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Evaluating the effect of anti-nausea drugs in IDO enzyme gene expression and preventing postoperative vomiting and nausea in patients undergoing general anesthesia: A Meta-analysis

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ABSTRACT

Nausea and vomiting are known as side effects after surgery. Since serotonin antagonist drugs are widely used to prevent nausea and vomiting after surgery, the present study was conducted to compare the effectiveness of this group's drugs, namely, ondansetron and palonosetron. On the other hand, recent studies have shown that the metabolites of the kynurenine pathway in the Suppression of the immune response play a role. Indoleamine 2,3 dioxygenase (IDO) is the main enzyme controlling this pathway. Therefore, the effect of these two drugs on IDO gene expression was evaluated. The present study is a systematic review with meta-analysis. The search was conducted in the Cochrane, PubMed, Clinical K, and CRD databases for randomized clinical trial articles that compared two drugs, palonosetron, and ondansetron, regarding nausea and vomiting in patients undergoing surgery with general anesthesia. In the end, eight studies were included in the meta-analysis. STATA13 statistical software was used to estimate the overall risk, relative risk, and data analysis. The results showed that the number of samples in all articles was 739. The analysis of the results between 0 and 24 hours showed that palonosetron reduces the incidence of nausea by 50% and the incidence of vomiting by 79% compared to ondansetron (p=0.001). Also, there was no difference between the IDO gene expression in the two drug groups (p>0.05). In general, the analysis of the results related to the effectiveness of palonosetron and ondansetron 24 hours after surgery with a dose of 0.075 mg of palonosetron versus 4 mg of ondansetron showed that palonosetron is more effective in reducing the incidence of nausea and vomiting in patients than ondansetron.

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Introduction

Despite the advancement of surgical methods and anesthesia, nausea and vomiting after surgery is still an unwilling complication for patients, which occurs in more than 30% of surgeries (1). Continuation of nausea and vomiting after surgery can create dangerous side effects for patients. Among these symptoms, we can mention electrolyte disturbances, lack of volume of body fluids, delay in the discharge of patients, and prolonged hospitalization (2). In addition to these cases, persistent nausea and vomiting after the operation can cause stretching of the suture line, increase in blood pressure, and increase in bleeding in the skin flaps, as well as in patients in whom the return of the swallowing reflex has not occurred, causing pulmonary aspiration (3). In the absence of prompt treatment, appropriately, pulmonary aspiration can lead to pneumonia, generating 15% to 20% of hospital infections and increasing costs by 39%. Patients who undergo abdominal, ear, nose, larynx, and eye surgeries have a high risk of nausea and vomiting after surgery and are considered a high-risk population (4). In addition to the type of surgery, the rate of nausea and vomiting after surgery is higher in women, people who do not smoke, and people who have a history of nausea and vomiting after surgery or a history of illness in the past. Nausea and vomiting in this high-risk population, who have not taken any preventive medicine, is approximately 70% to 80%.

Various antiemetic drugs are used to prevent nausea and vomiting. Since 1990, serotonin antagonists have been the basis of modern antiemetic drugs to prevent nausea and vomiting after surgery (5). Ondansetron is the first drug of this group, which doctors have widely used since 1991 after the approval of the Food and Drug Organization in nausea and vomiting after surgery due to its reasonable price and few side effects (3).

Then, with the emergence of other drugs in this group, finally, in 2008, the new generation of drugs of this group, namely palonosetron, was approved by the American Food and Drug Administration for preventing nausea and vomiting up to 24 hours after surgery with a dose of 0.075 mg. With its single isomeric structure, palonosetron drug can connect to serotonin receptors with more strength and time (5). Ondansetron drug is the gold standard of comparison of serotonin antagonist drugs. Various experimental studies have been conducted to compare two drugs, palonosetron and ondansetron. This study is a systematic review and meta-analysis of the results of randomized

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trial studies that have compared palonosetron and ondansetron and tries to answer the question of which one is more effective in preventing nausea and vomiting after 24 hours (4). Besides, recent studies have shown that kynurenine pathway metabolites play a role in immune response suppression. The main enzyme controlling this pathway is indoleamine 2,3 dioxygenase (IDO) (6). IDO is an intracellular enzyme that controls the breakdown of tryptophan in the kynurenine pathway (7). This study, as a systematic review and meta-analysis of the results of randomized trial studies that have compared palonosetron and ondansetron, the effect of palonosetron and ondansetron on the level of IDO gene expression in leukocytes was investigated.

