Systematic Review

Effectiveness and Safety of Hydromorphone Compared to Morphine for Postoperative Analgesia: A Systematic Review and Meta-analysis

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Disclaimer: Y Li and X Yue contributed equally to this work.
This work was supported by grants from the National Natural Science Foundation of China (No. 82171236 and 82372180) and the Key Research and Development Plan of Hunan Province, People's Republic of China (No. 2021SK2018).

Conflict of interest: Each author certifies that he or she, or a member of his or her immediate family, has no commercial association (i.e., consultancies, stock ownership, equity interest, patent/licensing arrangements, etc.) that might pose a conflict of interest in connection with the submitted article.

Article received: 03-09-2024
Revised article received: 06-01-2024
Accepted for publication: 06-10-2024

Free full article: www.painphysicianjournal.com

Background: Background: Because of its side effects, a morphine replacement has been searched for in the field of postoperative analgesia. Hydromorphone is a derivative of morphine with no active metabolites.

Objectives: We conducted a meta-analysis of hydromorphone and morphine to compare their clinical effects in postoperative analgesia.

Study Design: Systematic review and meta-analysis.

Methods: The methodological quality of the studies included in this meta-analysis was assessed according to the Cochrane risk-of-bias tool. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria were used to evaluate the quality of evidence and recommendation grade for inclusion of randomized controlled trials. The primary outcome was postoperative pain score. Secondary outcomes were severe sedation, nausea, vomiting, and pruritus. The meta-analysis was performed using RevMan 5.4 (The Nordic Cochrane Centre for The Cochrane Collaboration).

Results: Eight randomized controlled trials comprising 833 patients were found. There was no significant difference in pain scores between the hydromorphone and morphine groups at any measured postoperative time point: 8 hours (mean difference [MD] = -0.42; 95%CI, -2.08 to 1.24; $P = 0.62$); 12 hours (MD = -0.19; 95%CI, -0.62 to 0.24; $P = 0.39$); 24 hours (MD = -0.22; 95%CI, -0.54 to 0.09; $P = 0.17$); 36 hours (MD = 0.01; 95%CI, -0.67 to 0.69; $P = 0.98$) and 48 hours (MD = -0.14; 95%CI, -1.25 to 0.96; $P = 0.80$). There was no significant difference in the incidence of nausea and vomiting at 24 hours postoperative. The incidence of pruritus at 24 hours postoperative was lower in the hydromorphone group (relative risk = 0.24; 95%CI, 0.09 to 0.66; $P = 0.005$).

Limitations: The perioperative multimodal analgesia measures were varying in the included studies, such as different medication doses. The sample size was small for some outcomes and high heterogeneity was observed.

Conclusions: There was no significant statistical difference in postoperative analgesic effect between hydromorphone and morphine, as well as side effects, including severe sedation, nausea, and vomiting at 24 hours postoperative. However, the incidence of pruritus was lower in the hydromorphone group at 24 hours postoperative.

Key words: Hydromorphone, morphine, analgesia, intravenous, epidural, systematic review, meta-analysis, randomized controlled trial

Pain Physician 2024: 27:469-478

Postoperative analgesia is a challenging part of anesthesia management; effective postoperative analgesia not only reduces patients' pain, but also helps speed their recovery from their surgical procedure (1,2). Administering opioids is often necessary for postoperative analgesia. Morphine has long been considered a suitable and well-known opioid for treating pain, but morphine often causes adverse reactions, such as nausea, vomiting, and pruritus. The severity of adverse reactions and the obvious dependence on morphine limit its clinical application. Therefore, the search for morphine replacement products has become a focus in the field of postoperative analgesia (3-5).

Hydromorphone, a semisynthetic morphine derivative, which possesses similar pharmacokinetic and pharmacodynamic profiles, may be a suitable alternative (6). At the same time, we note that hydromorphone is more readily available clinically than morphine. Due to the change in the molecular structure of hydromorphone, the clinical analgesic effect is better than morphine, and its dosage is only one-eighth to one-fifth of morphine.

Morphine and hydromorphone are metabolized mainly in the liver. Their main metabolite, glucuronides, are eliminated via the kidney. Therefore, active 6-glucuronic acid metabolites produced after morphine metabolism may cause severe opioid side effects in patients with renal failure (7). Hydromorphone, on the other hand, is glucuronidated at position 3 on the phenanthrene morphine nucleus. So, in patients with renal insufficiency, hydromorphone may be better tolerated than morphine with fewer adverse effects (8).

Hydromorphone can be used both as a bolus and infusion. Another disadvantage of morphine is that it releases histamine (9-11). In our further study of the relationship between the 2 analgesics, we found that the use of hydromorphone and morphine in postoperative analgesia is a patient-centered selection. Whether hydromorphone is an effective alternative to morphine for postoperative analgesia remains controversial. Therefore, we conducted a meta-analysis of the evidence on the effectiveness and safety of hydromorphone and morphine in postoperative analgesia to provide a basis for clinical postoperative analgesia treatment.

