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Review Article

Efficacy and safety of intrathecal diamorphine: a systematic review and meta-analysis with meta-regression and trial sequential analysis

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Summary

Background Intrathecal diamorphine is believed to provide postoperative analgesia but is associated with adverse effects such as nausea and vomiting. There is little evidence of synthesis regarding intrathecal diamorphine in the contemporary literature. We performed a systematic review, meta-analysis with meta-regression and trial sequential analysis to determine the magnitude of intrathecal diamorphine efficacy and safety.

Methods We systematically searched the literature for trials comparing intrathecal diamorphine with a control group in patients undergoing all types of surgery. The primary efficacy and safety outcomes were intravenous morphine consumption and incidence of postoperative nausea and vomiting at 24 h following surgery, respectively.

Results Twelve trials were identified, which included data for 712 patients. Intrathecal doses of diamorphine ranged from 100 μg to 2500 μg. Intravenous morphine consumption at 24 h postoperatively was significantly reduced in the intrathecal diamorphine group, with a mean difference (95%CI) of -8 mg (-11 to -6), I^2 = 93%, $p < 0.001$. There was a significant difference between three intrathecal diamorphine dosing subgroups but without correlation: mean differences (95%CI) -1 mg (-3–0), -26 mg (-40 to -11) and -6 mg (-15–4) in patients receiving doses of 0–200 μg, 201–400 μg and > 400 μg, respectively ($p = 0.003$). Intrathecal diamorphine increased postoperative nausea and vomiting with a risk ratio (95%CI) of 1.37 (1.19–1.58), I^2 = 7%, $p < 0.001$. There were no differences in postoperative nausea and vomiting between the three intrathecal diamorphine dosing subgroups. There was no correlation observed with meta-regression of the primary efficacy and safety outcomes. The quality of evidence for all outcomes was very low.

Conclusion There is very low level of evidence that intrathecal diamorphine provides effective analgesia after surgery, while increasing postoperative nausea and vomiting with doses > 200 μg.

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Introduction

Neuraxial administration of hydrophilic opioids, such as morphine, hydromorphone and diamorphine, provides pain relief after surgery [1]. Diamorphine use is limited globally, but evidence suggests it remains widely used in the UK, accounting for nearly 90% of intrathecal opioid use [2]. Intrathecal diamorphine is recommended as standard practice in obstetric settings by the National Institute for Health and Care Excellence in the UK [3].

The evidence base for intrathecal morphine is more developed than diamorphine [4]; thus, clinicians often infer this evidence to apply to both drugs. Although previous studies suggested analgesic comparability [5], the pharmacokinetics and dynamics of these drugs vary. Moreover, there has been no contemporary synthesis of the evidence of the analgesic efficacy and safety of intrathecal diamorphine, with only dated clinical trials used to support its use [6].

We aimed to determine the magnitude of intrathecal diamorphine efficacy and safety by performing a systematic review and meta-analysis, with meta-regression and trial sequential analysis.

Methods

This study followed the PRISMA statement and the protocol was registered [7]. Searches were performed in Ovid Medline, Embase and the Cochrane Central Register of Controlled Clinical Trials from inception to 4 May 2023. There were no language restrictions. Supplemental searches were carried out on clinicaltrials.gov and Google Scholar (limited to the first 200 results). Search strategies (see online Supporting Information Appendix S1) were peer-reviewed by a second investigator and reported using the peer review of electronic search strategies (PRESS) checklist [8]. References were imported into EndNote™ 20 software (Clarivate™, London, UK) and deduplicated with Deduklick (Risklick AG, Bern, Switzerland) [9]. References of retrieved articles were assessed for potentially relevant clinical trials. The inclusion criteria were prospective, randomised controlled trials of adult patients undergoing any type of surgery under general or spinal anaesthesia, where intrathecal diamorphine was compared with a control. Data extraction was performed as described previously [10–12]. Trial characteristics extracted included: diamorphine dose; type of surgery; primary anaesthesia (general vs. spinal); and postoperative analgesic strategy. The primary efficacy outcome was intravenous morphine consumption at 24 h postoperatively. The primary safety outcome was the rate of nausea and vomiting within the first 24 h after surgery. Secondary analgesic outcomes included: at rest and dynamic pain scores at 0–2 h, 8–12 h and 24 h postoperatively; intravenous morphine consumption at 0–4 h and 8–12 h postoperatively; and duration of analgesia, defined as time to first pain reported, or if not reported, time to first analgesic request. Adverse effects sought were the incidence at 24 h postoperatively of: pruritus; urinary retention; sedation; respiratory depression; and hypoxaemia. Data were extracted from manuscript text, tables or images including number of participants; number of events; means; standard deviations; standard error of means; and 95%CI. Data presented graphically were extracted with plot digitising software (Plot Digitizer Version 2.1, Free Software Foundation, Boston, MA, USA). Where studies did not present sufficient data to allow synthesis, corresponding authors were emailed twice requesting access to the relevant data or the complete dataset. Where mean and SD were not reported, median and IQR were used as approximations 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. All opioids were converted to equianalgesic intravenous morphine doses. Intravenous morphine 10 mg was determined to be equivalent to oral morphine 30 mg; intravenous tramadol 100 mg; intravenous pethidine 75 mg; intravenous fentanyl 100 μg; intravenous nalbuphine 10 mg; oral hydrocodone 30 mg; oral codeine 165 mg; and systemic diamorphine 90 mg [13]. When pain scores were reported with an 11-unit graduation verbal, visual or numeric rating scale, results were transposed to a 0–10 analogue scale to allow synthesis. The GRADE system was used for each outcome to assess quality of evidence [14]. Methodological quality of included trials was assessed using the Cochrane Collaboration's Risk of Bias tool 2 [15]. Two authors (SG, EA) independently screened, evaluated and scored each trial, with disagreements settled by a third author (KE).

