5-HT$_3$ Receptor Antagonists for Propofol Injection Pain: A Meta-Analysis of Randomized Controlled Trials

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Published online: 10 February 2016
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Abstract

Background and Objectives 5-hydroxytryptamine$_3$ (5-HT$_3$) receptor antagonists have been commonly used to reduce propofol injection pain. The aim of this meta-analysis was to evaluate the efficacy and safety of 5-HT$_3$ receptor antagonists in decreasing the incidence and intensity of propofol injection pain.

Methods Online databases of Pubmed, Embase and the Cochrane Central Register of Controlled Trials were searched as well as reference lists of included studies and recent reviews. Eligible randomized controlled trials (RCTs) assessing the efficacy and safety of 5-HT$_3$ receptor antagonists for propofol injection pain were identified. The outcomes included the incidence and intensity of propofol injection pain and adverse effects. We calculated risk ratios (RR) with 95 % confidence intervals (CIs) for dichotomous data and adopted fixed or random-effects model when proper.

Results A total of eight RCTs were included in the final analysis. Compared with the control group, 5-HT$_3$ receptor antagonists were related to a decreasing incidence of propofol injection pain (RR 0.43, 95 % CI 0.33–0.56, $P < 0.05$). Besides, they also effectively alleviated the severity of propofol injection pain. They significantly reduced the number of patients with moderate (RR 0.21, 95 % CI 0.15–0.30, $P < 0.05$) and severe pain (RR 0.16, 95 % CI 0.10–0.25, $P < 0.05$) during propofol injection. 5-HT$_3$ receptor antagonists and lidocaine were equally effective in preventing propofol injection pain. Moreover, only one article mentioned the adverse effects of 5-HT$_3$ receptor antagonists in two patients.

Conclusion Our meta-analysis indicates that 5-HT$_3$ receptor antagonists can effectively reduce the incidence and severity of propofol injection pain. Additionally, 5-HT$_3$ receptor antagonists may become the alternatives to lidocaine in attenuating propofol injection pain. However, evidence is still limited for the safety of 5-HT$_3$ receptor antagonists on propofol injection pain.

Key Points

A total of eight full-text randomized controlled trials were selected in this meta-analysis to evaluate the efficacy and safety of 5-HT$_3$ receptor antagonists in decreasing the incidence and intensity of propofol injection pain.

The results indicate that 5-HT$_3$ receptor antagonists can effectively decrease the incidence and severity of propofol injection pain and they may become the alternatives to lidocaine in attenuating propofol injection pain.

Larger and better-designed randomized controlled trials are needed to assess the safety of 5-HT$_3$ receptor antagonists on propofol injection pain.
1 Introduction

Although propofol has been widely used in clinical practice and regarded as the most transformative agent in anesthesia over the last 25 years [1], it often has the common adverse effect of inducing pain on injection site after infusion, which was ranked seventh among the most important 33 low-morbidity clinical anesthesia problems [2]. The incidence of propofol injection pain (PIP) has been reported to be about 60% with no pretreatment [3].

Numerous factors appear to influence the incidence and the severity of PIP, such as menstrual cycle [4], temperature [5], injection rate [6], infusion equipment [7], concentration of propofol [8], age of patients [9], venous occlusion [10] and lots of pretreatment agents [3]. Although the exact mechanism of PIP is still unclear, plenty of methods have been put forward over the years to prevent and alleviate PIP with different results [3].

In clinical practice, 5-HT3 receptor antagonists (5-HT3-RAs) are often used for chemotherapy-induced and postoperative nausea and vomiting (PONV) [11]. Other therapeutic applications of 5-HT3-RAs that have been reported include the management of pain. Many studies have shown that some 5-HT3-RAs such as ondansetron can effectively prevent PIP. Therefore, we conducted this meta-analysis to evaluate the efficacy and safety of 5-HT3-RAs in decreasing the incidence and intensity of PIP.

