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Review Article

# Efficacy and safety of intrathecal morphine for analgesia after lower joint arthroplasty: a systematic review and meta-analysis with meta-regression and trial sequential analysis

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## Summary

Widespread adoption of intrathecal morphine into clinical practice is hampered by concerns about its potential side-effects. We undertook a systematic review, meta-analysis and trial sequential analysis with the primary objective of determining the efficacy and safety of intrathecal morphine. Our secondary objective was to determine the dose associated with greatest efficacy and safety. We also assessed the impact of intrathecal morphine on respiratory depression. We systematically searched the literature for trials comparing intrathecal morphine with a control group in patients undergoing hip or knee arthroplasty under spinal anaesthesia. Our primary efficacy outcome was rest pain score (0–10) at 8–12 hours; our primary safety outcome was the rate of postoperative nausea and vomiting within 24 hours. Twenty-nine trials including 1814 patients were identified. Rest pain score at 8–12 hours was significantly reduced in the intrathecal morphine group, with a mean difference (95%CI) of −1.7 (−2.0 to −1.3), $p < 0.0001$ (19 trials; 1420 patients; high-quality evidence), without sub-group differences between doses ($p = 0.35$). Intrathecal morphine increased postoperative nausea and vomiting, with a risk ratio (95%CI) of 1.4 (1.3–1.6), $p < 0.0001$ (24 trials; 1603 patients; high-quality evidence). However, a sub-group analysis by dose revealed that rates of postoperative nausea and vomiting within 24 hours were similar between groups at a dose of 100 μg, while the risk significantly increased with larger doses (p value for sub-group difference = 0.02). Patients receiving intrathecal morphine were no more likely to have respiratory depression, the risk ratio (95%CI) being 0.9 (0.5–1.7), $p = 0.78$ (16 trials; 1173 patients; high-quality evidence). In conclusion, there is good evidence that intrathecal morphine provides effective analgesia after lower limb arthroplasty, without an increased risk of respiratory depression, but at the expense of an increased rate of postoperative nausea and vomiting. A dose of 100 μg is a 'ceiling' dose for analgesia and a threshold dose for increased rate of postoperative nausea and vomiting.

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## Introduction

Since the first report in 1979 describing the intrathecal injection of morphine to achieve pain relief [1], this intervention has been successfully used in many surgical operations such as caesarean section [2], lower limb arthroplasty [3] and abdominal laparoscopy within an enhanced recovery protocol [4].

While hip and knee arthroplasty are increasingly performed on an ambulatory basis or with a short hospital stay, anaesthetists are reluctant to administer intrathecal morphine, despite its expected analgesic effect, for fear of potential side-effects, particularly postoperative nausea and vomiting (PONV) and respiratory depression. These complications might lead to hospital admission or prolonged length of stay, increase postoperative morbidity and impoverish patients' experience, thus undermining the analgesic efficacy and patient-centred benefits of this analgesic modality, particularly in the setting of enhanced recovery [5]. Intrathecal morphine has been shown to be superior to a range of regional anaesthetic techniques in various surgical procedures [6–8], though its effectiveness and safety when compared with control remain unclear. Previous meta-analyses have reported inconsistent conclusions regarding the risk-benefit balance of different intrathecal morphine doses. While optimal dosing may have been determined for women undergoing caesarean delivery [2], uncertainty remains when other surgical procedures are considered [9]. Notably, there have been no recent studies synthesising data on the efficacy and safety of intrathecal morphine in lower limb arthroplasty, with older data no longer representing current peri-operative practice [9]. One recent meta-analysis attempted to examine this question but failed to provide sufficient clinically useful evidence as the results were subject to significant bias, including the absence of registration before publication; incomplete literature search; exclusion of relevant studies; and no assessment of patient-centred outcomes such as pain score [10].

To address this gap in understanding, we undertook this systematic review and meta-analysis with trial sequential analysis with the primary objective of determining the efficacy and safety of intrathecal morphine after lower limb arthroplasty. Our secondary objective was to determine the dose of intrathecal morphine associated with the most favourable efficacy and safety profile.

## Methods

This study followed the PRISMA statement [11] and was prospectively registered on the International Prospective Register of Systematic Reviews.

With the assistance of a medical librarian, we searched the following electronic databases from inception to 25 November 2020: Ovid Medline; PubMed (search limited to non-indexed references for Medline); Embase; the Cochrane Central Register of Controlled Clinical Trials; and Web of Science. Supplemental searches were carried out on Clinicaltrials.gov; the World Health Organization International Clinical Trials Registry Platform; and Google Scholar (search limited to the first 200 results). Details of the literature search strategy are described in online Supporting Information Appendix S1. The searches were conducted in accordance with the Peer Review of Electronic Search Strategies (PRESS) checklist, which included peer review by another medical librarian [12]. No language or date limits were placed on the search. References were imported into EndNote™ X9 software (Clarivate™, London, UK) for deduplication. In addition, the authors examined the references of all retrieved articles for any applicable trials that might not have been captured by the above approach.