Meta-analyses were performed using RevMan 5.4.1 (The Nordic Cochrane Centre, The Cochrane Collaboration 2020, Copenhagen, Denmark). We estimated weighted mean differences for continuous data and risk ratios 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 to determine heterogeneity, setting predetermined limits for low (< 50%); moderate (50–74%); and high (> 75%) [16]. We used a random-effects model when moderate or high heterogeneity was observed, otherwise, a fixed-effects model was used [17]. To account for potential causes of heterogeneity, we performed subgroup analyses for primary outcomes according to the dose of intrathecal diamorphine (0–

200 μg, 201–400 μg or > 400 μg); type of surgery (caesarean section vs. other); and the use of multimodal analgesia, defined as prescribing at least two different analgesic modalities (dichotomised to yes or no). Risk of publication bias associated with our two primary outcomes was estimated by drawing a funnel plot of the standard error of the mean difference of intravenous morphine consumption at 24 h postoperatively and the rate of postoperative nausea and vomiting on the y-axis as a function of mean difference of intravenous morphine consumption at 24 h following surgery and risk ratio of postoperative nausea and vomiting on the x-axis. This was then confirmed with Duval and Tweedie's trim and fill test [18]. This assessment was performed using Comprehensive Meta-analysis version 2 (Biostat, Englewood, NJ, USA). Interactions between dose of neuraxial diamorphine and mean difference in intravenous morphine consumption at 24 h postoperatively, or the risk ratio of postoperative

