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Review Article

PAIN

Non-pulmonary complications of intrathecal morphine administration: a systematic review and meta-analysis with meta-regression

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Abstract

Background: Intrathecal morphine provides effective analgesia for a range of operations. However, widespread implementation into clinical practice is hampered by concerns for potential side-effects. We undertook a systematic review, meta-analysis, and meta-regression with the primary objective of determining whether a threshold dose for non-pulmonary complications could be defined and whether an association could be established between dose and complication rates when intrathecal morphine is administered for perioperative or obstetric analgesia.

Methods: We systematically searched the literature for randomised controlled trials comparing intrathecal morphine *vs* control in patients undergoing any type of surgery under general or spinal anaesthesia, or women in labour. Primary outcomes were rates of postoperative nausea and vomiting, pruritus, and urinary retention within the first 24 post-operative hours, analysed according to doses (1–100 μg; 101–200 μg; 201–500 μg; >500 μg), type of surgery, and anaesthetic strategy. Trials were excluded if doses were not specified.

Results: Our analysis included 168 trials with 9917 patients. The rates of postoperative nausea and vomiting, pruritus, and urinary retention were significantly increased in the intrathecal morphine group, with an odds ratio (95% confidence interval) of 1.52 (1.29–1.79), $P<0.0001$; 6.11 (5.25–7.10), $P<0.0001$; and 1.73 (1.17–2.56), $P=0.005$, respectively. Meta-regression could not establish an association between dose and rates of non-pulmonary complications. There was no subgroup difference according to surgery for any outcome. The quality of evidence was low (Grading of Recommendations Assessment, Development, and Evaluation [GRADE] system).

Conclusions: Intrathecal morphine significantly increased postoperative nausea and vomiting, pruritus, and urinary retention after surgery or labour in a dose-independent manner.

Systematic review protocol: PROSPERO (CRD42023387838).

Keywords: intrathecal morphine; non-pulmonary complications; postoperative nausea and vomiting; pruritus; urinary retention

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Editor's key points

- Intrathecal morphine is effective for postoperative analgesia, but is associated with respiratory depression and non-pulmonary side-effects.
- This systematic review, meta-analysis, and meta-regression was designed to determine whether a threshold dose for the non-pulmonary side-effects of intrathecal morphine administered for perioperative or obstetric analgesia could be defined.
- The rates of postoperative nausea and vomiting, pruritus, and urinary retention were significantly increased in the intrathecal morphine group.
- Meta-regression could not establish an association between dose and rates of non-pulmonary complications.
- Future studies should explore the safety profile of intrathecal morphine in specific types of surgery and patient populations.

Intrathecal morphine provides effective analgesia after a range of surgical procedures, including Caesarean delivery,[1] lower limb orthopaedic surgery,[2] or abdominal surgery.[3] However, widespread implementation into clinical practice is hampered by concerns for potential complications, such as postoperative nausea and vomiting (PONV), pruritus, and urinary retention. These adverse effects could prolong post-anaesthesia care unit (PACU) length of stay,[4] lead to unplanned hospital admission,[5] and increase healthcare expenses,[6] along with patient dissatisfaction.[7]

Two previous meta-analyses demonstrated that morphine 100 μg was a threshold dose for PONV after Caesarean delivery[1] and lower limb arthroplasty,[8] above which the incidence increases significantly. However, uncertainty remains about whether a threshold dose exists for other non-pulmonary complications, such as pruritus and urinary retention, and safety in a range of surgical settings. Therefore, we undertook this systematic review, meta-analysis, and meta-regression with the primary objective of determining whether a threshold dose for non-pulmonary complications could be defined, and whether an association could be established between dose and complication rates when morphine is administered intrathecally for analgesia after all types of surgery or labour.

