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Review Article

Pulmonary complications after intrathecal morphine administration: a systematic review and meta-analysis with meta-regression and trial sequential analysis

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Summary

Introduction Intrathecal morphine provides effective postoperative analgesia, but there are concerns about potential pulmonary complications influencing peri-operative management. We aimed to determine whether there is an association between intrathecal morphine administration and pulmonary complications after non-obstetric surgery. We also aimed to determine whether there was a dose-dependent effect on pulmonary complications.

Methods We searched the literature systematically for randomised controlled trials comparing intrathecal morphine vs. control in patients undergoing any type of non-obstetric surgery under general or spinal anaesthesia. Primary outcomes were rates of postoperative sedation, respiratory depression and hypoxaemia. We performed a meta-analysis and meta-regression for each of our outcomes of interest and conducted trial sequential analysis to assess whether the required information size was achieved.

Results We included 127 trials (7388 patients). Rates of sedation and hypoxaemia were not increased significantly in patients receiving intrathecal morphine (odds ratio 1.00, 95%CI 0.78–1.28, p = 0.98, moderate quality evidence; and 1.22, 95%CI 0.84–1.79, p = 0.30, moderate quality evidence, respectively). There were more episodes of respiratory depression in patients receiving intrathecal morphine than control (odds ratio 1.78, 95%CI 1.19–2.67, p = 0.005, very low-quality evidence), which was no longer significant when morphine doses > 500 μg were not included (odds ratio1.49, 95%CI 0.99–2.23, p = 0.06). Meta-regression revealed associations between dose and rate of sedation, respiratory depression and hypoxaemia, but when doses of > 500 μg were not included, these associations did not persist. Trial sequential analyses suggest that further data may still be required for all outcomes, but statistical significance was reached for respiratory depression.

Discussion There is moderate evidence that intrathecal morphine does not increase rates of sedation or hypoxaemia after non-obstetric surgery. There is very low-quality evidence that intrathecal morphine might increase the rate of respiratory depression.

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Introduction

Intrathecal morphine has a long history of peri-operative use in a wide range of surgical settings [1, 2]. The favourable efficacy profile achieved with this single-injection technique includes reduced pain; decreased analgesic requirement; improved quality of spinal anaesthesia; and improved mobilisation after surgery [3]. This has led to generalised implementation of this modality, particularly in lower limb arthroplasty [4] and abdominal surgery settings [5].

Despite the well-described benefits, intrathecal morphine is associated with several adverse effects [6] including nausea; vomiting; pruritus; and urinary retention [1, 7]. However, the most significant adverse consequences of intrathecal morphine are pulmonary complications such as sedation; respiratory depression; and hypoxaemia [8, 9], the incidences of which are variable and multifactorial [10, 11]. It also remains unclear if there are any dose-dependent respiratory consequences of intrathecal morphine. This uncertainty has led to significant variations in clinical practice, particularly with respect to postoperative monitoring. Peri-operative management ranges from no additional monitoring following administration to admission to a high-dependency unit bed [12–14]. Thus, synthesising the literature is an important step to standardise practice with such significant resource implications.

We performed a systematic review and meta-analysis with meta-regression aiming to assess any association between doses of intrathecal morphine and rates of pulmonary complications after all types of non-obstetric surgery. We also aimed to define any potential threshold dose for each of the above-mentioned pulmonary complications.

Methods

This study was conducted according to PRISMA guidelines [15]. A medical librarian searched MEDLINE, Embase, Cochrane Central Register of Controlled Clinical Trials, Wiley, clinicaltrials.gov and Google Scholar (search limited to the first 300 results) on 4 May 2023 (online Supporting Information Appendix S1). The searches were reviewed by another medical librarian in accordance with the peer review of electronic search strategies checklist [16]. No language or date limits were placed on the search. References were imported into EndNote™ 20 software (Clarivate™, London, UK) for deduplication. In addition, we examined the references of all retrieved articles for any applicable trials that might not have been captured by the above approach. We sought randomised controlled trials involving adult patients (aged > 18 y) having elective surgery who received intrathecal morphine compared with no intrathecal opioids. To be eligible, trials had to include any of the following outcomes of interest that we defined as primary in our review: sedation; respiratory depression; or hypoxaemia. Additional outcomes recorded were the need for additional oxygen therapy; the need for opioid antagonist administration (because of sedation, respiratory depression or hypoxaemia); or the need for any additional respiratory support or escalated levels of care or mortality.