We included prospective, randomised controlled trials of adult patients undergoing unilateral, elective hip or knee arthroplasty under spinal anaesthesia, comparing intrathecal morphine with a control group.

Defined outcomes were extracted from each article following the routine approach previously described in meta-analyses on acute postoperative pain [13–15]. We defined one efficacy and one safety primary outcome. Our efficacy primary outcome was rest pain score at 8–12 postoperative h, because the duration of action of intrathecal morphine is not expected to extend beyond this time-point [16]. Our second primary outcome was the rate of PONV within the first 24 postoperative h. This time-point was selected because most studies report this outcome for the first postoperative day [17]. Our secondary objective was to determine the dose of intrathecal morphine which best balanced efficacy and safety; therefore, dosing of intrathecal morphine was sought from all included studies. Secondary analgesic outcomes included: rest pain scores at 0–2 and 24 postoperative h; intravenous (i.v.) morphine equivalent consumption at 0–4, 8–12 and 24 postoperative h; and duration of analgesia. Other secondary outcomes sought were side-effects including pruritus; urinary retention; hypoxaemia; respiratory depression; and sedation, all recorded within the first 24 postoperative h. We also aimed to determine any differences in the hospital stay.

Extracted trial characteristics included doses of morphine injected; the joint undergoing replacement; local anaesthetic used for spinal anaesthesia; presence and type of an additional analgesic technique employed; and medication used for postoperative analgesia.

 

The text, tables or images from the source articles were evaluated to extract the number of participants, number of events, means, SDs, SEMs and 95%CI. Data presented graphically were extracted with plot digitising software (Plot Digitizer Version 2.1, Free Software Foundation, Boston, MA, USA). For articles that did not describe the sample size or results as a mean and SD or standard error of the mean and 95%CI, we contacted the corresponding author twice by electronic mail, requesting access to the relevant data or the complete dataset. If the corresponding author failed to reply, we took the median (IQR) as approximations of the mean (SD), by estimating the mean as equivalent to the median, and the SD as the IQR divided by 1.35, or the range divided by 4. When trials investigated different intrathecal doses, or performed sub-group analyses according to the joint replaced, data from all groups were included. All opioids were converted to equianalgesic i.v. morphine doses (i.v. morphine 10 mg = oral morphine 30 mg = i.v. tramadol 100 mg = i.v. pethidine 75 mg = i.v. fentanyl 100 μg = i.v. nalbuphine 10 mg = oral hydrocodone 30 mg = oral codeine 165 mg) [18]. For pain scores with an 11-point verbal, visual or numerical rating scale, results were transposed to a 0–10 analogue scale to permit statistical evaluation. In addition, the grades of recommendation, assessment, development and evaluation (GRADE) system was applied to each outcome to evaluate the quality of evidence [19].

For each randomised trial, the methodological quality was evaluated using the Cochrane Collaboration's Risk of Bias tool [20]. Two authors (EG and SG) used this method to independently screen, review and score the items for each trial. Disagreements in scoring or extracted data were adjudicated by a third author (EA).

All meta-analyses were conducted using RevMan 5.4.0 (Nordic Cochrane Centre, Cochrane Collaboration, 2020, Copenhagen, Denmark). For continuous data, this software estimates the weighted mean differences, and similarly the risk ratio for categorical data between groups, with an overall estimate of the pooled effect. A meta-analysis was conducted when two or more trials reported any given outcome. We calculated the $I^2$ coefficient in order to assess heterogeneity' and set predetermined limits for low (< 50%); moderate (50–74%); and high (> 75%) levels [21]. A random-effects model was applied in circumstances when moderate or high heterogeneity was observed; otherwise, we used a fixed-effects model [22]. To account for sources of heterogeneity, sub-group analyses were conducted for our primary outcomes according to the dose of intrathecal morphine (35–100 μg; 150–200 μg; or > 200 μg), the site of surgery (hip or knee) and whether multimodal analgesia (two different modalities) had been used. The risk of publication bias for our two primary outcomes was assessed by funnel plot analysis [23] and confirmed with Duval and Tweedie's trim and fill test [24]. This assessment was performed using Comprehensive Meta-analysis version 2 (Biostat, Englewood, NJ, USA). The interactions between the dose of intrathecal morphine and mean difference in pain score at 8–12 postoperative hours, or risk ratio of PONV within 24 postoperative hours, were investigated with meta-regression using the JMP 14 statistical package (SAS Institute, Cary, NC, USA). Finally, trial sequential analysis was performed for the two primary outcomes to confirm whether firm evidence was reached or not (TSA software version 0.9.5.10 Beta; Copenhagen Trial Unit, Center for Clinical Intervention Research, Rigshospitalet, Copenhagen, Denmark). A two-sided p value < 0.05 was deemed to be significant.

## Results

We identified 1198 trials, with 29 different trials published in 29 distinct manuscripts, including a total of 1814 patients, meeting the inclusion criteria [25–53] (see also Supporting Information Fig. S1). The risk of bias of the different trials is summarised in Figure 1. Fourteen authors were contacted [27,31,34,39,40,43–47,49–52] and five provided additional data [27,31,39,44,51].