Methods

This study adhered to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement[9] and was prospectively registered on PROSPERO. With the assistance of a medical librarian, we searched the following electronic databases from inception to May 5, 2023: Ovid Medline; Embase; and Cochrane Central Register of Controlled Clinical Trials Wiley. Supplemental searches were carried out on Clinicaltrials.gov and Google Scholar (search limited to the first 300 results). Details of the literature search strategy are described in the Supplementary material (Supplementary document 1). Searches were conducted in accordance with the Peer Review of Electronic Search Strategies (PRESS) checklist, which included peer review by another medical librarian.[10] 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 included prospective, randomised controlled trials of adult patients undergoing any type of surgery under general or spinal anaesthesia or labour, comparing intrathecal morphine with control, defined as injection of normal saline or no injection of any hydrophilic opioid. We excluded trials that compared intrathecal morphine with administration of intrathecal lipophilic opioids (e.g. fentanyl, sufentanil) or hydrophilic opioids (e.g. diamorphine, hydromorphone). Primary outcomes were rates of PONV, pruritus, and urinary retention within the first 24 postoperative hours. Records were screened by two authors independently with Rayyan software (Qatar Computing Research Institute, 2016, Doha, Qatar), and in cases of disagreement, a third author determined eligibility. For included studies, data were extracted onto a standardised spreadsheet. Extracted trial characteristics included: doses of morphine injected, type of surgery, anaesthetic technique (neuraxial, general, neuraxial, and general anaesthesia), and medication used for postoperative analgesia. Text, tables or images from the source articles were evaluated to extract the number of participants and number of events. Graphically presented data were extracted with plot digitising software (Plot Digitizer Version 2.1, Free Software Foundation, Boston, MA, USA). When 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. The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system was applied to each outcome to evaluate the quality of evidence.[11] For each randomised trial, the methodological quality was evaluated using the Cochrane Collaboration's Risk of Bias tool.[12]

Meta-analyses were done using RevMan 5.4.1 (The Nordic Cochrane Centre, The Cochrane Collaboration 2020, Copenhagen, Denmark) when more than one study reported any given outcome. We calculated the I^2 coefficient in order to determine heterogeneity, and set predefined limits for low (<50%), moderate (50–74%), and high (>75%) levels.[13] However, we elected to use a random-effects model, rather than a fixed-effects model, whatever the I^2 coefficient, because of the important clinical variability across studies.[14] 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, >500 μg), type of surgery (abdominal, cardiothoracic, gynaecological, orthopaedic, spinal, Caesarean delivery and labour, and other), and anaesthetic technique (general *vs* spinal *vs* combined). For studies assessing multiple doses, data from all groups were included and pooled in the predetermined dose categories. We then performed trial sequential analysis for the three 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). We also assessed the risk of publication bias for each outcome with a funnel plot of the sample size (y-axis) as a function of the odds ratio (OR) of each complication (x-axis).[15] This was then confirmed with Duval and Tweedie's trim and fill test.[16] This assessment was performed using Comprehensive Meta-analysis version 2 (Biostat, Englewood, NJ, USA).

We also assessed possible associations between dose and risk of PONV, pruritus, and urinary retention. For each

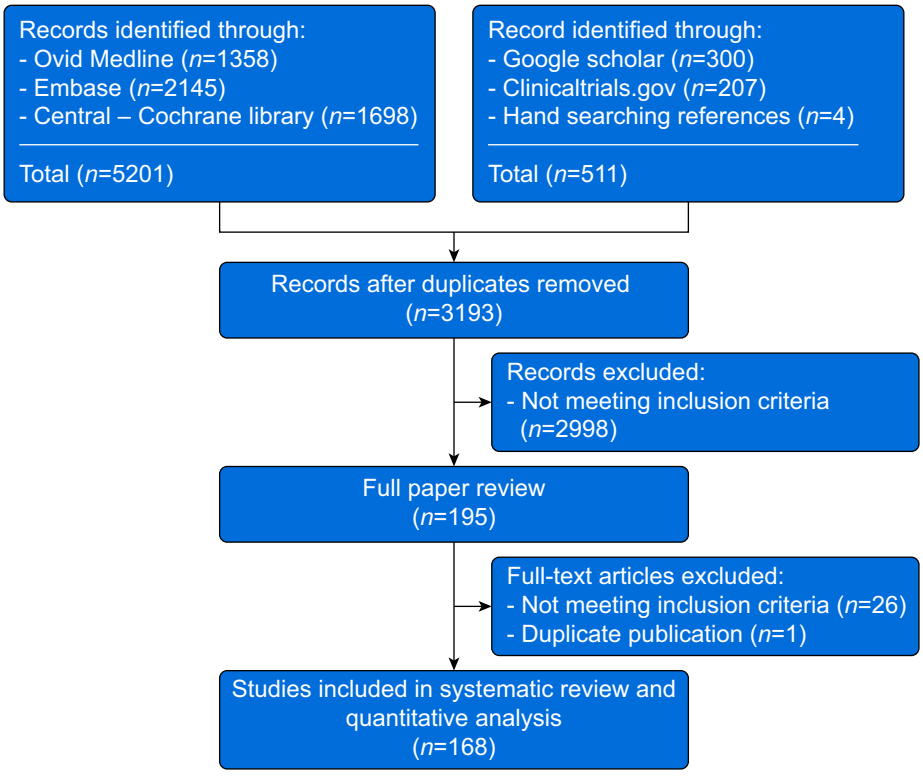

Fig 1. PRISMA flow diagram showing literature search results. The analysis included 169 prospective trials. ICTPR, International Clinical Trials Registry Platform (from the World Health Organization); PRISMA, Preferred Reporting Items for Systematic reviews and Meta-Analyses.

