

Original Article

Does droperidol have a good effect of preventing morphine-induced pruritus in adults? A meta-analysis

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Abstract: Objective: We systematically evaluated the efficacy of droperidol preventing morphine-induced pruritus. Methods: We searched Cochrane Library, EMBASE, EBSCO, Web of Science, PubMed, OVID, CNKI for full reports of randomized controlled trials that study the efficacy of droperidol for preventing morphine-induced pruritus. After screening for related studies according to the inclusion criteria and exclusion criteria, data extraction and quality evaluation, useful data were obtained and then analyzed with the help of RevMan 5.0. Results: In total, we included 9 RCTs and 802 patients. Results of meta-analysis revealed: for droperidol via intravenous injection, comparison of droperidol group and control group produced no statistical difference [RR=0.81, 95% CI (0.63, 1.03)]. However, for droperidol via epidural catheter, comparison of droperidol group and control group produced a statistical difference [RR=0.71, 95% CI (0.57, 0.89)]. There was a statistically significant effect on droperidol preventing nausea and vomiting [RR=0.57, 95% CI (0.38, 0.87)]. In addition, droperidol could increase the risk of somnolence [RR=3.13, 95% CI (1.83, 5.35)]. Conclusion: This meta-analysis revealed: high dose of droperidol via intravenous injection might not have an effect of preventing morphine-induced pruritus in adults; and it might increase the incidence of somnolence. But epidural droperidol significantly reduced the incidence of pruritus.

Keywords: Droperidol, morphine, pruritus, meta-analysis

Introduction

Morphine is one of opioid drugs which are mu-receptor agonists acting on the central nervous system thus producing analgesic effect. However, morphine can cause adverse reactions such as pruritus, nausea and vomiting. Some literature shows that the rates of nausea, vomiting and pruritus caused by morphine are respectively 21.5%, 21.5% and 59.5% [1] after retrospectively studying 1304 anesthesia records.

In clinical practice, droperidol is often applied in providing sedation and inhibiting vomiting, especially effective for gynecologic patients. Moreover, a meta-analysis [2] published 13 years ago included 22 randomized controlled trials and 4 of them concerned themselves with the interaction between morphine and pruritus, revealing that droperidol could effectively prevent morphine-induced pruritus ($P=0.53$, $RR=1.71$, 95% CI (1.28, 2.29)). However, this

study did not discuss the administration of droperidol, the effect of high dose of droperidol and its side effect. Therefore, our study re-performed a meta-analysis on the topic that involved droperidol and morphine-induced pruritus, aiming to explore whether droperidol has an effect of preventing morphine-induced pruritus and its side effect.

Materials and methods

Inclusion and exclusion criteria

(1) Only human randomized controlled trials (RCTs) were included, and there were no language restrictions in this meta-analysis. (2) Adult patients received droperidol for preventing the side effect of morphine induced, and the outcome included pruritus. (3) Types of interventions included: 1) Experiment: Morphine and droperidol; 2) Control: Morphine. (4) The main outcomes were the incidences of the skin pruritus of two groups. And other outcomes were nausea and vomiting and somnolence.