Table 1 shows the trial characteristics. In eight and 14 trials, authors included patients undergoing hip [25,32,36, 37,41,42,44,53] or knee arthroplasty [26–29,38–40,43,46, 47,49–52], respectively, while seven trials included both [30,31,33–35,45,48]. One trial presented separate results for hip and knee arthroplasties [48]. Most trials used bupivacaine for spinal anaesthesia, except in three studies where levobupivacaine [51] or tetracaine [30,48] were administered. Intrathecal morphine doses ranged from 35 μg [51] to 500 μg [30,36,37], while the most frequently investigated dose was 100 μg [25,27,31–35,38,40,42–44,47,48]. Eight trials allocated patients to different intervention groups with different intrathecal doses of morphine [31,34,35,38,40,44,47,48]. Among patients undergoing hip arthroplasty, local anaesthesia infiltration analgesia was used in one study [25]. In patients scheduled for knee arthroplasty, additional analgesic techniques employed were local infiltration analgesia [26,43,49]; local infiltration analgesia with adductor canal block [27]; femoral nerve block [39,40,46,47]; continuous femoral nerve block [51]; and epidural analgesia [38]. Finally, four studies reported the use of a multimodal analgesic regimen in the postoperative period [25–27,46].

Rest pain score at 8–12 postoperative h was significantly reduced in the intrathecal morphine group,

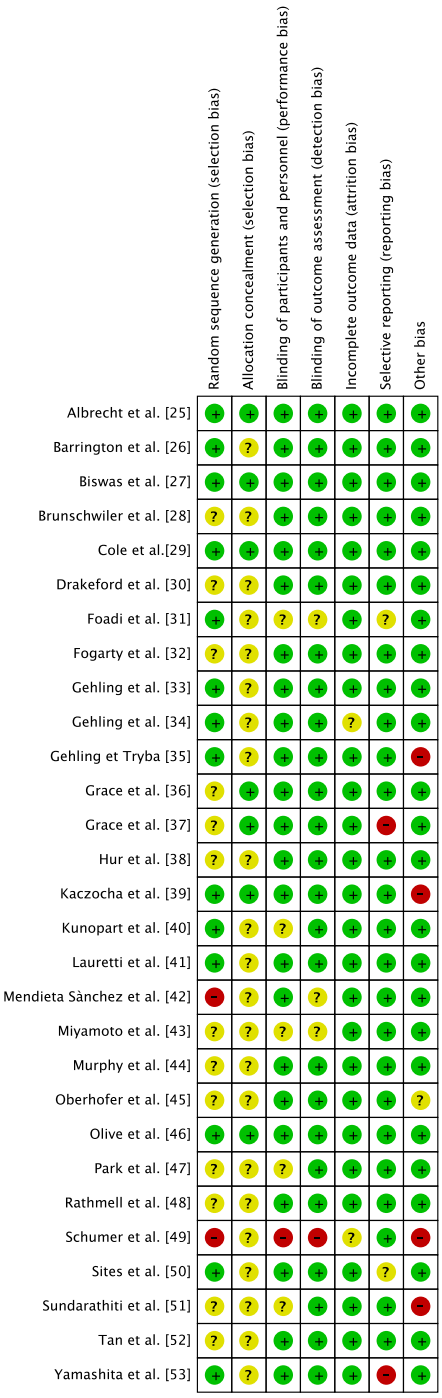


**Figure 1** Cochrane Collaboration Risk of Bias summary: evaluation of bias risk items for each included study. Green circle, low risk of bias; red circle, high risk of bias; and yellow circle, unclear risk of bias.

with a mean difference (95%CI) of −1.7 (−2.0 to −1.3), $I^2$ = 74%, p < 0.0001 (Fig. 2), without sub-group difference between doses (p = 0.35). Meta-regression confirmed the absence of a correlation between dose and mean differences in pain scores ($r^2$ = 0.06, p = 0.24, see also online Supporting Information Fig. S2). Sub-group analyses examining the use of multimodal analgesia did not reveal any differences when it was used or not (p for sub-group difference = 0.62). However, sub-group analyses demonstrated a greater mean difference (95%CI) analgesic effect of intrathecal morphine in patients undergoing knee arthroplasty (−2.1 (−2.5 to −1.6), $I^2$ = 48%, p < 0.0001) than those undergoing hip arthroplasty (−1.2 (−1.7 to −0.8), $I^2$ = 16%, p < 0.0001; p for sub-group difference = 0.04). Trial sequential analysis indicated that firm evidence was reached regarding the contribution of intrathecal morphine to decrease rest pain score at 8–12 postoperative h (see also Supporting Information Fig. S3). Duval and Tweedie's trim and fill test calculated the combined studies' point estimate (95%CI) to be −0.96 (−1.2 to −0.7) with a random-effects model. Using trim and fill, these values were unchanged, suggesting a low likelihood of publication bias.