2 Methods

2.1 Search Strategy

We searched online databases including Pubmed (from 1948), Embase (from 1974) and the Cochrane Central Register of Controlled Trials (from 1997) up to 10 October 2015 for articles that studied the efficacy and safety of 5-HT3-RAs on PIP. Search strategies for terms and keywords were as follows: (1) propofol; (2) 5-HT3 receptor antagonist, 5-hydroxytryptamine3 receptor antagonist, ondansetron, palonosetron, ramosetron, granisetron, tropisetron, dolasetron and alosetron; (3) pain; (4) induc*, relat*, infus*, inject*. All above terms were appropriately adjusted for each database. The limits or filters of “Humans”, “English”, “Clinical trial”, “Controlled clinical trial” and “Randomized controlled trial” were set for corresponding databases during our search process. The reference lists from the selected studies and reviews were also checked manually to identify additional eligible articles.

2.2 Selection Criteria

Two investigators (WW, LXW) independently reviewed the titles, abstracts, and full texts of selected articles to decide whether the study met the selection criteria. All controversies were settled by a third investigator.

2.2.1 Types of Studies

All full-text randomized controlled trials (RCTs) testing the effect of 5-HT3-RAs on propofol injection pain were included.

2.2.2 Types of Participants

Patients undergoing surgery with pain induced by propofol infusion were selected.

2.2.3 Types of Intervention

Articles studying 5-HT3-RAs were considered. 5-HT3-RAs included ondansetron, palonosetron, ramosetron, granisetron, tropisetron, dolasetron and alosetron. Studies that tested the mixed pain of propofol with other agents such as rocuronium were excluded. We also excluded articles that infused propofol by non-intravenous injection.

2.2.4 Types of Control

Control intervention, namely infusion with 0.9% saline, was considered.

2.2.5 Types of Outcome Measures

Trials with detailed data of the incidence and intensity of PIP assessed by a standard method were included. The adverse events of 5-HT3-RAs were considered as secondary outcomes.

2.3 Data Extraction

The data in eligible studies were extracted by two independent researchers (TW, CBZ) and any discrepancy in this process was resolved by a third investigator. The following data were extracted: first author, year of publication, country, sample size in each group, sex, intervention, injection site, catheter size, assessment, premedication, time for pretreatment infusion, way of venous occlusion, time for venous occlusion, time or rate for propofol injection, propofol induction dose and propofol injection dose.
2.4 Quality Assessment

Two reviewers (WW, LZ) independently evaluated the quality of all selected studies using the Cochrane Collaboration’s tool for assessing risk of bias [12] and settled disagreement by a third author. The tool contains the following seven types of biases: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. An assessment of high, unclear, or low risk of bias for each above items was made. According to a previous systematic review [13], other bias was regarded as a low risk if there was no statistical difference in the demographic characteristics between experimental and control groups.

2.5 Statistical Analysis

Review Manager (version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) and STATA software (version 11.2; Stata Corp LP, College Station, TX) were used for statistical analysis. Risk ratio (RR) and 95 % confidence intervals (CI) were calculated for the dichotomous data such as the incidence and intensity of propofol injection pain. Heterogeneity was evaluated by the Chi-square test and $I^2$ test. If the $P$ value of the Chi-square test was $>0.10$ or $I^2 < 50 \%$, a fixed-effects model was adopted, otherwise, a random-effects model was used in the meta-analysis. Subgroup analysis and sensitivity analysis were also conducted to explore the possible sources of heterogeneity and test the stability of the outcomes, which was performed by removing one study each time to reevaluate the influence of individual studies on the overall result. The Begg’s test [14] and Egger’s test [15] were applied to assess the potential publication bias.

3 Results

3.1 Research Results

We initially identified 225 articles (28 from Pubmed, 34 from Embase, and 163 from the Cochrane Central). After exclusion of duplicates and articles that did not meet the selection criteria, 13 potentially eligible articles were carefully reviewed. Subsequently five articles were excluded, two for assessing the incidence and intensity of PIP at four different times [16, 17], one for evaluating mixed efficacy of both propofol and rocuronium injection pain [18], one for having no saline control group [19] and one for infusing propofol by target controlled infusion [20]. Ultimately, eight articles with a total of 778 patients were included in the final analysis [21–28]. The detailed procedure of our selection is shown in Fig. 1.