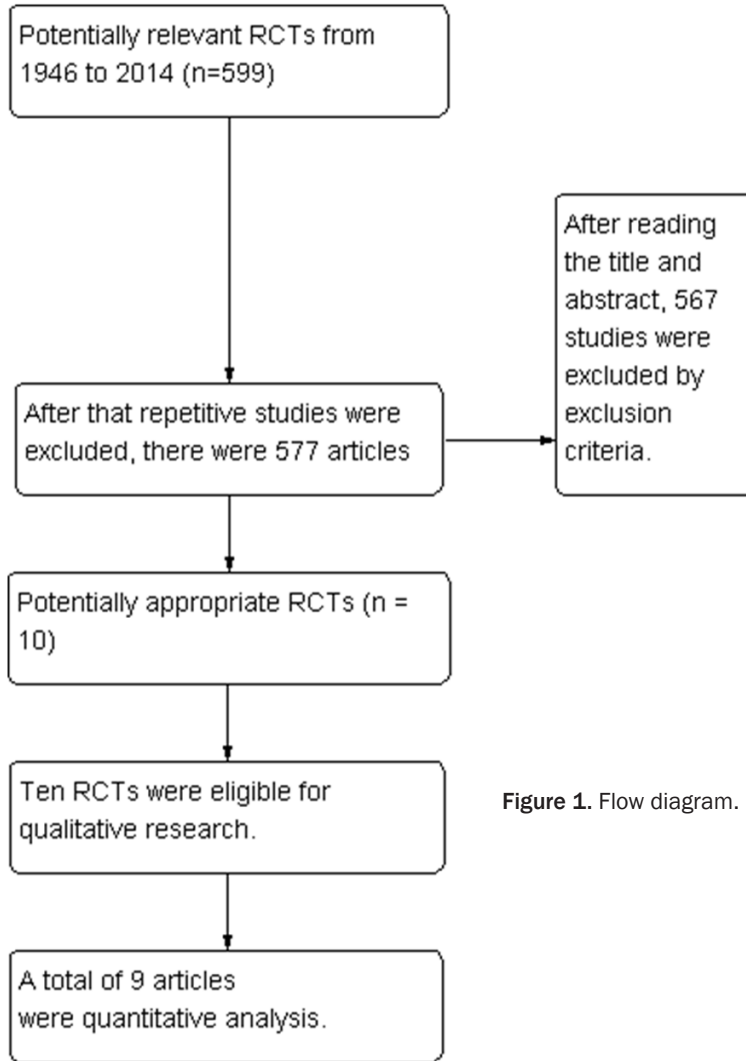


Figure 1. Flow diagram.

tion manual 5.0.1 [3]. All literatures were specifically evaluated according to the criteria. The evaluated content included the detailed description of RCT random sequence, allocation concealment methods, blinding, incomplete data, selective reporting and other bias and so on.

Data extraction

We drafted the registration form of basic information and documentation quality assessment form of each study. Data from the selected studies were extracted independently by two review authors (Cheng-Mao Zhou, Xiao-Dong Chen). If differences were in data extraction, we would discuss them with the third review author (Lin Ruan). The extracted content included the authors, the published year, the type of operation, the type of research, the interventions, the detailed description of RCT random sequence, allocation concealment methods, blinding, incomplete data, selective reporting and other bias and so on.

Search methods for identification of studies

We identified all studies by searching the following databases: Cochrane Library (Issue 9 of 12, September 2014), OVID (1946 to September Week 3 2014), EMbase (All years), PubMed (1980~2014.9), EBSCO (All years), CNKI (1980~2014.9).

The key words included “droperidol”, “morphine” and “pruritus”.

Literature selected and quality of the studies

Two reviewers (Cheng-Mao Zhou, Xiao-Dong Chen) independently screened and searched, extracted information and cross-checked the literature, and discussed with the third reviewer when the views were inconsistent. The quality method of this meta-study chose the quality evaluation criteria of RCT of the system evalua-

Statistical analysis

The Cochrane Collaboration’s RevMan 5.0.13 software was chose in the meta-analysis. We computed the relative risk (RR) with 95% confidence interval (CI) for dichotomous outcomes. A formal heterogeneity test was performed by the RevMan 5.0.13 software, and a P value was used to assess heterogeneity among trials. If $I^2 < 50%$, there was no homogeneity. If $I^2 > 50%$, there was a significant heterogeneity. The following techniques were used to solve the heterogeneity: sensitivity analysis, subgroup analysis or a random effects model.

Results

Literature search results

Initially detection of 599 documents, after excluding repeated ones, and there were 577

Droperidol and morphine-induced pruritus

Table 1. Baseline characteristics of the trials included in the meta-analysis

Author (Published year)	Country	Design	Treatment (Control)	The administration route of Dro	ASA	Surgical setting	Observation period
Sanansilp 1998 [7]	Thailand	RCT	MF 5 mg (MF 5 mg + Dro 2.5 mg)	Intravenous injection and Epidural injection	I II	Cesarean section	24 h
Horta 1993 [8]	Brazil	RCT	MF 2 mg (MF 2 mg + Dro 2.5 mg)	Intravenous injection	I II	Cesarean section	24 h
Horta 2006 [4]	Brazil	RCT	MF 2 mg (MF 2 mg + Dro 1.25 mg)	Intravenous injection	I II	Cesarean section	24 h
Almeida 1991 [9]	Brazil	RCT	MF 0.2 mg (MF 0.2 mg + Dro 2.5 mg)	Intravenous injection	I	Cesarean section	24 h
Culebras 2003 [5]	Switzerland	RCT	PCA MF 100 mg/100 ml of saline (Dro 50 ug/mg of MF)	Intravenous injection	I II III	Gynecological surgery	24 h
Cheng 2002 [11]	China	RCT	MF 2 mg (MF 2 mg + Dro 1 mg)	Epidural injection	I II	Cesarean section	24 h
Naji 1990 [10]	Switzerland	RCT	MF 4 mg (MF 4 mg + Dro 2.5 mg)	Epidural injection	I II III	Hip replacement	24 h
Horta 2000 [6]	Brazil	RCT	MF 2 mg (MF 2 mg + Dro 2.5 mg)	Epidural injection	I II	Cesarean section	24 h
Nakata 2002 [12]	Japan	RCT	MF 2 mg (MF 2 mg + Dro 2.5 mg)	Intravenous injection and Epidural injection	I II	Elective thoracic or abdominal surgery	24 h

Total data of relative study. RCT: Randomized controlled trial; MF: Morphine; Dro: Droperidol.