Methods

Our systematic review and meta-analysis is registered with the Prospective Register of Systematic Reviews (PROSPERO), registry number CRD42023472078. The best practice Cochrane Association guidelines (12) and Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines for systematic reviews (13,14) were followed during the data gathering and analysis processes. A PRISMA checklist is available as a supplement (Supplemental Table 1).

We searched the databases of PubMed, Cochrane Library, EMBASE, and Web of Science to include randomized controlled trials that examined the efficacy and safety of hydromorphone and morphine for postoperative analgesia. The search terms were "hydromorphone"; "morphine"; and "randomized controlled trial." The search was not limited by region, publication type, or language. Only articles published from the database's creation through October 16, 2023 were included in the search. The detailed search parameters are in Supplemental Table 2. To find other possibly suitable trials, we also looked through the reference lists of the full-text papers that had been screened.

Inclusion and Exclusion Criteria

Inclusion criteria were: 1) a randomized controlled trial; 2) adults receiving postoperative analgesia; 3) hydromorphone and morphine adminstered for postoperative analgesia; 4) postoperative analgesic measurement or side effects were reported.

Exclusion criteria were: 1) morphine and hydromorphone were not compared; 2) reviews, unpublished observations, correspondence, abstracts from scientific meetings, and trials with animals; 3) text that was repeated or from which information could not be gleaned; 4) there was no access to the entire text.

The references of the included studies were handsearched to identify any missed papers.

Every study that seemed to meet the requirements for inclusion in the whole review was independently found by 2 investigators. Independently, 2 reviewers chose which studies to include in the review. Disputes were settled by consensus after being sent to a third reviewer for resolution. We would get in touch with the authors and request that their data be made available if the data were supplied in a format that prevented them from being included in our meta-analysis.

Data Extraction

The following data were extracted from the included papers: 1) the study's basic information, including the author's or authors' names, the year it was published, and the author's or authors' nationalities; 2)

the patient ages and the study's sample size; 3) detailed information about the treatment plan and intervention methods; 4) essential components of a biased risk evaluation; 5) primary data of the relevant outcome indicators.

When multiple study samples were reported, the data were treated as subgroups of the same study. All studies comparing postoperative analgesia with hydromorphone were included. The primary outcome was postoperative pain score; Visual Analog Scale (VAS) scores can be combined and analyzed proportionally, which is the most commonly used measure to assess pain intensity. The rating ranges from 0 cm to 10 mm (0 cm = no pain, 10 cm = worst possible pain). For data processing, we believe that VAS and Numeric Rating Scale pain scores can be converted and combined for analysis. Secondary outcomes were severe sedation, nausea, vomiting, and pruritus. Subgroup analysis was performed according to the route of administration—intravenous or epidural.

Statistical Analysis

The outcomes of the included studies were subjected to a meta-analysis using RevMan 5.4 (The Nordic Cochrane Centre for The Cochrane Collaboration). Meta-analyses were conducted when the number of studies was 2 or more. Using a Mante-Haenszel χ^2 test, a risk ratio with 95%CI was calculated for dichotomous data. The mean difference with 95%CI was the expression of a Z-statistic for continuous data. The $P < 0.05$ was deemed significant in both situations. Q-statistics was used for heterogeneity analysis, with an α of 0.1 used for heterogeneity analysis and combined with the I^2 test (15). When $I^2 < 50\%$, $P > 0.1$, a fixed effect model was used. If heterogeneity exists ($I^2 > 50\%$, $P < 0.1$), a random-effects model was used.

We used the Cochrane risk-of-bias tool to evaluate the methodological quality of the papers in the meta-analysis (15,16). After a subjective review of all the studies, 2 investigators rated each one as "high," "low," or "unclear" for the following categories: creation of random sequences; concealing allocation; blinding of patients and staff; blinding outcome assessment; incomplete outcome data; selective reporting; and other biases. In order to assess the quality of evidence and recommendation grade for including the randomized controlled trials, 2 reviewers independently employed online software (https://gdt.gradepro.org/app) and adhered to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach.

Results

Study Selection

Through a systematic literature search, 8 randomized controlled trials met the inclusion criteria after excluding studies related to duplicate publications and full-text reviews (6,17-23). A total of 833 patients (422 in the hydromorphone group and 411 in the morphine group) were included in the quantitative synthesis (Fig. 1). Table 1 displays the characteristics for every study that was included. Since fewer than 10 randomized controlled trials were included, we did not conduct a publication bias analysis.

Risk of Bias Assessment

Figure 2 displays the methodological quality information. The specifics of random sequence creation were not covered in one study (19), and 4 studies did not describe the details hidden by random assignment schemes (18-20,23). Due to insufficient outcome data, selective reporting, and the blind nature of outcome evaluation, all studies carry an unknown risk of bias (6,17-23). Five original studies were unclear risks (18-21,23). and 3 original studies were high risk (6,17,22).

Meta-analysis Results

1. Postoperative Pain Score. Two studies provided data on patients' pain intensity scores at 8 hours postsurgery (18,19). Five studies provided pain intensity scores for patients at 12 hours postsurgery; one study had incomplete pain score data (22), so only 4 studies were included in the final analysis (19-21,23). Meta-analysis was performed after converting the 4 studies. Six studies provided pain intensity scores for patients at 24 hours postsurgery (6,17,19-21,23). Two studies provided pain intensity scores for patients at 36 hours postsurgery (20,23), and 2 studies provided pain intensity scores for patients at 48 hours postsurgery (19,20).