Following deduplication, title, abstract and full-text screening were performed using Rayyan (Qatar Computing Research Institute, Doha, Qatar) by two independent reviewers, with a third adjudicating in case of disagreement. Data were then extracted into a Microsoft Excel spreadsheet (Microsoft Inc., Redmond, WA, USA), which was piloted before use. Data extracted included study details; patient characteristics; intervention information; and outcomes of interest. Text, tables or images from the source articles were evaluated to extract the number of participants and the number of events. Graphically presented data were extracted with plot digitising software (Plot Digitizer Version 2.1, Free Software Foundation, Boston, MA, USA). Where data were missing, we contacted the corresponding author up to three times by email with a request for access to the relevant data or the complete dataset. In addition, the GRADE system was applied to each outcome to evaluate the quality of evidence [17].

Two authors performed the risk of bias assessment independently with the Cochrane Risk of Bias 2 tool [18]. Meta-analysis was then performed with RevMan 5.4.1 (Nordic Cochrane Center, the Cochrane Collaboration). A meta-analysis was conducted if two or more trials reported the same outcome of interest. The I^2 coefficient was used to assess heterogeneity with predetermined thresholds for low (25–49%); intermediate (50–74%); and high (75%) heterogeneity. A random effects model was used in case of intermediate or high heterogeneity; otherwise, a fixed effects model was used. To account for sources of heterogeneity, subgroup analyses were conducted for our primary outcomes according to the dose of intrathecal morphine (1–100 μg, 101–200 μg, 201–500 μg and > 500 μg); type of surgery (cardiothoracic, abdominal, gynaecological, orthopaedic and spine and other); and the anaesthetic strategy (general vs. spinal anaesthesia). When trials investigated multiple doses of morphine, data from each group were included in the relevant dose category.

We then performed trial sequential analysis for the three outcomes to control type 1 and type 2 errors, which can be affected by analysing data at multiple time-points (TSA software version 0.9.5.10 Beta;

Copenhagen Trial Unit, Copenhagen, Denmark). We calculated the Z-statistic with the DerSimonian and Laird random effects model. We set risks of type 1 and type 2 statistical errors at 5% and 20%, respectively, resulting in a power of 80%. The O'Brien Fleming alpha-spending function was used to adjust the threshold for statistical significance. The required information size was estimated following the incidences in the control and intrathecal morphine groups. The risk of publication bias associated with each of our primary outcomes was estimated by drawing a funnel plot of the rate of complication (y axis) as a function of the odds ratio (OR) of the complication (x-axis) [19]. This was then confirmed with Duval and Tweedie's trim and fill test [20]. This assessment was performed using Comprehensive Meta-analysis version 2 (Biostat, Englewood, NJ, USA).

We explored the potential correlation between the dose of intrathecal morphine and the risk of sedation, respiratory depression and hypoxaemia. For each complication and each study, we computed an OR using Haldane-Anscombe correction in case of zero cells. Due to the positive skewness of these ORs, we considered their logarithm (logOR) and we built regression models with logOR as the outcome and the dose as the predictor [21]. Each study was weighted according to the variance of logOR. We started with linear regression and checked if more complex models using fractional polynomials or restricted cubic splines might improve the goodness of fit [22].