Droperidol and morphine-induced pruritus

Table 2. Methodological quality of the trials included in the meta-analysis

Author (Published year)	Random sequence generation	Allocation concealment	Blinding	Incomplete outcome data	Selective reporting	Other bias
Sanansilp 1998 [7]	Unclear	Low	Low	Low	Low	Low
Horta 1993 [8]	Unclear	Low	Low	Low	Unclear	Unclear
Horta 2006 [4]	Low	Low	Low	Low	Low	Low
Almeida 1991 [9]	Unclear	Unclear	Low	Low	Low	Low
Culebras 2003 [5]	Low	Low	Low	Low	Unclear	Low
Cheng 2002 [11]	Unclear	Unclear	Unclear	Low	Low	Low
Naji 1990 [10]	Unclear	Unclear	Unclear	Low	Low	Low
Horta 2000 [6]	Low	Low	Low	Low	Low	Low
Nakata 2002 [12]	Low	Low	Low	Low	Low	Low

documents for further screening. After reading the title and abstract, there were only ten literatures. At last, 10 RCTs [4-13] were included, 8 RCTs [4-10, 12, 13] were English, 1 RCT was Chinese [11] (**Figure 1**).

Characteristics of included studies

Nine RCTs [4-12] of the included studies contains 802 patients. There were several patients withdrew the study in Horta 1993 [8], Culebras 2003 [5] and Nakata 2002 [12]. In addition, one article [13] was no full text (We have contacted the author, but there was no reply; and the result of our meta-analysis was similar with theirs), so it was as a descriptive analysis. Sanansilp (1) 1998, Sanansilp (2) 1998 and Sanansilp 1998 were from a same study [7]. And Nakata 2002, Nakata (1) 2002 and Nakata (2) 2002 were from a same study [12]. Basic information of each included study was shown in **Table 1**.

Evaluation of method quality of included study

In the 9 RCTs, only 4 studies [4-6, 12] described the true detail of RCT random sequence, and 5 RCTs [4-8, 12] described the true detail of allocation concealment methods; in addition to two studies [10, 11], other studies correctly described the blinding concrete implementation methods; there was no selective reporting result (**Table 2**).

Result of this meta-analysis

The incidences of pruritus were specifically reported in 9 RCTs [4-12]. The observation time was chose 24 hours in each study, and high dose of drug was chose in experiment group

and control group when mutil-group was existed. In this meta-analysis, no pruritus or pruritus was described by two categorical variables. Therefore, two different administrations were selected to make subgroup analyzes.

Five hundred and fifty patients were included in this subgroup analysis. There was no statistically significant within it [RR=0.81, 95% CI (0.63, 1.03)]. It showed that intravenous administration of droperidol had no effect of preventing morphine-induced pruritus. The random model was selected with a significant heterogeneity (**Figure 2**).

Two hundred and seventy-eight patients were included in this subgroup analysis. There was a statistically significant within it [RR=0.71, 95% CI (0.57, 0.89)]. It meant that epidural administration of droperidol might have an effect of preventing morphine-induced pruritus. The fixed model was selected without a significant heterogeneity (**Figure 3**).

The effect of droperidol on preventing the side effect of morphine

Three hundred and thirty-five patients were included in this meta-analysis. There was no statistically significant within it [RR=0.57, 95% CI (0.38, 0.87)]. It showed that droperidol also had an effect of preventing morphine-induced nausea and vomiting. The fixed model was selected without a significant heterogeneity (**Figure 4A**).

