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ORIGINAL RESEARCH

Efficacy of ondansetron for the prevention of propofol injection pain: a meta-analysis

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Aim: This review was performed to investigate the effect of ondansetron on the prevention of propofol injection pain.

Methods: PubMed, Cochrane Library, and China National Knowledge Infrastructure (CNKI) were searched for randomized controlled trials (RCTs) of ondansetron in preventing the pain on injection of propofol. Then, RevMan 5.2 was adopted to conduct a meta-analysis on propofol injection pain.

Results: Ten RCTs, totaling 782 patients, were included in this analysis. The meta-analysis showed that: 1) compared with the control group, the ondansetron group was related to a decreasing incidence of propofol injection pain, and it was statistically significant (risk ratio [RR] = 0.41, 95% confidence interval [CI, 0.34, 0.49], $P < 0.00001$); 2) compared with the incidence of propofol injection pain in the lidocaine group, there was no difference and no statistical significance (RR = 1.28, 95% CI [0.85, 1.93], $P = 0.25$); 3) no statistically significant differences were found between the ondansetron and magnesium sulfate groups in the incidence of propofol injection pain (RR = 1.20, 95% CI [0.87, 1.66], $P = 0.27$); and 4) the incidence of ondansetron group igniting moderate pain (RR = 0.37, 95% CI [0.26, 0.52], $P < 0.00001$) and severe pain (RR = 0.27, 95% CI [0.17, 0.43] $P < 0.00001$) was less likely to occur during the injection of propofol compared with the control group, but there was no difference between the ondansetron and control groups in the incidence of mild propofol injection pain (RR = 0.83, 95% CI [0.63, 1.10], $P = 0.20$).

Conclusion: Ondansetron can effectively prevent propofol injection pain, and the effect is similar to that of magnesium sulfate and lidocaine.

Keywords: ondansetron, propofol injection pain, meta-analysis

Introduction

Propofol, as an induction agent in general anesthesia, has been widely used in clinical anesthesia and sedation. Propofol can make one wake up quickly, and it is commonly used in the induction and maintenance of anesthesia. It has a few side effects, but injection pain is a common one.[1] A study[2] reported that the total incidence of propofol injection pain ranged from 40% to 86%.

Currently, lidocaine and opioid drugs have been used to prevent propofol injection pain, but they have generated several adverse reactions. In addition to preventing nausea and vomiting, ondansetron can also prevent propofol injection pain. In this study, a meta-analysis was performed to study the efficacy of ondansetron for the prevention of propofol injection pain.

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Methods

The following are the inclusion criteria:

1. Settings and design: randomized controlled trials (RCTs) of ondansetron for the prevention of propofol injection pain.
2. Study subjects: patients who received propofol-induced intravenous injection.
3. Interventions: the experimental group was given ondansetron, while the control group received placebo.
4. Outcome indicators: incidence of propofol injection pain.

The following are the exclusion criteria:

1. Incomplete data
2. People allergic to ondansetron.

Search strategy

We searched PubMed, Cochrane Library and China National Knowledge Infrastructure (CNKI) with the last search date of August 2016. Search terms included propofol, injection pain, and ondansetron.

Literature screening, data extraction, and quality assessment

Two researchers independently screened the articles and extracted data based on the inclusion and exclusion criteria and then cross-checked with each other. They consulted with a third party to decide whether to include the article when there was a disagreement. Extraction included the following: document title, author, source, year of publication, experimental group, sample size, surgical options, interventions, dose of administration, and incidence rate of propofol.

Quality assessment

Methodological quality of included studies was assessed according to Jadad scale.

Data processing

Review Manager 5.2 was used to conduct the meta-analysis. First, we adopted χ^2 test to test the heterogeneity of the included studies. A fixed-effects model was employed to conduct a meta-analysis when $P > 0.05$, indicating that there was no heterogeneity among the clinical studies; when heterogeneity was found among the studies ($P < 0.05$), we analyzed the cause for the heterogeneity and we also conducted a subgroup analysis of the factors that may lead to heterogeneity. A random-effects model was utilized when each study showed statistical heterogeneity rather than clinical heterogeneity or if the differences had no significance. To perform the statistical analysis, we used risk ratio (RR) for dichotomous variables and weighted mean difference (WMD) for continuous variables. Both were expressed with 95% confidence intervals (CIs).

Results

Search results and quality evaluation

According to the abovementioned strategy, first, 144 openly published articles were searched. By reading the literature and abstracts, excluding 134 articles based on the inclusion and exclusion criteria, we had 10 articles totaling 782 patients included in the study.[3–12] Patients in the 10 included articles were randomly assigned to groups (Figure 1). General information of all the included studies is presented in Table 1.