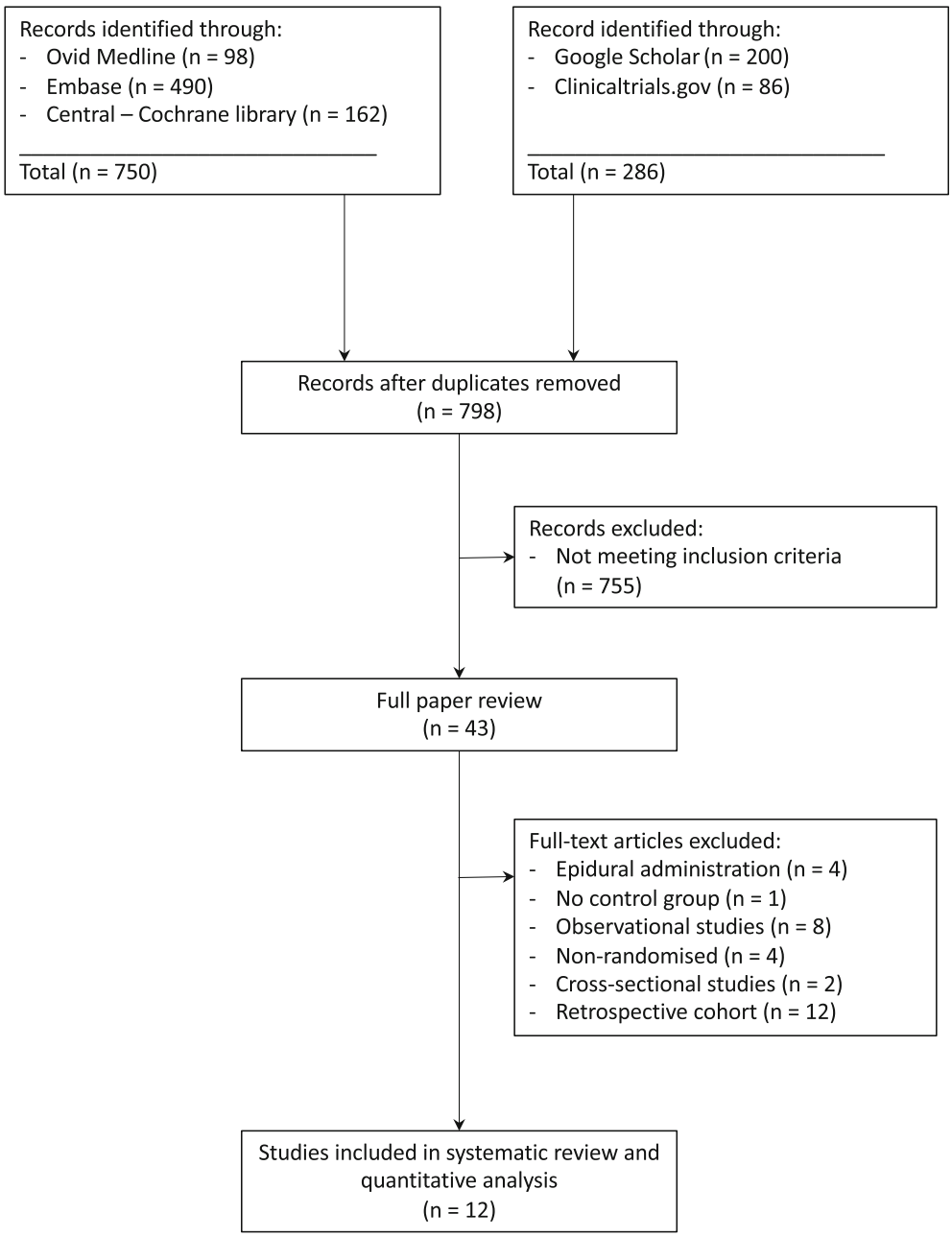

Figure 1 Study flow diagram showing literature search results.

nausea and vomiting within 24 h were investigated with meta-regression using the JMP 17 statistical package (SAS Institute, Cary, NC, USA). We then performed trial sequential analysis for the 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). Results are reported as mean difference or relative risk (RR) with 95%CI and a two-sided p-value < 0.05 was set to be significant.

Results

Of the 798 studies identified, 12 trials met inclusion criteria [6, 19–29], including a total of 712 patients (Fig. 1). Risk of bias is summarised in Fig. 2. No authors needed to be contacted for missing data. Characteristics of the included trials are reported in Table 1. Eight trials included patients undergoing caesarean section [20–24, 27–29], three were for hip or knee arthroplasty [6, 25, 26] and one included different types of surgery [19]. All surgery was performed under spinal anaesthesia. Intrathecal doses of diamorphine ranged from 100 µg [27–29] to 2500 µg [6]. Multimodal analgesia was prescribed in four studies [21, 23, 24, 29].

Morphine consumption 24 h postoperatively was significantly reduced in patients receiving diamorphine compared with control, with a mean difference (95%CI) of -8 mg (-11 to -6), I^2 = 93%, p < 0.001 (Fig. 3). There was a significant difference between three intrathecal diamorphine dosing subgroups but without correlation: mean differences (95%CI) -1 mg (-3–0); -26 mg (-40 to -11); and -6 mg (-15–4) in patients receiving doses of 0–200 µg, 201–400 µg and > 400 µg, respectively (p = 0.003). Meta-regression confirmed the absence of correlation between doses and mean differences in pain scores (r^2 = 0.14, p = 0.13, see online Supporting Information Figure S1). Subgroup analysis according to the type of surgery showed a mean difference of -9 mg (-12 to -7), I^2 = 94%, p < 0.001 for patients undergoing caesarean section and the mean difference (95%CI) for all other types of surgery was -5 mg (-12–3), I^2 = 78%, p = 0.22. A difference between subgroups was not seen (p = 0.27). Subgroup analysis according to the use of multimodal analgesia revealed a significant difference (p = 0.0006). The subgroup receiving multimodal analgesia demonstrated a mean difference (95%CI) of -2 mg (-3–0), I^2 = 91%, p = 0.04, while the mean difference in the subgroup who did not receive multimodal analgesia was -18 mg (-27 to -9), I^2 = 89%, p < 0.001. Trial sequential analysis indicated that firm evidence was reached (see online Supporting Information Figure S2). When assessing publication bias with Duval and Tweedie's trim and fill test, combined studies point estimate (95%CI) to be -1.00 (-1.30 to -0.71) with a random-effects model. Using trim and fill, these values are unchanged.