We conducted sensitivity analyses eliminating studies with a high risk of bias; restricting to doses of intrathecal morphine ≤ 500 μg; and both. To assess whether prolonged postoperative ventilation in certain trials, such as those involving cardiac surgery, could represent a confounding factor in the meta-analysis, we also conducted a sensitivity analysis after discounting trials using postoperative mechanical ventilation. These analyses were performed with Stata 18.0 (StataCorp, College Station, TX, USA). A

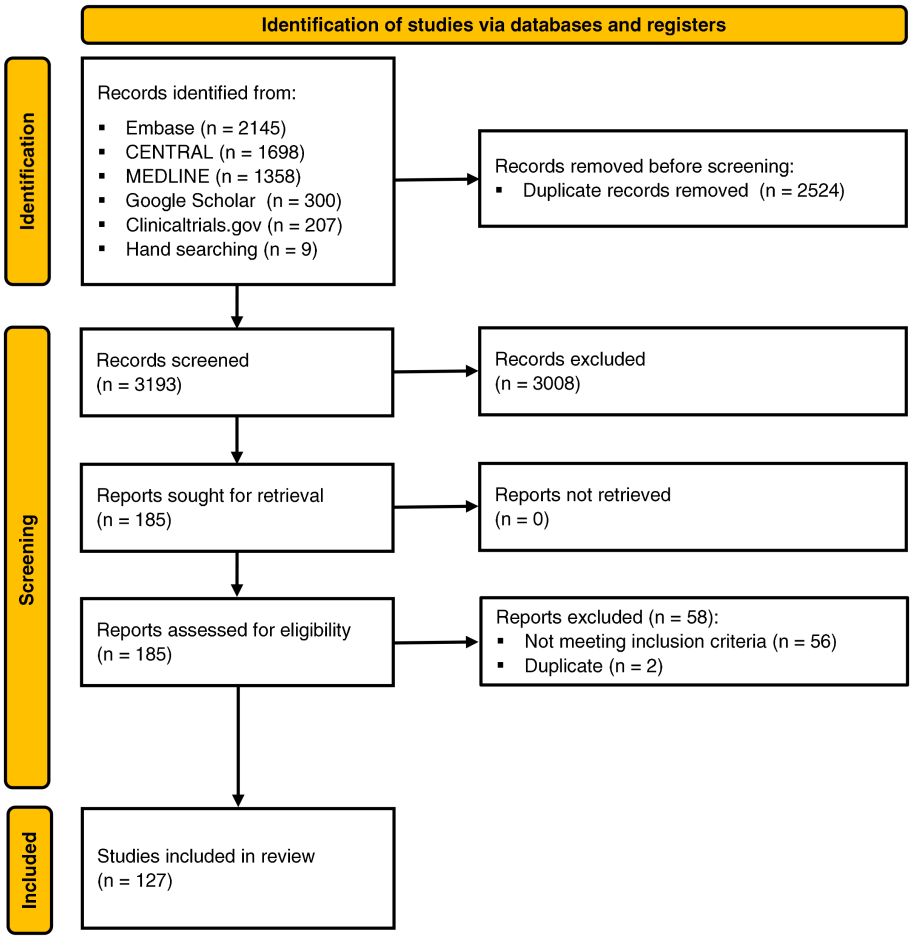

Figure 1 Study flow diagram of literature search results.

Table 1 Sedation reported in included studies investigating intrathecal morphine, analysed according to dose, type of surgery and anaesthetic strategy.