Meta-analysis

Propofol injection pain

A random-effects model was chosen because statistically significant heterogeneity was found between the ondansetron and control groups. The results showed that the ondansetron group has a lower incidence of propofol injection pain compared with the control group, and it was statistically significant (RR = 0.41, 95% CI [0.34, 0.49], $P < 0.00001$; Figure 2).

Level of propofol injection pain

Mild injection pain: Nine included studies reported the incidence of mild propofol injection pain. No statistical heterogeneity ($P = 0.24$, $I^2 = 23\%$) was found. A fixed-effects model was employed to perform a meta-analysis, indicating that

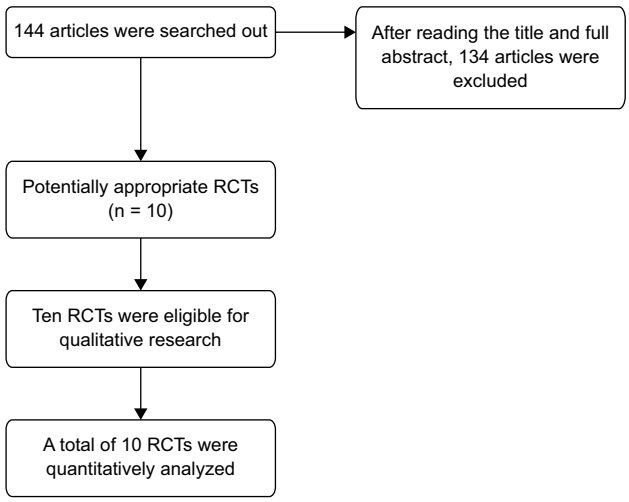

Figure 1 Flow diagram.
Abbreviation: RCTs, randomized controlled trials.

Table 1 Characteristics and Jadad score of the included studies in the meta-analysis

Study	Country	Head count	Group	Surgery	Jadad score
Kang et al[7]	Korea	90	Ondansetron 4 mg 1% lidocaine 2 mL Normal saline 10 mL	Elective surgery	4
Zahedi et al[6]	Iran	135	Ondansetron 4 mg 50 mg tramadol Normal saline	Elective eye surgeries	4
Ambesh et al[8]	India	80	Ondansetron 4 mg Normal saline	Elective gastrointestinal surgery	4
Drašković et al[5]	Serbian	120	Ondansetron 4 mg Alfentanil Nitric oxide and oxygen Normal saline	Elective surgery	4
Alipour et al[4]	Iran	336	Ondansetron 4 mg Paracetamol 2 mg/kg Magnesium sulfate 2 mmol Granisetron 2 mg lidocaine 40 mg Normal saline	Elective surgery	5
Rahimzadeh et al[3]	Iran	90	Ondansetron 4 mg Magnesium sulfate 2 mmol Normal saline	Elective surgery	4
Liu et al[11]	China	60	Ondansetron 4 mg Normal saline	Elective surgery	4
Lu[9]	China	80	Ondansetron 4 mg Normal saline	Elective surgery	4
Yan et al[10]	China	180	Ondansetron 4 mg Normal saline Lidocaine 40 mg	Elective surgery	5
Zhu et al[12]	China	90	Ondansetron 4 mg Normal saline Lidocaine 40 mg	Elective surgery	4