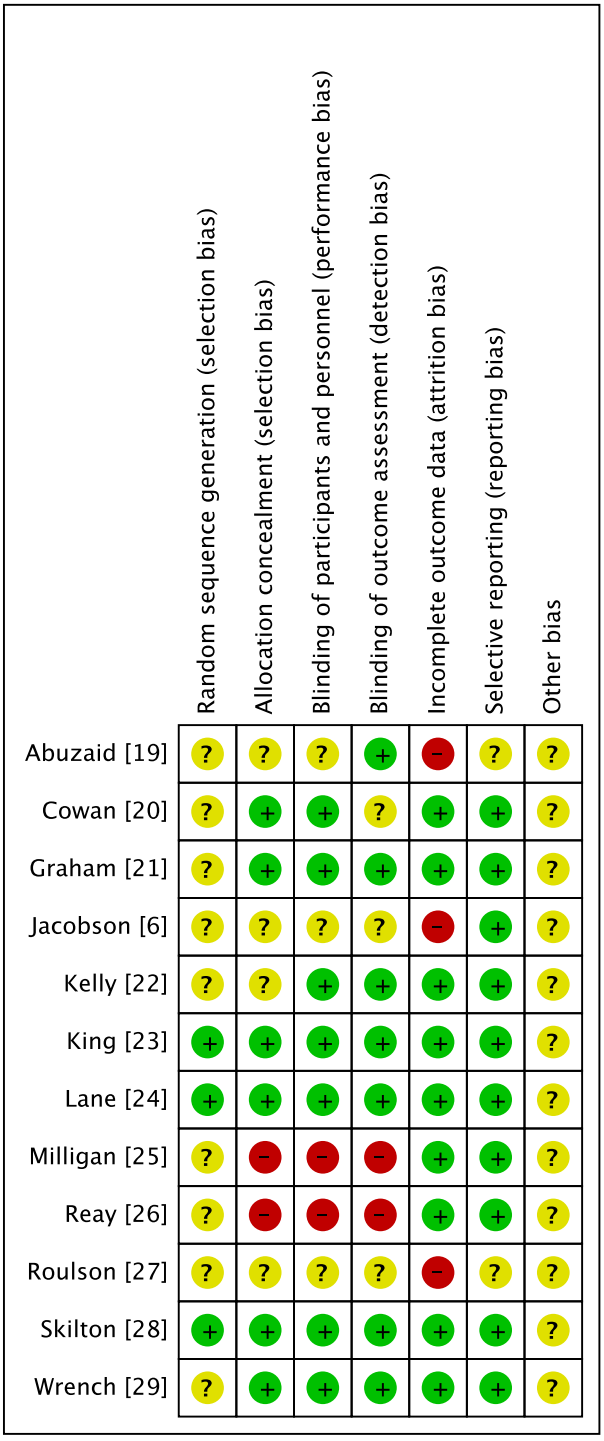

Figure 2 Cochrane Collaboration Risk of Bias 2 evaluation for the included studies. Green circle, low risk of bias; red circle, high risk of bias; yellow circle, unclear risk of bias.

Other than 24 h postoperative at rest and dynamic pain scores, all secondary pain-related outcomes were significantly reduced in patients receiving intrathecal diamorphine (Table 2). The incidence of 24-h postoperative nausea and vomiting was significantly increased in the diamorphine group, with a risk ratio (95%CI) of 1.37 (1.19–1.58), I^2 = 7%, p < 0.001 (Fig. 4). There were no differences shown on subgroup analysis for different intrathecal doses (p = 0.13) or different types of surgery (p = 0.48). However, there was a subgroup difference based on the use of multimodal analgesia (p = 0.003), where the risk ratio (95% CI) was 1.08 (0.9–1.30), I^2 = 52%, p = 0.39 in patients who received multimodal analgesia compared with 1.66 (1.34–2.05), I^2 = 0%, p < 0.001 in those who did not.