The incidence (95%CI) of PONV in the intrathecal morphine and control groups was 42.4 (39.0–45.9)% and 29.9 (26.8–33.2)%, respectively. While the difference was significant between groups with a risk ratio (95%CI) of 1.4 (1.3–1.6), $I^2$ = 0%, p < 0.0001, sub-group analysis according to intrathecal morphine dose revealed that rates of PONV were similar between groups with doses up to 100 μg. The risk of PONV significantly increased with doses above 150 μg (p for sub-group difference = 0.02; Fig. 3). Meta-regression indicated the absence of correlation between PONV and dose of intrathecal morphine ($r^2$ = 0.09, p = 0.07, see also Supporting Information Fig. S4). Of note, risk ratio (95%CI) of PONV was reduced when patients received multimodal analgesia (1.1 (0.8–1.3), $I^2$ = 0%, p = 0.67) compared with patients who did not (1.5 (1.3–1.8), $I^2$ = 0%, p < 0.0001; p for sub-group difference = 0.009). Finally, there were no sub-group differences based on the site of surgery (p = 0.50). Firm evidence was confirmed with the trial sequential analysis (see also Supporting Information Figure S5). Duval and Tweedie's trim and fill test calculated the combined studies point estimate (95%CI) to be 1.5 (1.1–2.0) with a random-effects model. Using trim and fill, these values were unchanged, suggesting that one study might be missing.

All secondary pain-related outcomes were consistently reduced in the intrathecal morphine group (Table 2). Patients receiving intrathecal morphine suffered more pruritus, urinary retention and sedation, but without increased risk of respiratory depression or hypoxaemia (Table 3). Hospital length of stay, reported in four studies [26,27,31,49], was similar between groups, with a mean difference (95%CI) of 0.0 days (−0.2 to 0.3), $I^2$ = 0%, p = 0.68.

 

**Table 1** Characteristics of studies included in the systematic review.

| Reference | Group (n) | Joint arthroplasty | Local anaesthetic for spinal anaesthesia | Type of control | Additional analgesic technique | Medication used for the additional analgesic technique | Postoperative analgesia |
|---|---|---|---|---|---|---|---|
| Albrecht et al. [25] | Control (30)<br>Morphine 100 μg (30) | Hip | Bupivacaine 0.5%, 3 ml | Saline | Local infiltration analgesia | Ropivacaine 0.2%, 50 ml | Paracetamol; ibuprofen; oxycodone |
| Barrington et al. [26] | Control (38)<br>Morphine 200 μg (41) | Knee | Bupivacaine 0.75%, 1.2 ml | No intervention | Local infiltration analgesia | Ropivacaine 0.5%, 50 ml; ketorolac 30 mg; adrenaline 1 mg | Paracetamol; celecoxib |
| Biswas et al. [27] | Control (68)<br>Morphine 100 μg (64) | Knee | Bupivacaine 0.5%, 3 ml | No intervention | Local infiltration analgesia and adductor canal block | Local infiltration analgesia: ropivacaine 0.2%, 150 ml; ketorolac 30 mg; adrenaline 0.6 mg;<br>Adductor canal block: ropivacaine 0.5%, 30 ml | Acetaminophen; celecoxib; hydromorphone; oxycodone |
| Brunschwiler et al. [28] | Control (12)<br>Morphine 150 μg (12) | Knee | Bupivacaine 0.5%, 2 ml | Saline | None | n/a | Diclofenac; morphine |
| Cole et al. [29] | Control (15)<br>Morphine 300 μg (17) | Knee | Bupivacaine 0.5%, 2 ml | Saline | None | n/a | Diclofenac; morphine |
| Drakeford et al. [30] | Control (20)<br>Morphine 500 μg (20) | Hip, knee | Tetracaine 1%, volume unknown | No intervention | None | n/a | Acetaminophen; oxycodone; morphine |
| Foadi et al. [31] | Control (17)<br>Morphine 100 μg (16)<br>Morphine 200 μg (16) | Hip, knee | Bupivacaine 0.5%, volume unknown | Saline | None | n/a | Metamizole; morphine |
| Fogarty et al. [32] | Control (30)<br>Morphine 100 μg (30) | Hip | Bupivacaine 0.5%, 2.75 ml | Saline | None | n/a | Morphine |
| Gehling et al. [33] | Control (15)<br>Morphine 100 μg (15) | Hip, knee | Bupivacaine 0.5%, 3 ml | Saline | None | n/a | Metamizole; piritramide |
| Gehling et al. [34] | Control (66)<br>Morphine 100 μg (63)<br>Morphine 200 μg (59) | Hip, knee | Bupivacaine 0.5%, 3 ml | Saline | None | n/a | Metimazole; morphine |
| Gehling and Tryba [35] | Control (15)<br>Morphine 50 μg (15)<br>Morphine 100 μg (15)<br>Morphine 200 μg (15) | Hip, knee | Bupivacaine 0.5%, 3 ml | Saline | None | n/a | Metimazole; piritramide |
| Grace et al. [36] | Control (30)<br>Morphine 500 μg (30) | Hip | Bupivacaine 0.5%, 2.75 ml | Saline | None | n/a | Morphine |
| Grace et al. [37] | Control (30)<br>Morphine 500 μg (30) | Hip | Bupivacaine 0.5%, 2.75 ml | Saline | None | n/a | Morphine |
| Hur et al. [38] | Control (20)<br>Morphine 50 μg (16)<br>Morphine 100 μg (18) | Knee | Bupivacaine 0.5%, volume unknown | Saline | Patient-controlled epidural analgesia | Levobupivacaine 0.1%; fentanyl 0.0002% | Patient-controlled epidural analgesia; ketorolac |
| Kaczocha et al. [39] | Control (25)<br>Morphine 200 μg (17) | Knee | Bupivacaine 0.5%, 3 ml | Saline | Femoral nerve block | Not specified | Morphine |
| Kunopart et al. [40] | Control (15)<br>Morphine 100 μg (15)<br>Morphine 200 μg (15)<br>Morphine 300 μg (15) | Knee | Bupivacaine 0.5%, 3 ml | No intervention | Femoral nerve block | Bupivacaine 0.5%, 20 ml | Morphine |
| Lauretti et al. [41] | Control (20)<br>Morphine 200 μg (20) | Hip | Bupivacaine 0.5%, 3 ml | Saline | None | n/a | Ketoprofen; tramadol |
| Mendieta Sànchez et al. [42] | Control (15)<br>Morphine 100 μg (15) | Hip | Bupivacaine 0.5%, 2–3 ml | Saline | None | n/a | Morphine |
| Miyamoto et al. [43] | Control (32)<br>Morphine 100 μg (31) | Knee | Bupivacaine 0.5%, 4 ml | No intervention | Local infiltration analgesia | Levobupivacaine 0.5%, 20 ml; dexamethasone 3.3 mg | Diclofenac; pentozacine; flurbiprofen |
| Murphy et al. [44] | Control (15)<br>Morphine 50 μg (15)<br>Morphine 100 μg (15)<br>Morphine 200 μg (15) | Hip | Bupivacaine 0.5%, 3 ml | Saline | None | n/a | Diclofenac; morphine |
| Oberhofer et al. [45] | Control (19)<br>Morphine 200 μg (21) | Hip, knee | Bupivacaine 0.5%, 3 ml | Saline | None | n/a | Diclofenac; morphine |