One study used the Numeric Rating Scale to score pain intensity on a 0-10 scale (6). Another study used the Verbal Rating Scale, in which patients verbally rated pain intensity on a scale of 0-10 (17). We suggest that these 6 pain score ratings can be combined in this meta-analysis.

Our meta-analysis showed that there was no significant difference in pain scores at 8 hours postsurgery between the hydromorphone and morphine groups (mean difference [MD] = -0.42; 95%CI, -2.08 to 1.24; $P = 0.62$; $I^2 = 87\%$) (Fig. 3). There was no significant difference in pain scores at 12 hours postsurgery (MD = -0.19; 95%CI, -0.62 to 0.24; $P = 0.39$; $I^2 = 83\%$) (Fig. 3).

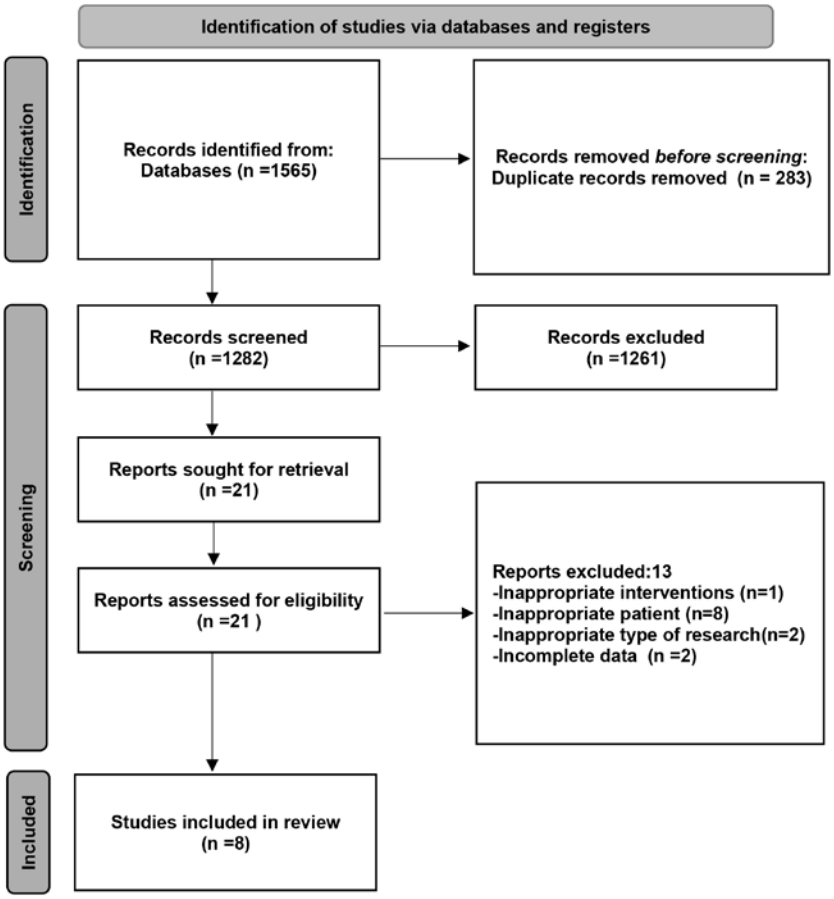

Fig. 1. *Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow chart of study screening.*

No significant difference was found in pain scores at 24 hours postsurgery (MD = -0.22; 95%CI, -0.54 to 0.09; P = 0.17; I^2 = 89%) (Fig. 3). There was no significant difference in pain scores at 36 hours postsurgery (MD = 0.01; 95%CI, -0.67 to 0.69; P = 0.98; I^2 = 54%) (Fig. 3). Finally, there was no significant difference in pain scores at 48 hours postsurgery (MD = -0.14; 95%CI, -1.25 to 0.96; P = 0.80; I^2 = 86%) (Fig. 3).

A subgroup analysis was performed of the analgesic scores at 12 and 24 hours postsurgery according to the route of administration. At 12 hours postsurgery, the results showed that there was no statistical difference between intravenous administration (MD = -0.19; 95%CI, -1.17 to 0.78; P = 0.70; I^2 = 90%) and epidural administration (MD = -0.18; 95%CI, -0.40 to 0.04; P = 0.12; I^2 = 0%). At 24 hours postsurgery, there was no statistical difference between intravenous administration (MD = -0.11; 95%CI, -0.39 to 0.17; P = 0.45; I^2 = 78%) and epidural administration (MD = -0.52; 95% CI, -1.24 to 0.21; P = 0.16; I^2 = 82%).

2. Postoperative Sedation Intensity. Five studies reported data on postoperative sedation (6,18-20,22). One study did not describe sedation measures (19), 2 studies measured sedation using the Ramsay Sedation Scale with different study time points (6,18), one study measured sedation using the VAS (20), and the rest of the studies measured sedation with the Modified Observer's Assessment of Alertness/Sedation Scale (22). Only Ying's and Li's article (19) concluded that sedation within 12 hours postsurgery was more significant in the morphine group. The other 4 articles all concluded that the difference in sedation intensity between hydromorphone and morphine was not statistically significant (6,18,20,22).