Table 1 Characteristics of included studies comparing the use of spinal anaesthesia plus intrathecal diamorphine with control.

Reference	Diamorphine dose and group size (n)	Surgical intervention	Postoperative analgesia
Abuzaid [19]	Control (30) Diamorphine 1000 μg (30)	Miscellaneous	Paracetamol, intramuscular papaveretum or oral dextropropoxyphene
Cowan [20]	Control (25) Diamorphine 300 μg (25)	Caesarean section	Intravenous morphine PCA
Graham [21]	Control (20) Diamorphine 300 μg (19)	Caesarean section	Paracetamol, NSAID, intravenous morphine PCA
Jacobson [6]	Control (7) Diamorphine 250 μg (7) Diamorphine 750 μg (7) Diamorphine 1500 μg (7) Diamorphine 2500 μg (7)	Total knee replacement	Intramuscular morphine on demand
Kelly [22]	Control (20) Diamorphine 125 μg (19) Diamorphine 250 μg (20) Diamorphine 375 μg (19)	Caesarean section	Intravenous morphine PCA
King [23]	Control (19) Diamorphine 300 μg (19)	Caesarean section	Paracetamol, NSAID, intravenous morphine PCA
Lane [24]	Control (32) Diamorphine 250 μg (32)	Caesarean section	Paracetamol, NSAID, intravenous morphine PCA
Milligan [25]	Control (30) Diamorphine 750–1000 μg (30)	Total hip replacement	Intravenous morphine PCA
Reay [26]	Control (20) Diamorphine 250 μg (20) Diamorphine 500 μg (20)	Total hip/knee replacement	Intramuscular diamorphine
Roulson [27]	Control (20) Diamorphine 100 μg (16) Diamorphine 200 μg (21) Diamorphine 300 μg (21)	Caesarean section	Not specified
Skilton [28]	Control (10) Diamorphine 100 μg (10) Diamorphine 200 μg (10) Diamorphine 300 μg (10)	Caesarean section	Intravenous morphine PCA
Wrench [29]	Control (26) Diamorphine 100 μg (29) Diamorphine 200 μg (27) Diamorphine 300 μg (28)	Caesarean section	Paracetamol, NSAID, subcutaneous diamorphine

PCA, patient-controlled analgesia; NSAID, non-steroidal anti-inflammatory drugs.

Meta-regression showed the absence of correlation between postoperative nausea and vomiting and dose of intrathecal diamorphine (r^2 = 0.04, p = 0.38, see online Supporting Information Figure S3). Trial sequential analysis indicated that firm evidence was reached (see online Supporting Information Figure S4). With respect to the risk of publication bias, Duval and Tweedie's trim and fill test calculated the combined studies point estimate (95%CI) to be 2.12 (1.44–3.13) with a random-effects model. Using trim and fill, the imputed point estimate is 1.55 (1.02–2.36), suggesting that eight studies are missing. Except for pruritus, the incidence of other postoperative adverse effects at 24 h was similar between groups (Table 3).

According to the GRADE system, the quality of evidence was very low for both the primary and secondary outcomes (see online Supporting Information Table S1).

Discussion

This systematic review and meta-analysis with meta-regression and trial sequential analysis aimed to determine the magnitude of intrathecal diamorphine efficacy and safety. Based on data from 12 trials and 712 patients, we conclude that there is a very low level of evidence that intrathecal diamorphine reduced: 0–4 h, 8–12 h and 24 h postoperative intravenous morphine consumption; 0–4 h postoperative rest and dynamic pain scores; and 8–12 h postoperative pain scores at rest. Intrathecal diamorphine did increase the incidence of postoperative nausea and vomiting and pruritus. Interestingly, while the difference in intravenous morphine consumption at 24 h reached significance for patients undergoing caesarean section, the current evidence does not show any benefit of intrathecal diamorphine for other types of surgery. Moreover, we found no correlation between intrathecal doses and mean difference in 24 h postoperative intravenous morphine consumption or the incidence of nausea and vomiting at 24 h following surgery. This could reflect the limited number of trials found: 12 studies over a 35-year period reporting the outcomes of interest. Of note, the absence of analgesic efficacy with doses above 400 µg could be due to a type 2 error as only two trials included patients in this subgroup. Regarding the incidence of 24 h postoperative nausea and vomiting, our data suggest this adverse effect occurs with doses above 200 µg. Based on these two findings, the existing data suggests that an intrathecal diamorphine dose of 200 µg