complication and study, we calculated the OR using Haldane-Anscombe correction in case of zero cells in the corresponding contingency table. As there was a positive skew to ORs, we generated regression models with logOR as the outcome and dose as the predictor,[17] weighting studies based on the variance of their logOR. To reduce the impact of clear outliers and to ensure relevance to contemporary clinical practice, we focused on studies reporting intrathecal morphine doses <1 mg. We performed linear regression to assess association, but also used fractional polynomials and restricted cubic splines to determine whether these latter two approaches improved goodness of fit.[18] Statistical analyses were performed with Stata 18.0 (Stata Statistical Software Release 18; StataCorp, College Station, TX, USA, 2023). Data are presented as OR or logOR with the 95% confidence interval (CI). A two-sided *P*-value <0.01 was set as statistically significant, allowing for multiple comparisons.

Results

Of the 3197 studies found, 168 met the inclusion criteria[19–186] (Fig. 1), with a total of 9917 patients. Risk of bias assessments are summarised in Supplementary Figure S1. We contacted 43 authors,[25,26,30,31,36–38,42,44,57,62,63,68,69,74–76,81,83,85,86,90,96–98,100,113,114,124,133,139,140,149,150,159,167,168,173,179–181,184,186] and eight provided additional data.[25,42,83,86,124,133,173,181]

Study characteristics are reported in Supplementary Table S1. Twenty-five trials (15%) involved cardiothoracic surgery[26,30,32,40,44,48–51,58,64,90,113,116,121,142,145,146,151,163–165,169,172,179]; 17 (10%) abdominal surgery[34,35,37,42,43,56,60,62,63,84,95,101,102,114,150,177,183]; 39 (23%) Caesarean delivery and labour[19–24,31,45,52,67,75,76,81,86–88,92,99,100,112,115,117,123,128,129,136,139,140,149,154,156,159,161,166,167,170,171,176,180]; 15 (9%) gynaecological surgery[27,38,47,71,78,83,85,97,98,104,109,147,148,152,182]; and 60 (36%) orthopaedic and spinal surgery.[25,28,33,36,39,41,46,53,55,57,59,61,66,68–70,72–74,79,80,82,89,91,93,94,105–107,110,111,118–120,122,124,127,131–134,137,138,141,143,153,155,157,158,160,162,168,173–175,178,181,184–186] Twelve (7%) trials included a range of other surgical procedures.[29,54,65,77,96,103,108,125,126,130,135,144] Studies reported the use of intrathecal morphine doses ranging from 25 μg[92,136] to 4000 μg.[32,51,151] Postoperative multimodal analgesia was prescribed in 19 (11%) trials.[25,27,41,42,62,66,83,104,109,119,124,126,130,133,138,154,170,174,175]

The rates of PONV (Table 1), pruritus (Table 2), and urinary retention (Table 3) were all significantly increased in patients receiving intrathecal morphine with an OR (95% CI) of 1.52 (1.29–1.79), *P*<0.0001; 6.11 (5.25–7.10), *P*<0.0001; and 1.73 (1.17–2.56), *P*=0.005, respectively. With both linear or complex models, meta-regressions for PONV, pruritus, and urinary retention did not reveal any association between dose and risk of complications (Fig. 2). Trial sequential analysis indicated that firm evidence was reached for each of the outcomes (Supplementary Figs. S2–S4).

Rates of PONV were significantly increased with doses of 1–100 μg and 201–500 μg, but not with doses of 101–200 μg and 501–4000 μg. The rate was significantly increased with

Table 1 Postoperative nausea and vomiting reported in included studies analysed according to dose, type of surgery, and anaesthetic strategy. Numbers are number/total and odds ratio (95% CI). CI, confidence interval.

