

REVIEW ARTICLES

 **Benefit and risk of intrathecal morphine without local anaesthetic in patients undergoing major surgery: meta-analysis of randomized trials**

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Intrathecal morphine without local anaesthetic is often added to a general anaesthetic to prevent pain after major surgery. Quantification of benefit and harm and assessment of dose–response are needed. We performed a meta-analysis of randomized trials testing intrathecal morphine alone (without local anaesthetic) in adults undergoing major surgery under general anaesthesia. Twenty-seven studies (15 cardiac–thoracic, nine abdominal, and three spine surgery) were included; 645 patients received intrathecal morphine (dose-range, 100–4000 µg). Pain intensity at rest was decreased by 2 cm on the 10 cm visual analogue scale up to 4 h after operation and by about 1 cm at 12 and 24 h. Pain intensity on movement was decreased by 2 cm at 12 and 24 h. Opioid requirement was decreased intraoperatively, and up to 48 h after operation. Morphine-sparing at 24 h was significantly greater after abdominal surgery {weighted mean difference, –24.2 mg [95% confidence interval (CI) –29.5 to –19.0]}, compared with cardiac–thoracic surgery [–9.7 mg (95% CI –17.6 to –1.80)]. The incidence of respiratory depression was increased with intrathecal morphine [odds ratio (OR) 7.86 (95% CI 1.54–40.3)], as was the incidence of pruritus [OR 3.85 (95% CI 2.40–6.15)]. There was no evidence of linear dose-responsiveness for any of the beneficial or harmful outcomes. In conclusion, intrathecal morphine decreases pain intensity at rest and on movement up to 24 h after major surgery. Morphine-sparing is more pronounced after abdominal than after cardiac–thoracic surgery. Respiratory depression remains a major safety concern.

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Intrathecal opioid administration is an attractive analgesic technique since the opioid is injected directly into the cerebrospinal fluid, close to the structures of the central nervous system where the opioid acts. The procedure is simple, quick, and with a relatively low risk of technical complications or failure. Opioids are often added to intrathecally injected local anaesthetics in patients undergoing surgery without general anaesthesia, for instance, females undergoing Caesarean section.<sup>16</sup> In some institutions, an opioid alone, typically morphine,<sup>23</sup> is administered intrathecally as a single-dose injection before operation in patients undergoing major surgery under general anaesthesia. This adjuvant analgesic technique is expected to decrease postoperative pain intensity and opioid requirements, and to fasten recovery. The first clinical study testing intrathecal morphine in this context was published in 1979.<sup>49</sup> Since

then, this analgesic method has been the subject of a large number of trials and reviews,<sup>11 32 37</sup> illustrating an ongoing interest in the technique. Although most relevant studies have reported some decrease in postoperative pain intensity, the magnitude of the analgesic effect remains unclear and data on dose-responsiveness controversial,<sup>1 3 8 18 22 39</sup> and there has been no consensus on the optimal dose of intrathecal morphine when used alone. It has been suggested that the optimal dose depends on the surgical setting and that there is a ceiling analgesic effect above which the risk of adverse effects outweighed the benefits of improved analgesia.<sup>37</sup> This, however, has never been shown formally. Morphine, which is relatively less hydrophobic than other opioids, has a longer residence time in the cerebrospinal fluid and therefore may reach rostral sites over a longer period than other opioids.<sup>47</sup> Consequently, there is a

potential of achieving adequate and long-lasting analgesia with an intrathecal injection of morphine.<sup>32</sup> However, the downside of this less hydrophobic character is an increased risk of adverse effects, especially postoperative respiratory depression,<sup>29</sup> which remains a particular concern.

The primary aim of this systematic review and meta-analysis was to quantify the analgesic effect of intrathecal morphine (without local anaesthetic) in patients undergoing surgery with a general anaesthetic. Secondary objectives were to quantify the harmful effects and to test for dose-responsiveness.

## Methods

### *Literature search*

We conducted a systematic search for published full reports of randomized, controlled trials that compared a single intrathecal dose of morphine with intrathecal placebo, a sham-injection, or no treatment in patients undergoing major surgery (abdominal, thoracic, orthopaedic, and spinal) under general anaesthesia. Relevant studies had to report on pain outcomes or adverse effects that were possibly related to the intrathecal morphine. We excluded studies with <10 patients per group,<sup>28</sup> that were performed in awake patients without a general anaesthetic, that tested the efficacy of morphine as an adjunct to intrathecal local anaesthetic, or that tested combinations of intrathecal opioids.

We searched in Medline, the Cochrane Library, and Embase using the terms 'opiates', 'opioid\*', 'morphine', 'pain', 'intrathecal', 'injection', 'an(a)esthesia', 'analgesia', and combinations of those, without language restriction and up to November 2007. Additional studies were identified from the bibliographies of retrieved reports. Authors were contacted to obtain additional information if necessary.

We applied a modified Oxford scale (four items, seven points) to assess the quality of data reporting.<sup>20</sup> As we included only randomized trials, the minimum score was 1. One author scored all the studies to be included (N.M.). The scores were independently checked by two other authors (N.E. and C.L.). Any disagreement was resolved through discussion with the fourth author (M.R.T.).

### *Data extraction*

One author (N.M.) extracted information on number of patients, surgery, dose of intrathecal morphine, intra- and postoperative analgesic regimens, outcomes, and adverse events; two authors (N.E. and C.L.) independently checked all extracted data. Relevant pain outcomes were pain intensity at rest or on movement or on coughing, and intra- or postoperative opioid-sparing. Definitions of adverse effects were taken as reported in the original trials.

Variable morphine doses were extrapolated to a fixed dose using the average body weight of the patient

population reported in the study. When no bodyweight was reported, we assumed that it was 70 kg.

We extrapolated 0–100 mm visual analogue scales to a 0 (no pain) to 10 (worst pain) cm scale. Other numerical scales or verbal scales were not considered.