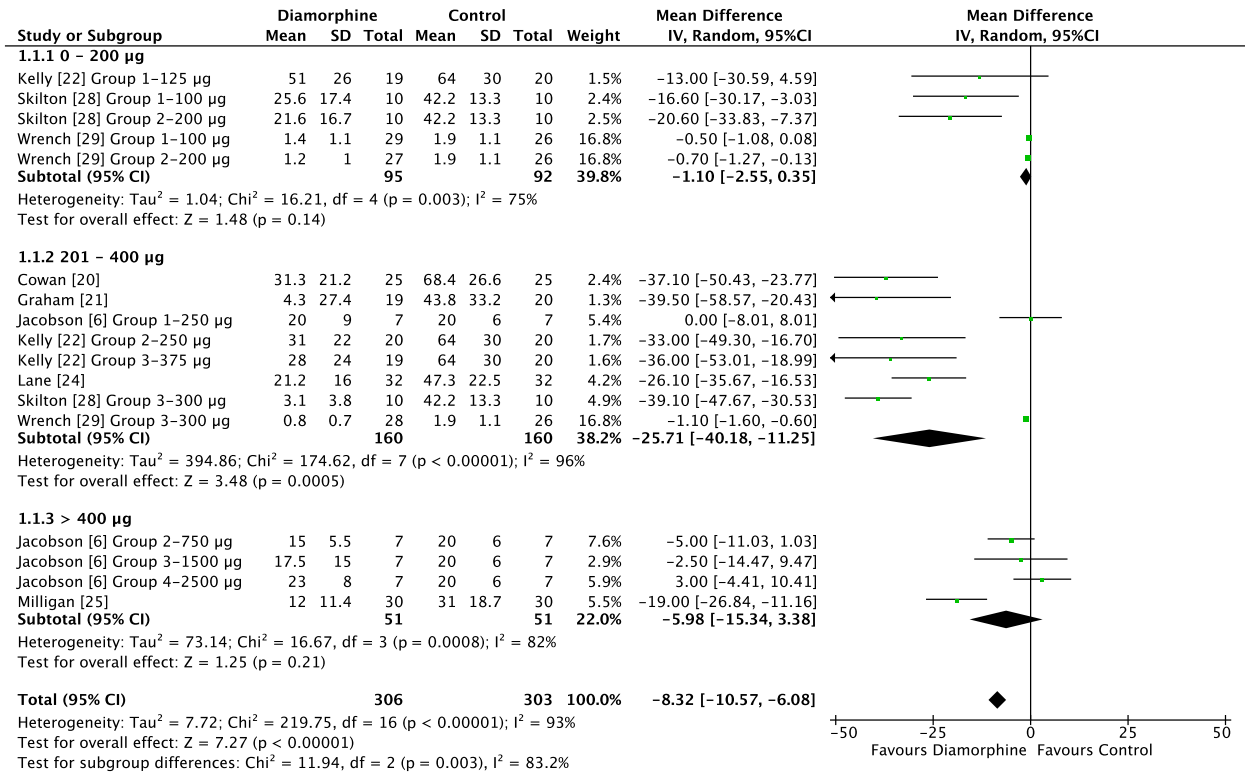

Figure 3 Intravenous morphine consumption 24 h postoperatively according to the dose of intrathecal diamorphine (0–200 µg, 201–400 µg or > 400 µg).

Table 2 Secondary pain-related outcomes.

Outcome	Number of trials	Studies	Number of patients		Mean difference (95%CI)	I^2	p value for overall effect
			Diamorphine	Control			
0–4 h postoperative pain at rest; analogue scale 0–10	5	Cowan [20], Graham [21], Kelly [22], Milligan [25], Wrench [29]	216	213	-1.34 (-2.1 to -0.6)	70%	< 0.001
8–12 h postoperative pain at rest; analogue scale 0–10	3	Cowan [20], Graham [21], Milligan [25]	74	75	-0.9 (-1.4 to -0.3)	0%	0.001
24 h postoperative pain at rest; analogue scale 0–10	5	Cowan [20], Graham [21], Kelly [22], Milligan [25], Wrench [29]	216	213	-0.4 (-0.7–0.04)	65%	0.08
0–4 h postoperative dynamic pain; analogue scale 0–10	1	Wrench [29]	84	78	-3.0 (-4.0 to -2.0)	53%	< 0.001
24 h postoperative dynamic pain; analogue scale 0–10	1	Wrench [29]	84	78	0.5 (-0.2–1.1)	43%	0.17
0–4 h postoperative intravenous morphine consumption; mg	6	Cowan [20], Graham [21], Kelly [22], King [23], Lane [24], Skilton [28]	183	186	-6 (-8 to -3)	89%	< 0.001
Intravenous morphine consumption at 8–12 postoperative hours; mg	4	Cowan [20], Graham [21], Lane [24], Skilton [28]	106	107	-21 (-24 to -17)	29%	< 0.001
Duration of analgesia; min	7	Graham [21], Jacobson [6], Kelly [22], Milligan [25], Reay [26], Skilton [28], Wrench [29]	289	286	142 (94–189)	88%	< 0.001

