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Review

Efficacy and safety of neuraxial hydromorphone: A systematic review and meta-analysis with trial sequential analysis

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HIGHLIGHTS

- The objective of this study is to clarify the magnitude of the analgesic efficacy of neuraxial hydromorphone and the optimal dose.
- We performed a systematic review and meta-analysis with trial sequential analysis, and included six articles, 436 patients.
- Neuraxial hydromorphone reduced rest pain score at 24 postoperative hours with a mean difference (95 %CI) of −0.4 (−0.8 to −0.1), $I^2 = 74$ %, $p = 0.01$, without impact on postoperative nausea and vomiting (risk ratio [95 %CI]: 1.2 [0.8–1.8], $I^2 = 27$ %, $p = 0.47$), but at the expense of increased pruritus (risk ratio [95 %CI]: 3.1 [1.6–5.9].
- Trials focusing on the optimal dose and side-effects should be performed before widely administering this medication into the neuraxial space.

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ABSTRACT

Study objective: Neuraxial hydromorphone provides postoperative pain relief. However, the magnitude of this effect and the optimal dose remain unknown. The objective of this study is to clarify these uncertainties.
Design: Systematic review and meta-analysis with trial sequential analysis.
Setting: Postoperative recovery area and ward, up to 24 h.
Patients: Any patient undergoing any type of surgery or being in labor.
Interventions: Neuraxial hydromorphone versus control.
Measurements: Our primary outcome was rest pain score (analogue scale, 0–10) at 24 h according to route of administration (epidural versus spinal) and type of surgery (orthopedic versus other). Secondary outcomes included rest pain score at 0–4 and 8–12 h; rates of postoperative nausea and vomiting, and pruritus at 24 h.
Main results: Six trials, including 436 patients, were identified. Rest pain score at 24 postoperative hours was significantly reduced in the hydromorphone group, with a mean difference (95 %CI) of −0.4 (−0.8 to −0.1), $I^2 = 74$ %, $p = 0.01$. Neuraxial hydromorphone did not increase postoperative nausea and vomiting (risk ratio [95 % CI]: 1.2 [0.8–1.8], $I^2 = 27$ %, $p = 0.47$), but increases pruritus (risk ratio [95 %CI]: 3.1 [1.6–5.9], $I^2 = 0$ %, $p = 0.0005$). The quality of evidence was very low for our primary and secondary outcomes. In conclusion, there is very low level of evidence that neuraxial hydromorphone provides effective analgesia after surgery or labor, at the expense of an increased rate of pruritus. The improvement in pain scores appears to be clinically insignificant. With only six trials published over a period of 30 years, we were unable to perform a meta-regression.
Conclusions: If neuraxial hydromorphone is to be used regularly, trials focusing on the optimal dose and side-effects should be performed before widely administering this medication into the neuraxial space.
More trials focusing on the optimal dose and side-effects should be performed before widely administering this medication into the neuraxial space.

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1. Introduction

Hydrophilic opioids, such as morphine, hydromorphone or diamorphine, provide pain relief after surgery when administered neuraxially [1]. The advantage of neuraxial rather than intravenous routes of administration is the deep and sustained analgesia provided [2]. Although morphine is widely used and investigated, drug shortages and regional practice variation mean there is currently a role for neuraxial hydromorphone. Comparative studies suggest that neuraxial injection of hydromorphone may provide similar analgesia to morphine [3]. The emerging role of hydromorphone has also led to retrospective dose-finding studies, which were hampered by methodological weaknesses [4]. More specifically, data suggest that neuraxial hydromorphone provides adequate postoperative analgesia, though the significance of these differences appears to be variable [5–10].

Given the traction it is increasingly receiving, there is a need to determine safety and efficacy of neuraxial hydromorphone for postoperative analgesia. We therefore aimed to assess the magnitude of the postoperative analgesic effect of neuraxial hydromorphone and its optimal dose, along with drug-related side-effects with a systematic review and meta-analysis with meta-regression and trial sequential analysis. This would establish whether further work is required and if hydromorphone truly has a position in perioperative pain management.