3. Rate of Unfavorable Reactions Following Surgery. Any postsurgical adverse event was recorded in

Table 1. *Main characteristics of the included studies.*

Reference	Sample Size	Route of Administration	Dosing		Outcomes*
			Hydromorphone Group	Morphine Group	
Chaplan, et al 1992 (20)	52	Epidural	0.05mg/mL in normal saline	0.15mg/mL in normal saline	V, n, p
Halpern, et al 1996 (21)	46	Epidural	0.6 mg epidural hydromorphone in 6 mL normal saline	3.0 mg epidural morphine in the same volume	V, n, p
Rapp, et al 1996 (17)	57	Intravenous.	Morphine/hydromorphone computed in l/5 ratio	Morphine/hydromorphone computed in l/5 ratio	V, n, v, p
Hong, et al 2008 (18)	50	Intravenous	0.2 mg/mL of hydromorphone one mL demand dose, 6 min lockout, and 10 mL hourly limit, with 3 mL boluses for breakthrough pain to a limit of 4 boluses per hour	one mg/mL of morphine one mL demand dose, 6 min lockout, and 10 mL hourly limit, with 3 mL boluses for breakthrough pain to a limit of 4 boluses per hour	N, R, n, v, p
Liu, et al 2018 (19)	80	Intravenous	The first dose for the hydromorphone group was 0.9% saline 5 mL + hydromorphone injection 0.4 mg, maintenance dose was 0.9% saline 100 mL + hydromorphone hydrochloride injection 3.6 mg, intravenous infusion pump drip rate was 2 mL/hour, continuous analgesia for 48 hours	The first dose of morphine group was 0.9% saline 5 mL + morphine hydrochloride injection 2 mg; the maintenance dose was 0.9% saline 100 mL + morphine injection 18 mg, intravenous infusion rate 2 mL/h, continuous analgesia for 48 hours	V, R, n, v
Shanthanna, et al 2019 (6)	401	Intravenous	Hydromorphone 0.2 mg + normal saline = 1 mL	Morphine one mg + normal saline = 1 mL	N, p
Bai, et al 2019 (23)	106	Intravenous	Bolus: 0.002 mg/kg Lockout interval: 8 min	Bolus: 0.015 mg/kg Lockout interval: 8 min	V, n, v
Wehrfritz, et al 2022 (22)	41	Intravenous	Deliver bolus doses of 0.2 mg of hydromorphone chloride within one minute, with a lock-out time of 10 minutes	Deliver bolus doses of 2 mg of morphine hydrochloride within one minute, with a lock-out time of 10 minutes	N, n, v

* V = Visual Analog Scale score; N =Numeric rating Scale; R = Ramsay Sedation Scale score; n = nausea; v = vomiting; p = pruritus.

all 8 investigations (6,17-23). The main adverse events were postoperative nausea, vomiting, and pruritus. Six studies provided data on nausea for patients at 24 hours postsurgery (6,17,19,20,22,23). Four studies provided data on vomiting at 24 hours postsurgery (6,17,22,23). Two studies provided data on pruritus at 24 hours postsurgery (17,22).

Nausea severity at 24 hours postsurgery was similar in the hydromorphone and morphine groups (relative risk [RR] = 0.87; 95%CI, 0.70 to 1.09; $P = 0.22$; $I^2 = 44\%$) (Fig. 4). There was no significant difference in the incidence of vomiting (RR = 1.59; 95%CI, 0.95 to 2.65; $P = 0.08$; $I^2 = 0\%$) (Fig. 4). In our meta-analysis, the only significant difference observed was a lower incidence of pruritus at 24 hours postsurgery in the hydromorphone group (RR = 0.24; 95%CI, 0.09 to 0.66; $P = 0.005$; $I^2 = 0$ %) (Fig. 4).

GRADE Certainty of Evidence

Supplemental Table 3 shows the GRADE evidence profile. The likelihood of evidence was very low for the postsurgery pain score, low for the incidence of pruritus, moderate for the incidence of vomiting, and high for the incidence of nausea at 24 hours postsurgery.

Discussion

Our meta-analysis shows there was no statistically significant difference for postsurgery analgesia between the hydromorphone and morphine groups, as did subgroup analyses based on route of administration, which showed no statistical difference for postsurgery analgesia, whether through intravenous or epidural administration. Due to the different measurements and acquisition times of sedation data in the 8 included studies, a meta-analysis could not be

