Review Article

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Efficacy of 5-HT₃ receptor antagonists (ondansetron) vs dopamine receptor antagonists (droperidol) for preventing postoperative nausea, vomiting and headache: a meta-analysis

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Abstract: Objective To investigate the effects of 5-hydroxytryptamine 3 receptor antagonists (ondansetron [OND]) versus dopamine receptor antagonists (droperidol [DRO]) in the prevention of postoperative nausea, vomiting (PONV) and headache by pooling data from open published studies. **Methods** Performed systematic electronic searches of PubMed, Embase, Google scholar and CNKI, to identify open-published prospective randomized controlled trials (RCTs) relevant to the comparison of OND versus DRO for preventing PONV and headache to be included in the present study. The pooled PONV, headache, dizziness and drowsiness were calculated based on the original data of each included study. The pooled data was presented with risk ratio (RR) and 95% confidence interval (95%CI). **Results** Thirteen prospective randomized clinical trials were included in this meta-analysis. The pooled PONV, post-operative nausea (PON) and positive operative vomiting (POV) were 0.67 (95%CI:0.48-0.93, $p < 0.05$), 0.88 (95%CI:0.67-1.14, $p > 0.05$) and 0.56 (95%CI:0.39-0.82, $p < 0.05$) respectively for OND vs. DRO. And the overall pooled positive operative nausea and vomiting was 0.71(95%CI:0.60-0.86) by fixed effects model for OND vs. DRO. The pooled risk of post-operative headache, dizziness and drowsiness were 4.33 (95%CI:0.76-24.69, $p > 0.05$), 0.63 (95%CI:0.21-1.87, $p > 0.05$) and 0.48(0.28-0.81, $p < 0.05$) respectively by fixed effect model for OND vs. DRO. **Conclusion** The post-operative

nausea, vomiting and dizziness risks were significant decreased for patients receiving OND compared to patients receiving DRO.

Keywords: 5-hydroxytryptamine 3 receptor antagonists; dopamine receptor antagonists; ondansetron; droperidol; meta-analysis.

Introduction

Post-operative nausea and vomiting (PONV) is common complication in patients who receive general anesthesia [1-3]. Clinical studies have indicated that this complication develops in one of ten patients who undergo general anesthesia [4, 5]. PONV not only causes anxiety in the post-operative patients, but also increases the risk of aspiration pneumonia. Therefore, a postoperative antiemetic is generally given to patients who received general anesthesia. The most commonly used postoperative antiemetic drugs were 5-hydroxytryptamine 3 receptor antagonists (ondansetron [OND]) and dopamine receptor antagonists (droperidol [DRO]). Previous clinical trials have proven that ondansetron [6, 7] and droperidol were safe and effective for the prevention of PONV. Several studies have evaluated the clinical efficacy of both ondansetron [8-10] and droperidol [11, 12] in the prevention of PONV. However, the conclusions from the published studies have been inconsistent and unconvincing. Therefore, we performed a meta-analysis by pooling the data of relevant open-published studies, with the goal of strengthening the statistical power of analyses to quantify the clinical efficacy of ondansetron versus droperidol in preventing PONV.

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Material and Methods

Publication electronic searching

Open-published prospective randomized controlled trials (RCTs) relevant to efficacy of 5-hydroxytryptamine 3 receptor antagonists (ondansetron) versus dopamine receptor antagonists (droperidol) for preventing postoperative nausea, vomiting and headache were screened in the electronic databases of PubMed, Embase, Google scholar and CNKI by the text word of ondansetron, droperidol, post-operative, nausea, vomiting. The publication searching was limited to prospective randomized clinical trials, with the language restriction of English and Chinese. The references of the included publications were also screened to identify additional suitable studies.

Ethical approval: The conducted research is not related to either human or animals use.

Publication inclusion and exclusion criteria

Inclusion criteria: (i) Study type: prospective randomized clinical trials; (ii) Subjects: patients who received general anesthesia; (iii) Drug: 5-hydroxytryptamine 3 receptor antagonists (ondansetron) versus dopamine receptor antagonists (droperidol); (iv) Outcome: Post-operative nausea/vomiting, headache, dizziness or drowsiness; (v) Language: English or Chinese.

Exclusion criteria: (i) Study type: retrospective study, case report or review; (ii) Subject: Not human beings; (iii) Duplicated publications or data; (iv) Not enough data to calculate the pooled PONV.

Data and information extraction

The main information and data of each included publication were independently extracted by two reviewers (Xiaoyun Chen and Yinying Qin). Any disagreements in data extraction were resolved through consulting a third reviewer (Xiaoyun Wu). The main information and data of authors, the paper publication year, journal, number of subjects, ondansetron/droperidol dosage, surgery type, frequency of PONV, headache, dizziness and drowsiness were extracted from each included publication.