	Number of trials	References	Number of patients		Odds ratio (95%CI)	I^2	p value for overall effects	p value for subgroup differences
			Morphine	Control				
Morphine dose								0.01
1–100 μg	17	[38, 61, 62, 66, 67, 69, 74–76, 81, 88, 90, 92, 102, 106, 113, 114]	46/499	37/456	1.08 (0.65–1.78)	2%	0.77	
101–200 μg	16	[32, 39, 62, 67, 75, 81, 88–90, 92, 106, 109, 113, 114, 117, 139]	50/363	19/341	2.59 (1.49–4.48)	52%	< 0.001	
201–500 μg	17	[31, 34, 40, 51, 58, 75, 78, 82, 84, 88, 95, 97, 104, 117, 126, 128, 129]	110/394	123/402	0.87 (0.62–1.22)	0%	0.42	
501–4000 μg	7	[29, 49, 64, 78, 104, 135, 137]	28/184	19/127	0.91 (0.47–1.75)	0%	0.78	
Surgery								0.30
Cardiothoracic	4	[29, 95, 97, 137]	21/84	22/73	1.00 (0.51–1.98)	0%	0.34	
Abdominal	8	[31, 32, 34, 39, 40, 51, 58, 84]	65/224	75/225	0.79 (0.52–1.22)	2%	0.29	
Gynaecological	4	[74, 75, 82, 92]	47/176	36/97	0.93 (0.52–1.66)	11%	0.80	
Orthopaedic and spinal	22	[38, 61, 62, 64, 66, 67, 76, 78, 88–90, 102, 106, 109, 113, 114, 117, 126, 128, 129, 135, 139]	99/823	48/531	1.38 (0.91–2.11)	30%	0.13	
Other	4	[49, 69, 81, 104]	2/133	0/99	2.35 (0.23–23.75)	0%	0.47	
Anaesthetic strategy								0.33
General anaesthesia	22	[29, 31, 32, 34, 39, 40, 51, 58, 64, 75, 78, 82, 84, 90, 92, 95, 97, 117, 129, 135, 137, 139]	158/719	137/527	0.92 (0.69–1.23)	5%	0.58	
Spinal anaesthesia	30	[38, 49, 61, 62, 66, 67, 69, 74, 76, 81, 88, 89, 102, 104, 106, 109, 113, 114, 126, 128]	76/721	44/498	1.21 (0.76–1.93)	23%	0.42	
Total	42		234/1440	181/1025	1.00 (0.78–1.28)	9%	0.98	

two-sided p value < 0.01 was deemed to be significant to correct for multiple comparisons.

Results

We identified 3193 trials and 127 met the inclusion criteria [23–149] (Fig. 1), including a total of 7388 patients. The risk of bias of included trials is summarised in online Supporting Information Figure S1. Thirty-one authors were contacted [23, 24, 28, 33–35, 39, 41, 52, 58, 59, 62, 63, 68, 74, 75, 77, 81–83, 95, 96, 103, 110, 123, 135, 138, 143, 144, 147, 149] and seven provided additional data [23, 39, 74, 103, 110, 138, 144].

Among the 127 trials of intrathecal morphine, 25 (20%) were performed on patients having cardiothoracic surgery [24, 28, 29, 37, 41, 44–47, 53, 57, 77, 95, 97, 101, 116, 119, 120, 124, 132–134, 136, 137, 143]; 15 (12%) having abdominal surgery [31, 32, 34, 39, 40, 51, 55, 58, 59, 84, 85, 96, 123, 141, 146]; 15 (12%) having gynaecological surgery [25, 35, 43, 65, 70, 74, 75, 82, 83, 87, 92, 121, 122, 125, 145]; and 60 (47%) on patients undergoing orthopaedic and spine surgery [23, 26, 30, 33, 36, 38, 42, 48, 50, 52, 54, 56, 61–64, 66–68, 71–73, 76, 78–80, 88–90, 93, 94, 98–100, 102, 103, 106, 108–111, 113–115, 117, 126–131, 135, 138–140, 142, 144, 147–149] (online Supporting Information Table S1). Twelve (9%) trials assessed patients having other types of surgery [27, 49, 60, 69, 81, 86, 91, 104, 105, 107, 112, 118]. Authors used intrathecal morphine with doses ranging from 35 μg [127] to 4000 μg [29, 45, 124].

Tables 1–3 present rates of sedation, respiratory depression and hypoxaemia after intrathecal morphine

Table 2 Respiratory depression reported in included studies investigating intrathecal morphine, analysed according to dose, type of surgery and anaesthetic strategy.