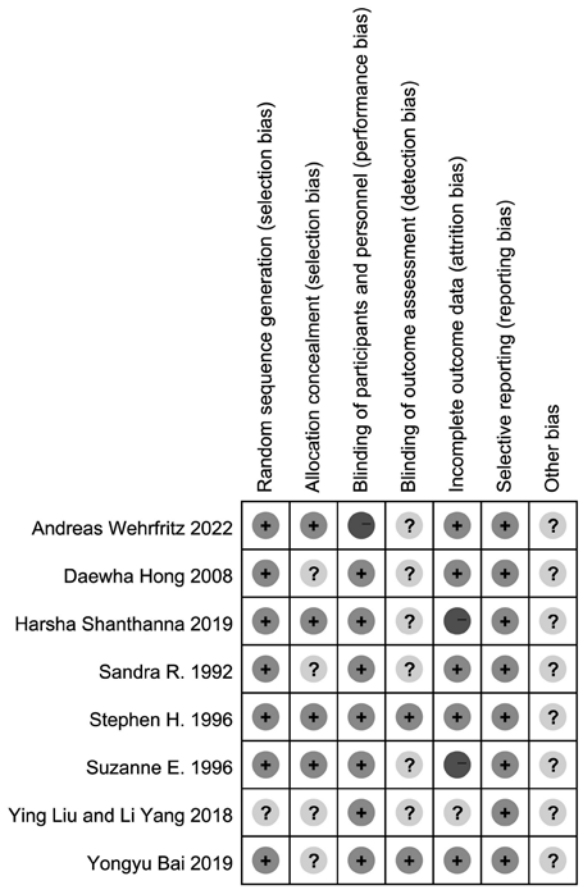

Fig. 2. *Risk of bias graph for the included studies.*

performed. At 24 hours postsurgery, there was no statistically significant difference in adverse events, which included nausea and vomiting. The only observation was a lower incidence of pruritus at 24 hours postsurgery in the hydromorphone group.

The lower pruritus incidence in the hydromorphone group may be because morphine releases more histamine. What's more, the μ1 receptor is a pure analgesic receptor, the mechanism of opioid itch may not be histamine release; there is evidence that pruritus is usually associated with selective μ2 receptor activation (20). Opioid receptor antagonists are not usually used to treat itching in the clinic. The use of opioid receptor antagonists may also cause withdrawal symptoms, which include restlessness, sweating, insomnia, nausea, vomiting, tachycardia, increased respiratory rate, and other symptoms (24).

These results of our meta-analysis were surprising given previous clinical bias. Most clinicians believe that hydromorphone has a better analgesic effect and fewer side effects. They believe this because hydromorphone has no active metabolites that cause opioid side effects and it is more readily available clinically with a lower incidence of pruritus in postoperative analgesia, which makes it seem that hydromorphone is a good alternative to morphine. However, our study did not further investigate the efficacy and safety of postoperative analgesia between the 2 groups in patients with renal insufficiency caused by active metabolites.

In the process of meta-analysis, we found a possible research focus on hydromorphone and morphine in the field of postoperative analgesia in the future, that is, opioid rotation analgesia. Some studies suggest that opioid rotation can improve the analgesic effect in patients who experience severe pain or side effects with a given opioid (25-27). In Hong, et al's study (18), 2 patients experienced relief from refractory postsurgery pain or intense pruritus with opioid rotation. Therefore, they believe that opioid rotation may be a good option for postsurgery analgesia; but a different study (28) demonstrated that both an increase in dosage and the opioid rotation approach itself may have an effect on successful symptom control. More clinical trials are needed to provide evidence on opioid rotation, which could be a focus of postsurgery analgesia in the future.

A similar meta-analysis discussed the analgesic effects and side effects of hydromorphone and morphine on acute and chronic pain (29). Our meta-analysis includes comparing studies on acute pain with more recent studies on acute pain than were included in previous meta-analyses, which was more controversial and innovative. A subgroup analysis was conducted according to drug routes, with more and higher quality original research on acute pain. Currently, there are many original studies and meta-analyses on the analgesic effects and safety of hydromorphone and morphine for chronic pain, and the controversies are relatively small. However, the effects and side effects of hydromorphone and morphine for acute pain are varied. Therefore, our study only conducted a meta-analysis on the effectiveness and safety of hydromorphone and morphine for postsurgical analgesia during the perioperative period. A similar meta-analysis showed that the solubility of hydromorphone was nearly 10 times more than morphine, and the speed of its passage through the blood-brain barrier was accelerated, so the time of effect was accelerated, and the time of peak effect was significantly shortened. Furthermore, unlike with morphine, the concentrations at the site of action do