(continued)

**Table 1** (*continued*)

| Reference | Group (n) | Joint arthroplasty | Local anaesthetic for spinal anaesthesia | Type of control | Additional analgesic technique | Medication used for the additional analgesic technique | Postoperative analgesia |
|---|---|---|---|---|---|---|---|
| Olive et al. [46] | Control (27)<br>Morphine 175 μg (28) | Knee | Bupivacaine 0.5%, 3.5 ml | No intervention | Femoral nerve block | Ropivacaine 0.75%, 20 ml | Paracetamol; celecoxib; morphine |
| Park et al. [47] | Control (20)<br>Morphine 50 μg (20)<br>Morphine 100 μg (20)<br>Morphine 150 μg (20)<br>Morphine 200 μg (20) | Knee | Bupivacaine 0.5%, 2–3 ml | No intervention | Femoral nerve block | Bupivacaine 0.25%, 20ml then bupivacaine 0.125%, 2 ml.h$^{-1}$ | Diclofenac; butorphanol; morphine |
| Rathmell et al. [48] | Control (20)<br>Morphine 100 μg (20)<br>Morphine 200 μg (20)<br>Morphine 300 μg (18) | Hip, knee | Tetracaine 1%, volume unknown | No intervention | None | n/a | Morphine |
| Schumer et al. [49] | Control (64)<br>Morphine dosage unknown (65) | Knee | Bupivacaine, concentration and volume unknown | Not specified | Local infiltration analgesia | Bupivacaine, dosage unknown | Ketorolac; opioid not specified |
| Sites et al. [50] | Control (21)<br>Morphine 250 μg (20) | Knee | Bupivacaine 0.5%, 3 ml | Saline | None | n/a | Morphine |
| Sundarathiti et al. [51] | Control (33)<br>Morphine 35 μg (35) | Knee | Levobupivacaine 0.5%, 2.8 ml | No intervention | Continuous femoral nerve block | Levobupivacaine 0.125%, 5–7 ml.h$^{-1}$ | Acetaminophen; tramadol |
| Tan et al. [52] | Control (20)<br>Morphine 300 μg (20) | Knee | Bupivacaine 0.5%, 3 ml | Saline | None | n/a | Diclofenac |
| Yamashita et al. [53] | Control (10)<br>Morphine 50 μg (10) | Hip | Bupivacaine 0.5%, 2.8 ml | No intervention | None | n/a | Diclofenac |

n/a, not applicable.

According to the GRADE system, the quality of evidence was high for our primary outcomes and moderate-to-high for our secondary outcomes (see also Supporting Information Table S1).

## Discussion

This meta-analysis demonstrates that intrathecal morphine provides effective analgesia after lower limb arthroplasty under spinal anaesthesia, but brings a higher risk of PONV, pruritus, urinary retention and sedation. When stratifying by dose of intrathecal morphine, we found that a dose of 100 μg best balanced analgesia and side-effects. The overall quality of evidence was high for both of our primary outcomes and moderate-to-high for our secondary outcomes, indicating that practitioners should consider adapting their practice in keeping with these findings.