Outcome	Number of trials	References	Total number of patients		Odds ratio (95% CI)	I^2 (%)	P-value for overall effects	P-value for subgroup differences
			Morphine	Control				
According to dose								0.54
1–100 μg	53	19, 27, 41, 47, 52, 66, 68, 72, 73, 77, 82, 83, 85, 87, 89, 92, 96, 100, 102–105, 107, 109, 112, 115, 120, 122, 123, 126–128, 136–138, 140, 141, 144, 147, 148, 155, 156, 161, 166, 167, 170, 173, 176–178, 184–186	432/1587	300/1332	1.56 (1.19–2.05)	37	0.001	
101–200 μg	50	20–25, 33, 35, 42, 46, 55, 57, 67, 68, 72, 78, 85, 86, 88, 92, 96, 103, 105–107, 109, 110, 127–130, 132, 133, 136–138, 141, 143, 148, 152, 159, 166, 167, 171–175, 178, 180	492/1425	351/1276	1.43 (1.09–1.89)	41	0.01	
201–500 μg	45	19, 26, 28, 29, 31, 34, 36–40, 43, 53, 56, 58, 62–64, 79, 80, 85, 91, 97, 98, 101, 105, 108, 111, 113, 115, 116, 119, 125, 134, 136, 141–143, 147, 153, 157, 158, 162, 169, 183	335/1101	212/1003	1.71 (1.29–2.27)	29	0.0002	
501–4000 μg	11	32, 48, 54, 69, 71, 91, 115, 118, 125, 165, 168	80/256	39/212	2.46 (1.18–5.13)	45	0.02	
According to type of surgery								0.13
Caesarean delivery and labour	30	19–24, 31, 52, 67, 86–88, 92, 100, 112, 115, 123, 128, 129, 136, 140, 156, 159, 161, 166, 167, 170, 171, 176, 180	242/1056	139/763	1.44 (1.08–1.92)	14	0.01	
Abdominal surgery	12	34, 35, 37, 42, 43, 56, 62, 63, 101, 102, 177, 183	98/442	77/324	1.15 (0.65–2.06)	54	0.63	
Cardiothoracic surgery	12	26, 32, 40, 48, 58, 64, 113, 116, 142, 165, 169, 172	65/275	37/253	1.74 (1.06–2.86)	0	0.03	
Gynaecological surgery	14	27, 38, 47, 71, 78, 83, 85, 97, 98, 104, 109, 147, 148, 152	208/534	112/343	1.14 (0.76–1.72)	23	0.52	
Orthopaedic and spinal surgery	50	25, 28, 33, 36, 39, 41, 46, 53, 55, 57, 66, 68, 69, 72, 73, 79, 80, 82, 89, 91, 105–107, 110, 111, 118–120, 122, 127, 132–134, 137, 138, 141, 143, 153, 155, 157, 158, 162, 168, 173–175, 178, 184–186	669/1800	371/1322	1.70 (1.32–2.20)	40	<0.0001	
Other	10		57/262	21/202	2.66 (0.77–9.14)	65	0.12	

Continued

Table 1 Continued

Outcome	Number of trials	References	Total number of patients		Odds ratio (95% CI)	I^2 (%)	P-value for overall effects	P-value for subgroup differences
			Morphine	Control				
		29, 54, 77, 96, 103, 108, 125, 126, 130, 144						
According to anaesthetic technique								0.02
General anaesthesia	41	26, 32, 34, 35, 37, 38, 40, 42, 43, 48, 53, 56–58, 62–64, 85, 91, 97, 98, 101, 107, 109, 113, 116, 130, 134, 142, 143, 147, 152, 158, 165, 168, 169, 172, 174, 177, 184, 186	423/1357	294/1005	1.15 (0.86–1.55)	41	0.34	
Spinal anaesthesia	87	19–25, 27–29, 31, 33, 36, 39, 41, 46, 47, 52, 54, 55, 66–69, 71–73, 77–80, 82, 83, 86–89, 92, 96, 100, 102–106, 108, 110–112, 115, 118–120, 122, 123, 125–129, 132, 133, 136–138, 140, 141, 144, 148, 153, 155–157, 159, 161, 162, 166, 167, 170, 171, 173, 175, 176, 178, 180, 183, 185	916/3012	463/2202	1.73 (1.42–2.09)	30	<0.0001	
Total	128		1339/4369	757/3207	1.52 (1.29–1.79)	35	<0.0001	

Table 2 Pruritus reported in included studies analysed according to dose, type of surgery, and anaesthetic strategy. Numbers are number/total and odds ratio (95% CI). CI, confidence interval.