	Number of trials	References	Number of patients		Odds ratio (95%CI)	I^2	p value for overall effects	p value for subgroup differences
			Morphine	Control				
Morphine dose								0.05
1–100 μg	35	[43, 56, 61, 62, 66–69, 74–76, 81, 85–88, 90, 92, 100, 102, 103, 106, 112–115, 118, 121, 122, 138, 141, 142, 147–149]	12/1014	8/906	1.36 (0.60–3.06)	0%	0.46	
101–200 μg	27	[32, 39, 42, 62, 67, 68, 70, 75, 81, 86, 88–90, 92, 106, 107, 109, 113–115, 117, 122, 125, 137–139, 141]	26/685	8/644	2.68 (1.26–5.73)	0%	0.01	
201–500 μg	35	[24, 26, 27, 31, 34–37, 40, 51, 53, 54, 57, 59, 71, 72, 75, 78, 83, 84, 88, 91, 94, 97, 104, 115–117, 119–121, 128, 129, 136, 144]	25/871	22/821	1.02 (0.55–1.89)	30%	0.96	
501–4000 μg	10	[49, 64, 65, 78, 98, 101, 104, 124, 134, 143]	30/233	7/200	3.40 (1.62–7.13)	27%	0.001	
Surgery								0.02
Cardiothoracic	14	[24, 37, 53, 57, 97, 101, 116, 119, 120, 124, 134, 136, 137, 143]	6/315	12/304	0.39 (0.13–1.23)	63%	0.11	
Abdominal	10	[31, 32, 34, 39, 40, 51, 59, 84, 85, 141]	14/403	1/285	4.11 (0.87–19.36)	0%	0.07	
Gynaecological	12	[35, 43, 65, 70, 74, 75, 83, 87, 92, 121, 122, 125]	28/494	12/303	1.30 (0.62–2.71)	0%	0.48	
Orthopaedic and spine	38	[26, 36, 42, 54, 56, 61, 62, 64, 66–68, 71, 72, 76, 78, 88–90, 94, 98, 100, 102, 103, 106, 109, 113–115, 117, 128, 129, 138, 139, 142, 144, 147–149]	38/1316	8/921	2.39 (1.25–4.57)	0%	0.008	
Other	10	[27, 49, 69, 81, 86, 91, 104, 107, 112, 118]	7/275	0/214	8.36 (1.06–66.29)	35%	0.04	
Anaesthetic strategy								0.66
General anaesthesia	39	[24, 31, 32, 34, 35, 37, 39, 40, 51, 53, 57, 59, 64, 75, 78, 83, 84, 90, 92, 97, 101, 107, 116, 117, 119–121, 124, 125, 129, 134, 136, 137, 139, 141, 143, 144, 147, 149]	55/1187	18/893	1.63 (0.91–2.91)	36%	0.10	
Spinal anaesthesia	45	[26, 27, 36, 42, 43, 49, 54, 56, 61, 62, 65–72, 74, 76, 81, 85–89, 91, 94, 98, 100, 102–104, 106, 109, 112–115, 118, 122, 128, 138, 142, 148]	38/1616	15/1134	1.95 (1.12–3.39)	0%	0.02	
Total	84		93/2803	33/2027	1.78 (1.19–2.67)	8%	0.005	

injection with subgroup analyses. Forest plots of these outcomes are shown in online Supporting Information Figures S2–S4. There were no significant differences between intrathecal morphine and control in the OR (95% CI) of sedation (1.00 (0.78–1.28), p = 0.98) or hypoxaemia (1.22 (0.84–1.79), p = 0.30). The quality of evidence was deemed moderate for both outcomes (online Supporting Information Table S2). Subgroup analysis according to dose revealed a significant increased rate of sedation with doses of 101–200 μg, but not in the other dose subgroups. There were more episodes of respiratory depression in patients receiving intrathecal morphine than control (OR (95%CI) 1.78 (1.19–2.67), p = 0.005), with very low-quality evidence (online Supporting Information Table S2). Sensitivity analyses omitting studies at high risk of bias and/or restricted to doses of ≤ 500 μg showed no significant association between intrathecal morphine and control in the OR of sedation, hypoxaemia and respiratory depression

Table 3 Hypoxaemia reported in included studies investigating intrathecal morphine analysed according to dose, type of surgery and anaesthetic strategy.