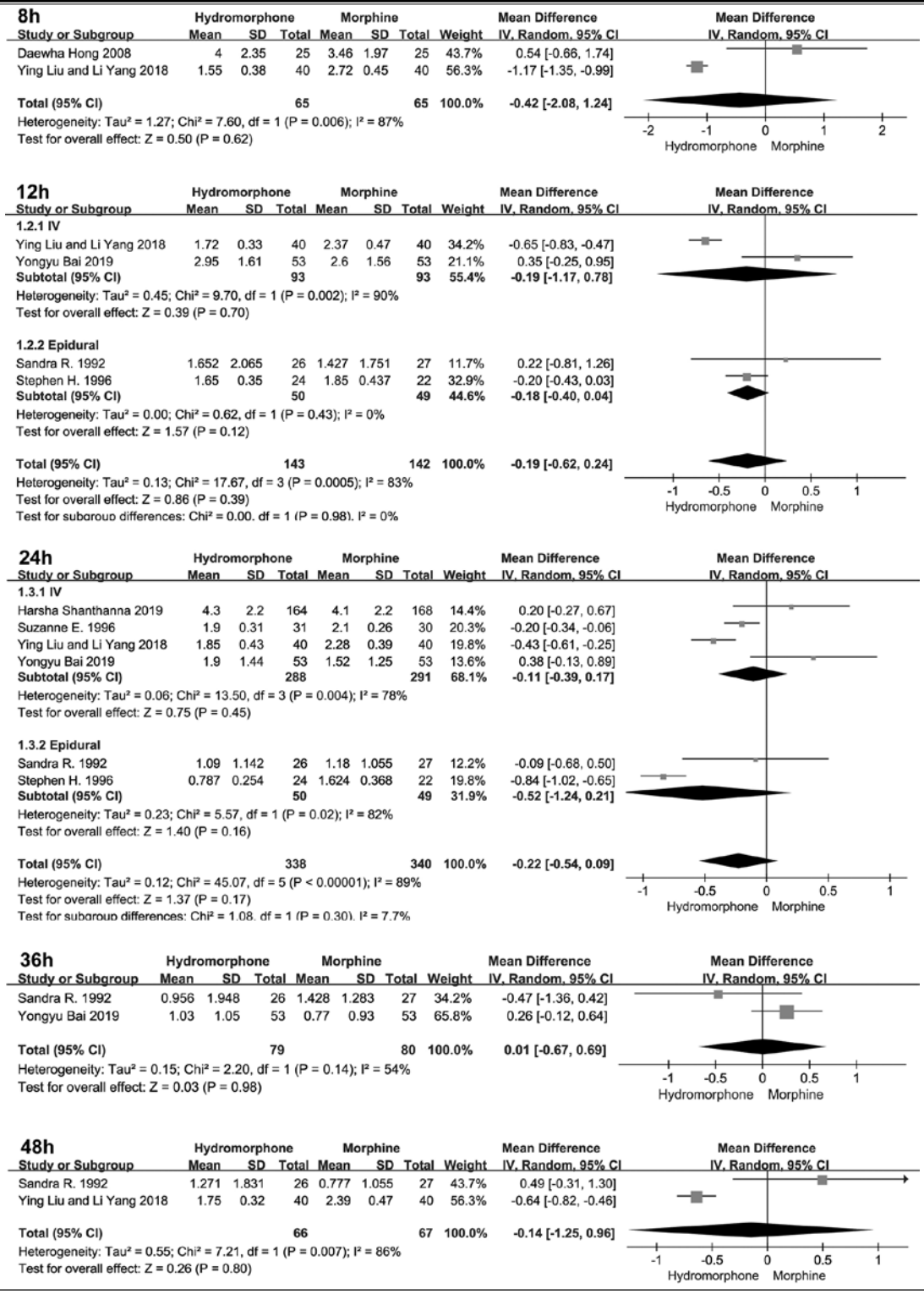

Fig. 3. *Comparative evaluation of pain scores of hydromorphone and morphine at 8 hours, 12 hours, 24 hours, 36 hours and 48 hours postsurgery. The comparison of pain scores at 12 and 24 hours postsurgery was performed by subgroup analysis of different routes of administration.*

