Research Article

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Clinical efficacy of 5-hydroxytryptamine 3 receptor antagonists in reducing propofol injection pain, postoperative nausea/vomiting and shivering: A meta-analysis

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Abstract: Objective To investigate the clinical efficacy of 5-hydroxytryptamine 3 (5-HT3) receptor antagonists in reducing propofol injection pain, postoperative nausea/vomiting, and shivering through pooling the available published data.

Methods Prospective randomized clinical studies relevant to 5-HT3 receptor antagonists in reducing propofol injection pain published before June 2019 were identified from four electronic databases, Pubmed, the Cochrane central register of controlled trials, EMBASE and Wanfang. The incidence of propofol injection pain, postoperative nausea/vomiting, and shivering in patients after 5-HT3 receptor antagonists were compared to relevant control groups by pooling the individual data through random or fixed-effect models. The publication bias was assessed by funnel plot and Egger’s line regression test.

Results After screening, a total of 19 publications relevant to 5-HT3 receptor antagonists in reducing propofol injection pain and prevention of postoperative nausea/vomiting or shivering were included for analysis. The pooled results demonstrated that 5-HT3 receptor antagonists could significantly reduce the total propofol injection pain compared to placebo (RR=0.49, 95%CI:0.45-0.54, P<0.05). For mild propofol injection pain, there was no statistical difference between 5-HT3 receptor antagonists and control groups (RR=1.07, 95%CI:0.89-1.29, P>0.05). However, for moderate (RR=0.37, 95%CI: 0.31-0.46, P<0.05) and severe (RR=0.19, 95%CI:0.14-0.27, P<0.05) propofol injection pain, the incidence in 5-HT3 receptor antagonists was significantly lower than that of control groups. The pooled results also indicated that incidence of postoperative nausea/vomiting (RR=0.28, 95%CI:0.17-0.44, P<0.05) and postoperative shivering (RR=0.33, 95%CI:0.23-0.48, P<0.05) were significantly reduced in 5-HT3 receptor antagonists group compared to control group with a statistical difference.

Conclusion: In this meta-analysis, 5-HT3 receptor antagonists effectively reduced propofol injection pain, postoperative nausea/vomiting, and shivering.

Keywords: 5-HT3, receptor antagonists; propofol injection pain; postoperative nausea/vomiting; meta-analysis

Introduction

Propofol is one of the most widely used clinical intravenous anesthetics with the advantages of rapid onset, complete recovery, no accumulation, and good controllability. However, local injection pain is a common adverse reaction, with an incidence rate of 28% to 90% in adults and 28% to 85% in children [1]. Propofol injection pain can cause obvious discomfort and distress to the patient, affecting blood pressure and heart rate [2-4].

The preventive effect of 5-HT3 receptor antagonists (such as ondansetron, granisetron, and tropisetron) on nausea and vomiting after surgery had been confirmed by the previous publications [5, 6]. Compared with other antiemetic drugs, 5-HT3 receptor antagonists have fewer side effects and no sedative and hypnotic effects. Several publications have shown that 5-HT3 receptor antagonists can effectively prevent propofol injection pain compared to the placebo [7, 8]. In order to provide more reliable evidence for the clinical application of 5-HT3 receptor antagonists for reducing propofol injection pain, we performed this meta-analysis by pooling the available published data relevant to 5-HT3 receptor antagonists on prevention propofol injection pain.

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Material and methods

Search Strategy

The publications were electronically searched according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement flow chart in the relevant databases (Figure 1). Prospective randomized clinical studies relevant to 5-hydroxytryptamine 3 receptor antagonists in reducing propofol injection pain published before June 2019 were systematically searched in the electronic databases of Pubmed, the Cochrane central register of controlled trials, EMBASE and Wanfang. The databases were searched using the following terms: propofol injection pain; 5-hydroxytryptamine 3 receptor antagonists/5-HT$_3$ receptor antagonists; ondansetron; granisetron; tropisetron; palonosetron; ramosetron. The search was confined to humans, and in either English or Chinese language only.

Data extraction and quality assessment

The data was extracted from each of the included studies by two independent reviewers and cross-checked. The general information such as named first author, publication date, sample size, 5-HT$_3$ receptor antagonist dosage, and administration in each study were extracted. The incidence of propofol injection pain, postoperative nausea/vomiting, and shivering were also extracted from each included publication.