	Number of trials	References	Number of patients		Odds ratio (95%CI)	I^2	p value for overall effects	p value for subgroup differences
			Morphine	Control				
Morphine dose								0.22
1–100 μg	10	[43, 90, 92, 100, 106, 115, 118, 121, 138, 142]	31/230	27/195	0.92 (0.48–1.73)	11%	0.79	
101–200 μg	8	[23, 89, 90, 92, 106, 115, 138, 139]	34/181	29/181	1.30 (0.70–2.40)	66%	0.40	
201–500 μg	12	[35, 40, 48, 51, 53, 78, 83, 97, 99, 115, 121, 126]	49/263	39/264	1.27 (0.77–2.11)	0%	0.35	
501–4000 μg	1	[78]	6/12	0/8	17.00 (0.80–359.81)	N/A	0.07	
Surgery								0.33
Cardiothoracic	2	[53, 97]	1/43	1/56	1.13 (0.07–18.73)	N/A	0.93	
Abdominal	2	[40, 51]	10/70	15/70	0.50 (0.18–1.42)	N/A	0.19	
Gynaecological	5	[35, 43, 83, 92, 121]	14/133	5/82	1.20 (0.39–3.71)	0%	0.75	
Orthopaedic and spine	13	[23, 48, 78, 89, 90, 99, 100, 106, 115, 126, 138, 139, 142]	95/412	39/282	1.46 (0.93–2.29)	48%	0.10	
Other	1	[118]	0/28	0/14	N/A	N/A	N/A	
Anaesthetic strategy								0.75
General anaesthesia	12	[35, 40, 48, 51, 53, 78, 83, 90, 92, 97, 121, 139]	38/347	24/269	1.13 (0.61–2.10)	5%	0.70	
Spinal anaesthesia	11	[23, 43, 89, 99, 100, 106, 115, 118, 126, 138, 142]	82/339	36/235	1.28 (0.79–2.08)	56%	0.31	
Total	23		120/686	60/504	1.22 (0.84–1.79)	34%	0.30	

NA, not applicable.

(online Supporting Information Table S3). Meta-regression revealed an association between dose and rate of sedation, respiratory depression and hypoxaemia (Fig. 2). However, this effect appeared to be driven by very large doses given in earlier studies and restricting to a range now used commonly in clinical practice (≤ 500 μg), these associations were no longer present (online Supporting Information Figures S5–S7). Sensitivity analysis which did not include patients who underwent postoperative ventilation did not alter the findings of our primary analyses (online Supporting Information Table S3).

Low-quality evidence suggested that there was no difference in the need for additional oxygen administration, the need for opioid antagonist administration, additional respiratory support or an escalated level of care (Table 4). No deaths were reported.

Trial sequential analyses reported that insufficient evidence has been reached for sedation and hypoxaemia, but sufficient evidence has been reached for statistical significance for respiratory depression (see online Supporting Information Figures S8–S10).

With respect to the risk of publication bias for the rate for sedation, Duval and Tweedie's trim and fill test calculated the combined studies point estimate (95%CI) to be 0.90 (0.69–1.18) with a random-effects model. Using trim and fill, the imputed point estimate was 0.75 (0.55–1.01), suggesting that 10 studies were missing. For respiratory depression, Duval and Tweedie's trim and fill test calculated the combined studies point estimate (95%CI) to be 1.58 (1.01–2.46) with a random-effects model. Using trim and fill, the imputed point estimate was 1.12 (0.70–1.81), suggesting that nine studies were missing. Finally, for hypoxaemia, the combined studies point estimate (95%CI) was 1.52 (1.29–1.78) with a random-effects model. Using trim and fill, the imputed point estimate was 1.26 (1.06–1.51), suggesting that 20 studies were missing. Funnel plots are shown in online Supporting Information Figure S11.