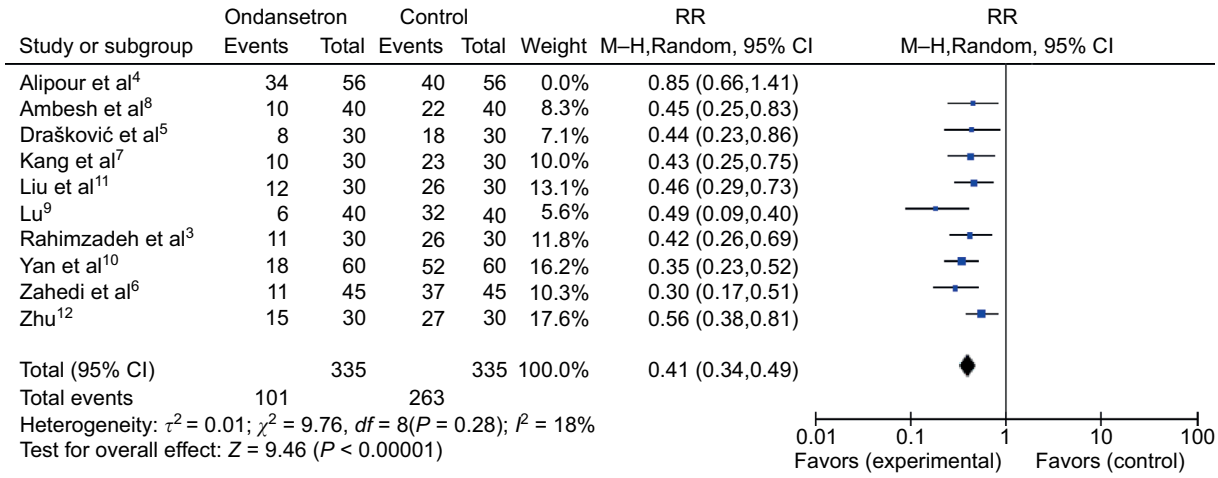

Figure 2 The incidence of propofol injection pain of the ondansetron group compared with the control group.
Abbreviations: CI, confidence interval; RR, risk ratio; M–H, Mantel–Haenszel.

the incidence of propofol injection pain in the ondansetron group was not better than that in the control group (RR = 0.83, 95% CI [0.63, 1.10], $P = 0.20$; Figure 3).

Moderate pain: Nine included studies reported the incidence of moderate propofol injection pain. No statistical heterogeneity ($P = 0.21$, $I^2 = 28\%$) was found. A fixed-effects model was adopted to conduct a meta-analysis, showing that the incidence of propofol injection pain in the ondansetron group was lower than that in the control group (RR = 0.37, 95% CI [0.26, 0.52], $P < 0.00001$; Figure 4).

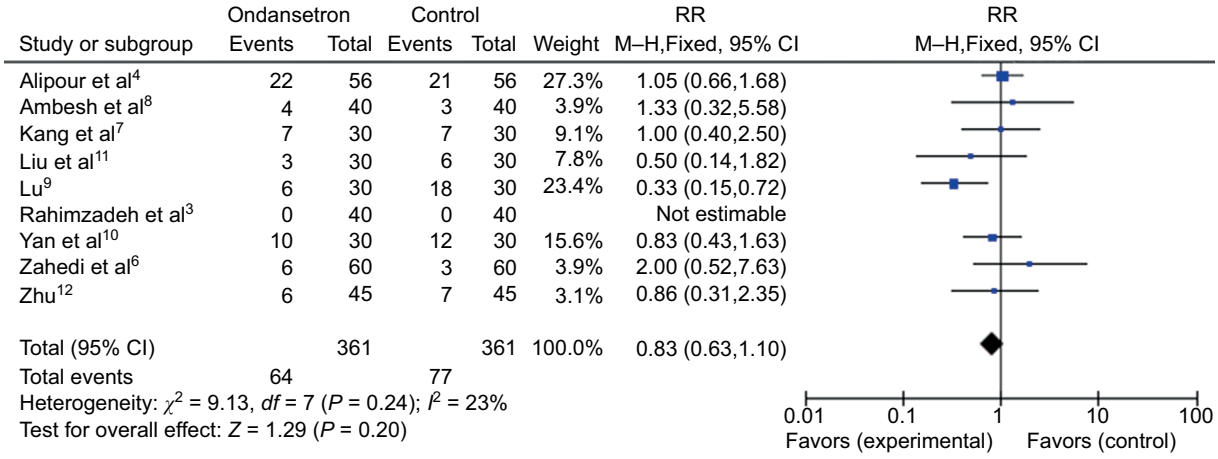

Figure 3 The incidence of mild propofol injection pain of the ondansetron group compared with the control group.
Abbreviations: CI, confidence interval; RR, risk ratio; M–H, Mantel–Haenszel.