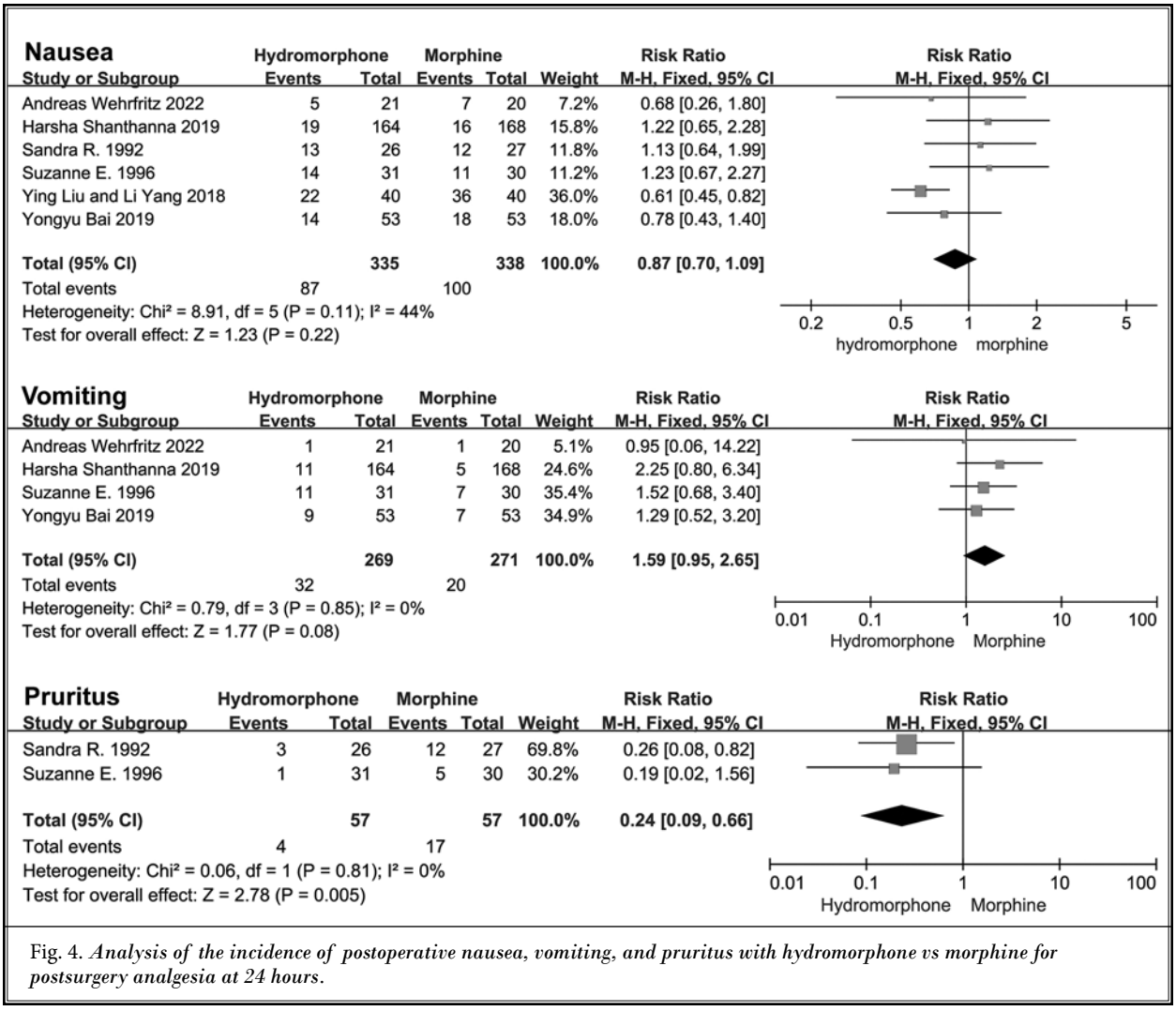

Fig. 4. *Analysis of the incidence of postoperative nausea, vomiting, and pruritus with hydromorphone vs morphine for postsurgery analgesia at 24 hours.*

not rise when titration is halted. Thus, hydromorphone may be a more appropriate option than morphine for the titration of acute analgesia, according to Felden, et al's meta-analysis (29).

The results of our meta-analysis provide a higher level of evidence for this dispute because higher quality original studies were included. Some of the conclusions drawn in our study are different from those drawn in other, similar meta-analyses in China and elsewhere, which may be because our study included not just Chinese studies, and did not set any language limit for retrieval.

Limitations

There are limitations to our study. Among the 8 studies included in this meta-analysis, there are several articles with fuzzy data and special research methods, and little of their data can be included in the study. Some of the data in the included studies only have graphs without providing detailed data. The studies in this meta-analysis all used VAS scores to evaluate pain intensity, but a VAS score is a subjective indicator, which may cause bias. There were some differences in drug dosage, measurement time, and measurement methods among the included studies. We did not conduct a subgroup analysis of doses; we only conducted a subgroup analysis of the administration route. The 8 randomized controlled trials we included had a limited sample size, and analgesic effect studies had a high degree of variability (6,17-23). Compared to larger samples, smaller trials are more prone to overestimate the treatment effect.

Because of the variations in the included studies, care should be taken when interpreting the data. Our study provides a clinical preference for using these two medicines for postsurgical analgesia, but clinical decisions also should be based on individual patient responses.

Conclusions

The analgesic effects of hydromorphone and morphine are similar, but hydromorphone's incidence of pruritus is lower at 24 hours postsurgery. This indicates that hydromorphone is an effective substitute for morphine and can provide better clinical results. Some clinical studies are old and of relatively low quality, and most of them vary widely in dose, outcome, and data measurement. Therefore, high-quality multicenter, randomized, parallel-controlled and blind trials are needed to investigate the effect and side effects of hydromorphone and morphine on postsurgery analgesia.

Author Contributions

YL: This author helped with conceptualization, data curation, formal analysis, investigation, methodology, project administration, resources, software, visualization, writing the original draft, and reviewing and editing the manuscript.

XY: This author helped with data curation and formal analysis.

FR: This author helped with data curation and formal analysis.

SL: This author helped with data curation, formal analysis, investigation, methodology, resources, software, visualization, and reviewing and editing the manuscript.

QG: This author helped with revising the manuscript.

WZ: This author helped with conceptualization, data curation, formal analysis, funding acquisition, methodology, project administration, resources, software, supervision, validation, visualization, and reviewing and editing the manuscript.

All authors reviewed the manuscript and approved it for publication.

Supplemental material is available at www.painphysicianjournal.com

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Supplemental Table 1. *Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) checklist.*

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	1-2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	3-4
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	3-4
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	5
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	5-6
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Supplemental Table 2
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	6
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	6-7
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	6-7
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	6-7
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	7
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	6
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	6
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	6
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	6
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	6-7
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	6-7
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	

Supplemental Table 1 cont. ***Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) checklist.***

Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	6-7
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	8, Figure 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	8, Figure 1
Study characteristics	17	Cite each included study and present its characteristics.	8, Figure 1
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	8-10
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	8-10
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	8-10
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	8-10
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	12-15
	23b	Discuss any limitations of the evidence included in the review.	15
	23c	Discuss any limitations of the review processes used.	12-15
	23d	Discuss implications of the results for practice, policy, and future research.	12-15
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Authorship Form
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Authorship Form
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	Authorship Form
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Authorship Form
Competing interests	26	Declare any competing interests of review authors.	Authorship Form
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	

Supplemental Table 2. ***Database search strategy (PubMed)***.