Outcome	Number of trials	References	Total number of patients		Odds ratio (95% CI)	I^2 (%)	P-value for overall effects	P-value for subgroup differences
			Morphine	Control				
According to dose								0.76
1–100 μg	54	19, 27, 41, 47, 52, 61, 66, 68, 72, 73, 77, 82, 83, 85, 87, 89, 92, 96, 100, 102–105, 107, 109, 112, 115, 117, 120, 122–124, 126–128, 136–138, 140, 141, 144, 147, 156, 161, 166, 167, 170, 173, 176–178, 184–186	540/1613	121/1326	6.43 (4.54–9.13)	32	<0.0001	
101–200 μg	48	20–25, 35, 42, 46, 55, 57, 67, 68, 72, 78, 85, 86, 88, 92, 96, 103, 105–107, 109, 110, 127–130, 132, 133, 136–138, 141, 143, 152, 159,	488/1337	135/1187	6.81 (4.15–11.18)	62	<0.0001	

Continued

Table 2 Continued

Outcome	Number of trials	References	Total number of patients		Odds ratio (95% CI)	I^2 (%)	P-value for overall effects	P-value for subgroup differences
			Morphine	Control				
		166, 167, 171–175, 178, 180						
201–500 μg	46	19, 26, 28, 29, 31, 34, 36–40, 43, 53, 56, 58, 60, 62, 64, 79, 80, 85, 91, 97, 98, 101, 105, 108, 111, 115, 116, 119, 125, 134, 136, 141–143, 145–147, 153, 157, 158, 162, 169, 183	315/1125	43/1026	7.20 (4.76–10.89)	26	<0.0001	
501–4000 μg	13	32, 48, 54, 69–71, 91, 115, 118, 121, 125, 165, 168	108/351	8/283	10.75 (4.51–25.66)	32	<0.0001	
According to type of surgery								0.28
Caesarean delivery and labour	31	19–24, 31, 52, 67, 86–88, 92, 100, 112, 115, 117, 123, 128, 129, 136, 140, 156, 159, 161, 166, 167, 170, 171, 176, 180	501/1141	118/809	7.04 (4.36–11.38)	55	<0.0001	
Abdominal surgery	12	34, 35, 37, 42, 43, 56, 60, 62, 101, 102, 177, 183	91/442	19/324	6.76 (3.81–12.01)	0	<0.0001	
Cardiothoracic surgery	14	26, 32, 40, 48, 58, 64, 116, 121, 142, 145, 146, 165, 169, 172	40/353	6/324	3.88 (1.77–8.48)	0	0.0007	
Gynaecological surgery	13	27, 38, 47, 71, 78, 83, 85, 97, 98, 104, 109, 147, 152	160/390	39/272	9.51 (4.34–20.82)	30	<0.0001	
Orthopaedic and spinal surgery	51	25, 28, 36, 39, 41, 46, 53, 55, 57, 61, 66, 68–70, 72, 73, 79, 80, 82, 89, 91, 105–107, 110, 111, 118–120, 122, 124, 127, 132–134, 137, 138, 141, 143, 153, 157, 158, 162, 168, 173–175, 178, 184–186	587/1839	104/1349	5.89 (3.79–9.15)	56	<0.0001	
Other	10	29, 54, 77, 96, 103, 108, 125, 126, 130, 144	72/261	0/200	16.87 (6.18–46.03)	0	<0.0001	
According to anaesthetic technique								<0.0001
General anaesthesia	43	26, 32, 34, 35, 37, 38, 40, 42, 43, 48, 53, 56–58, 62, 64, 70, 85, 91, 97, 98, 101, 107, 109, 116, 121, 130, 134, 142, 143, 145–147, 152, 158, 165, 168, 169, 172, 174, 177, 184, 186	322/1447	81/1072	4.03 (3.07–5.29)	35	<0.0001	
Spinal anaesthesia	88	19–25, 27–29, 31, 36, 39, 41, 46, 47, 52, 54, 55, 60, 61, 66–69, 71–73, 77–80, 82, 83, 86–89, 92, 96, 100, 102–106, 108, 110–112, 115, 117–120, 122–129,	1129/2979	205/2206	7.23 (6.03–8.67)	47	<0.0001	

Continued

Table 2 Continued

Outcome	Number of trials	References	Total number of patients		Odds ratio (95% CI)	I^2 (%)	P-value for overall effects	P-value for subgroup differences
			Morphine	Control				
		132, 133, 136–138, 140, 141, 144, 153, 156, 157, 159, 161, 162, 166, 167, 170, 171, 173, 175, 176, 178, 180, 183, 185						
Total	131		1451/4426	286/3278	6.11 (5.25–7.10)	46	<0.0001	

Table 3 Urinary retention reported in included studies analysed according to dose, type of surgery, and anaesthetic strategy. Numbers are number/total and odds ratio (95% CI). CI, confidence interval; NA, not applicable.