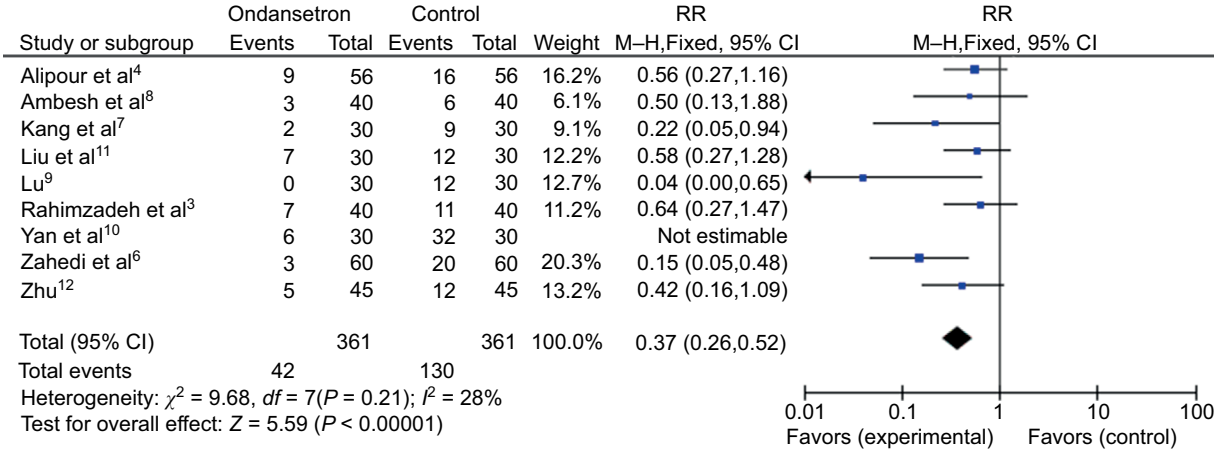

Figure 4 The incidence of moderate propofol injection pain of the ondansetron group compared with the control group.
Abbreviations: CI, confidence interval; RR, risk ratio; M–H, Mantel–Haenszel.

Severe pain: Nine included studies reported the incidence of severe propofol injection pain. No statistical heterogeneity (P = 0.75, I^2 = 0%) was found. A fixed-effects model was used to conduct a meta-analysis, showing that the incidence of propofol injection pain in the ondansetron group was lower than that in the control group (RR = 0.27, 95% CI [0.17, 0.43], P <0.00001; Figure 5).

Ondansetron group and lidocaine group

A random-effects model was employed because statistically significant heterogeneity was found between the ondansetron and lidocaine groups. The results suggested that the efficacy of lidocaine in preventing propofol injection pain is similar to that with ondansetron, and no statistical significance was found (RR = 1.28, 95% CI [0.85, 1.93], P = 0.25; Figure 6).

Ondansetron group and magnesium sulfate group

A fixed-effects model was applied because no statistically significant heterogeneity was found between the ondansetron and magnesium sulfate groups. The results indicated that the efficacy of lidocaine in preventing propofol injection pain was as effective as that with magnesium sulfate, and there was no significant significance (RR = 1.20, 95% CI [0.87, 1.66], P = 0.27; Figure 7).

Sensitivity analysis

As heterogeneity was found between the ondansetron and control groups, sensitivity analysis was conducted. After excluding a study,[5] the heterogeneity was I^2 = 18%, and a fixed-effects model was used to conduct a meta-analysis. The results were (RR = 0.41, 95% CI [0.34, 0.49], P < 0.00001) consistent with the previous ones. This indicated that the

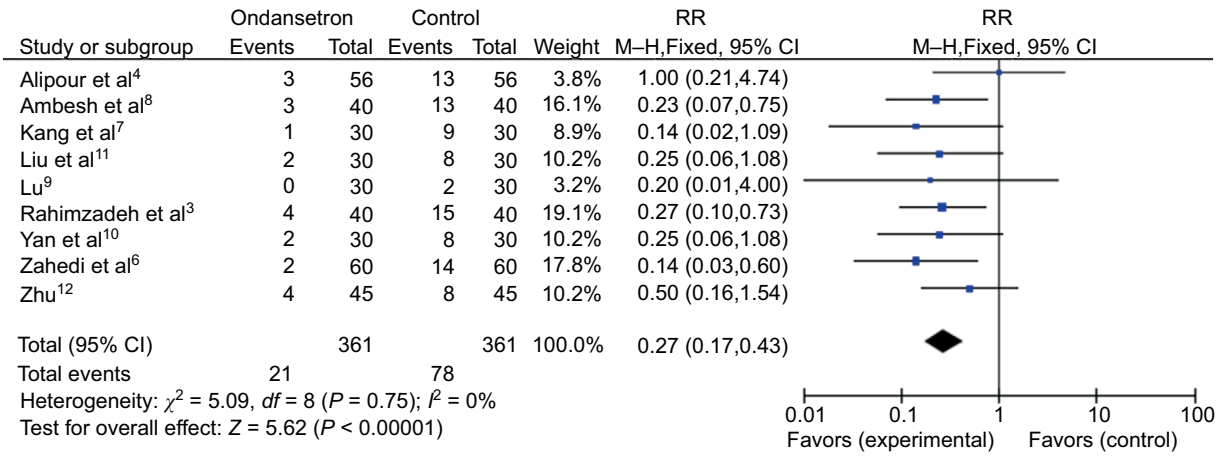

Figure 5 The incidence of severe propofol injection pain of the ondansetron group compared with the control group.
Abbreviations: CI, confidence interval; RR, risk ratio; M–H, Mantel–Haenszel.