For our primary efficacy outcome, we found clear evidence that intrathecal morphine provided both statistically and clinically important [54,55] analgesia at 8–12 h, with a mean difference of 1.7 units when compared with control. This effect was consistent at earlier time-points, and when opioid consumption was assessed. Moreover, intrathecal morphine was associated with an increase in analgesic duration by nearly 9 h. The consistency with which this efficacy was demonstrated is pertinent. Notably, the duration of effect of intrathecal morphine is estimated to be up to 16 h [16], which may be the underlying reason for clinically unimportant differences in analgesic outcomes at 24 h. We also demonstrated that postoperative analgesia was more effective in patients undergoing knee arthroplasty, even in the presence of other regional anaesthetic techniques, which may be because knee arthroplasty is generally thought to be more painful [56]. However, both statistically and clinically important differences were reported for hip and knee arthroplasty, underlining the efficacy of this intervention. Of note, sub-group analysis and meta-regression indicated that it would be futile to administer an intrathecal dose of morphine greater than 100 μg as there does not appear to be additional analgesic benefits at 8–12 postoperative hours.

However, intrathecal morphine was associated with an increased risk of PONV, worse pruritus and more urinary retention, but without impact on hospital length of stay. Notwithstanding, our sub-group analyses concluded that there was a dose threshold of 100 μg, above which the rate of PONV statistically increased, with an absolute risk of 12%. This increased risk of PONV was greater in the absence of reported prescribing of postoperative multimodal analgesia. Of note, none of the included patients received i.v. dexamethasone, which has been reported to decrease PONV secondary to intrathecal long-acting opioids from 54% down to 22% [57].

When synthesising the findings of both our primary outcomes, it is apparent that a dose of up to 100 μg

 