Three hundred and eighty-seven patients were included in this meta-analysis. There was no statistically significant within it [RR=3.13, 95% CI (1.83, 5.35)]. It showed that droperidol could

Droperidol and morphine-induced pruritus

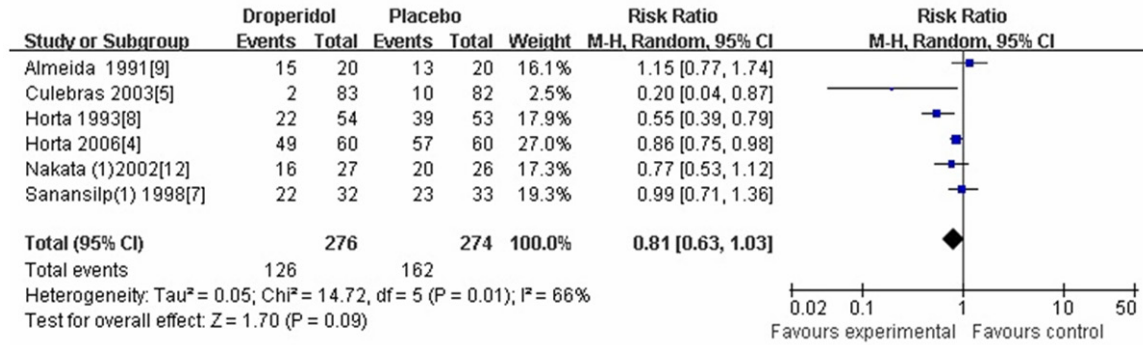


Figure 2. The incidence of pruritus in the intravenous administration of droperidol.

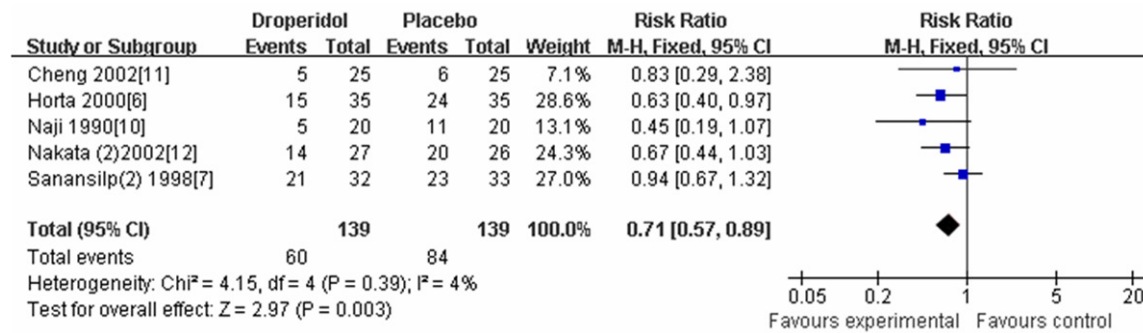


Figure 3. The incidence of pruritus in the epidural administration of droperidol.

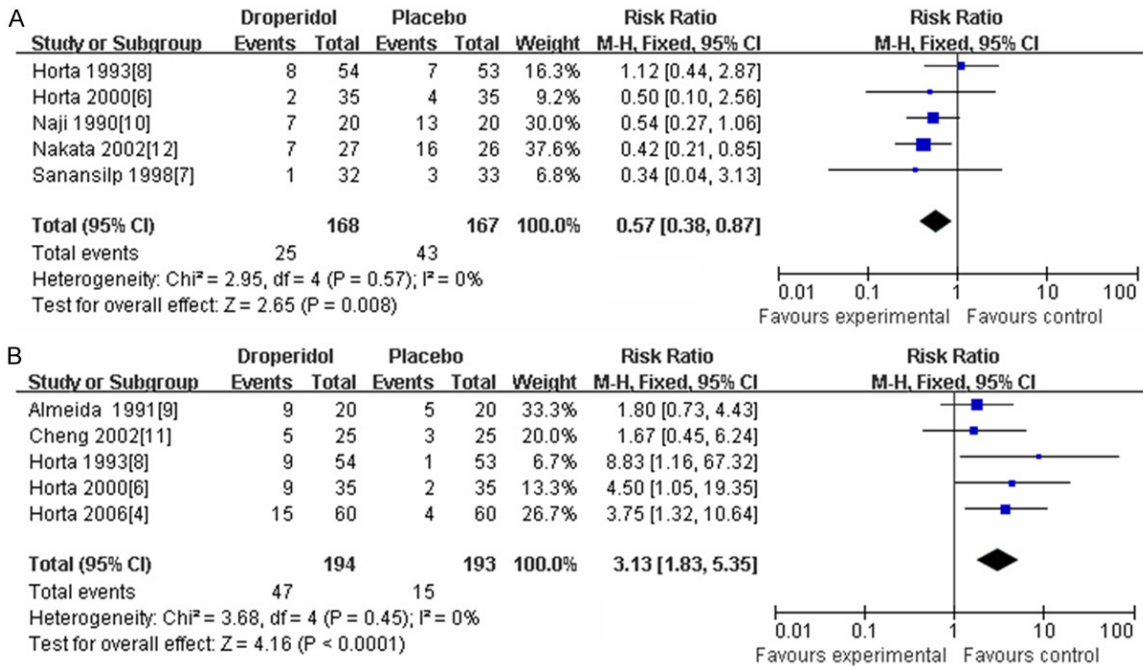


Figure 4. The incidence of nausea and vomiting (A) and somnolence (B). (A) Droperidol and morphine-induced nausea and vomiting; (B) Droperidol and somnolence.

increase the risk of somnolence. The fixed model was selected without a significant heterogeneity (Figure 4B).