Statistical analysis

Stata 11.0SE (Stata Corporation, College Station, TX) was used to perform data analysis. The risk of developing PONV, headache, dizziness and drowsiness were expressed by risk ratio (RR) and 95% confidence interval (CI). Statistical heterogeneity across the 13 studies was evaluated using a chi-square (χ^2) test, and demonstrated by I^2 [13, 14]. When I^2 50%, the statistical heterogeneity was considered significant, and the data was pooled through random effect method. Otherwise, the data was pooled through fixed effect method. The Begg's funnel plot and Egger's line regression test were used to evaluate any potential publication bias [13].

Results

Main features of the included clinical trials

Through systematic searching the electronic databases, 88 studies were initially identified for inclusion in our meta-analysis. After reviewing the title and abstract, 57 trials were excluded as duplicated publication, not prospective randomized studies, or for other reasons based on the inclusion and exclusion criteria described previously. After reviewing the full text manuscripts, 18 studies were further excluded for lacking sufficient data for our analyses. Ultimately, 13 clinical trials [8-10, 15-24] were included in the final meta-analysis.

Figure 1. The main features of the included 13 publications were shown in **Table 1**.

Pooled POVA, PON and POV

The pooled PONV, PON and POV were calculated as 0.67 (95%CI:0.48-0.93, $p<0.05$), 0.88 (95%CI:0.67-1.14, $p>0.05$) and 0.56 (95%CI:0.39-0.82, $p<0.05$) respectively for OND vs. DRO. The overall pooled positive operative nausea and vomiting was 0.71 (95%CI:0.60-0.86) as calculated through the fixed effects method (**Figure 2**). These analyses indicate that the post-operative nausea and vomiting risk in OND-treated patients was lower than that in the DRO group, and this difference is statistically significant

Pooled headache, dizziness and drowsiness

The pooled risk of post-operative headache, dizziness and drowsiness were calculated by the fixed effect method

Figure 1: The RCTs electronic searching flow-chart.

as 4.33 (95%CI:0.76-24.69, $p>0.05$), 0.63 (95%CI:0.21-1.87, $p>0.05$) and 0.48 (0.28-0.81, $p<0.05$) respectively for OND vs. DRO. These results indicate that the post-operative risk of dizziness in the OND-treated group was statistically significantly lower than that of the DRO-treated group. However, the post-operative headache and dizziness risks were not statistically different between the OND- and DRO-treated groups ($p>0.05$) (Figure 3).

Publication bias evaluation

The Begg’s funnel plot (Figure 4) and Egger’s line regression test ($t=-1.16$, $p=0.27$) indicated no obvious publication bias.

Figure 2: Forest plot of ondansetron vs droperidol for preventing PONV. The gray squares and horizontal lines indicate the RR and 95% CI, respectively. The area of the squares reflects the study specific weight (inverse of the variance). The blue diamond represents the pooled RR and 95% CI.

Table 1: The main features of the included clinical trials (n=13).

First author	Year	No of subjects (OND/DRO)	Administration		Operation type	Induced anesthesia	Maintenance anesthesia	Postoperative analgesia
			OND	DRO				
Ekinçi	2010	20/20	4 mg	2.5 mg	Gynecologic surgery	Thiopentone, fentanyl, vecuronium	Isoflurane	Negative
Fabling	2000	20/20	4 mg	0.62 mg	Neurosurgery	Thiopentone, fentanyl, vecuronium	Isoflurane	Negative
Reihner	2000	67/69	8 mg	1.25 mg	Breast surgery	Thiopentone, fentanyl, atracurium	Isoflurane	Positive
Swiatkowski	1999	67/67	4 mg	75 µg/kg	Abdominal surgery	Thiopentone, fentanyl, atracurium	Isoflurane	Positive
Bugedo	1999	57/57	4 mg	1.25 mg	Gynecologic/ Abdominal surgery	Thiopentone, fentanyl, vecuronium	Isoflurane	Positive
Peixoto	2000	30/30	4 mg	1.25 mg	Gynecologic surgery	Thiopentone, fentanyl, vecuronium	Isoflurane	Positive
Sharma	2000	25/25	4 mg	2.5 mg	Gynecologic surgery	Thiopentone, fentanyl, succinylcholine	Isoflurane	Positive
Wu	2000	37/38	4 mg	1.25 mg	Gynecologic surgery	Propofol, midazolam	Isoflurane	Negative
Helmy	1999	40/40	4 mg	1.25 mg	Abdominal surgery	Thiopentone, Sufentanil, atracurium	Sufentanil, propofol	Positive
Ma	2006	30/30	8 mg	2.5 mg	Gynecologic surgery	Fentanyl, atracurium, etomidate	Isoflurane	Positive
Charton	2018	84/87	4 mg	1.25 mg	Ambulatory surgery	NA	NA	Positive
Yao	2007	22/22	8 mg	2.5 mg	Abdominal surgery	NA	NA	Positive
Liu	2017	40/40	8 mg	2.5 mg	Abdominal surgery	Sufentanil	NA	Positive