Outcome	Number of trials	References	Total number of patients		Odds ratio (95% CI)	I^2 (%)	P-value for overall effects	P-value for subgroup differences
			Morphine	Control				
According to dose								0.37
1–100 μg	15	41, 47, 72, 73, 82, 89, 100, 102, 122, 124, 126, 127, 140, 184, 185	81/463	43/402	2.06 (1.07–3.98)	19	0.03	
101–200 μg	10	35, 57, 72, 110, 127, 132, 143, 160, 174, 175	169/447	110/349	1.21 (0.54–2.73)	62	0.64	
201–500 μg	15	22, 29, 38, 58, 59, 62, 65, 90, 91, 108, 111, 116, 119, 143, 162	73/350	44/363	2.10 (1.29–3.43)	0	0.003	
501–4000 μg	1	91	9/9	5/9	15.55 (0.70–346.72)	NA	0.08	
According to type of surgery								0.94
Caesarean delivery and labour	3	22, 100, 101	13/90	4/92	4.72 (0.36–62.08)	61	0.24	
Abdominal surgery	3	35, 62, 102	12/123	3/103	2.74 (0.37–20.16)	39	0.32	
Cardiothoracic surgery	3	58, 90, 116	8/65	9/77	1.99 (0.15–26.45)	52	0.6	
Gynaecological surgery	2	38, 47	3/43	2/44	1.61 (0.24–10.59)	0	0.62	
Orthopaedic and spine surgery	22	41, 57, 59, 72, 73, 82, 89, 91, 110, 111, 119, 122, 124, 127, 132, 143, 160, 162, 174, 175, 184, 185	279/879	169/687	1.52 (0.93–2.50)	51	0.1	
Other	4	29, 65, 108, 126	17/69	8/69	2.18 (0.81–5.90)	0	0.12	
According to anaesthetic technique								0.38
General anaesthesia	11	35, 38, 57, 58, 62, 90, 91, 116, 143, 174, 184	61/347	44/334	1.31 (0.60–2.89)	43	0.5	
Spinal anaesthesia	26	22, 29, 41, 47, 59, 65, 72, 73, 82, 89, 100, 102, 108, 110, 111, 119, 122, 124, 126, 127, 132, 140, 160, 162, 175, 185	271/922	151/738	1.98 (1.23–3.18)	40	0.005	
Total	37		332/1269	195/1072	1.73 (1.17–2.56)	38	0.005	