3.2 Study Characteristics

The characteristics of eight selected studies are presented in Tables 1 and 2. They were all conducted in Asia (two in Korea [21, 23], two in Iran [26, 27], four in India [22, 24, 25, 28]) published from 1999 to 2014. Participants in every included study were all adults. Four types of 5-HT3RAs were tested in the eight articles: one studied palonosetron [21], two ramusorot [22, 23], two granisetron [24, 25], two ondansetron [27, 28] and one article tested both ondansetron and granisetron [26]. As for the study with two interventions [26], each intervention group was considered as a study and compared with control group. We marked this study as studya and studyb in our meta-analysis. Patients were given premedication orally two hours before the induction in two studies [22, 28]. One trial included only women [24] and one did not mention the ratio of men to women in each group [27]. In one study, 18-gauge catheters were used [23] while 20-gauge catheters were used in the other seven studies. Propofol was injected into the vein on the dorsum of the hand in all involved trials. The 5-HT3RAs were administrated intravenously before propofol injection in experimental groups. Five studies reported the time for pretreatment infusion [21, 24, 25, 27, 28] and only one study did not mention time or rate for propofol injection [23]. All trials performed venous occlusion before propofol injection but only two exactly gave the way of using a tourniquet with the pressure of 70 mmHg [25, 27]. All included studies adopted a four-point scale (a point of 0 to 3, respectively, corresponding to no, mild, moderate, severe pain) to evaluate the incidence and the severity of PIP and reported no difference in the baseline characteristics between the experiment and control groups. Among these eight studies, one [24] recruited only females, which obviously showed the selection bias. The outcomes of sensitivity analyses were consistent before and after we excluded this study, which showed the robustness of our results. Thus, we included this study in our meta-analysis. In the process of data extraction, we found that four studies reported the efficacy of lidocaine on PIP [22, 23, 25, 26]. Three studies used 40 mg lidocaine [22, 25, 26] and 20 mg lidocaine was used in one study [23]. Other interventions in lidocaine group were all the same as those for 5-HT3RAs and control group in each study. Thus, we decided to compare 5-HT3RAs with lidocaine about their effectiveness on PIP.
Fig. 1 Flowchart of the selection process. TCI target controlled infusion

225 articles identified through database searching:
PubMed: 28
Embase: 34
Cochrane Central: 163

212 articles excluded for overlap, unrelated studies according to title and abstract

13 full-text articles assessed for eligibility

5 full-text articles excluded:
- 2 for assessing the incidence and intensity of propofol injection pain at four different times
- 1 for assessing the incidence and intensity of both propofol and rocuronium injection pain
- 1 for no saline control group
- 1 for infusing propofol by TCI

8 studies finally included in meta-analysis

Table 1 Characteristics of individual studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Country (year)</th>
<th>Sample size (EG/CG)</th>
<th>Sex (M:F) (EG/CG)</th>
<th>Intervention</th>
<th>Injection site</th>
<th>Catheter size</th>
<th>Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ryu [21]</td>
<td>Korea (2014)</td>
<td>40/40</td>
<td>20:20/20:20</td>
<td>P 75 μg IV NS 2 mL IV</td>
<td>The dorsum of hand</td>
<td>20-gauge</td>
<td>A four-point scale</td>
</tr>
<tr>
<td>Singh [22]</td>
<td>India (2014)</td>
<td>40/40</td>
<td>22:18/21:19</td>
<td>R 0.3 mg IV NS 2 mL IV</td>
<td>The dorsum of hand</td>
<td>20-gauge</td>
<td>A four-point scale</td>
</tr>
<tr>
<td>Lee [23]</td>
<td>Korea (2011)</td>
<td>50/50</td>
<td>32:18/32:18</td>
<td>R 0.3 mg IV NS 5 mL IV</td>
<td>NA</td>
<td>18-gauge</td>
<td>A four-point scale</td>
</tr>
<tr>
<td>Ahmed [24]</td>
<td>India (2012)</td>
<td>40/40</td>
<td>0:40/0:40</td>
<td>G 2 mg IV NS 2 mL IV</td>
<td>The dorsum of hand</td>
<td>20-gauge</td>
<td>A four-point scale</td>
</tr>
<tr>
<td>Dubey [25]</td>
<td>India (2003)</td>
<td>50/50</td>
<td>19:31/18:32</td>
<td>G 2 mg IV NS 5 mL IV</td>
<td>The dorsum of hand</td>
<td>20-gauge</td>
<td>A four-point scale</td>
</tr>
<tr>
<td>Alipour [26]</td>
<td>Iran (2014)</td>
<td>56/56</td>
<td>27:29/36:20</td>
<td>G 2 mg IV NS 5 mL IV</td>
<td>The dorsum of hand</td>
<td>20-gauge</td>
<td>A four-point scale</td>
</tr>
<tr>
<td>Alipour [26]</td>
<td>Iran (2014)</td>
<td>56/56</td>
<td>25:31/36:20</td>
<td>O 4 mg IV NS 5 mL IV</td>
<td>The dorsum of hand</td>
<td>20-gauge</td>
<td>A four-point scale</td>
</tr>
<tr>
<td>Zahedi [27]</td>
<td>Iran (2012)</td>
<td>45/45</td>
<td>NA</td>
<td>O 4 mg IV NS 2 mL IV</td>
<td>The dorsum of hand</td>
<td>20-gauge</td>
<td>A four-point scale</td>
</tr>
<tr>
<td>Ambesh [28]</td>
<td>India (1999)</td>
<td>40/40</td>
<td>NA</td>
<td>O 4 mg IV NS 2 mL IV</td>
<td>The dorsum of hand</td>
<td>20-gauge</td>
<td>A four-point scale</td>
</tr>
</tbody>
</table>