2. Material and methods

This study adhered to the PRISMA statement [11] and was prospectively registered on PROSPERO (CRD42023459099). With the assistance of a medical librarian, we searched the following electronic databases from inception to May 4, 2023: Ovid Medline ALL, Embase.com, 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 200 results). Details of the literature search strategy are described in Supporting Information Appendix S1. The search strategies were peer-reviewed by another librarian in accordance with the Peer Review of Electronic Search Strategies (PRESS) checklist [12]. No language or date limits were placed on the search, and adapted filters for randomized trials were used in Medline and Embase. References were imported into EndNote™ 20 software (Clarivate™, London, UK) and deduplicated with Deduklick (Risklick AG) [13]. 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, randomized controlled trials of adult patients undergoing any type of surgery under general or neuraxial anesthesia or patients being in labor, comparing neuraxial hydromorphone with a control group receiving no hydromorphone or normal saline. Defined outcomes were extracted from each article following the routine approach previously described in meta-analyses on acute postoperative pain [14–16]. Our primary outcome was rest pain score at 24 postoperative hours. Secondary pain-related outcomes included: rest, dynamic pain scores at 0–4 and 8–12 postoperative hours; intravenous morphine consumption at 0–4, 8–12 and 24 postoperative hours; and duration of analgesia. Other secondary outcomes sought were side-effects including rates of postoperative nausea and vomiting; pruritus; urinary retention; sedation; respiratory depression; and hypoxemia, all recorded within the first 24 postoperative hours. Extracted trial characteristics included route of administration (intrathecal or epidural) and doses of hydromorphone injected; type of surgery; anesthetic strategy and medication used for postoperative analgesia.

Text, tables or images from the source articles were evaluated to extract the number of participants, number of events, means, standard deviations, standard error of means, and 95 % confidence interval (CI). Data presented graphically were extracted with plot digitizing software (Plot Digitizer Version 2.1, Free Software Foundation, Boston, USA). For studies that did not describe the sample size or results as a mean and standard deviation or standard error of the mean and 95 %CI, we contacted the corresponding author twice by email with a request for access to the relevant data or the complete dataset. If the corresponding author failed to reply, we employed the median and interquartile range as approximations of the mean and standard deviation, by estimating the mean as equivalent to the median, and the standard deviation as the interquartile range divided by 1.35 or the range divided by 4 [17]. All opioids were converted to equianalgesic intravenous (IV) morphine doses (IV morphine 10 mg = oral morphine 30 mg = IV tramadol 100 mg = IV pethidine 75 mg = IV fentanyl 100 μg = sufentanil 10 μg = IV nalbuphine 10 mg = oral hydrocodone 30 mg = oral codeine 165 mg) [18]. For pain scores employing an 11-unit graduation verbal, visual or numeric 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 randomized trial, the methodologic quality was evaluated using the Cochrane Collaboration's Risk of Bias 2 tool [20]. Two authors (SG, EA) employed 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 (KE).

All meta-analyses were conducted using RevMan 5.4.1 (The Nordic Cochrane Centre, The Cochrane Collaboration 2020, Copenhagen). 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 %) [21]. A random-effects model was applied in circumstances when moderate or high heterogeneity was observed; otherwise, a fixed-effects model was employed [22]. To account for sources of heterogeneity, subgroup analyses were conducted for our primary outcome according to the route of administration (epidural vs intrathecal), type of surgery (orthopedic versus other surgeries), and whether a multimodal analgesic treatment was prescribed (yes or no). These subgroup analyses were performed even with the presence of one trial per subgroup. The risk of publication bias associated with our primary outcome was estimated by drawing a funnel plot of the mean difference standard error of rest pain score at 24 postoperative hours and confirmed with Duval and Tweedie's trim and fill test [23]. This assessment was performed using Comprehensive Meta-analysis version 2 (Biostat, Englewood, NJ, USA). We planned to investigate the interactions between dose of intrathecal and epidural hydromorphone and mean difference in pain score at 24 postoperative hours with a meta-regression using the JMP 17 statistical package (SAS Institute, Cary, NC, USA) if more than 5 studies with different doses were published for each route of administration. Finally, trial sequential analysis was performed 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). We present results as the mean difference or relative risk (RR) with 95 %CI, and a two-sided p-value <0.05 was deemed to be significant.

3. Results

We identified 798 studies, and six met inclusion criteria [5–10], with a total of 436 patients (Fig. 1). Two authors were contacted and did not provide requested data [6,7]. The risk of bias of included studies is summarized in Fig. 2.