In some trials, the presence or absence of pruritus was reported; in others, the intensity of pruritus was recorded on an intensity scale, or it was classified as mild, moderate, or severe. Since scales were different across trials, we dichotomized the data as the number of patients having any degree of pruritus.

### *Meta-analysis*

We analysed outcomes only when they were reported in at least five trials, or in at least 100 patients receiving intrathecal morphine. Continuous outcomes were extracted as means and standard deviations or standard errors. When these data were not reported, we contacted the authors. If they did not respond, and the data were presented graphically, we extracted the data from the graphs. We computed weighted mean differences (WMD) with 95% confidence interval (CI) using a fixed effect model when the studies showed homogeneous results ( $P$  for heterogeneity  $>0.1$ ). When the results were heterogeneous ( $P < 0.1$ ), we searched for the source of heterogeneity. As in similar previous analyses,<sup>21</sup> there was an intention to investigate whether differences in reported effects could be explained by differences in the dose of the intrathecal morphine. When there was no evidence of dose-responsiveness, a summary estimate using the random effects model was computed.

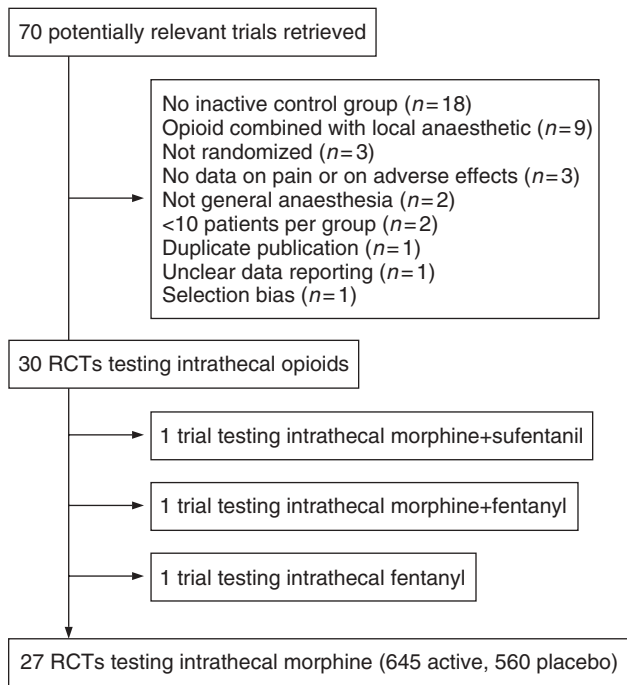
Binary outcomes were extracted as the presence or absence of an effect. We computed Peto odds ratios (OR) with 95% CI. If the 95% CI did not include 1, we assumed that the difference between intrathecal morphine and control was statistically significant at the 5% level. To estimate the clinical relevance of a beneficial or harmful effect, we computed numbers needed to treat or to harm (NNT/NNH) with 95% CI using the OR and the control event rate. CIs around the NNT/NNH point estimates were computed only, when the result was statistically significant.<sup>44</sup> For binary outcomes showing heterogeneous results across trials, we searched for dose-responsiveness using meta-regression.

Analyses were conducted using Microsoft<sup>®</sup> Excel<sup>®</sup> 11.3 for Mac<sup>®</sup>, Review Manager [RevMan (computer program) version 4.2, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration], Maple 9.5 (University of Geneva, Switzerland), and STATA 9 (Version 9, STATA Corp., College Station, TX, USA).

## Results

### *Retrieved trials*

We identified 70 trials and subsequently excluded 43 (Fig. 1). Of the excluded studies, one was published



**Fig 1** Flow chart of retrieved, excluded, and analysed trials. RCT, randomized, controlled trial. Relevant trials tested intrathecal morphine alone (without a local anaesthetic) in patients undergoing a general anaesthetic for major surgery.

twice.<sup>45 46</sup> We contacted 21 authors for supplementary data, 12 answered. We eventually analysed 27 valid trials with data on 1205 adult patients, of whom 645 received intrathecal morphine (Table 1).<sup>1–3 5 6 10 12–15 17 18 25 27 30 31 34 36 39–43 46 48 50 51</sup> Doses ranged from 100 to 4000  $\mu\text{g}$ . Twenty-three trials tested a single dose, and four were dose-finding studies that compared two<sup>1 3 18</sup> or three<sup>39</sup> doses with an inactive control group.

The studies were published between 1985 and 2007; seven had been published since 2005. Since the earliest trials, the tested doses have consistently decreased (Fig. 2). The studies were performed in 12 countries: Turkey (six trials), France (five), the UK and USA (three each), Canada and Thailand (two each), and Saudi Arabia, Egypt, India, Japan, The Netherlands, and Sweden (one each). Group sizes ranged from 10 to 47 patients. The median quality score was 3 (range, 1–6). All except four trials (14.8%) were properly blinded.<sup>2 17 40 43</sup> Surgery was cardiac (13 studies), abdominal (five), hysterectomy (four), spine (three), thoracic (one), or cardiac and thoracic (one).

#### *Intraoperative fentanyl or sufentanil consumption*

Nine trials reported on intraoperative fentanyl or sufentanil consumption.<sup>1 3 5 6 14 17 31 34 40</sup> Intrathecal morphine (280–4000  $\mu\text{g}$ ) was always administered before surgery. Median time of surgery was 226 min (range, 132–252). We computed fentanyl equivalents of sufentanil doses by multiplying the average sufentanil doses by 10.<sup>9</sup> In control groups,

average intraoperative fentanyl equivalents ranged from 300 to 3800  $\mu\text{g}$  (median, 883). Overall, there was a significant decrease in fentanyl equivalents during surgery with intrathecal morphine, WMD,  $-145 \mu\text{g}$  (95% CI  $-181$  to  $-109$ ). The data were homogeneous ( $P=0.13$ ), indicating lack of dose-responsiveness.