Materials and Methods

This meta-analysis study aims to compare the effectiveness of palonosetron and ondansetron in preventing nausea and vomiting after surgery. In this study, randomized clinical trial studies were selected. Also, due to the limitation of time and resources, the selection of studies was limited to English articles that were done from 2008 to 2021. Searching and finding available evidence, based on Pico's four criteria, which include:

Population: adults who undergo surgery with general anesthesia.

Intervention: Intravenous injection of palonosetron

Comparison: intravenous infusion of ondansetron

Result: Nausea and vomiting occurred after surgery. Then, based on other research limitations, entry criteria and exit criteria were formulated.

From the point of view of searching for studies, one of the most critical stages of carrying out the design is the comprehensive search of the available evidence and using them to answer the designed questions. For a comprehensive search, the following four methods were used:

1. Search electronic databases (3282 new items were found)
2. Checking the sources mentioned in related articles (3 new items)
3. Review of cited information (5 new cases)
4. Contacting the authors (no new items found)

Cochrane review, PubMed, Clinical K, and CRD were searched in electronic databases under the headings of medical subjects. The medical titles included the words: nausea, vomiting, nausea and vomiting after surgery, general anesthesia, ondansetron, and palonosetron, and the English equivalent of these words were used, and the search strategy for articles was developed according to the instructions of each electronic database, and at the end Search procedures, nine studies were selected. Figure 1 shows the number and method of selecting articles in different stages.

Afterward, the selected studies were evaluated based on the critical evaluation checklist specific to clinical trial studies. This checklist includes ten three-choice questions. This checklist discusses articles in 10 areas. Eight questions out of 10 examined areas have been presented as a test with three options: yes, can't say, and no. The first option of high power, the second option of medium strength, and the third option of low power show the studies comparing these two drugs. In this order, the scoring of the articles is between 8 and 24. In this research, articles with medium and high power are included in the meta-analysis study, and reports with low power, i.e., a score of less than 16, are excluded from the meta-analysis (8). Table 1 shows the scoring of the studies mentioned in the table with the names of their authors. Except for the Laha study (9), all the studies have sufficient power to enter the meta-analysis, and the average score of the articles is 20.

Among the nine studies, one study was excluded due to its low power. It should be mentioned that all these stages, i.e., search and critical evaluation of the articles, were done by two people, and at the end of each step, the researchers' results were compared. The information of the articles that had sufficient power to enter the meta-analysis, including prescribing the drugs and their dosage, the incidence of nausea and vomiting, and the duration of follow-up of patients for the occurrence of nausea and vomiting after surgery, were extracted. Table 2 shows the articles and the results of their extraction.

To check the distribution network, a funnel plot was drawn. To combine the results of quantitative studies, two methods of fixedness and randomness were used. The fixed method was used for the condition of homogeneity, and the random method was used in the heterogeneous conditions. In estimating the overall risk for meta-analysis studies, the relative risk was estimated. The relative risk shows that the risk of nausea and vomiting after the operation in the palonosetron group is several times the risk of occurrence in the ondansetron group. To analyze the data of the results obtained from the review of the studies and to determine the homogeneity and heterogeneity of the results of the studies, the statistical software STATA13 was used.

Results

The analysis of the bias caused by the publication of articles was done using the funnel plot diagram. Considering that the bias points of most studies are located on one

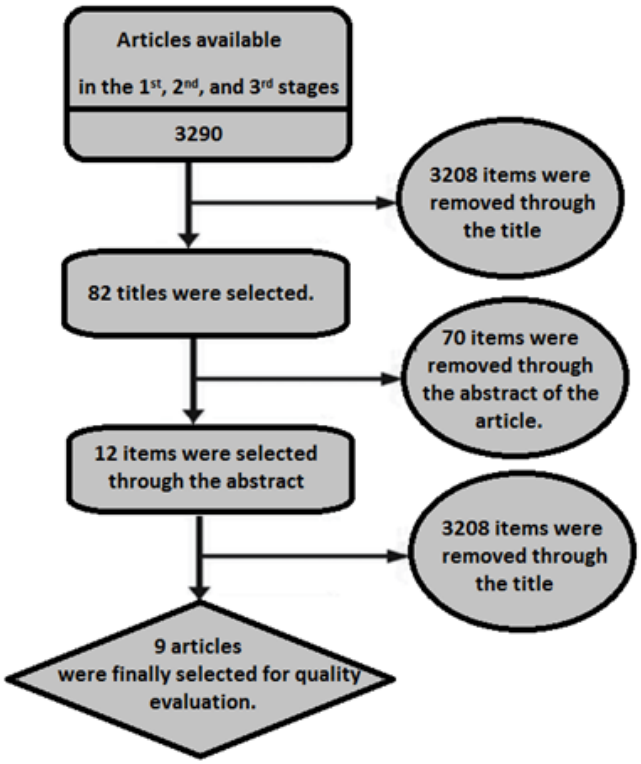

Figure 1. The number of articles found in different phases of the study.