Table 1 presents the study characteristics. Three studies included patients undergoing elective orthopedic surgery [5,7,8], one partial hepatectomy [6], one cesarean section [10] and one, labor analgesia [9]. Operations were performed under spinal anesthesia in two studies [7,8], under epidural anesthesia in one [10] and under general anesthesia in two others [5,6]. Hydromorphone was injected epidurally in two studies

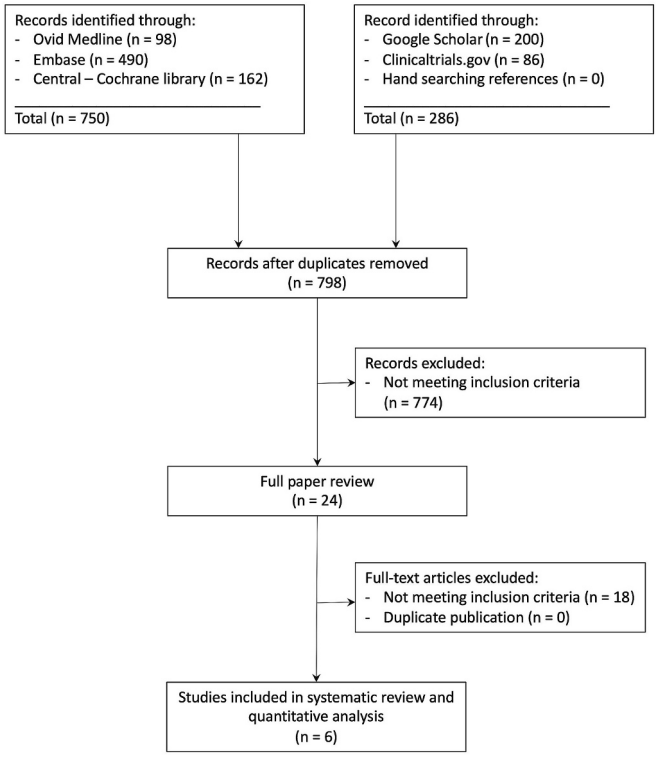

Fig. 1. PRISMA flow diagram showing literature search results. Five prospective trials were included in the analysis.

with doses between 200 and 600 μg [10] and intrathecally in the four others with doses ranging from 2.5 [8] to 200 μg [7]. In four studies, patients in the control group received an equivalent volume of normal saline [5,8–10]; in one study, patients received the local anesthetic only [7]; and in one study, patients did not receive any injection [6].

Rest pain score at 24 postoperative hours was significantly reduced in the hydromorphone group, with a mean difference (95 %CI) of −0.4 (−0.8 to −0.1), $I^2 = 74$ %, $p = 0.01$ (Fig. 3), without subgroup differences between route of administration ($p = 0.29$), prescription or not of multimodal analgesia ($p = 0.39$) and type of surgery (p = 0.39). With four and two trials on intrathecal and epidural administration, respectively, we were unable to perform any meta-regression. Trial sequential analysis indicated that firm evidence was not reached regarding the decreased rest pain score at 24 h (see also Supporting Information Appendix S2). 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 −0.46 (−0.75 to −0.17) with a random-effects model. Using trim and fill, these values were unchanged suggesting no studies are missing.

Regarding secondary pain-related outcomes, rest pain scores at 0–4 and 8–12 h, dynamic pain scores at 0–4 and at 24 h, along with morphine consumption at 24 h were also significantly reduced in patients receiving hydromorphone (Table 2). Intravenous morphine consumption and dynamic pain scores at 8–12 h were not reported at all. There was no difference in side-effects between groups except for pruritus (Table 2).

According to the GRADE system, the quality of evidence was downgraded to very low for our primary and secondary outcomes due mainly to the limited number of trials investigating the predefined outcome and to serious inconsistency and imprecision (Table 3).

4. Discussion

With this systematic review and meta-analysis with trial sequential analysis, we aimed to determine the magnitude of the postoperative analgesic effect of neuraxial hydromorphone and its optimal dose. We also aimed to capture any hydromorphone-related side-effect. Based on six trials only and 436 patients, we concluded that there is very low level of evidence that neuraxial hydromorphone reduced rest pain score at 0–4, 8–12 and 24 postoperative hours, as well as dynamic pain scores at 0–4 and 24 h, along with morphine consumption at 24 h. Side-effects were not increased, except for pruritus. Notably, the differences found did not meet the minimum clinically important differences expected for acute postoperative pain [24,25], thought to be around 10 mm on a 100 mm scale. That said, the trial sequential analysis did not demonstrate that firm evidence was achieved, therefore further data are awaited.