Quality assessment

The methodological qualities of the included 19 publications were evaluated by two reviewers Wenjie Zhou & Jie Zhou independently by using the Cochrane Reviews Handbook 5.0. Six questionnaires, including randomization, allocation concealment, blinding, withdraw, free of selective reporting and other bias according were used in the quality evaluation analysis [9].

Statistical analysis

Stata12.0 software was used for data analysis. Dichotomous data such as propofol injection pain postoperative nausea and vomiting were expressed as a number and combined by the effect size of risk ratio (RR) with a 95% confidence interval (CI). Statistical heterogeneity across the included

Results

General characteristics of the included publications

A total of 19 publications [7, 8, 12-28] relevant to 5-HT$_3$ receptor antagonists in reducing propofol injection pain and prevention of postoperative nausea and vomiting or shivering were included in this study. Of the 19 studies, five 5-HT$_3$ receptor antagonists, ondansetron, granisetron, tropisetron, palonosetron, and ramosetron, were included for reducing propofol injection pain. The general characteristics of the included 19 publications were shown in Table 1.

The quality of the included studies

The methodological quality of the included 19 studies were assessed by six questionnaires including, randomization, allocation concealment, blinding, withdraw, free of selective reporting, and other bias according to the Cochrane Reviews Handbook 5.0. Generally, the methodological quality of the included 19 was of moderate risk of bias. The detailed quality results of each included study were demonstrated in Table 2.
Table 1: Study design and cohort characteristics of included studies.

| First author | Year | No of subjects(5-HT3RA/Control) | Administration | Operation | Induced anesthesia |
|--------------|------|---------------------------------|----------------|-----------|--------------------|
| Arnbesh      | 1999 | 40/40                            | Ondansetron 4mg 0.9\%NaCl 2mL | NA        | Local venous reflux was blocked by ligation of forearm with tourniquet for 10 seconds followed by 5 mL pretreatment solution injected into vein, then tourniquet was loosened, and 25\% of the amount of propofol was injected into vein (2.5 mg/kg) in 20 seconds. |
| Dubey        | 2003 | 50/50                            | Granisetron 2mg 0.9\%NaCl 2mL | Laparoscopic surgery | Local venous reflux was blocked by ligation of forearm with tourniquet for 10 seconds followed by 5 mL pretreatment solution injected into vein, then tourniquet was loosened, and 25\% of the amount of propofol was injected into vein (2.5 mg/kg) in 20 seconds. |
| Cao DH       | 2005 | 29/30                            | Ondansetron 4mg 0.9\%NaCl 2mL | NA        | Intravenous injection of 3 mL of pretreatment solution and 0.5 mL/s of propofol 180 mg after 30 seconds. |
| Liu F        | 2006 | 31/31                            | Tropisetron 2mg 0.9\%NaCl 2mL | NA        | Intravenous injection of pretreatment solution 2 mL, 60 seconds followed by injection of 2 mg/kg propofol |
| Ma YS        | 2009 | 50/50                            | Granisetron 2mg 0.9\%NaCl 3mL | Gynecological laparoscopy | Intravenous injection of 3 mL of pretreatment solution, release tourniquet after 1 minute, and inject propofol at a speed of 0.5 mL/s. Pain score was assessed when the dose was 0.5 mg/kg. |
| Xu XX        | 2010 | 30/30                            | Tropisetron 2mg 0.9\%NaCl 2mL | NA        | 2 mL of pretreatment solution was injected intravenously, and 1.5-2 mg/kg of propofol was injected at a speed of 5 mg/s after 60 seconds. |
| Fu HQ        | 2010 | 100/100                          | Granisetron 2mg 0.9\%NaCl 3mL | Laparoscopic cholecystectomy | Intravenous injection of 3 mL of pretreatment solution, release tourniquet after 1 minute, and inject propofol at a speed of 0.5 mL/s. Pain score was assessed when the dose was 0.5 mg/kg. |
| Liu QM       | 2011 | 30/30                            | Ondansetron 4mg 0.9\%NaCl 3mL | Painless gastroscopy | 3 mL of pretreatment solution was injected intravenously, and 1.5-2 mg/kg of propofol was injected at the speed of 0.5 mL/S after 30 seconds. |
| Yan YX       | 2011 | 60/60                            | Ondansetron 4mg 0.9\%NaCl 2mL | Painless gastroscopy | Intravenous injection of 2 mL pretreatment solution and 60 seconds followed by injection of 2.5 mg/kg propofol |
| Lu H         | 2011 | 40/40                            | Ondansetron 4mg 0.9\%NaCl 2mL | Painless gastroscopy | Intravenous injection of pretreatment solution 2 mL, 30 seconds followed by injection of 2mg/kg propofol |
Propofol injection pain incidence