Table 1. Evaluating articles using a critical evaluation checklist.

Studies	Clarity of the study question	Randomization	Allocation of participants in study groups	Blinding	Study design and method	Data collection and analysis	Sampling	Practical results of the study	Total scores
Joshi *et al*. (10)	3	3	3	3	3	3	2	1	21
Gupta *et al*. (11)	3	3	1	3	3	3	2	1	19
Gan *et al*. (12)	3	3	3	2	3	3	2	1	20
Kim *et al*. (13)	3	3	1	3	3	2	2	2	19
Laha *et al*. (9)	3	3	2	1	1	1	2	1	14
Jeyabalan *et al*. (14)	3	3	3	3	3	3	3	2	23
Yoo *et al*. (15)	3	3	3	3	1	3	2	2	20
Lee *et al*. (16)	3	3	3	3	3	3	2	2	22
Dey *et al*. (17)	3	3	3	3	1	3	2	2	20
Park *et al*. (18)	3	3	3	3	3	3	3	1	22

Table2. Evaluating articles using a critical evaluation checklist.

Authors	Study Sample	Follow-up period	intervention	comparator	Extracted results
Joshi *et al*. (10)	100 patients/ age group: 18-60 years old/ male and female/ All types of surgery/ Classified by the American Society of Anesthesiology 1 and 2	24 hours	Palonosetron 0.075mg before anesthesia	Ondansetron 4mg before anesthesia	Occurrence of nausea and vomiting in time intervals 0-1, 2-6, 6-12, 12-24, and 0-24 hours after the surgery
Gupta *et al*. (11)	120 patients/ age group: 18-58 years old/ male and female/ All types of surgery/ Classified by the American Society of Anesthesiology 1 and 2	12 hours	Palonosetron 0.075mg before anesthesia	Ondansetron 2mg and Granisetrone 4mg before anesthesia	Occurrence of nausea and vomiting in time intervals 0-4, 4-12, and 0-12 hours after the surgery
Gan *et al*. (12)	100 patients/ age group: more than 18 years old/ male and female/ laparoscopy/ Classified by the American Society of Anesthesiology 1 and 2	72 hours	Palonosetron 0.075mg before anesthesia	Ondansetron 8mg before anesthesia and 16 mg of infusion injection	Occurrence of nausea and vomiting in time intervals 0-2, 2-24, 0-24, 24-72, and 0-72 hours after the surgery
Kim *et al*. (13)	109 patients/ age group: 20-65 years old/ Female/ laparoscopy/ Classified by the American Society of Anesthesiology 1 and 2	48 hours	Palonosetron 0.075mg before anesthesia	Ondansetron 4mg and Romestrone 0.3mg before anesthesia	Occurrence of nausea and vomiting 0-48 hours after the surgery
Jeyabalan *et al*. (14)	60 patients/ age group: 20-50 years old/ Tympanoplasty	24 hours	Palonosetron 0.075mg before anesthesia	Ondansetron 4mg before anesthesia	Occurrence of nausea and vomiting in time intervals 0-6, 6-24, and 0-24 hours
Yoo *et al*. (15)	100 patients/ age group: 20-60 years old/ Female/ Thyroidectomy surgery/ Classified by the American Society of Anesthesiology 1 and 2	24 hours	Palonosetron 0.075mg before anesthesia	Ondansetron 8mg before anesthesia and 16 mg of infusion injection	Occurrence of nausea and vomiting in time intervals 0-2 and 2-24 hours
Lee *et al*. (16)	60 patients/ age group: 25-40 years old/ Female/ All types of surgery/ Classified by the American Society of Anesthesiology 1 and 2	72 hours	Palonosetron 0.075mg before anesthesia	Ondansetron 8mg before anesthesia	Occurrence of nausea and vomiting in time intervals 0-1, 1-6, 6-12, 12-24, 24-72 and 0-72 hours
Park *et al.* (18)	90 patients/ Female/ laparoscopy/ Classified by the American Society of Anesthesiology 1 and 2	24 hours	Palonosetron 0.075mg before anesthesia	Ondansetron 8mg before anesthesia	Occurrence of nausea and vomiting in time intervals 0-2, 2-6, 6-24, and 0-24 hours