Noteworthy, the clinical impact of neuraxial hydromorphone in the setting of multimodal analgesia was assessed by only two trials. With only four trials investigating intrathecal, and two epidural hydromorphone, and what is more over a period of 30 years, we were unable to perform a meta-regression and define the optimal dose. While doses injected via the epidural route ranged from 200 to 600 μg, we noted inconsistency in the doses administered intrathecally, from 2.5 to 200 μg. Before the widespread use of hydromorphone occurs, more trials investigating the safety profile and dose-response of both epidural and intrathecal hydromorphone should be performed, particularly in the setting of multimodal analgesia.

A word of caution is required regarding pulmonary complications. While there was no increased risk of sedation, respiratory depression and hypoxemia, it is important to understand that these outcomes were sought in a total of only 67, 348 and 65 patients, respectively. As no robust conclusions can be drawn, we suggest clinicians follow the local guidelines regarding postoperative monitoring following administration of neuraxial opioids [26].

Notably, we did not compare efficacy of hydromorphone with other hydrophilic opioids. Indeed, there remains minimal data to answer this question, and while initial studies suggest similar efficacy [3,27], more studies are required before drawing any definitive conclusions. Given the substantial evidence base for neuraxial morphine in particular, any alternative must demonstrate at least equivalence, if not superiority, for either safety or efficacy. The evidence we currently report suggests that pruritus appears particularly prevalent with hydromorphone use, with a relative risk of 3.1, and the efficacy appears clinically modest. Another

Fig. 2. Cochrane Collaboration Risk of Bias 2 summary: evaluation of bias risk items for each included study. Green circle, low risk of bias; red circle, high risk of bias; yellow circle, unclear risk of bias. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 1
Characteristics of studies included in this study. NSAID, non-steroidal anti-inflammatory drugs.

Reference	Group (n)	Mode of administration	Type of intervention	Anesthetic strategy	Postoperative analgesia
Aglio et al., 2018 [5]	Control (32) Hydromorphone 500 μg (33)	Epidural	Spine surgery	General anesthesia	Opioids
Ding et al., 2022 [6]	Control (62) Hydromorphone 100 μg (61)	Intrathecal	Partial hepatectomy	General anesthesia	Opioids
Drakeford et al., 1991 [7]	Control (20) Hydromorphone 100–200 μg (20)	Intrathecal	Hip or knee arthroplasty	Spinal anesthesia	Paracetamol, opioids
Lee et al., 2012 [8]	Control (15) Hydromorphone 2.5 μg (15) Hydromorphone 5 μg (15) Hydromorphone 10 μg (15)	Intrathecal	Knee arthroscopy	Spinal anesthesia	Paracetamol, NSAID
Mhyre et al., 2013 [9]	Control (32) Hydromorphone 100 μg (35)	Intrathecal	Labor analgesia	Not applicable	Epidural analgesia
Yang et al., 2019 [10]	Control (20) Hydromorphone 200 μg (20) Hydromorphone 400 μg (20) Hydromorphone 600 μg (20)	Epidural	Cesarean section	Epidural anesthesia	Opioids

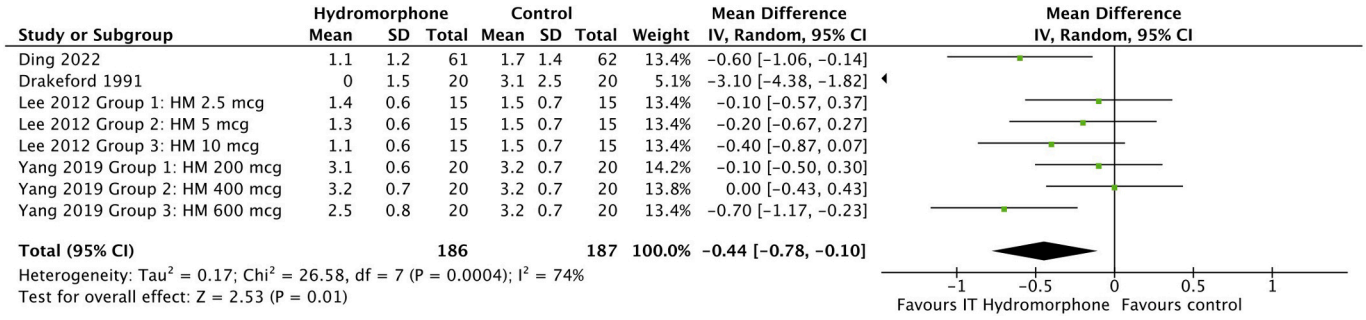

Fig. 3. Rest pain score at 24 postoperative hours.