#### *Postoperative morphine consumption*

Eleven trials reported postoperative cumulative morphine consumption at 24 h.<sup>1 5 6 10 13 14 17 30 32 42 46</sup> In controls, median consumption was 36 mg. When all trials were combined independent of the type of surgery, 24 h morphine consumption was significantly decreased with intrathecal morphine, WMD,  $-16.9 \text{ mg}$  (95% CI  $-23.7$  to  $-10.1$ ) (Fig. 3). The data were heterogeneous ( $P<0.001$ ); however, there was no evidence of dose-responsiveness.

In an attempt to identify the source of heterogeneity, we performed a subgroup analysis, taking into account the type of surgery (Fig. 3). In six trials, patients underwent thoracic or cardiac surgery; the median dose of intrathecal morphine was 500  $\mu\text{g}$  (range, 250–700).<sup>1 13 14 30 31 46</sup> Median 24 h morphine consumption in controls was 34.5 mg; with intrathecal morphine, this was significantly decreased (WMD,  $-9.7 \text{ mg}$ ). In five trials, patients underwent abdominal surgery including hysterectomy; the median dose of intrathecal morphine was 300  $\mu\text{g}$  (range, 100–400).<sup>5 6 10 17 42</sup> Median 24 h morphine consumption in controls was 34.8 mg. In this subgroup, postoperative morphine-sparing was more pronounced (WMD,  $-24.2 \text{ mg}$ ). The 95% CI of the point estimates of the two subgroups did not overlap. In both subgroups, heterogeneity was decreased (thoracic and cardiac surgery,  $P=0.005$ ; abdominal surgery,  $P=0.04$ ).

Six studies reported on morphine consumption during the second postoperative day;<sup>5 6 13 14 17 41</sup> median 24–48 h morphine consumption in controls was 21 mg. When these trials were combined, 24–48 h morphine consumption was significantly decreased with intrathecal morphine, WMD  $-6.5 \text{ mg}$  (95% CI  $-9.9$  to  $-3.2$ ). There were not enough studies to allow a subgroup analysis by the type of surgery.

#### *Postoperative pain intensity*

Pain intensity at rest was reported in four trials during cardiac surgery,<sup>30 34 36 46 48</sup> in two for abdominal surgery,<sup>6 10</sup> and in two for spinal surgery.<sup>41 51</sup> With intrathecal morphine, pain intensity was significantly decreased at 2, 4, 12, and 24 h (Fig. 4). Up to 4 h after surgery, pain intensity at rest was decreased by about 2 cm on the 10 cm visual analogue scale. At 12 and 24 h, pain intensity was decreased by about 1 cm. At all time points, the data were heterogeneous; however, there was no evidence for dose-responsiveness.

Pain intensity on movement or during coughing at 12 or at 24 h was reported in two studies in abdominal surgery<sup>6 10</sup> and two in cardiac surgery.<sup>34 46</sup> Pain intensity was

**Table 1** Included randomized trials of intrathecal morphine alone in patients undergoing surgery with a general anaesthetic. PCA, patient-controlled analgesia; i.v., intravenous; i.m., intramuscular; s.c., subcutaneous

First author, year of publication	Comparisons, all regimens are intrathecal unless otherwise stated (no. of analysed patients) [data not analysed]	Administration of intrathecal morphine before or after surgery	Type of surgery	Duration of surgery, range of means unless otherwise stated (min)	Intraoperative rescue analgesic	Postoperative rescue analgesic	Randomization	Concealment	Blinding	Drop outs
Alhashemi, 2000 <sup>1</sup>	1. Morphine 250 µg (16) 2. Morphine 500 µg (15) 3. Lidocaine s.c. (considered as sham treatment) (19)	Before	Cardiac	198–216	Fentanyl	Morphine i.v.	2	0	1	0
Askar, 2007 <sup>2</sup>	1. Morphine 10 µg kg <sup>-1</sup> (17) 2. No treatment (16)	Before	Thoracic and cardiac	246–269	Remifentanyl	Morphine PCA	1	0	0	0
Aun, 1985 <sup>3</sup>	1. Morphine 2000 µg (20) 2. Morphine 4000 µg (20) 3. No treatment, sticky plaster (20)	Before	Cardiac	Not reported	Fentanyl	Papaveretum	1	0	1	0
Beaussier, 2006 <sup>5</sup>	1. Morphine 300 µg (26) 2. NaCl s.c. (26)	Before	Abdominal	240–252	Sufentanil	Morphine PCA	2	1	1	2
Blay, 2006 <sup>6</sup>	1. Morphine 200 µg (15) 2. NaCl s.c. (15)	Before	Abdominal	Not reported	Sufentanil	Acetaminophen i.v. Tramadol i.v. Morphine i.v. Morphine PCA	1	0	1	2
Boonmak, 2007 <sup>10</sup>	1. Morphine 300 µg (40) 2. No treatment (40)	Before	Abdominal	146–150	Not reported	Morphine PCA	2	0	1	0
Casey, 1987 <sup>12</sup>	1. Morphine 20 µg kg <sup>-1</sup> (19) 2. NaCl (21)	Before	Cardiac	Not reported	Fentanyl	Morphine i.v.	1	0	2	0
Chaney, 1996 <sup>15</sup>	1. Morphine 4000 µg (30) 2. NaCl (30)	Before	Cardiac	Not reported	Fentanyl	Morphine PCA	1	0	1	0
Chaney, 1997 <sup>13</sup>	1. Morphine 10 µg kg <sup>-1</sup> (19) 2. NaCl (21)	Before	Cardiac	Not reported	Fentanyl	Morphine PCA	1	0	1	0
Chaney, 1999 <sup>14</sup>	1. Morphine 10 µg kg <sup>-1</sup> (20) 2. NaCl (20)	Before	Cardiac	Not reported	Fentanyl	Morphine PCA	1	0	1	1
Devys, 2003 <sup>17</sup>	1a. Morphine 300 µg for submesocolic surgery (15) 1b. Morphine 400 µg for supramesocolic surgery (15) 2. No treatment (30)	Before	Abdominal	193–222 (median)	Sufentanil	Morphine PCA	2	0	0	2
El-Hakeem, 2003 <sup>18</sup>	1. Morphine 250 µg (15) 2. Morphine 500 µg (15) 3. NaCl (15)	Before	Cardiac	218–220	Fentanyl	Morphine i.v.	2	0	1	0
Jacobsohn, 2005 <sup>25</sup>	1. Morphine 6 µg kg <sup>-1</sup> of ideal body weight (22) 2. NaCl (21)	Before	Cardiac	202–228	Sufentanil	Morphine PCA	1	0	1	1
Karaman, 2006 <sup>27</sup>	1. Morphine 5 µg kg <sup>-1</sup> (12) 2. No treatment (12)	Before	Hysterectomy	101–105	Remifentanyl	Morphine PCA	2	0	1	0