In the aspect of general injection pain incidence, there was significant statistical heterogeneity across the 19 studies. Therefore, the data were pooled by random-effects methods. The pooled results demonstrated that the 5-HT\textsubscript{3} receptor antagonists could significantly reduce the total propofol injection pain compared to placebo (RR=0.49, 95%CI:0.45-0.54, P<0.05). For the different 5-HT\textsubscript{3} receptor antagonists ondansetron, granisetron, tropisetron, palonosetron, and ramosetron, the propofol injection pain incidence was also statistically significantly reduced (Pall<0.05), Figure 2.
Propofol injection pain degree analysis

According to the pain degree, we performed a subgroup analysis for mild, moderate, and severe propofol injection pain comparing incidence between 5-HT\textsubscript{3} receptor antagonists and control groups. For mild propofol injection pain, there was no statistical difference between 5-HT\textsubscript{3} receptor antagonists and control groups (RR=1.07, 95%CI:0.89-1.29, P>0.05). However, for moderate (RR=0.37, 95%CI:0.31-0.46, P<0.05) and severe (RR=0.19, 95%CI:0.14-0.27, P<0.05) propofol injection pain, the incidence in 5-HT\textsubscript{3} receptor antagonists was significantly lower than that of control groups, Figure 3.

Postoperative nausea/vomiting and shivering

There was no statistical heterogeneity in the aspects of postoperative nausea/vomiting and shivering; therefore the data was combined through fixed-effect model. The pooled results indicated that incidence of postoperative nausea/vomiting (RR=0.28, 95%CI:0.17-0.44, P<0.05) and postoperative shivering (RR=0.33, 95%CI:0.23-0.48, P<0.05) was significantly reduced in the 5-HT\textsubscript{3} receptor antagonists group compared to the control group with a statistical difference, Figure 4.

Publication bias evaluation

A funnel plot was used to evaluate publication bias for 5-HT\textsubscript{3} receptor antagonists in reducing propofol injection pain. The funnel plot was asymmetric at the bottom, and Egger’s line regression test also demonstrated significant publication bias (t=-7.53, P<0.05), Figure 5.