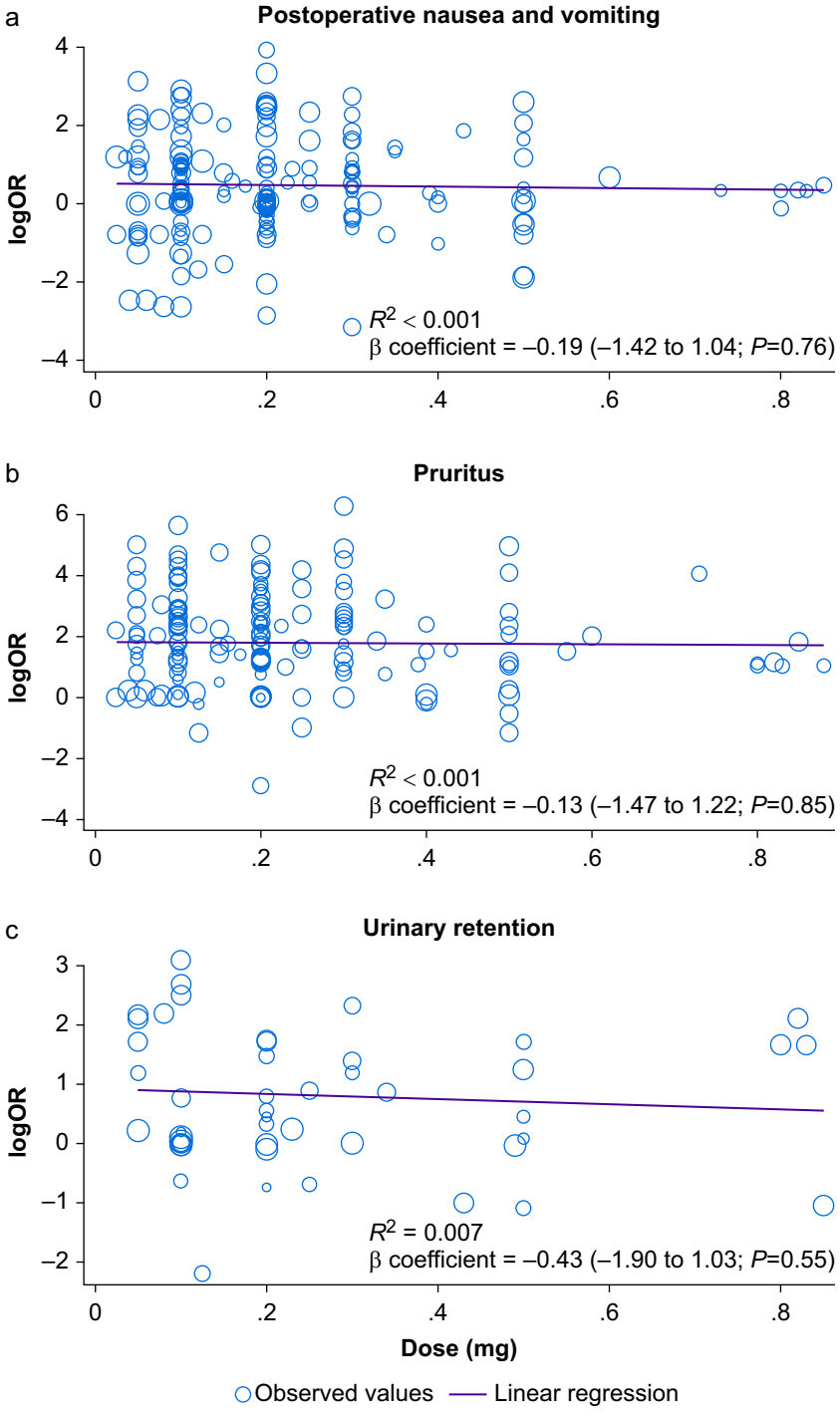

Fig 2. Meta-regression with linear model for (a) postoperative nausea and vomiting, (b) pruritus, and (c) urinary retention according to the dose of intrathecal morphine.

orthopaedic and spinal surgery but not with other types of surgery; patients having surgery under general anaesthesia, as opposed to those under spinal anaesthesia, did not have an increased rate of PONV (Table 1). Rates of pruritus were significantly increased in all doses, type of surgery, and anaesthetic techniques (Table 2). Regarding urinary retention, rate was significantly increased only when patients received a dose of 201–500 μg, confirming an absence of association between dose and risk; subgroup analysis revealed no increased risk regardless of surgery or anaesthetic type (Table 3). Funnel plots for the three outcomes are shown in Supplementary Figure S5. With respect to the risk of publication bias for rate

Table 4 Quality of evidence assessment for each non-pulmonary complication. GRADE, Grading of Recommendations Assessment, Development, and Evaluation. *As a few studies suffered from a high risk of bias, we downgraded by one level for major limitation. †I^2 <50%. ‡Consistent definition of the reported outcome. ¶No serious imprecision as the clinical decision would not be modified whether the upper or lower boundary limit of the confidence interval represented the truth. §Decision was made to downgrade by one level for publication bias.

Quality assessment							Summary of findings	
Outcome	Limitations	Inconsistency	Indirectness	Imprecision	Publication bias	Total number of participants	Conclusion	Quality of evidence (GRADE)
Rate of postoperative nausea and vomiting	High risk of bias in a few trials*	No inconsistency†	No serious indirectness‡	No serious imprecision¶	20 Studies are missing§	7576	Increased risk	Low quality (⊕⊕OO)
Rate of pruritus	High risk of bias in a few trials*	No inconsistency†	No serious indirectness‡	No serious imprecision¶	42 Studies are missing§	7704	Increased risk	Low quality (⊕⊕OO)
Rate of urinary retention	High risk of bias in a few trials*	No inconsistency†	No serious indirectness‡	No serious imprecision¶	6 Studies are missing§	2341	Increased risk	Low quality (⊕⊕OO)

of PONV, Duval and Tweedie's trim and fill test calculated the combined studies point estimate (95% CI) to be 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. For pruritus, Duval and Tweedie's trim and fill test calculated the combined studies point estimate (95% CI) to be 6.57 (5.11–8.44) with a random-effects model. Using trim and fill, the imputed point estimate was 3.32 (2.54–4.34), suggesting that 42 studies were missing. Finally, for urinary retention, the combined studies point estimate (95% CI) was 2.08 (1.31–3.33) with a random-effects model. Using trim and fill, the imputed point estimate was 1.53 (0.89–2.62), suggesting that six studies were missing. According to the GRADE criteria, the quality of evidence was rated as low (Table 4).

Discussion

Based on 168 trials and 9917 patients, this systematic review and meta-analysis with meta-regression demonstrated that intrathecal morphine significantly increased rates of PONV, pruritus, and urinary retention, with a low quality of evidence after all types of surgery and labour. We were unable to define a threshold dose and an association between dose and rate for non-pulmonary complications. This is the largest analysis in this setting and provides information to guide future clinical decision-making to mitigate adverse effects of intrathecal morphine.