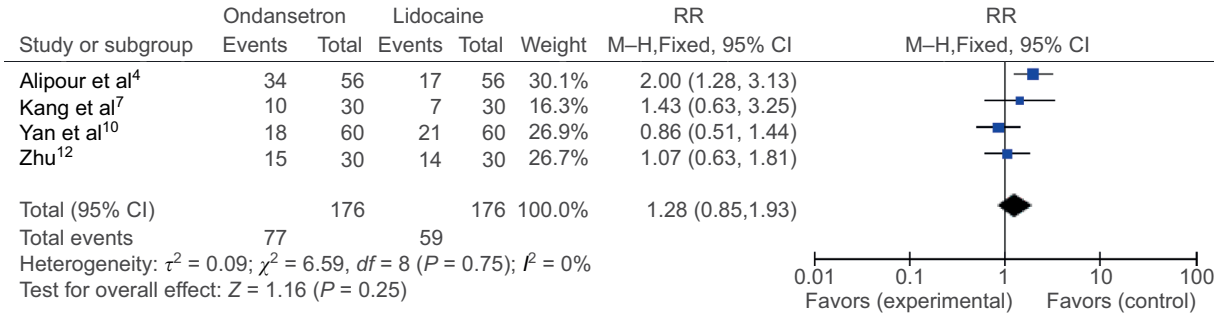

Figure 6 The incidence of propofol injection pain of the ondansetron group compared with the lidocaine group.
Abbreviations: CI, confidence interval; RR, risk ratio; M–H, Mantel–Haenszel.

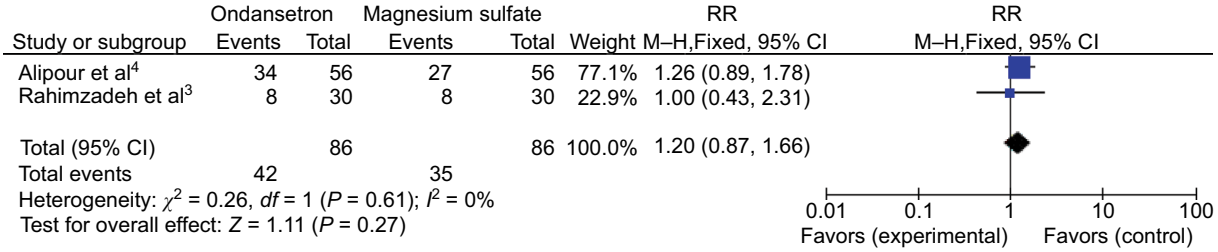

Figure 7 The incidence of propofol injection pain of the ondansetron group compared with the magnesium sulfate group.
Abbreviations: CI, confidence interval; RR, risk ratio; M–H, Mantel–Haenszel.

stability was good. The funnel plot analysis demonstrated that the results were symmetrical.

Discussion

Several studies have shown the underlying mechanism of propofol-induced pain.[13] The possible mechanism may be that propofol can activate the kallikrein–kinin system and release bradykinin, resulting in venous dilation and increased permeability, thereby increasing contacts between propofol aqueous phase and free nerve endings, causing propofol injection pain. However, recent studies showed that compared with saline, propofol did not increase the plasma concentrations of bradykinin.[14,15]

Ondansetron, as a distinctive 5-HT3 antagonist, is an antiemetic commonly used for preventing postoperative nausea and vomiting (PONV). The dose for an adult is 4 mg. Ye et al[16] showed that the effect of subcutaneous injection of ondansetron was 15 times than that of local anesthesia with lidocaine. The molecular structure of 5-HT3 receptor blockers was completely different from that of local anesthetic, but it has a similar effect to that of local anesthetic. However, the mechanism is not yet entirely clear; it may be blocking the

Na^+ channels and peripheral 5-HT3 receptors that are related to pain pathways. Meanwhile, ondansetron can be combined with the body of micro-receptors to activate.

The study collected 10 RCTs to conduct the meta-analysis. The results showed that ondansetron can effectively prevent propofol injection pain, and the effect is similar to that of magnesium sulfate and lidocaine.

Shortcomings and limitations of this study are as follows: 1) standard literature was limited, and the sample size was relatively insufficient, these factors could make the power of test insufficient; and 2) differences existed among surgeries, the drug concentration, doses of administration, and outcome indicators of the included RCTs. These factors are likely to affect the comprehensive analysis and conclusion. Therefore, more rigorously designed and high-quality studies are needed to reduce or lower the effect of bias on study results.

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Disclosure

The authors report no conflicts of interest in this work.

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