EG experimental group, CG control group, M male, F female, P palonosetron, R ramosetron, G granisetron, O ondansetron, IV intravenously, NS normal saline, NA not available
3.3 Study Quality

Among all selected trials, four clearly showed the methods of randomized sequence generation [22–24, 26]. The main problem experienced in these included studies was lack of detailed information on allocation concealment method. Only one [25] explicitly demonstrated while others were unclear. One research did not clearly report the blinding of participants and personnel [22] and seven reported the blinding of outcomes assessment [21, 22, 24–28]. All studies had low risk of bias for incomplete outcome data due to no dropout or withdrawal. Because we could not get the initial protocol of each trial, the risk of bias for selective reporting was considered as unclear. Other bias of each study was regarded as a low risk because there was no statistically significant difference in the demographic characteristics between experimental and control groups. The details of quality assessment were illustrated in Table 3.

3.4 Clinical Outcomes

3.4.1 Efficacy of 5-HT₃RAs

The outcomes of our analysis showed that pretreatment with 5-HT₃RAs was related to a decreasing incidence of PIP (RR 0.43, 95 % CI: 0.33 to 0.56, \( P < 0.05 \)) with obvious heterogeneity across trials (\( P = 0.001, I^2 = 69 \% \), Fig. 2). Thus, we applied a random-effects model for analysis. In addition, 5-HT₃RAs also alleviated the severity of PIP. Compared with the control group, 5-HT₃RAs allowed more patients to experience mild pain (RR 1.63, 95 % CI: 1.21 to 2.20, \( P = 0.001 \), Fig. 3) while significantly decreased the number of patients with moderate (RR 0.21, 95 % CI 0.15–0.30, \( P < 0.05 \), Fig. 4) and severe pain (RR 0.16, 95 % CI 0.10–0.25, \( P < 0.05 \), Fig. 5) during propofol injection. In the analysis of the severity of PIP, the fixed-effects model was applied for no major heterogeneity detected.

3.4.2 Safety of 5-HT₃RAs

No patient in the included trials experienced pain or discomfort during the injection of 5-HT₃RAs. One study [28] reported that eight patients suffered from skin rashes in the upper limb, as did 12 in ondansetron group. Ten patients in the control group had myoclonic movements after propofol injection. Only one article [25] mentioned that two patients in granisetron group complained of headache in the immediate postoperative period. No significant side effects were seen in any group that needed active intervention after propofol injection.