Continued

Table 1. Continued

First author, year of publication	Comparisons, all regimens are intrathecal unless otherwise stated (no. of analysed patients) [data not analysed]	Administration of intrathecal morphine before or after surgery	Type of surgery	Duration of surgery, range of means unless otherwise stated (min)	Intraoperative rescue analgesic	Postoperative rescue analgesic	Randomization	Concealment	Blinding	Drop outs
Lena, 2003 <sup>30</sup>	1. Morphine 4 µg kg <sup>-1</sup> (14) [2. Morphine 4 µg kg <sup>-1</sup> + clonidine 1 µg kg <sup>-1</sup> (15)] 3. No treatment (16)	Before	Cardiac	212–292 (median)	Sufentanil	Morphine PCA	2	0	1	0
Liu, 2001 <sup>31</sup>	[1. Sufentanil 50 µg (10)] 2. Morphine 500 µg (10) [3. Sufentanil 50 µg+morphine 500 µg (10)] 4. Lidocaine s.c. (considered as sham treatment) (19)	Before	Thoracic	132	Fentanyl	Morphine PCA	2	0	1	2
Mehta, 2004 <sup>34</sup>	1. Morphine 8 µg kg <sup>-1</sup> (53) 2. NaCl s.c., adhesive band on back (47)	Before	Cardiac	226–236	Fentanyl	Tramadol i.v. Diclofenac i.m.	1	0	1	0
O'Neil, 1985 <sup>36</sup>	1. Morphine 1000 µg (24) 2. No treatment (22)	After	Spinal	Not reported	Not reported	Morphine i.v. Papaveretum i.m.	1	0	1	0
Sarma, 1993 <sup>39</sup>	1. Morphine 100 µg (20) 2. Morphine 300 µg (20) 3. Morphine 500 µg (20) 4. No treatment (20)	After	Hysterectomy	Not reported	Fentanyl	Meperidine i.m.	2	0	1	0
Sebel, 1985 <sup>40</sup>	1. Morphine 4000 µg (10)  2. No treatment (10)	Before	Cardiac	Not reported	Fentanyl	Papaveretum (route not reported)	1	0	0	0
Techanivate, 2003 <sup>41</sup>	1. Morphine 300 µg (20) 2. NaCl (20)	After	Spinal	214–240	Fentanyl	Morphine PCA	2	0	2	0
Togal, 2000 <sup>43</sup>	1. Morphine 10 µg kg <sup>-1</sup> (10) 2. No treatment (10)	Before	Abdominal	Not reported	Fentanyl	Meperidine i.m.	1	0	0	0
Togal, 2004 <sup>42</sup>	1. Morphine 100 µg (25) 2. NaCl (25)	After	Hysterectomy	Not reported	Not reported	Morphine PCA	1	0	1	0
Turker, 2005 <sup>46</sup>	1. Morphine 10 µg kg <sup>-1</sup> (22) 2. No treatment (21)	Before	Cardiac	182–194	Remifentanyl	Morphine PCA	2	0	1	2
Vanstrum, 1988 <sup>48</sup>	1. Morphine 500 µg (16)  2. NaCl (14)	Before	Cardiac	Not reported	None	Morphine i.v.	2	0	1	0
Yokota, 2004 <sup>50</sup>	1. Morphine 500 µg (10) [2. Morphine 500 µg+norepinephrine 5 µg (10)]  3. NaCl (10)	Before	Hysterectomy	95–102	Not reported	Diclofenac Indomethacine (route not reported)	1	0	1	0
Yorukoglu, 2005 <sup>51</sup>	1. Morphine 100 µg (20)  [2. Morphine 2000 µg in epidural space (20)] [3. Bupivacaine in paraspinal muscle (20)] 4. NaCl in paraspinal muscle (20)	After	Spinal	91–101	Not reported	Meperidine i.m.	2	0	1	1



significantly decreased in patients receiving intrathecal morphine at 12 h [WMD, -2.0 (95% CI -3.1 to -1.0)] and at 24 h [WMD, -1.7 (95% CI -2.7 to -0.8)]. The data were heterogeneous; however, there was no evidence for dose-responsiveness. For postoperative pain intensity, subgroups were too small to allow for sensitivity analysis according to the type of surgery.