Discussion

This systematic review establishes that intrathecal morphine does not increase rates of sedation and hypoxaemia with a moderate level of evidence. Whilst our primary analyses showed that intrathecal morphine was associated with respiratory depression with a very low level of evidence, this association was not apparent in several sensitivity analyses,

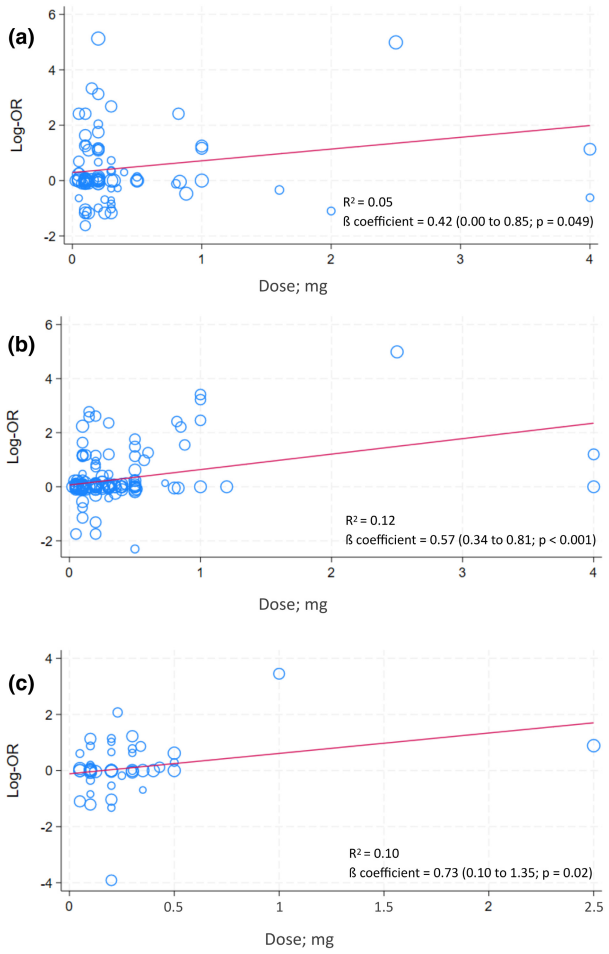

Figure 2 Meta-regression with linear model of (a) sedation; (b) respiratory depression; and (c) hypoxaemia according to the dose of intrathecal morphine. Red lines, linear regression; blue circles, observed values in each study.

nor did it persist with doses used in routine clinical practice (≤ 500 μg). Meta-regression analyses showed an association between sedation, respiratory depression and hypoxaemia and the dose of morphine. This association did not persist when restricting to doses ≤ 500 μg. However, as this threshold was set arbitrarily, the actual threshold might differ. That said, the 500 μg threshold was defined based on the maximum dose administered typically in contemporary clinical practice. Interestingly, there was no increased need for oxygen therapy, antagonism of opioids or any additional respiratory support or escalated levels of care. Additionally, no trials reported any mortality. Finally, the type of surgery or anaesthetic strategy did not impact the results.

The lack of a clear association between typical intrathecal morphine doses and pulmonary complications deserves to be considered. While there might be no true association, another explanation might be the pulmonary effects of systemic opioids administered in patients who did not receive intrathecal morphine and who may have developed moderate-to-severe postoperative pain. Pulmonary complications in these patients might eliminate differences observed in patients receiving intrathecal morphine. Data showing a difference in pulmonary outcomes comparing systemic opioids and intrathecal administration are required.

Concerns regarding the risk of respiratory depression also warrant further consideration. In our primary analysis, there appears to be a significant difference in outcome. However, when high doses of intrathecal morphine were not included, this difference was no longer significant. The trial sequential analysis suggested that sufficient information had been reached; however, the GRADE quality of evidence undermines this confidence, as does a more critical assessment of the outcome. Adding to this, respiratory depression usually warrants treatment with either antagonism of opioids or treatment with additional oxygen therapy or respiratory support, but our results show no evidence of increased requirement in these additional treatments. This could be caused by high-risk studies not detecting or reporting additional support, or by the fact that there were variable definitions of respiratory depression, some of which may not require such interventions.

