that the study cohorts and surgical settings were not necessarily the same. For instance, mean duration of postoperative analgesia in controls in trials testing intrathecal morphine was about 4.7 h; in fentanyl trials, it was little more than 3 h. Looking at absolute values, morphine prolonged duration of analgesia by more than 8 h, and fentanyl by 2 h only. Relative to the average duration of postoperative analgesia in the respective control groups, morphine prolonged analgesia by about 180%, fentanyl by 60% only. Similarly, incidences of nausea and urinary retention in controls were higher in trials that tested morphine compared with trials that tested fentanyl. The addition of morphine to bupivacaine significantly increased both risks. This was not the case with fentanyl.

4.4. Respiratory depression

Curiously, only a minority of trials reported on respiratory depression which remains the most important opioid-related adverse effect. We do not know whether in the others, no episodes of respiratory depression occurred, or whether they did but were missed by the trialists, or whether the authors deemed it not important enough to report them. Also, we may assume that patients at high risk of respiratory depression, for instance, obese patients, were not included in these trials. Finally, definition of respiratory depression varied between, and even within, trials. Indirect comparisons suggested that the risk of respiratory depression was more pronounced with intrathecal morphine than with fentanyl. This may have an impact on the way these patients are followed up postoperatively.

4.5. Limitations

Our systematic review has 3 main limitations. First, the trials were performed in a variety of surgical settings, using different regimens of local anesthetics and opioids. Obviously, this resulted in considerable heterogeneity. We have arbitrarily chosen to limit our analyses to subgroups that allowed combining data from at least 5 trials or 100 patients. As a consequence, we were able to provide valid data on morphine and fentanyl added to bupivacaine only. The impact of these 2 opioids added to other local anesthetics, or the impact of further opioids added to bupivacaine or other local anesthetics, remains unknown. Second, most studies included a limited number of patients; maximum group size was 60 patients. The main problem with small trials is that they are likely to report on results by random chance and, as a result of potential publication bias, they may overestimate treatment effect. Third, in the original trials, a large variety of endpoints was reported. Some endpoints were not always clearly defined. It may then be problematic to combined data from independent trials. Also, the trials inconsistently reported on endpoints. Arterial hypotension or motor blockade were regularly reported, probably by convenience. However, these data do not improve our understanding of the usefulness of intrathecal opioids; there is no biological basis as to why an intrathecal opioid should have any impact on these outcomes. Other endpoints that may be useful for clinical decision making and that are regularly reported in acute pain trials—for instance, pain intensity at 24 h—were only rarely reported.

4.6. Ethics of intrathecal injection of unapproved drugs

Many adjuvants have been used for intrathecal administration in surgical patients [22]. For a large number of opioids, the quantity of available data was deemed insufficient by us to allow for appropriate meta-analysis. As a consequence, the benefit and harm of

these substances when administered intrathecally remain unclear. Perhaps most importantly in this context, for most of these opioids, neurotoxicity after intrathecal administration cannot be excluded; as a consequence, they should not be used [67].

4.7. Research agenda

The lack of evidence of dose responsiveness with intrathecal morphine and fentanyl for any of the reported endpoints, with the exception of some positive results that were reported in small trials with a limited number of patients, is clearly unsatisfactory. It may mean that doses that are smaller than the smallest investigated doses in these trials should be tested in randomized dose-finding studies. For morphine this would be doses below 0.05 mg and for fentanyl below 10 μg. Future trials would have to report on clinically relevant endpoints including a clear definition of respiratory depression. Also, we still do not know whether adding an opioid to a local anesthetic for spinal anesthesia allows for reducing the dose of the local anesthetic and, subsequently, reducing the adverse effects of the local anesthetic, as, for instance, prolonged motor blockade or arterial hypotension which are likely to interfere with postoperative recovery and mobilization.

4.8. Conclusions

Meta-analytically combined data from systematically searched randomized trials suggest that morphine and fentanyl, added to intrathecal bupivacaine, prolong postoperative analgesia—with morphine by more than 8 h, with fentanyl by about 2 h. With morphine added to intrathecal bupivacaine, there is also evidence of opioid sparing and of a decrease in pain intensity up to 12 h after surgery. Morphine increases the risk of nausea, vomiting, pruritus, and urinary retention; fentanyl increases the risk of pruritus. Finally, with morphine, respiratory depression cannot be excluded. For all these effects, beneficial or harmful, there is a lack of evidence of dose responsiveness. The impact of adding fentanyl or morphine to other intrathecally administered local anesthetics remains obscure. Other opioids should not be used as adjuvants to intrathecal local anesthetics unless further valid data provide evidence of efficacy and lack of neurotoxicity. It is now time to start a rational clinical research program that aims to identify minimal effective doses of intrathecal opioids—that is, doses that exert a maximum effect without increasing the risk of unacceptable adverse effects.

Conflict of interest statement

The authors declare that they have no conflict of interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.pain.2011.11.028. and are also freely accessible on the author's Web site at http://www.hcuge.ch/anesthesia/data.htm.

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