*Further beneficial outcomes*

Duration of hospital stay was decreased by 0.5 days (Table 2). The incidence of pulmonary complications (defined as radiological evidence of atelectasis or consolidation, need for oxygen therapy, or hypoxaemia) showed a

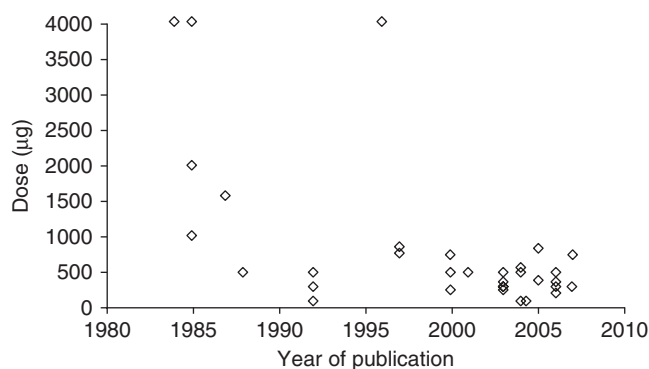
tendency in favour of intrathecal morphine (OR, 0.62) (Table 3). Intrathecal morphine had no effect on time to tracheal extubation (Table 2).

*Adverse effects related to intrathecal morphine*

In 21 trials, the authors monitored the patients for signs of respiratory depression.<sup>1 2 5 6 10 13 17 18 27 30 31 34 36 39-43</sup>

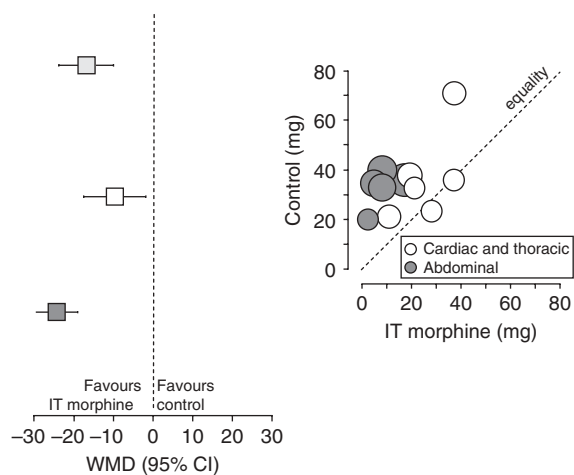
Definitions of respiratory depression included a respiratory frequency <8 or <10 breaths min<sup>-1</sup> (bpm), oxygen saturation <85% or <96%, or the need for naloxone to maintain an adequate tidal volume. Some trials did not provide a clear definition of respiratory depression.

Six cases of respiratory depression were reported in three trials.<sup>5 34 40</sup> Respiratory depression occurred exclusively in patients who had received intrathecal morphine and not in controls. One study was double-blinded, included patients aged >70 yr (average, 78 yr), the dose of intrathecal morphine was 300 µg, and postoperative pain treatment was with patient-controlled analgesia with morphine.<sup>5</sup> Four patients had a ventilatory frequency <10 bpm.<sup>5</sup> The second study was also double-blinded, the average age of the patients was 58 yr, the dose of intrathecal morphine was 560 µg, and postoperative pain treatment was with i.v. tramadol or morphine.<sup>34</sup> One patient had a ventilatory frequency <8 bpm and needed naloxone.<sup>34</sup> The third study had an open design, the average age of the patients was 54 yr, the dose of intrathecal morphine was 4000 µg, and postoperative pain treatment was with papaveretum.<sup>40</sup> One patient required naloxone to maintain an adequate tidal volume.<sup>40</sup> When these data were combined, the risk of respiratory depression was significantly