#1	"Hydromorphone"[Mesh]
#2	Dihydromorphinone[Title/Abstract]
#3	Hydromorphon[Title/Abstract]
#4	Palladone[Title/Abstract]
#5	Laudacon[Title/Abstract]
#6	Dilaudid[Title/Abstract]
#7	Hydromorphone Hydrochloride[Title/Abstract]
#8	"Morphine"[Mesh]
#9	Morphia[Title/Abstract]
#10	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 ((((((("Hydromorphone"[Mesh]) OR (Dihydromorphinone[Title/Abstract])) OR (Hydromorphon[Title/Abstract])) OR (Palladone[Title/Abstract])) OR (Laudacon[Title/Abstract])) OR (Dilaudid[Title/Abstract])) OR (Hydromorphone Hydrochloride[Title/Abstract])
#11	#8 OR #9 ("Morphine"[Mesh]) OR (Morphia[Title/Abstract])
#12	(randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR placebo[tiab] OR clinical trials as topic[mesh:noexp] OR randomly[tiab] OR trial[ti]) NOT (animals[mh] NOT humans[mh])
#13	#10 AND #11 AND #12 (((((((("Hydromorphone"[Mesh]) OR (Dihydromorphinone[Title/Abstract])) OR (Hydromorphon[Title/Abstract])) OR (Palladone[Title/Abstract])) OR (Laudacon[Title/Abstract])) OR (Dilaudid[Title/Abstract])) OR (Hydromorphone Hydrochloride[Title/Abstract])) AND (("Morphine"[Mesh]) OR (Morphia[Title/Abstract]))) AND ((randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR placebo[tiab] OR clinical trials as topic[mesh:noexp] OR randomly[tiab] OR trial[ti]) NOT (animals[mh] NOT humans[mh]))

Supplemental Table 3. *The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) evidence profile.*

Certainty assessment							No. of patients		Effect			
No. of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Hydromorphone**	**Morphine**	**Relative (95% CI)**	**Absolute (95% CI)**	**Certainty**	**Importance**
visual analog scale(8h)												
2	randomized trials	not serious	very serious[a]	not serious	very serious[c]	publication bias strongly suspected[f]	65	65	-	MD 0.42 lower (2.08 lower to 1.24 higher)	⨁◯◯◯ Very low	CRITICAL
visual analog scale(12h)												
4	randomized trials	not serious	very serious[a]	not serious	very serious[c]	none	143	142	-	MD 0.19 lower (0.62 lower to 0.24 higher)	⨁◯◯◯ Very low	CRITICAL
visual analog scale(24h)												
6	randomized trials	not serious	very serious[a]	not serious	serious[d]	none	338	340	-	MD 0.22 lower (0.54 lower to 0.09 higher)	⨁◯◯◯ Very low	CRITICAL
visual analog scale(36h)												
2	randomized trials	not serious	serious[b]	not serious	very serious[c]	publication bias strongly suspected[f]	79	80	-	MD 0.01 higher (0.67 lower to 0.69 higher)	⨁◯◯◯ Very low	CRITICAL
visual analog scale(48h)												
2	randomized trials	not serious	very serious[a]	not serious	very serious[c]	publication bias strongly suspected[f]	66	67	-	MD 0.14 lower (1.25 lower to 0.96 higher)	⨁◯◯◯ Very low	CRITICAL
Incidence of nausea at 24 hours after surgery												
6	randomized trials	not serious	not serious	not serious	not serious	none	87/335 (26.0%)	100/338 (29.6%)	RR 0.87 (0.70 to 1.09)	38 fewer per 1,000 (from 89 fewer to 27 more)	⨁⨁⨁⨁ High	CRITICAL
Incidence of vomiting at 24 hours after surgery												
4	randomized trials	not serious	not serious	not serious	serious[d]	none	32/269 (11.9%)	20/271 (7.4%)	RR 1.59 (0.95 to 2.65)	44 more per 1,000 (from 4 fewer to 122 more)	⨁⨁⨁◯ Moderate	CRITICAL
Incidence of pruritus at 24 hours after surgery												
2	randomized trials	not serious	not serious	not serious	serious[e]	publication bias strongly suspected[f]	4/57 (7.0%)	17/57 (29.8%)	RR 0.24 (0.09 to 0.66)	227 fewer per 1,000 (from 271 fewer to 101 fewer)	⨁⨁◯◯ Low	CRITICAL

CI: confidence interval; MD: mean difference; RR: risk ratio

[a]: Heterogeneity test is very large; [b]: Heterogeneity is present but not very large; [c]: The sample size is small and the 95% CI crosses the push clinical decision threshold; [d]: The 95% CI crosses the push clinical decision threshold; [e]: The sample size is small; [f]: Only few studies were included.