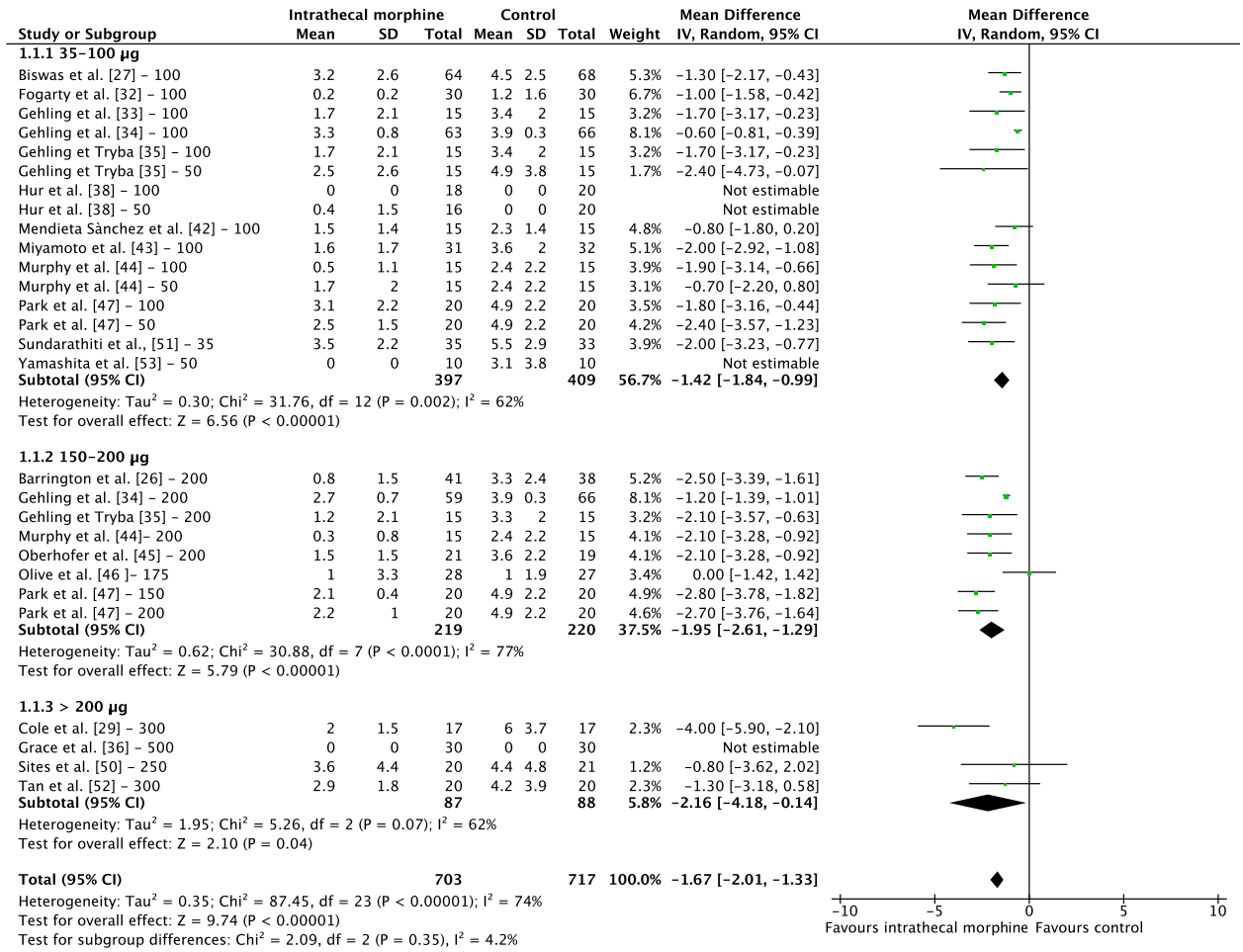


**Figure 2** Sub-group analyses for resting pain score at 8–12 postoperative hours in patients undergoing lower joint arthroplasty by intrathecal dose of morphine.

provides optimal analgesia without increasing the rate of PONV. We recommend an intrathecal dose of 100 µg for improving patient comfort without increasing the risk of PONV.

One particular area worthy of discussion is the posited risk of postoperative hypoventilation. Even if more patients demonstrated a greater degree of sedation in the intrathecal morphine group, there was no effect on the rates of hypoxaemia or respiratory depression. This is important, as many physicians believe that continuous monitoring is necessary, following recommendations from the American Society of Anesthesiologists [58]. While respiratory depression might have been a clinical problem with intrathecal morphine doses of 2.5 mg, as reported in the late 1980s [59], recent evidence highlights the absence of respiratory depression with doses below 150 µg [60,61], even in older people undergoing hip arthroplasty [25]. Thus, an intrathecal morphine dose of 100 µg for lower limb arthroplasty seems to warrant no more than standard postoperative care.

Several weaknesses hamper this meta-analysis. First, our sub-group analyses could only partly explain the elevated coefficient of heterogeneity. Second, we only focused on morphine, while other long-acting opioids might also be administered intrathecally such as diamorphine, meperidine or hydromorphone. The analgesic and safety dynamics of these drugs could potentially vary from morphine, and thus uncertainty exists in optimal dosing regimens for other hydrophilic opioids. Third, we did not examine pain scores on movement, as we expected these to be inconsistently reported, and the definitions of movement vary. Fourth, functional outcomes and quality of recovery scores were not examined in this meta-analysis, and this remains an important avenue of future investigation. Finally, we did not examine