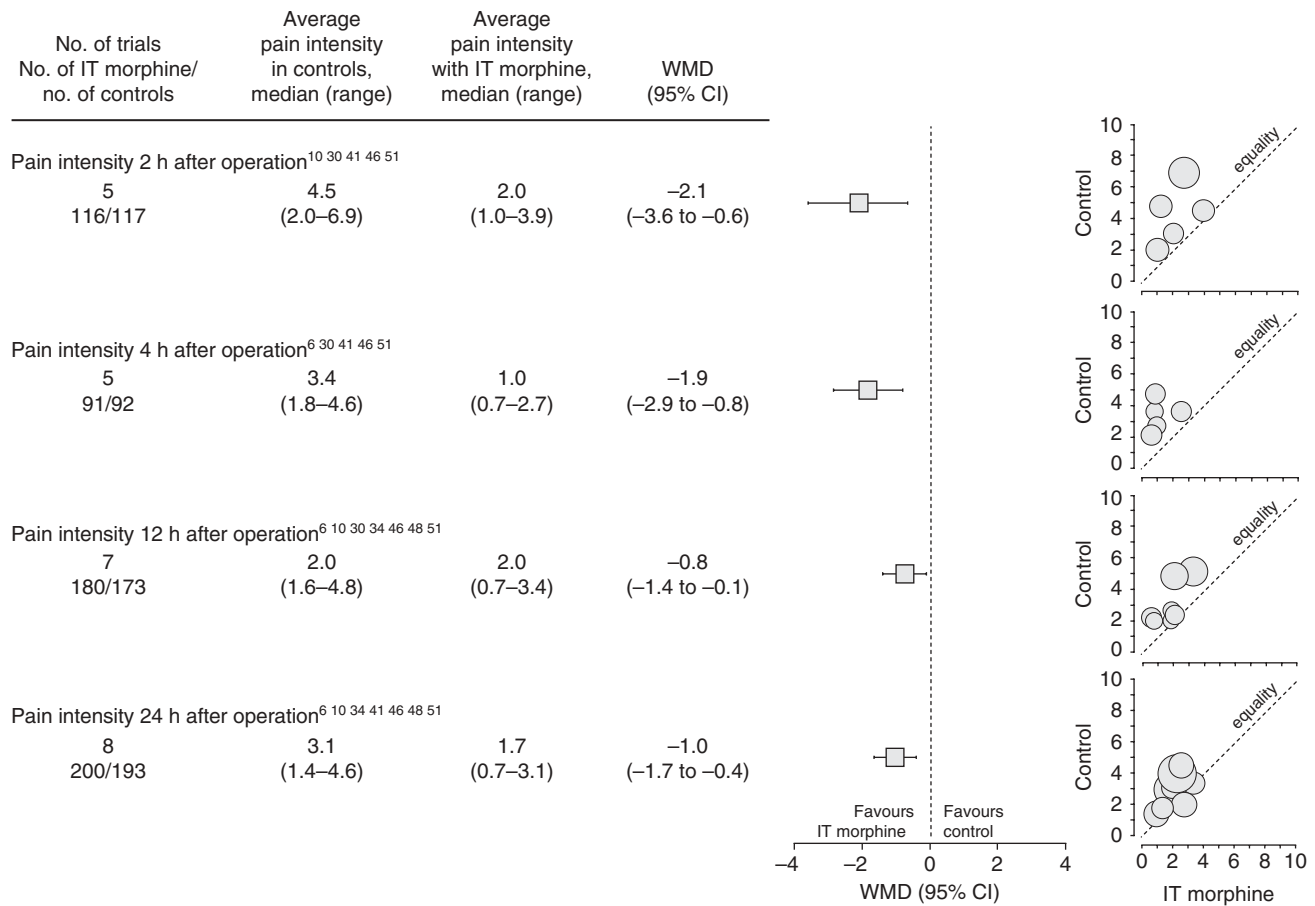


**Fig 2** Relationship between the year of publication of the trials and the doses of intrathecal morphine that were investigated in the trials. Data are from 27 placebo-controlled randomized trials. Each symbol represents one trial arm that tested intrathecal morphine; number of symbols does not add up since some trials tested more than one morphine dose.

No. of trials no. of IT morphine/ no. of controls	Average morphine consumption in controls (mg), median (range)	Average morphine consumption with IT morphine (mg), median (range)	WMD (95% CI)
<b>All surgeries combined</b>			
11 239/243	36.0 (20.1-71.0)	20.0 (3.20-37.7)	-16.9 (-23.7 to -10.1)
<b>Cardiac and thoracic<sup>1 13 14 30 31 46</sup></b>			
6 103/107	34.5 (21.3-71.0)	24.4 (12.7-37.7)	-9.69 (-17.6 to -1.80)
<b>Abdominal<sup>5 6 10 17 42</sup></b>			
5 136/136	34.8 (20.1-40.0)	9.00 (3.20-18.8)	-24.2 (-29.5 to -19.0)



**Fig 3** Cumulative 24 h consumption of i.v. morphine (in milligrams) for break-through pain after operation. IT, intrathecal; WMD, weighted mean difference; CI, confidence interval. On the bubble graph, each bubble represents one trial; sizes of the bubbles are proportional to sizes of the trials.



**Fig 4** Pain intensity (0–10-point scale, ranging from 0, no pain, to 10, maximum pain) at rest at 2, 4, 12, and 24 h after operation. IT, intrathecal; WMD, weighted mean difference; CI, confidence interval. On the bubble graphs, axes are pain intensities (0–10-point scale). Each bubble represents one trial; sizes of the bubbles are proportional to sizes of the trials.

**Table 2** Summary statistics of beneficial continuous outcomes. WMD, weighted mean difference; CI, confidence interval; IT, intrathecal; hetero, heterogeneity; N/A, not applicable (i.e. dose-responsiveness was sought only when the result was statistically significant and when the data appeared to be heterogeneous)

Outcome	No. of trials	No. of patients receiving IT morphine/no. of controls	Outcome in controls, median (range)	WMD (95% CI)	P hetero	P dose-response
Time to extubation (min), cardiac surgery only	8	180/180	564 (312–1374)	-12.3 (-75.2 to 50.7)	0.030	N/A
Duration of hospital stay (days)	8	210/173	7 (5–14)	-0.49 (-0.89 to -0.09)	0.950	N/A

increased in patients receiving intrathecal morphine; OR 7.86 (95% CI 1.54–40.3) (Table 3). When data from all 21 trials that reported on the presence or absence of respiratory depression were combined (i.e. including those that searched for, but did not report on, respiratory depression), the NNH was 84. When only the three trials that reported on patients who had respiratory depression were considered, the NNH decreased (i.e. worsened) to 15. There were no reports of patients who needed re-intubation of the trachea due to respiratory depression.

Eighteen studies reported on pruritus.<sup>1 3 5 6 12–15 17 18 27 31 39 42 43 46 48 51</sup> The incidence of pruritus was significantly increased with intrathecal morphine (Table 3), OR 3.85

(95% CI 2.40–6.15), NNH 6. The data were heterogeneous; however, there was no evidence of dose-responsiveness. Four trials reported on the number of patients requiring treatment for pruritus.<sup>13 34 41 42</sup> None of the control patients required treatment, compared with an average of 5.1% of those receiving intrathecal morphine (Table 3). This difference was statistically significant, OR 7.39 (95% CI 1.48–37.0), NNH 20. The data were homogeneous.

The incidence of urinary retention was slightly increased in patients receiving intrathecal morphine; the 95% CI around the OR (2.35) included 1 (Table 3). The incidence of sedation and nausea and vomiting was not affected (Table 3).

**Table 3** Summary statistics of further dichotomous outcomes. IT, intrathecal; OR, odds ratio; CI, confidence interval; NNT/H, number needed to treat or to harm (a negative number needed to treat is a number needed to harm); hetero, heterogeneity; N/A, not applicable (i.e. dose-responsiveness was sought only when the data appeared to be heterogeneous). \*95% CI around the NNT/H point estimate is shown only for statistically significant results