Discussion

The methodological quality of the included studies

The 9 studies included didn't address the sources of other literatures and one of them whose full vision wasn't obtained. Thus, publication bias was perhaps produced, although we tried comprehensive document retrieval.

Droperidol for morphine-induced pruritus

Analgesia using morphine could produce some adverse reactions and pruritus is one of common complications. This meta-analysis included 9 RCTs. Subgroup analysis had to be performed due to heavy heterogeneity. However, subgroup analysis didn't completely eliminate heterogeneity and therefore random model was adopted. Our study reveals that droperidol administration via intravenous injection has no effect of preventing morphine-induced pruritus; droperidol administration via epidural catheter has an effect of preventing morphine-induced pruritus either. Allergic reactions could also result in different outcomes. Finally, different persons have different responses to drugs, which further results in different rates of post-operative pruritus.

The technique of grouping was applied in several studies included. The outcome in intravenous administration of droperidol was similar with this literature [13], which also found high-dose intravenous administration of droperidol has no effect of preventing morphine-induced pruritus. However, the outcome in epidural administration of droperidol was reversed.

And the most types of operation were cesarean section in this meta-analysis, which showed that droperidol did not prevent morphine-induced pruritus. Meanwhile, ondansetron, another antagonist on preventing morphine-induced pruritus, also showed a similar effect in cesarean section [14]. The administration of ondansetron also was intravenous injection.

In addition, for the side effect of morphine, high dose of droperidol had a good effect of preventing nausea and vomiting. At a previous

study [15], droperidol also had a good effect of preventing nausea and vomiting. And for the aspect of somnolence, droperidol could increase it in our result. There was a similar result in other study [16]. Low-dose droperidol (≤ 1 mg or $\leq 15 \mu\text{g kg}^{-1}$), however, had little risk of dizziness, and it had a good efficacy on preventing nausea and vomiting [17].

Several clinical problems with this meta-analysis: 1) Regarding to the different grouping methods of time quantum, this meta-analysis chooses only one common time quantum-24 h. However, the efficacy in different time quanta may vary, which produces possible bias [9]; 2) The sorts and doses of anesthetics or different drug collocations may interfere the results. (Some literature reveals that the rate of pruritus produced by opioids combined with lidocaine is lower than that of opioids combined with bupivacaine [18]). 3) Morphine-induced pruritus may differ due to different administration routes-via iv and via epidural catheter. 4) Other adverse reactions may cover up pruritus: some study has pointed out the strength of pain may disturb the sensation of pruritus [19]. 5) The patients included are mostly female adults. It indicates that the representativeness of this meta-analysis is limited.

Limitations of this meta-analysis

The limitations of this meta-analysis lie in: 1) studies included are not many and the sample size is not large enough; 2) for the studies included, not all of them concretely describe the randomization, blinding and allocation concealment. This may lead to selection bias or false positive result; 3) the studies included are all published literatures without any other sources, which may cause bias; 4) doses of morphine and droperidol are different between the studies included. This meta-analysis only analyzes data of high doses, which may cause selection bias; 5) the incomplete measurement indexes: small sample size, different anesthetic techniques, different local anesthetics and analgesic techniques. This may influence the results; 6) several studies are from the same researcher, which may influence the results; 7) heavy heterogeneity exists between studies included. Adopting techniques like subgroup analysis and random model for meta-analysis doesn't eliminate heterogeneity, which possibly influences the results.

Conclusion

This systematic review shows that high dose of droperidol via intravenous injection may not prevent morphine-induced pruritus. Meantime, it might not have a good efficacy for prevent the side effect of morphine included somnolence. But epidural droperidol significantly reduced the incidence of pruritus.

More high-quality clinical prospective RCTs on the topic whether droperidol has an effect of preventing morphine-induced pruritus are needed. More efforts can be made to try different combinations of drug administrations and doses, because conclusion drawn whether droperidol has an effect of preventing morphine-induced pruritus based on only one combination will inevitably exaggerate or underrate such effect.

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Disclosure of conflict of interest

None.

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Droperidol and morphine-induced pruritus

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