Table 2
Secondary pain-related outcomes and side-effects. Numbers are number, number/total, and mean difference or risk ratio (95 %CI).

Outcome	Number of trials	Studies	Total number of patients		Mean difference or Risk ratio (95 %CI)	I^2; %	p-value for overall effect
			Hydromorphone	Control			
Secondary pain-related outcomes							
Rest pain score at 0–4 h; analogue scale 0–10	5	Aglio 2018 [5], Ding 2022 [6], Lee 2012 [8], Mhyre 2013 [9], Yang 2019 [10]	234	231	−0.7 (−1.1 to −0.2)	89	0.006
Rest pain score at 8–12 h; analogue scale 0–10	2	Lee 2012 [8], Yang 2019 [10]	105	105	−0.8 (−1.4 to −0.2)	88	0.01
Dynamic pain score at 0–4 h; analogue scale 0–10	1	Ding 2022 [6]	61	62	−1.0 (−1.5 to −0.5)	NA	<0.0001
Dynamic pain score at 24 h; analogue scale 0–10	1	Ding 2022 [6]	61	62	−0.7 (−1.2 to −0.2)	NA	0.003
Intravenous morphine consumption at 0–4 h; mg	1	Aglio 2018 [5]	33	32	−2.7 (−7.7 to 2.3)	NA	0.29
Intravenous morphine consumption at 24 h; mg	4	Aglio 2018 [5], Ding 2022 [6], Drakeford 1991 [7], Yang 2019 [10]	174	174	−22.4 (−34.6 to −10.0)	96	0.0003
Duration of analgesia; minutes	2	Ding 2022 [6], Mhyre 2013 [9]	96	94	95 (−47 to 238)	84	0.19
Side-effects							
Postoperative nausea and vomiting	4	Ding 2022 [6], Lee 2012 [8], Mhyre 2013 [9], Yang 2019 [10]	38/201	32/199	1.2 (0.8 to 1.8)	27	0.47
Pruritus	4	Ding 2022 [6], Lee 2012 [8], Mhyre 2013 [9], Yang 2019 [10]	34/201	10/199	3.1 (1.6 to 5.9)	0	0.0005
Urinary retention	2	Drakeford 1991 [7], Lee 2012 [8]	17/65	12/65	1.4 (0.8 to 2.3)	6	0.23
Sedation	1	Mhyre 2013 [9]	10/35	9/32	1.0 (0.5 to 2.2)	NA	0.97
Respiratory depression	3	Aglio 2018 [5], Ding 2022 [6], Drakeford 1991 [7], Yang 2019 [10]	3/174	3/174	1.0 (0.2 to 4.4)	NA	1.00
Hypoxemia	3	Aglio 2018 [5]	8/33	6/32	1.3 (0.5 to 3.3)	NA	0.59

important consideration is the off-label character of neuraxial administration of hydromorphone. Many drugs used in anesthesiology are employed with an off-label route of administration, such as intrathecal fentanyl or perineural dexamethasone for decades. While this is admitted in clinical practice, we stress to use a preservative-free solution as the preservative itself can be neurotoxic [28,29].

This study has limitations. First, we initially intended to focus this project on intrathecal hydromorphone, as registered on PROSPERO; due to the paucity of trials published, we elected to broaden the scope of this review to neuraxial hydromorphone. However, we do not believe this limitation reduces the validity of our conclusions. Then, some secondary pain-related outcomes that we intended to examine, such as dynamic

Table 3
GRADE quality of evidence assessment for each outcome. NA, Not applicable.