might provide the greatest balance of safety and efficacy, albeit the level of evidence is very low.

Only two trials investigated sedation, one evaluated hypoxaemia and six recorded respiratory depression. Therefore, it is not possible to draw meaningful conclusions regarding the respiratory profile of intrathecal diamorphine in the first 24 h postoperatively. As such, we would advocate caution with respect to intrathecal administration, until more dose–response trials are published to better specify the efficacy and safety profile of intrathecal diamorphine in contemporary practice.

The data found appear to be most relevant to patients having caesarean section. However, it is notable that these studies are less contemporary than would have been hoped, particularly given the scale of intrathecal diamorphine use in some countries. For example, the most recent study included was published in 2007. Since then, postoperative analgesia has benefitted from a number of advancements, including more established understanding of the role of multimodal analgesia [30]; enhanced recovery [31]; and regional anaesthesia [32]. Thus, continued use of diamorphine should be in parallel with contemporary clinical trial data, or alternatively, the use of intrathecal morphine may be more appropriate given the robust recency in the evidence base. The current practice of inferring outcomes from diamorphine based on evidence from morphine might not be appropriate.

This study has some limitations. We intended to evaluate secondary pain-related outcomes such as 8–12 h postoperative dynamic pain scores, but these were not reported by any of the included trials. We encourage researchers, when investigating intrathecal diamorphine, to include relevant secondary pain-related outcomes, such as those reported by a recent core outcome set for regional anaesthesia [33]. We changed our initial primary outcome from 8 to 12 h postoperative pain scores at rest to 24 h postoperative intravenous morphine consumption, as only three trials captured our predefined primary outcome. However, we do not believe this limitation lessens the validity of our conclusions. Three included trials did not use intravenous morphine patient-controlled analgesia for postoperative pain, instead prescribing intramuscular