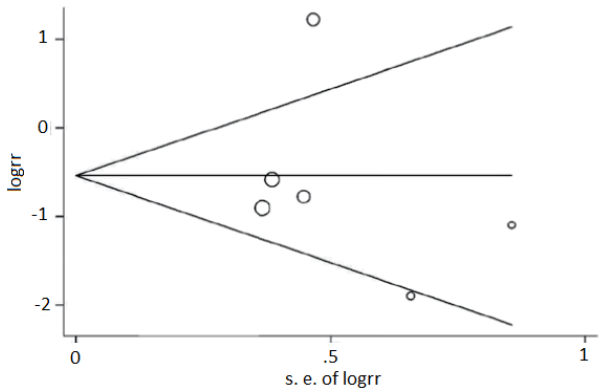

Figure 2. Results due to publication bias.

side of the curve and are mostly close to the outside of the curve, there is a bias of the studies in this research, due to which the results of the studies should be analyzed with more caution. Figure 2 shows the bias caused by articles with a 95% confidence interval.

As mentioned before, eight studies entered the meta-analysis stage. The results of these studies have been reported separately as the incidence of nausea and the incidence of vomiting. Meta-analysis of studies was done in two ways:

A: The analysis of all the results of the studies included in the meta-analysis that examines the incidence of nausea and vomiting separately after surgery. In this analysis, the results of the studies include time intervals from 0 to 72 hours after surgery.

B: Analysis of studies that have reported their results between 0 and 24 hours after the operation and prescribed the same dose of ondansetron, i.e., 4 mg, as a bolus to the patients. Only four studies have these conditions.

Meta-analysis for the occurrence of nausea regardless of time

Among the eight studies, one did not have information about the occurrence of nausea, which was not included in the meta-analysis. Table 2 shows the results of the meta-analysis for seven studies. According to the value of the heterogeneity index (I=8703%, p=0.001), we conclude that more than 90% of the observed differences between the relative risk of the studies are due to inconsistencies between the studies. This level is a sign of high heterogeneity between studies. According to this result, using the random effects method is necessary. These results are given in Table 3. As can be seen in the table3, the overall relative risk of 0.55 with a 95% confidence interval (0.26-1.15) obtained shows that the use of Palonosetron compared to Ondansetron has a 0.55 probability of nausea. It reduces among individuals. But the confidence interval related to the relative risk shows that this difference is not statistically significant. In other words, there is no significant difference between the two drugs in reducing nausea.

Meta-analysis for incidence of vomiting without taking into account time

The results of the homogeneity test (I=9.34%, p = 0.188) showed that the relative risk levels of the studies do not have a statistically significant difference. In other words, they are homogeneous. Therefore, the total fixed effects method is used to estimate the relative risk. For the five studies for which the incidence of vomiting was recorded, the total relative risk for the five studies was equal to 0.38 with a confidence interval (of 0.82 and 0.14), and the percentage obtained from this plan is greater than 64%. Ondansetron reduces the incidence of vomiting (Table 4).

Table 3. The results of the meta-analysis of the effect of pharmaceutical intervention of palonosetron and ondansetron based on the occurrence of nausea.

Studies	Relative risk	Confidence Interval		Weight
Joshi et al. (10)	0.405	0.257	0.638	19.19
Gupta et al. (11)	0.150	0.048	0.456	13.92
Kim *et al*. (13)	3.403	1.807	6.409	17.95
Jeyabalan *et al*. (14)	0.458	0.277	0.758	18.87
Yoo *et al*. (15)	0.333	0.073	1.521	11.03
Lee *et al*. (16)	0.556	0.345	0.895	19.04
Park *et al*. (18)	0.550	0.263	1.150	100.00

Chi-square of heterogeneity of studies = 27.39 (degree of freedom= 5) and significance (p = 0.001). Heterogeneity index value between the relative risk of studies: 87.3%. The significant level of overall relative risk (p=0.112).

Table 4. The results of the meta-analysis of the effect of pharmaceutical intervention of palonosetron and ondansetron based on the occurrence of vomiting.