| Author   | Year | Randomization | Allocation concealment | Blinding | Withdraw | Free of selective reporting | Other bias |
|----------|------|---------------|------------------------|----------|----------|-----------------------------|------------|
| Liu QM   | 2011 | Unclear       | Unclear                | Unclear  | No       | Unclear                     | Unclear    |
| Zhu M    | 2012 | Unclear       | Unclear                | Yes      | No       | Unclear                     | Unclear    |
| Yan YX   | 2011 | Unclear       | Unclear                | Yes      | No       | Unclear                     | Unclear    |
| Lu H     | 2011 | Unclear       | Unclear                | Unclear  | Unclear  | Unclear                     | Unclear    |
| Cao DH   | 2005 | Unclear       | Unclear                | Yes      | No       | Unclear                     | Unclear    |
| Ma YS    | 2009 | Yes           | Unclear                | Yes      | No       | Yes                         | Unclear    |
| Fu HQ    | 2010 | Unclear       | Unclear                | No       | No       | Yes                         | Unclear    |
| Liu F    | 2006 | Yes           | Unclear                | Yes      | Unclear  | Yes                         | Unclear    |
| Shao LL  | 2011 | Unclear       | Unclear                | Unclear  | Unclear  | Unclear                     | Unclear    |
| Xu XX    | 2010 | Unclear       | Unclear                | Unclear  | No       | Unclear                     | Unclear    |
| Singh    | 2011 | Yes           | Yes                    | Yes      | No       | Yes                         | Unclear    |
| Arnbesch | 1999 | Unclear       | Unclear                | Unclear  | Unclear  | Unclear                     | Unclear    |
| Ahmed    | 2012 | Yes           | Yes                    | Yes      | No       | Unclear                     | Unclear    |
| Dubey    | 2003 | Yes           | Yes                    | Yes      | No       | Unclear                     | Unclear    |
| Zahedi   | 2011 | Unclear       | Unclear                | Unclear  | Unclear  | Unclear                     | Unclear    |
| Ryu      | 2014 | Yes           | Unclear                | Unclear  | Unclear  | Unclear                     | Unclear    |
| Singh    | 2014 | Yes           | Unclear                | Unclear  | Unclear  | Unclear                     | Unclear    |
| Lee      | 2011 | Yes           | Unclear                | Unclear  | No       | Unclear                     | Unclear    |
| Alipour  | 2014 | Yes           | Unclear                | Yes      | No       | Unclear                     | Unclear    |
In the present work, we systematically searched and reviewed electronic databases and included a total of 19 studies relevant to 5-HT\textsubscript{3} receptor antagonists in reducing propofol injection pain. The general methodical quality of the included 19 individual studies was moderate. The combined results indicated that 5-HT\textsubscript{3} receptor antagonists could effectively reduce moderate and severe propofol injection pain, postoperative nausea/vomiting, and shivering. Injection pain is a common side effect in the clinical use of propofol [2, 29]. Among the 33 low-mortality clinical anesthesia problems, anesthesiologists ranked propofol injection pain as seventh according to the importance and incidence. The clinical manifestation of propofol injection pain is a burning pain at the injection site when propofol is injected intravenously, however, the mechanism has yet to be elucidated [30].

5-HT\textsubscript{3} receptor antagonists have a central antiemetic effect, which can effectively reduce the possibility of reflux and aspiration caused by intravenous anesthetics, and have fewer other adverse reactions [31-33]. Therefore, 5-HT\textsubscript{3} receptor antagonists, including ondansetron, granisetron, tropisetron, palonosetron, and ramosetron,

**Figure 2:** A forest plot of the propofol injection pain incidence between 5-hydroxytryptamine 3 receptor antagonists and control groups. (RR, risk ratio).
**Figure 3:** A forest plot of the propofol injection pain incidence between 5-hydroxytryptamine 3 receptor antagonists and control groups according to the pain degree. (RR, risk ratio).
Figure 4: A forest plot of postoperative nausea/vomiting and shivering incidence between 5-hydroxytryptamine 3 receptor antagonists and control groups according to the pain degree. (RR, risk ratio).

Figure 5: A funnel plot was used to evaluate the publication bias for 5-hydroxytryptamine 3 receptor antagonists in reducing propofol injection pain. (SE, standard error; RR, risk ratio).
have better application prospects than lidocaine and opioids. Clinically, 5-HT$_3$ receptor antagonists are mainly used to prevent nausea and vomiting after anesthesia with good clinical efficacy [34-36].

In addition to anti-nausea and vomiting effects, 5-HT$_3$ receptor antagonists can prevent propofol injection pain according to the previously published studies. Its effect on reducing propofol injection may be related to its antagonism of peripheral 5-HT$_3$ receptors and blockade of Na$^+$ channels in nerve cells, or possibly due to the activation of endorphin IV receptors [37]. Previous experiments in rats have shown that ondansetron can block Na$^+$ channels in brain neurons, and its local anesthetic effect is approximately 15 times that of lidocaine.

In conclusion

Based on the present publications, our meta-analysis demonstrated that 5-HT$_3$ receptor antagonists could effectively reduce propofol injection pain, postoperative nausea/vomiting, and shivering. However, there are several limitations in our present work, which should be taken into consideration when interpreting our results. Firstly, only publications written in English or Chinese were included; Secondly, significant publication bias was found in the present meta-analysis; Thirdly, the general methodology quality was not high. Therefore, well designed multicenter prospective randomized clinical trials relevant to 5-HT3 receptor antagonists in reducing propofol injection pain and prevention of postoperative nausea and vomiting are needed to further verify our findings.

Conflict of interest: Authors state no conflict of interest

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