3.4.3 Subgroup Analysis

Four types of 5-HT₃RAs were tested in the included eight trials. We conducted a subgroup analysis by the type of 5-HT₃RAs to explore the possible source of heterogeneity (Fig. 6). Four subgroups (palonosetron group, ramosetron group, granisetron group and ondansetron group) were included. Results of subgroup analysis indicated that a high heterogeneity still existed in the ondansetron group

Table 2 Characteristics of individual studies (continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Premedication</th>
<th>Time for pretreatment infusion (s)</th>
<th>Method of venous occlusion</th>
<th>Time for venous occlusion (s)</th>
<th>Time or rate for propofol injection</th>
<th>Propofol induction dose (mg/kg)</th>
<th>Propofol injection dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ryu [21]</td>
<td>No</td>
<td>5</td>
<td>Manual occlusion</td>
<td>60</td>
<td>5 s</td>
<td>2.0</td>
<td>25 % of ID</td>
</tr>
<tr>
<td>Singh [22]</td>
<td>Yes</td>
<td>NA</td>
<td>Manual occlusion</td>
<td>60</td>
<td>5–15 s</td>
<td>2.5</td>
<td>25 % of ID</td>
</tr>
<tr>
<td>Lee [23]</td>
<td>No</td>
<td>NA</td>
<td>Manual occlusion</td>
<td>30</td>
<td>NA</td>
<td>2.0</td>
<td>25 % of ID</td>
</tr>
<tr>
<td>Ahmed [24]</td>
<td>No</td>
<td>5</td>
<td>Manual occlusion</td>
<td>60</td>
<td>4 s</td>
<td>2.5</td>
<td>2 mL of ID</td>
</tr>
<tr>
<td>Dubey [25]</td>
<td>No</td>
<td>10</td>
<td>Manual occlusion</td>
<td>120</td>
<td>5 s</td>
<td>2.5</td>
<td>25 % of ID</td>
</tr>
<tr>
<td>Alipour [26]</td>
<td>NA</td>
<td>NA</td>
<td>Manual occlusion</td>
<td>60</td>
<td>4 mg/s</td>
<td>2.5</td>
<td>25 % of ID</td>
</tr>
<tr>
<td>Zahedi [27]</td>
<td>No</td>
<td>10</td>
<td>Manual occlusion</td>
<td>20</td>
<td>10 s</td>
<td>2.0</td>
<td>NA</td>
</tr>
<tr>
<td>Ambesh [28]</td>
<td>Yes</td>
<td>5</td>
<td>Manual occlusion</td>
<td>60</td>
<td>5 s</td>
<td>2.5</td>
<td>25 % of ID</td>
</tr>
</tbody>
</table>

NA not available, ID induction dose
### Table 3  Risk of bias of included studies

<table>
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<tr>
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<td>Random sequence generation</td>
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<td>L</td>
<td>L</td>
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<tr>
<td>Allocation concealment</td>
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<td>U</td>
<td>U</td>
<td>U</td>
<td>L</td>
<td>U</td>
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</tr>
<tr>
<td>Blinding of participants and personnel</td>
<td>L</td>
<td>U</td>
<td>L</td>
<td>L</td>
<td>L</td>
<td>L</td>
<td>L</td>
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<tr>
<td>Blinding of outcome assessment</td>
<td>L</td>
<td>L</td>
<td>U</td>
<td>L</td>
<td>L</td>
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<td>L</td>
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<tr>
<td>Incomplete outcome data addressed</td>
<td>L</td>
<td>L</td>
<td>L</td>
<td>L</td>
<td>L</td>
<td>L</td>
<td>L</td>
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</tr>
<tr>
<td>Free of selective reporting</td>
<td>U</td>
<td>U</td>
<td>U</td>
<td>U</td>
<td>U</td>
<td>U</td>
<td>U</td>
<td>U</td>
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<tr>
<td>Free of other bias</td>
<td>L</td>
<td>L</td>
<td>L</td>
<td>L</td>
<td>L</td>
<td>L</td>
<td>L</td>
<td>L</td>
</tr>
</tbody>
</table>

*U* low risk of bias, *U* unclear

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**Fig. 2** Forest plot of RR. 5-HT₃RAs group and control group on preventing propofol injection pain with 95% CI. **RR** risk ratios, **5-HT₃RAs** 5-hydroxytryptamine₃ receptor antagonists, **CI** confidence intervals, **M–H** Mantel–Haenszel

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**Fig. 3** Forest plot of RR. 5-HT₃RAs group and control group on reducing the mild propofol injection pain with 95% CI. **RR** risk ratios, **5-HT₃RAs** 5-hydroxytryptamine₃ receptor antagonists, **CI** confidence intervals, **M–H** Mantel–Haenszel

△ Adis
(P = 0.01, I² = 76 %), whereas no obvious heterogeneity was seen in the other three groups. Then we further conducted subgroup analysis on the basis of the volume of solution in ondansetron group. Finally, there was no heterogeneity in this subgroup analysis (P = 0.3; I² = 6 %). The subgroups’ results of the incidence of PIP were in accordance with the general results using a random-effects model.