Outcome	No. of trials	No. of patients with event/ total no. of patients (%)		OR (95% CI)	NNT/H (95% CI)	P hetero	P dose-response
		IT morphine	Control				
Pulmonary complications (any)	5	25/160 (15.6)	33/153 (21.6)	0.62 (0.34–1.16)	17*	0.610	N/A
Number of patients who are sedated at 24 h	5	26/136 (19.1)	26/125 (20.8)	0.64 (0.31–1.36)	59*	0.285	N/A
Respiratory depression							
All studies reporting on the absence or presence of respiratory depression	21	6/502 (1.2)	0/440 (0)	7.86 (1.54–40.3)	–84 (–409 to –47)	0.990	N/A
Only studies reporting on the presence of respiratory depression	3	6/89 (6.7)	0/83 (0)	7.86 (1.54–40.3)	–15 (–65 to –8)	0.994	N/A
Pruritus							
Any pruritus	18	93/435 (21.4)	19/358 (5.3)	3.85 (2.40–6.15)	–6 (–9 to –5)	0.041	0.753
Pruritus needing treatment	4	6/117 (5.1)	0/113 (0)	7.39 (1.48–37.0)	–20 (–88 to –11)	1.000	N/A
Urinary retention	8	18/155 (11.6)	14/164 (8.5)	2.35 (1.00–5.51)	–33*	0.130	N/A
Emesis							
Nausea	10	60/197 (30.5)	47/194 (24.2)	1.22 (0.77–1.95)	–16*	0.612	N/A
Vomiting	10	48/202 (23.8)	43/190 (22.6)	1.05 (0.63–1.73)	–88*	0.230	N/A

### Sensitivity analyses

We performed sensitivity analyses to test the impact of the quality of data reporting (i.e. the modified Oxford scale) and the age of the trials (i.e. year of publication) on outcomes. We selected outcomes that were reported in the majority of trials; these were cumulative 24 h morphine consumption and 24 h pain intensity at rest. We compared trials that had a score <3 (i.e. the median of all trials) with those that had a score >3, and we compared trials that were older than 15 yr with those that were younger. None of these sensitivity analyses revealed any statistically significant difference between subgroups (data not shown).

### Discussion

Comprehensive reviews have tried to summarize the role of intrathecal opioids alone without local anaesthetics for the control of postoperative pain after major surgery.<sup>32–37</sup> These reviews have not provided quantitative estimates of beneficial and harmful effects of intrathecal morphine. However, for rational decision-making, it is not only important to know whether an intervention works, but how well it works. Similarly, we not only need to know whether there are intervention-related adverse effects, but how often these occur. Intrathecal morphine without a local anaesthetic seems to be still a popular analgesic technique in many institutions around the world; the 27 analysed trials were conducted in 12 countries, and seven were published within the last 3 yr.

Several results emerge from our analysis, some of which confirm what has already been reported about intrathecal morphine, some add more precise knowledge, and some refute what is generally believed in this context.

It is known that intrathecal morphine, when injected alone in patients undergoing major surgery under general anaesthesia, provides postoperative analgesia. However, the degree of the analgesic efficacy is less clear. Our analysis allows for quantification of this beneficial effect and, consequently, for indirect comparison with the efficacy of alternative analgesic techniques that are frequently used in similar surgical settings. In adults undergoing major abdominal or cardio-thoracic surgery under general anaesthesia, a single dose of intrathecal morphine decreases 24 h pain intensity at rest by about 1 cm on the 10 cm scale. The effect is more pronounced on movement. This degree of analgesic efficacy appears to be greater than with intraoperative low-dose ketamine (reduction in pain intensity at 24 h, about 0.4 cm),<sup>20</sup> and similar to postoperative non-steroidal anti-inflammatory drugs or the gold-standard neuraxial analgesia technique, that is, epidural analgesia with local anaesthetic (with both, reduction in pain intensity at 24 h, about 1 cm).<sup>7–19</sup>

Intra- and postoperative opioid-sparing may be regarded as surrogates of the true efficacy of an analgesic. Patients who received intrathecal morphine needed less fentanyl equivalents intraoperatively and they received considerably less i.v. morphine for rescue analgesia after operation. It is a new finding that the morphine-sparing effect was weaker after cardio-thoracic than after abdominal surgery, even though the dose of intrathecal morphine used in cardio-thoracic surgery patients was considerably higher. Morphine-sparing after abdominal surgery was greater than with intraoperative ketamine (about 16 mg per 24 h)<sup>20</sup> or postoperative non-steroidal anti-inflammatory drugs (range, 10–20 mg per 24 h, depending on the regimen).<sup>19–33</sup> The limited amount of morphine that was spared after cardio-thoracic surgery was only comparable with the perioperative usage of acetaminophen (about 8



mg per 24 h).<sup>19 38</sup> Thus, the appropriateness of intrathecal morphine in patients undergoing thoracic or cardiac surgery may be questioned. The surgery-related difference could not be attributed to differences in the baseline risks; the average 24 h morphine consumption in control patients was almost identical in both subgroups. A reasonable hypothesis relates to the different distances from the drug administration site (which is always lumbar) to the spinal cord segments receiving the nociceptive input (which may be lumbar or thoracic).

A further unexpected finding was the lack of an analgesic dose–response. This does not mean that there is none. However, it implies that the published literature does not allow the establishment of a dose–response relationship with confidence, and hence the minimal effective dose of intrathecal morphine when used alone in patients undergoing major surgery remains unknown. This is remarkable as a large dose range was tested. We cannot exclude that all doses were on the upper horizontal part of the sigmoid-shaped dose–response curve. Consequently, very low doses of intrathecal morphine should be tested. The inability to show a dose–response challenges the conclusions of two previously published reviews<sup>32 37</sup> and three dose-finding studies.<sup>3 8 39</sup> Three further dose-finding studies were unable to find an analgesic dose–response.<sup>1 18 22</sup>