The lack of dose-dependence of intrathecal morphine on outcome is worth considering further. It is possible that no dose-related adverse effects truly exist. The mechanisms for PONV after intrathecal opioids are unclear, but are thought to be related to action at the chemoreceptor trigger zone in the area postrema, increasing vestibular sensitivity and delaying gastric emptying.[187] It remains to be mechanistically demonstrated whether this is an all-or-none mechanism, but based on the data we present here, this could be the cause.

Given the complexity of risk factors for PONV, it is also plausible that the heterogeneity in the data, both in terms of patient cohorts and types of surgery, mean that it is difficult to generalise our findings. Some types of surgery are likely to be associated with a high risk of PONV, which would mean that patients might have PONV regardless of intrathecal morphine dose. For example, gynaecological surgery is a recognised risk factor for PONV, in part because all patients are female,[188] and our data show no significant increase in rate of PONV based on dose of intrathecal morphine. Furthermore, patients having particularly painful procedures and not receiving intrathecal morphine, or those receiving low doses, might require supplementary systemic opioid analgesia, which itself is emetogenic. Other procedures that might be amenable to good analgesic management with multimodal analgesia, including regional anaesthesia, might exhibit a dose–response association with PONV, as seen with lower limb arthroplasty.[8]

There have also been significant changes to clinical practice in the previous 40 yr, which could impact interpretation of our results. For example, anaesthetic techniques are now less emetogenic, as the use of thiopental for induction or volatile anaesthetics for maintenance has largely been replaced by propofol. Furthermore, multimodal analgesia in the postoperative period is now a key component in contemporary practice,[189] which leads to reduced use of systemic morphine, and could unmask complications secondary to intrathecal administration. Finally, rates of PONV, pruritus, and urinary retention were all measured as secondary outcomes and

therefore are exploratory in nature. Based on our results, we encourage researchers to perform prospective dose-safety trials of intrathecal morphine for each of these complications in specific surgeries and populations.

An important element to consider is the use of routine prophylaxis for PONV. For example, routine administration of 5-hydroxytryptamine-3 (5-HT_3) receptor antagonists mitigates the incidence of PONV and might be considered routinely in patients who have received intrathecal morphine. Systemic dexamethasone has also been shown to provide effective analgesia[190] whilst significantly reducing PONV after intrathecal morphine administration, with a risk ratio (95% CI) of 0.42 (0.35–0.51).[191]

The mechanisms of pruritus and urinary retention remain subjects of investigation. Pruritus might involve GABAergic neuronal disinhibition in the spinal cord, allowing gastrin-releasing peptide receptor activity to trigger itch.[192] Urinary retention is believed to be attributable to spinal cord inhibitory effects on the release of acetylcholine causing detrusor contraction.[193] There have been few high-quality studies demonstrating the dose dependency of intrathecal morphine on these outcomes. As with PONV, it is possible that limitations in data synthesis were responsible for this finding, but it might also be that there is no true dose–response relationship. Importantly, this lack of relationship refers to incidence rather than severity, which is also an area of significant uncertainty. Regardless, our data robustly demonstrate that intrathecal morphine use is associated with an increased risk of pruritus and urinary retention, which would need to be considered in routine clinical practice.

This meta-analysis has several weaknesses. Firstly, we only partly explain the important heterogeneity coefficient. Secondly, we elected to centre our meta-analysis on morphine, whereas other hydrophilic opioids might be injected intrathecally including hydromorphone or diamorphine. The safety profile of these drugs could possibly differ from morphine, warranting further research in this area. Thirdly, we did not consider the severity of our three outcomes of interest but focused on a binary quantitative analysis. Severity might have been more patient-centred, but there was significant heterogeneity in the measurement instruments used to report each outcome making this analysis challenging. Fourthly, we could not assess the role of postoperative systemic opioids on our outcomes of interest because of limited reporting in the included trials, and therefore we could not adjust our results for this covariate. Finally, we did not examine pulmonary complications such as respiratory depression, which is a more complex complication and one potentially associated with significant resource utilisation.

In conclusion, we found low-quality evidence that intrathecal morphine significantly increases rates of PONV, pruritus, and urinary retention when all types of surgery and labour are considered. We found no clear evidence of a dose–response relationship. Further research should explore the safety profile of intrathecal morphine in specific types of surgery and patient populations.

Authors' contributions

Conception of the work: YR, EA
Design of the work and interpretation of data: YR, KE, EA
Acquisition of data: YR, CJ, AN, EA
Analysis of data: YR, JBR, KE, EA
Writing and review of the work: KE, EA, YR

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Declarations of interest

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Appendix A. Supplementary data

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