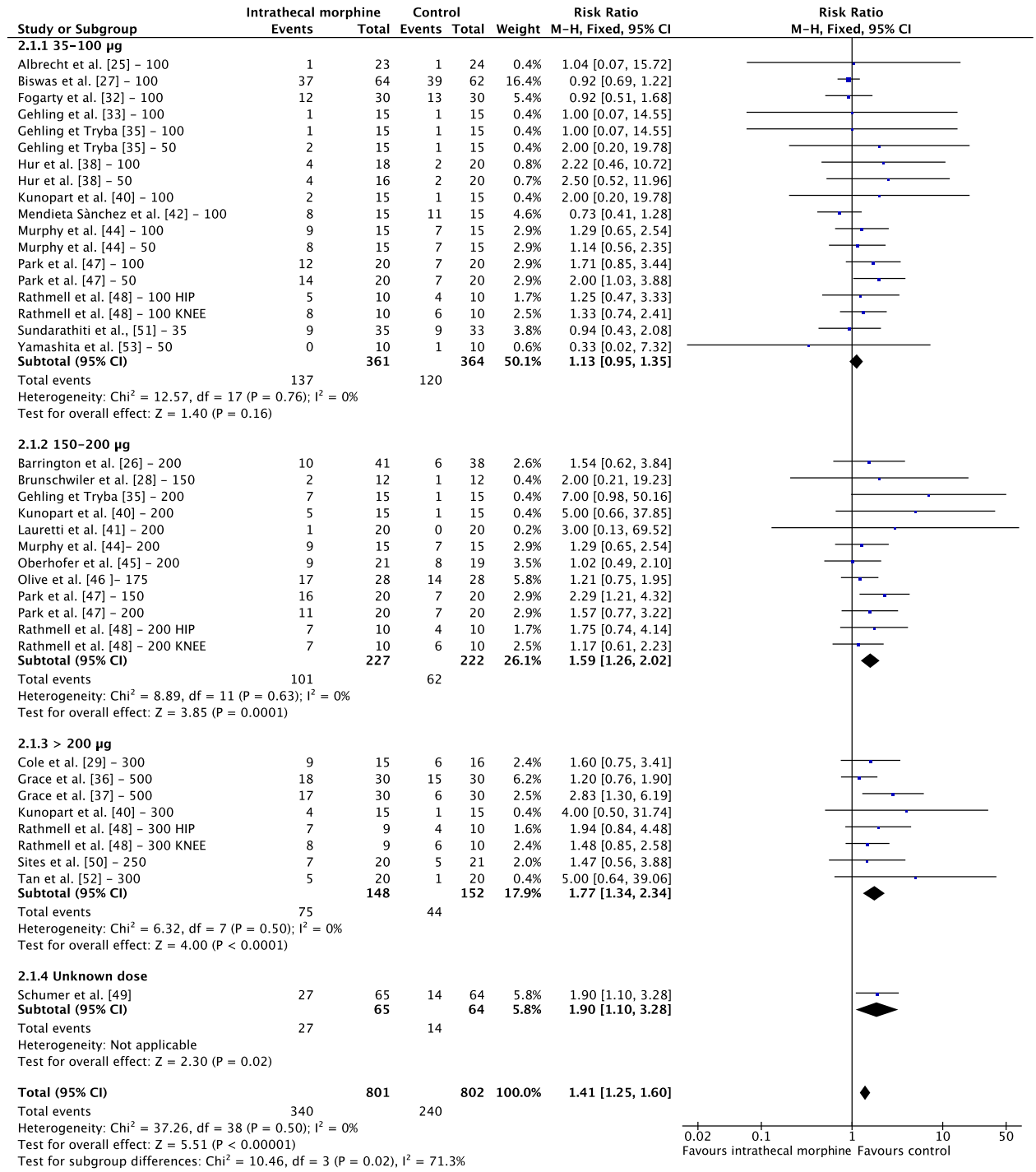


**Figure 3** Sub-group analyses for postoperative nausea and vomiting within 24 postoperative hours in patients undergoing lower joint arthroplasty by intrathecal dose of morphine.

the role of intrathecal morphine in ankle arthroplasty surgery, which warrants independent consideration.

In conclusion, there is high-level evidence that intrathecal morphine provides analgesia after lower limb arthroplasty, but at the expense of an increased profile of side-effects. However, a dose of 100 µg represents a 'ceiling' dose for analgesia and a threshold dose for increased rate of PONV.

 

**Table 2** Secondary pain-related postoperative outcomes.

| Outcome | Number of trials | Studies | Total number of patients | | Mean difference (95%CI) | $I^2$% | p value |
|---|---|---|---|---|---|---|---|
| | | | Morphine | Control | | | |
| Rest pain score at 0-4 h; analogue scale 0–10 | 16 | [25–27,29,32,34,36–39, 42,44,47,51–53] | 634 | 655 | -1.6 (−1.8 to −1.3) | 86 | <0.0001 |
| Rest pain score at 24 h; analogue scale 0–10 | 21 | [25–27,29–32,34,37,38, 41–47,50–53] | 737 | 753 | -0.6 (−0.9 to −0.3) | 85 | <0.0001 |
| i.v. morphine equivalent consumption at 0–4 h; mg | 7 | [25,32,40,42,46,48,50] | 219 | 222 | -5.5 (−8.1 to −2.8) | 91 | <0.0001 |
| i.v. morphine equivalent consumption at 8–12 h; mg | 8 | [27,32,39,40,42,46,48,50] | 277 | 286 | -10.9 (−15.1 to −6.8) | 83 | <0.0001 |
| i.v. morphine equivalent consumption at 24 h; mg | 18 | [25,27,29–33,35–37, 40–42,44–46,48,50] | 560 | 558 | -9.5 (−11.8 to −7.1) | 87 | <0.0001 |
| Duration of analgesia; h | 7 | [33,35–38,44,45] | 220 | 224 | 8.8 (6.2–11.4) | 87 | <0.0001 |

i.v., intravenous.

**Table 3** Side-effects reported in included studies. Values are number or risk ratio (95%CI).

| Outcome | Number of trials | References | Total number of patients | | Risk ratio (95%CI) | $I^2$% | p value |
|---|---|---|---|---|---|---|---|
| | | | Morphine | Control | | | |
| Pruritus | 24 | [25–29,31–33,35–38,40–42,44–50,52,53] | 272/782 | 55/782 | 4.4 (3.4–5.6) | 12 | < 0.0001 |
| Urinary retention | 10 | [27,30,33,35,38,41–44,49] | 76/353 | 54/358 | 1.4 (1.1–1.8) | 21 | 0.02 |
| Hypoxaemia | 6 | [29,44,48–50,53] | 45/215 | 33/215 | 1.4 (1.0–2.0) | 0 | 0.07 |
| Respiratory depression | 16 | [29,30,33–38,40,42–45,47,52,53] | 15/580 | 16/593 | 0.9 (0.5–1.7) | 0 | 0.78 |
| Sedation | 10 | [27,33,35,38,40,42,44,45,47,50] | 55/384 | 33/387 | 1.6 (1.1–2.3) | 20 | 0.009 |

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## Supporting Information

Additional supporting information may be found online via the journal website.

**Fig S1.** PRISMA flow diagram showing literature search results.

**Fig S2.** Meta-regression for rest pain score at 8–12 postoperative hours according to the dose of intrathecal morphine.

**Fig S3.** Trial sequential analysis for rest pain score at 8–12 postoperative hours.

**Fig S4.** Meta-regression for postoperative nausea and vomiting according to the dose of intrathecal morphine.

**Fig S5.** Trial sequential analysis for postoperative nausea and vomiting within 24 postoperative hours.

**Table S1.** Quality of evidence assessment for each outcome sought.

**Appendix S1.** Details of the literature search strategy.