3.4.4 Sensitivity Analysis

We also performed sensitivity analysis to assess potential sources of heterogeneity and test the robustness of our results. The relevant results were in agreement with the initial outcomes by taking out any single study, indicating the stability of our outcome.

3.4.5 Publication Bias

The shape of the Begg’s funnel plot was asymmetrical, suggesting the existence of publication bias (Fig. 7). Then, we applied the Egger’s test to provide statistical evidence, which showed publication bias for the incidence of PIP (t = -3.76, P = 0.007). The results of our study were not materially changed in the process of sensitivity analysis, suggesting that our outcomes are statistically robust.

3.4.6 Lidocaine Versus 5-HT₃RAs

Our analysis showed that there was no statistical significance between intravenous administration of 5-HT₃RAs and lidocaine on alleviation of the incidence of PIP (RR 1.10, 95 % CI 0.73–1.65, P = 0.66). We adopted a
random-effects model for analysis because obvious heterogeneity existed across studies \((P = 0.01; \hat{I}^2 = 69\%)\). Besides, lidocaine did not demonstrate superiority in reducing mild, moderate and severe PIP when compared with 5-HT\(_3\)RAs \((RR 1.13, 95\% CI 0.85–1.50, P = 0.41; \hat{I}^2 = 69\%\); \((RR 1.15, 95\% CI 0.65–2.03, P = 0.63; \hat{I}^2 = 0\%\)) with no considerable heterogeneity \((P = 0.65, \hat{I}^2 = 0\%\); \((P = 0.08, \hat{I}^2 = 51\%\); \(P = 0.46, \hat{I}^2 = 0\%\), respectively). Thus, we applied a fixed-effects model for mild and severe PIP and a random-effects model for moderate PIP. A subgroup analysis based on the type of 5-HT\(_3\)RAs was undertaken to find the possible source of heterogeneity. Results of subgroup analysis indicated that type of 5-HT\(_3\)RAs was the source of heterogeneity. Both subgroup analysis and sensitivity analysis were in accordance with the initial outcomes.

### 4 Discussion

Since ondansetron was first reported to effectively alleviate propofol injection pain in 1999 [28], many types of 5-HT\(_3\) receptor antagonists have been well tested. We carried out this meta-analysis of RCTs to study the effectiveness and safety of 5-HT\(_3\) receptor antagonists in reducing propofol injection pain. The guidelines recommended in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [29] were followed to conduct this meta-analysis.

Though propofol injection pain is the common side effect of this intravenous anesthetic, the underlying mechanism of PIP has still not been fully illustrated. Different kinds of methods have been studied to deal with the problem of PIP including using a tourniquet for venous occlusion [10], 4 or 37 °C propofol [5, 30], rapid...
administration of propofol [31], premedication [32], dilution of propofol [33], pretreatment with agents such as lidocaine [34], flurbiprofen axetil [35], magnesium sulfate [36] or paracetamol [37]. However, none of these methods can remove PIP completely.

In clinical anesthesia 5-HT₃RAs are commonly used as antiemetic drugs for preventing PONV [38]. Seven types of 5-HT₃RAs are commercially available: ondansetron, granisetron, dolasetron, palonosetron, alosetron, tropisetron and ramosetron [11]. Besides, many studies have shown that 5-HT₃RAs can effectively reduce the pain produced by propofol injection. The possible mechanisms of ondansetron have been well studied and suggested as follows: (1) ondansetron can block sodium channels exhibiting the property of a local anesthetic [39]; (2) 2s peripheral 5-HT₃ receptors are involved in the nociceptive pathway [39], 5-HT₃RAs can impair nociceptive pathway and therefore be used for the management of pain; (3) ondansetron can activate μ opioid receptors in humans showing analgesic effect [40]. Farouk [41] found that adding ondansetron to the lidocaine can improve the quality of intravenous regional anesthesia and prolong postoperative analgesia in patients undergoing hand surgery. Honarmand and colleagues [42] found that the addition of ondansetron 8 mg to lidocaine for intravenous regional anesthesia reduced intraoperative and postoperative analgesic use till 24 h and showed that ondansetron has local anesthesia properties. Besides, pretreatment with intravenous ondansetron can also significantly reduce the pain on injection of etomidate [43]. Although the mechanism of alleviation of PIP by other 5-HT₃RAs has not been known, it is presumed that the mechanism is similar to that of ondansetron.