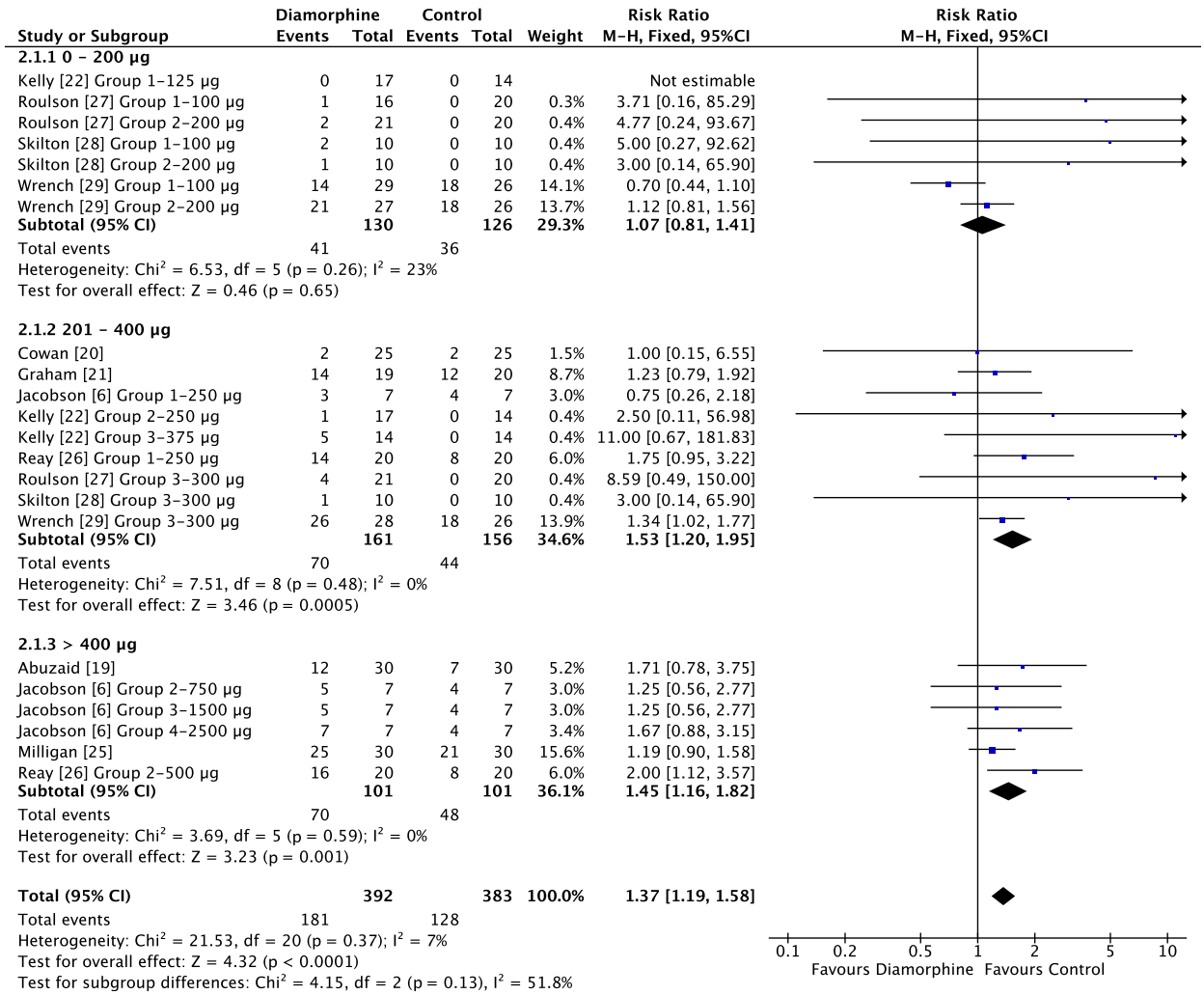

Figure 4 Nausea and vomiting with 24 h postoperatively according to the dose of intrathecal diamorphine (0–200 µg, 201–400 µg or > 400 µg).

Table 3 Adverse effects reported 24 h postoperatively. Values are number (proportion), risk ratio (95%CI) or proportion.

Outcome	Number of trials	References	Number of patients		Risk ratio (95%CI)	I^2	p value for overall effect
			Diamorphine	Control			
Pruritus	9	Abuzaid [19], Cowan [20], Graham [21], Jacobson [2], Kelly [22], Milligan [25], Reay [26], Skilton [28], Wrench 2007 [29]	182 (52.9%)	90 (26.4%)	2.0 (1.6–2.4)	23%	< 0.001
Urinary retention	4	Graham [21], Jacobson [2], Milligan [25], Reay [26]	44 (37.6%)	34 (28.8%)	1.3 (0.9–1.9)	0%	0.15
Sedation	2	Cowan [20], Milligan [25]	17 (30.9%)	16 (29.1%)	1.1 (0.7–1.7)	N/A	0.80
Respiratory depression	6	Cowan [20], Graham [21], Jacobson [2], Kelly [22], Milligan [25], Reay [26]	2.0 (1%)	4 (2.0%)	0.6 (0.2–2.2)	0%	0.48
Hypoxaemia	1	Milligan [25]	0	0	N/A	N/A	N/A

N/A, not applicable.

morphine on demand [6], subcutaneous diamorphine [29] or intramuscular papaveretum [19], and one trial did not specify postoperative opioid use [27]. These different routes of administration and drugs may have impacted overall opioid consumption and secondary outcomes. Finally, we did not compare the efficacy or safety of diamorphine with other hydrophilic intrathecal opioids, and thus these results only apply to diamorphine compared with control.

In conclusion, there is very low level of evidence that intrathecal diamorphine provides effective analgesia after surgery, while increasing postoperative nausea and vomiting with doses above 200 μg. With only 12 trials published over 35 years, more dose–response trials are needed to better specify the efficacy and safety profiles of intrathecal diamorphine.

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Supporting Information

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

Appendix S1. Literature search strategy.

Figure S1. Meta-regression for 24 h postoperative morphine consumption according to the dose of intrathecal diamorphine.

Figure S2. Trial sequential analysis for 24 h postoperative intravenous morphine consumption.

Figure S3. Meta-regression for postoperative nausea and vomiting according to the dose of intrathecal diamorphine.

Figure S4. Trial sequential analysis for incidence of 24 h postoperative nausea and vomiting.

Table S1. Quality of evidence assessment for each outcome.