Discussion

Statistical analysis showed the general incidence rate of PONV to be about 25% for patients received operation. The incidence of PONV has been estimated to be as high as 10%-35% for patients who have undergone general anesthesia. Not only can PONV increase the risk of the patient developing inhalation pneumonia, but PONV is also a common cause of patient anxiety, which may prolong hospitalization time. Therefore, treatment with

an effective postoperative antiemetic was necessary for patients receiving general anesthesia or subjects with high risk of PONV. The reasons for increased PONV risk were complex, with genetic susceptibility, application of different anesthetics intra-operation, operation procedure, and patients' demographic characteristics (such as gender, age, and BMI) all playing potential roles in ultimate PONV susceptibility.

Ondansetron, a 5-hydroxytryptamine 3 receptor antagonist, is the most clinically used post-operative

Figure 3: Forest plot of the risk of positive-operative headache, dizziness and drowsiness for ondansetron and droperidol groups. The gray squares and horizontal lines represent the RR and 95% CI, respectively. The area of the squares reflects the study specific weight (inverse of the variance). The blue diamond represents the pooled RR and 95% CI.

Figure 4: Begg's Funnel Plot depicting evaluation of potential publication bias for the studies included in the meta-analysis. Each blue dot represents an individual study included in the meta-analysis.

antiemetic drug. Ondansetron is a highly specific and selective serotonin 5-HT₃ receptor antagonist, with low affinity for dopamine receptors. The 5-HT₃ receptors are present both peripherally on vagal nerve terminals and centrally in the chemoreceptor trigger zone of the area postrema. Serotonin is released by the enterochromaffin cells of the small intestine in response to chemotherapeutic agents and may stimulate vagal afferents (via 5-HT₃ receptors) to initiate the vomiting reflex. It is believed that ondansetron's antiemetic action is mediated primarily via antagonism of vagal afferents, with a minor contribution from antagonism of central receptors [25]. Therefore, ondansetron was effective in controlling postoperative nausea and vomiting. It has been shown to be both more effective than metoclopramide in preventing PONV and less sedating than cyclizine, as reported by a meta-analysis^[26] published 20 years ago that evaluated the prophylaxis of postoperative vomiting by ondansetron. The authors included all prospectively randomized trials in which ondansetron and placebo had been administered for prevention of postoperative vomiting and found that ondansetron was effective for prophylaxis of postoperative vomiting.

Droperidol is an antidopaminergic drug used as an antiemetic for treatment and prevention of PONV. It has a central antiemetic action and effectively prevents postoperative nausea and vomiting in adults at doses as low as 0.625 mg. Another meta-analysis [27] published in 1999 evaluated the prevention of postoperative vomiting and nausea by droperidol as compared to placebo. The results showed droperidol can be administered to patients with an increased risk of suffering from PONV without antiemetic prophylaxis. However, the efficacy of 5-hydroxytryptamine 3 receptor antagonists (ondansetron) vs dopamine receptor antagonists (droperidol) for preventing postoperative nausea remained unclear, although several studies had compared the PONV preventive effects of the two drugs.

Therefore, we performed a meta-analysis by pooling the relevant published studies. In this meta-analysis, we included 13 prospective randomized clinical trials relevant to our ultimate goal of comparing the efficacy of 5-HT₃ receptor antagonists (ondansetron) and dopamine receptor antagonists (droperidol) for the prevention of PONV and headache. Our results indicate that ondansetron is more effective in preventing PONV as compared to droperidol. A possible explanation for this finding could be that the antiemetic effects of ondansetron are mediated mostly via antagonism of vagal afferents, with a minor contribution from antagonism of central receptors. In addition, patients receiving ondansetron also had less risk of developing

drowsiness. However, the post-operative headache and dizziness risk was not statistically different between OND- and DRO-treated patients. Therefore, the results of our meta-analysis suggest that ondansetron should be recommended as an effective treatment for patients who undergo general anesthesia.

However, this meta-analysis was limited in the following ways: (i) Only English or Chinese publication were screened and included, leading to a potential language selection bias; (ii) The administration dosage of ondansetron and droperidol were different for the included 13 publications. This is an important source of clinical heterogeneity.

Conflict of interest: Authors state no conflict of interest

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