Outcome	Limitations	Inconsistency	Indirectness	Imprecision	Publication bias	Total number of participants	Conclusion	Quality of evidence
Rest pain score at 0–4 h	Small sample size[a]	Serious inconsistency[b]	No serious indirectness	Serious imprecision[c]	None	395	Hydromorphone superior to control group	Very low quality (⊕OOO)
Rest pain score at 8–12 h	Small sample size[a]	Serious inconsistency[b]	No serious indirectness	Serious imprecision[c]	None	140	Hydromorphone superior to control group	Very low quality (⊕OOO)
Rest pain score at 24 h	Small sample size[a]	Moderate inconsistency[b]	No serious indirectness	Serious imprecision[c]	None	307	Hydromorphone superior to control group	Very low quality (⊕OOO)
Dynamic pain score at 4 h	Small sample size[a]	NA	No serious indirectness	Serious imprecision[c]	None	123	Hydromorphone superior to control group	Very low quality (⊕OOO)
Dynamic pain score at 12 h	NA	NA	NA	NA	NA	NA	None	NA
Dynamic pain score at 24 h	Small sample size[a]	NA	No serious indirectness	Serious imprecision[c]	None	123	No difference between groups	Very low quality (⊕OOO)
Intravenous morphine consumption at 0–4 h	Small sample size[a]	NA	No serious indirectness	Serious imprecision[c]	None	67	No difference between groups	Very low quality (⊕OOO)
Intravenous morphine consumption at 8–12 h	NA	NA	NA	NA	NA	NA	None	NA
Intravenous morphine consumption at 24 h	Small sample size[a]	Serious inconsistency[b]	No serious indirectness	Serious imprecision[c]	None	308	Hydromorphone superior to control group	Very low quality (⊕OOO)
Duration of analgesia	Small sample size[a]	Serious inconsistency[b]	No serious indirectness	Serious imprecision[c]	None	190	No difference between groups	Very low quality (⊕OOO)
Postoperative nausea and vomiting	Small sample size[a]	No inconsistency	No serious indirectness	Serious imprecision[c]	None	330	No difference between groups	Very low quality (⊕OOO)
Pruritus	Small sample size[a]	No inconsistency	No serious indirectness	Serious imprecision[c]	None	330	More pruritus in patients receiving hydromorphone	Very low quality (⊕OOO)
Urinary retention	Small sample size[a]	No inconsistency	No serious indirectness	No serious imprecision	None	100	No difference between groups	Very low quality (⊕OOO)
Sedation	Small sample size[a]	NA	No serious indirectness	Serious imprecision[c]	None	67	No difference between groups	Very low quality (⊕OOO)
Respiratory depression	Small sample size[a]	NA	No serious indirectness	Serious imprecision[c]	None	308	No difference between groups	Very low quality (⊕OOO)
Hypoxemia	Small sample size[a]	NA	No serious indirectness	Serious imprecision[c]	None	65	No difference between groups	Very low quality (⊕OOO)

[a] Five trials or less specifically sought this outcome; Final decision to rate down quality of evidence by two levels for serious limitation.
[b] I^2 was above 50 % with wide variance of point estimates across studies. Final decision to rate down quality of evidence by one level for moderate or serious inconsistency.
[c] Wide confidence interval with potential clinical impact. Final decision to rate down quality of evidence by one level for serious imprecision.

pain scores at 8–12 postoperative hours, were not sought by the included trials. We encourage researchers, when investigating neuraxial hydromorphone, to properly include all secondary pain-related outcomes. As some research databases such as Scopus were not interrogated, it is possible that we might have not included some relevant articles. However, according to the Cochrane Handbook, Medline, Embase and the Cochrane Central Register of Controlled Clinical Trials are the most relevant databases to be searched. While we initially registered on PROSPERO a timeframe at 0–2 h, we decided to enlarge to 4 h to avoid taking into account the residual effect of the local anesthetic, whenever possible. Furthermore, we did not analyze any risks of neurotoxicity with the neuraxial use of hydromorphone, which remains an interesting avenue of future research for all drugs administered via this route. Finally, and as already mentioned, we could not perform any meta-regression due to the scarcity of studies published.

In conclusion, there is very low level of evidence that neuraxial hydromorphone provides effective analgesia after surgery or labor, without increasing postoperative nausea and vomiting or urinary retention but with an increased risk of pruritus. The efficacy is unlikely to be clinically significant, but there appears to be insufficient studies in this field to draw definitive conclusions. More trials focusing on the optimal dose and side-effects should be performed before widely introducing this medication into the clinical practice.

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CRediT authorship contribution statement

Sina Grape: Writing – review & editing, Methodology, Formal analysis. **Kariem El-Boghdadly:** Writing – review & editing, Validation, Methodology, Formal analysis. **Cécile Jaques:** Writing – review & editing, Software, Formal analysis. **Eric Albrecht:** Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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