We performed this meta-analysis considering that the use of 5-HT₃RAs can alleviate PIP with the added advantage of preventing PONV in clinical anesthesia. The outcomes of our meta-analysis suggested that 5-HT₃RAs could significantly decrease the incidence and the severity of PIP. As compared with the saline control group, pretreatment with 5-HT₃RAs allowed fewer patients to experience pain during propofol injection and decreased the number of patients with moderate and severe PIP. Thus, it is very encouraging for anesthesiologists to use 5-HT₃RAs before propofol injection for preventing both PIP and PONV.

In our analysis, we performed subgroup analysis according to the type of 5-HT₃RAs to investigate potential source of heterogeneity in the overall incidence of PIP. However, a high heterogeneity still existed in the ondansetron group with no heterogeneity in the other three groups. Then, further subgroup analysis was conducted on the basis of the volume of solution in ondansetron group without obvious heterogeneity. The subgroups’ results of the incidence of PIP and the outcomes of sensitivity analysis were in accordance with the general results.

During our data extraction, four articles were found to include lidocaine as another intervention besides 5-HT₃RAs. As the use of lidocaine is thought to be the most popular method to alleviate propofol injection pain, we were eager to know whether lidocaine was superior to 5-HT₃RA. Thus, we performed analysis to compare 5-HT₃RAs with lidocaine regarding their effectiveness on PIP. Given that 5-HT₃RAs and lidocaine showed equal effectiveness in attenuating PIP in our analysis, 5-HT₃RAs may become the substitutes for lidocaine in alleviating pain induced by propofol injection.

Pretreatment with 5-HT₃RAs produced few adverse effects in preventing propofol injection pain. As headache and constipation are common adverse effects of 5-HT₃RAs [44], only one article in our meta-analysis mentioned that two patients in the granisetron group complained of headache in the postoperative period, which was perhaps related to granisetron. Other side effects like skin rashes and myoclonic movements after propofol injection may be associated with propofol. Besides, no patient felt discomfort due to 5-HT₃RAs injection.

There are still some limitations to our analysis which should be taken into consideration when interpreting our results. First, the number and sample size of included studies are not enough and small number of studies (only four) were included in the process of comparing lidocaine with 5-HT₃RA on PIP. As for the safety evaluation, it is impossible to use a meta-analysis to assess for lack of sufficient data. Second, because all data in our study were from adults, we know little about the efficacy of 5-HT₃RAs on PIP in children. Third, we set the limitation on language during our search of eligible trials. Only studies written in

![Fig. 7 Begg's funnel plot of publication bias test. 5-HT₃RAs vs. control. Each point represents a separate study included in the meta-analysis. 5-HT₃RAs 5-Hydroxytryptamine₃ receptor antagonists, RR risk ratios, logRR natural logarithm of RR, s.e. standard error](image-url)
English were included in our meta-analysis and some studies written in other languages were excluded. Besides, conference abstracts and unpublished studies were also excluded in our meta-analysis. Finally, all included trials come from the same continent (Asia).

5 Conclusion

In conclusion, our meta-analysis indicated that pretreatment with 5-HT3RAs can effectively reduce the incidence and severity of pain induced by propofol injection in Asian countries. Besides, 5-HT3RAs may become the alternatives to lidocaine in reducing propofol injection pain. Moreover, pretreatment with 5-HT3RAs produced few adverse effects in preventing propofol injection pain. However, evidence is limited for the safety of 5-HT3RAs for propofol injection pain. Thus, larger and better-designed randomized controlled trials, especially from other continents, are needed in future trials. And more high-quality RCTs should be conducted in future to confirm our result of lidocaine and 5-HT3RAs on propofol injection pain.

References