Studies	Relative risk	Confidence Interval		Weight
Joshi et al. (10)	0.405	0.257	0.638	19.19
Gupta et al. (11)	0.150	0.048	0.456	13.92
Kim *et al*. (13)	3.403	1.807	6.409	17.95
Jeyabalan *et al*. (14)	0.458	0.277	0.758	18.87
Yoo *et al*. (15)	0.333	0.073	1.521	11.03
Lee *et al*. (16)	0.556	0.345	0.895	19.04
Park *et al*. (18)	0.550	0.263	1.150	100.00

Chi-square of heterogeneity of studies = 27.39 (degree of freedom= 5) and significance (p = 0.001). Heterogeneity index value between the relative risk of studies: 87.3%. The significant level of overall relative risk (p=0.112).

Discussion

The present study is the first meta-analysis conducted on clinical trial studies comparing the efficacy of palonosetron and ondansetron in preventing nausea and vomiting after surgery. The results of this study indicate that palonosetron prevents 50% and 79% more nausea and vomiting 24 hours after the operation than ondansetron.

Among the articles found, 1 study had low power to enter the meta-analysis after quality assessment. The total number of samples in the eight reviewed studies was 739 patients, and the studies were conducted between 2011 and 2021. Studies have been carried out on different surgeries, including laparoscopy, tympanoplasty, and gynecological surgeries. In these studies, the period that the patients were observed for the occurrence of nausea and vomiting varied from 12 hours to 72 hours. The prescribed doses of ondansetron and its injection method are also different. In the analysis of 8 studies for the comparison of the occurrence of nausea, the heterogeneity rate was 87.3%, which is in the category of studies with high heterogeneity. Therefore, a random model was used for further analysis, and for the comparison of the occurrence of vomiting in all the studies, the heterogeneity rate was calculated as 9.34. It used the method of fixed effects model.

The analysis of all studies showed that the two drugs, palonosetron, and ondansetron, do not significantly differ in reducing the incidence of nausea. Still, palonosetron minimizes the incidence of vomiting by 64% more than ondansetron. The study of Kim *et al*. (13) confirms this result in 0 to 24 hours and 0 to 72 hours after the operation, and contrary to that, the study of Joshi *et al*. (10) does not confirm this result.

In another analysis, studies that reported their results 24 days after the operation and prescribed the same doses of ondansetron were used. Only two studies have used the same dose of 8 mg in their study method, so the analysis of the results of only two studies does not have good statistical power (9). The analysis of the results of 4 studies to compare the incidence of nausea and vomiting in 24 hours after surgery for the comparison of the dose of 0.075 mg of palonosetron against the dose of 4 mg of ondansetron, except for the studies, is considered to have low heterogeneity, for which the fixed effects model was used for its analysis.

The study by Gupta *et al*. (11) was conducted to evaluate the comparisons of palonosetron, granisetron, and ondansetron drugs to prevent nausea and vomiting up to 12 hours after surgery. The results of this study showed that there is the highest rate of nausea and vomiting in the granisetrone group and the lowest rate of nausea and vomiting in the palonosetron group, and palonosetron prevents nausea and vomiting after surgery more effectively than ondansetron. The study's results by Joshi *et al*. (10) also indicate that palonosetron with a dose of 0.075 mg prevents nausea and vomiting caused by surgery up to 24 hours after the operation more effectively than ondansetron with a dose of 4 mg.

Park *et al*. (18) also compared ondansetron and palonosetron in women's laparoscopic surgeries and showed that the incidence of nausea and vomiting in the palonosetron group is lower than that of the ondansetron group. The results of the present study also indicate that palonosetron prevents nausea and vomiting 24 hours after the operation to a greater extent than ondansetron. Since palonosetron drug, with its single isomeric structure, can bind to serotonin receptors with more strength and time and binds to these receptors for up to 72 hours, the US Food and Drug Administration has confirmed this effectiveness drug only 24 hours after surgery. It has been stated (7) that the results of the meta-analysis performed 24 hours after the operation and the studies of Park *et al*. (18), Joshi *et al*. (10), and Gupta *et al*. (11) confirm the greater effectiveness of the drug palonosetron compared to ondansetron 24 hours after the surgery. In general, the results related to palonosetron's efficacy and ondansetron (24 hours after surgery) with a dose of 0.075 mg of palonosetron versus 4 mg of ondansetron show that palonosetron is more effective in terms of reducing nausea and vomiting in patients which was statistically significant.

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