It is known that intrathecal morphine, alone or as an adjuvant to a local anaesthetic, increases the risk of respiratory depression. As respiratory depression is a major risk,<sup>29</sup> it is important to quantify that risk. None of the control patients experienced respiratory depression, although they were, on average, given more opioids intraoperatively and substantially more i.v. morphine for breakthrough pain after operation. To estimate the risk that was related to the intrathecal morphine, we used two denominators. When we considered exclusively the studies that reported cases of respiratory depression, the rate with intrathecal morphine was 6.7%. Since none of the controls had symptoms of respiratory depression, this incidence translated into an NNH of 15. This may be seen as a worst-case scenario, and it is likely to overestimate the true additional risk. When we considered all studies that reported the presence or absence of respiratory depression (i.e. including those that did not find any), the rate with intrathecal morphine decreased to 1.2%, and accordingly, the NNH improved to 84. We must, therefore, assume that between 15 and 84 patients undergoing surgery with a general anaesthetic and receiving i.v. morphine for breakthrough pain after operation need to receive intrathecal morphine for one additional patient to develop respiratory depression who would not have done so had they not received the morphine intrathecally. Our estimate matches a previously reported estimate from a large case series where patients received intrathecal morphine 200–800 µg before operation and patient-controlled analgesia with i.v. morphine or meperidine after operation.<sup>24</sup> This result is alarming but has to be interpreted cautiously. Respiratory

depression due to intrathecal morphine is a rare event and none of these studies was designed to study that risk. Some cases of respiratory depression may have been missed, which could have affected our estimate in either ways. Also, one of the trials that reported cases of respiratory depression was not blinded. Observer bias may lead to the overestimation of the beneficial effects of a treatment,<sup>26</sup> but it is not clear if this applies to harmful effects. Finally, in four of the six cases, the definition of respiratory depression was a ventilatory frequency <10 bpm, which may not necessarily be perceived as a real threat. None of the patients required tracheal re-intubation. Previous studies on the impact of the dose of intrathecal morphine alone on the risk of respiratory depression have inconsistent results.<sup>4 8 22</sup> The decreasing doses tested over the years (Fig. 2) suggest that investigators have tried to further decrease the risk of respiratory depression but to maintain analgesic efficacy. However, there is evidence from trials that were included in our analysis,<sup>5</sup> and from others,<sup>24</sup> that respiratory depression may occur with doses as low as 200 or 300 µg of intrathecal morphine.

A major concern is the uncertainty as to how, where, and for how long these patients need to be monitored. It has been suggested that after intrathecal morphine administration (200–600 µg), clinical signs or symptoms including ventilatory frequency, level of sedation, or pupil size were not reliable predictors of respiratory depression.<sup>4</sup> In addition, hypercarbia may occur despite a normal ventilatory frequency, and a sedation score may be more sensitive for detection of respiratory depression than capillary oxygen saturation or expired carbon dioxide levels.<sup>29</sup> The most practical and effective method for detection of respiratory depression is unknown. Whether these patients should be monitored in a high-dependency post-anaesthetic care area or whether they may be transferred to a regular surgical ward is an essential question<sup>23</sup> which raises important logistic and financial issues. These are likely to challenge the use of intrathecal morphine in settings where limited resources do not allow for appropriate postoperative surveillance.

There were further outcomes and for some, the results were surprising. For instance, there was no significant beneficial effect of intrathecal morphine on postoperative pulmonary complications. This may be explained by the limited number of trials reporting this endpoint. Intrathecal morphine is believed to be particularly emetogenic.<sup>37</sup> However, there was no evidence to support this view. Similarly, there was no evidence that intrathecal morphine increased the risk of sedation. Finally, there was a statistically significant shortening of the duration of hospital stay of about 0.5 days, although this was probably not clinically relevant.

Our meta-analysis has limitations. First, in only two studies did the group size exceed 30 patients. Small pain studies are likely to find results by random chance<sup>35</sup> and they are unlikely to identify rare but clinically relevant

adverse effects. Secondly, most treatment effects showed large variability that could not be explained by differences in dose and we were unable to identify other sources of heterogeneity, for instance, trial age or quality. The only identifiable source of heterogeneity was the type of surgery for the outcome '24 h morphine consumption'. The lack of consistency in study design and outcome measurement illustrated the lack of a research agenda. Thirdly, our analysis concentrated on patients undergoing major surgery under general anaesthesia and receiving an additional intrathecal injection of morphine without local anaesthetic. Thus, the results may not be applicable to other settings, for instance, patients undergoing knee arthroscopy, varicose vein stripping, or inguinal hernia repair receiving a small dose of opioid as an adjuvant to an intrathecally injected local anaesthetic and without general anaesthetic. Finally, we were unable to demonstrate a linear dose–response neither for beneficial nor harmful effects, but we cannot exclude that a non-linear dose–response exists.

In conclusion, in patients undergoing major surgery under general anaesthesia and receiving systemic opioids for break-through pain after operation, the additional use of intrathecal morphine decreases pain intensity after operation. It also decreases systemic morphine consumption for break-through pain after operation, but does not decrease the risk of morphine-related adverse effects. The extent of the analgesic efficacy is similar to postoperative non-steroidal anti-inflammatory drugs. The postoperative morphine-sparing is significantly weaker in patients undergoing cardio-thoracic compared with abdominal surgery, and the risk of respiratory depression remains finite. Finally, there is a lack of evidence of dose-responsiveness, neither for beneficial nor for harmful effects, and even though a large range of doses has been tested. Despite 30 yr of clinical research, we still do not know the optimal dose of intrathecal morphine when used alone. Different conclusions may be arrived at. The usefulness of intrathecal morphine in patients undergoing cardiothoracic surgery should be questioned. In patients undergoing abdominal surgery, there may be an argument for further research to quantify benefits and risks of very low doses of intrathecal morphine. Clinicians who wish to continue to use intrathecal morphine should consider that the optimal dose (i.e. the dose that has adequate analgesic efficacy without causing life-threatening respiratory depression) remains unknown, as does method and adequate length of monitoring of respiratory function. In view of all these caveats, the most radical, and perhaps most appropriate, conclusion would be that this analgesic intervention that reduces postoperative morphine consumption but not morphine-related adverse effects, that only slightly improves postoperative pain intensity, that significantly increases the risk of pruritus, and that is associated with a finite risk of respiratory depression should be abandoned.

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