This meta-analysis has several limitations. The lack of continuous monitoring to measure respiratory depression or hypoxaemia in some of the trials could have led to underreporting of potential events. Another limitation was the variability in definitions applied across trials for each of our three outcomes. For instance, regarding respiratory depression, trials used cut-off values including < 6, 8, 10 and 13 breaths.min^{-1}. However, consistent with the equipoise principle, we do not consider this limitation to affect the validity of our results significantly. That said, we urge researchers to perform prospective dose-safety trials of intrathecal morphine for each of these complications in specific surgeries and populations, with consistent definitions, to confirm the results of this meta-analysis. Although we initially registered on PROSPERO that we aimed to include other hydrophilic opioids such as hydromorphone or diamorphine, we focused this meta-analysis on intrathecal morphine given the volume of evidence and the difficulty with comparing other drugs [7]. As the safety profile of these opioids might possibly diverge from morphine, future research in this area is needed, especially with head-to-head comparisons between hydrophilic opioids, to determine whether one molecule for the intrathecal administration should be favoured in clinical practice. Some of the subgroup and sensitivity analyses

Table 4 Secondary outcomes reported in included studies investigating intrathecal morphine.

Outcome	Number of trials	References	Number of patients		Odds ratio (95%CI)	I^2	p value for overall effects
			Morphine	Control			
Need for oxygenation	12	[42, 48, 51, 61, 68, 71, 72, 88, 99, 113, 115, 116]	41/468	27/391	1.31 (0.74–2.30)	22%	0.35
Need for opioid antagonist	19	[34–36, 41, 42, 52, 64, 68, 72, 75, 79, 84, 101, 109, 113, 121, 124, 136, 149]	5/793	1/565	1.94 (0.52–7.32)	0%	0.33
Need for any additional respiratory support or escalated levels of care	13	[24, 34, 35, 37, 52–54, 66, 68, 77, 119, 120, 149]	3/482	4/404	0.85 (0.20–3.59)	0%	0.82

were not pre-registered, as their completion became necessary during the analysis and review processes to refine our results. Finally, we did not include observational studies, which may provide invaluable evidence in the setting of intrathecal morphine and pulmonary outcomes [150].

In conclusion, there is moderate evidence that intrathecal morphine does not increase rates of sedation or hypoxaemia after all types of non-obstetric surgery, though more data may be needed. There was evidence of an association between intrathecal morphine and respiratory depression, but this association did not persist in the range of doses used commonly in contemporary clinical practice. Intrathecal morphine does not appear to influence the need for oxygenation, administration of opioid antagonists or the need for any additional respiratory support or escalated levels of care. Variability in outcome definitions warrants caution when translating these results into clinical practice. These findings could inform future clinical guidelines and management.

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Supporting Information

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

Figure S1. Cochrane Risk of Bias 2 summary.
Figure S2. Forest plot for sedation.
Figure S3. Forest plot for respiratory depression.
Figure S4. Forest plot for hypoxaemia.
Figure S5. Sensitivity analysis without high-risk studies.
Figure S6. Sensitivity analysis with doses of ≤ 500 μg only.
Figure S7. Sensitivity analysis without high-risk studies and doses of ≤ 500 μg only.

Figure S8. Trial sequential analysis for rate of sedation.
Figure S9. Trial sequential analysis for rate of respiratory depression.
Figure S10. Trial sequential analysis for rate of hypoxaemia.
Figure S11. Funnel plot for (a) sedation; (b) respiratory depression; and (c) hypoxaemia according to the dose of intrathecal morphine.

Table S1. Characteristics of studies included in this study.
Table S2. Quality of evidence assessment for each primary outcome with intrathecal morphine.
Table S3. Sensitivity analyses.
Appendix S1. Literature search strategy.