ID Design Press, Skopje, Republic of Macedonia
Open Access Macedonian Journal of Medical Sciences. 2019 Oct 15; 7(19):3195-3200.
https://doi.org/10.3889/oamjms.2019.795
eISSN: 1857-9655
Clinical Science

Comparison of Ondansetron and Granisetron Effects for Prevention of Nausea and Vomiting Following Strabismus Surgery

Shirin Salajegheh[1], Soodeh Kuhestani[2*], Mahdieh Sharifzadeh Kermani[1], Omid Taheri[2], Naeimeh Naeimi Bafghi[1]

[1]Department of Anesthesiology, Shafa Hospital, Kerman University of Medical Sciences, Kerman, Iran; [2]Department of Anesthesiology, Bahonar Hospital, Kerman University of Medical Sciences, Kerman, Iran

Citation: Salajegheh S, Kuhestani S, Sharifzadeh Kermani M, Taheri O, Naeimi Bafghi N. Comparison of Ondansetron and Granisetron Effects for Prevention of Nausea and Vomiting Following Strabismus Surgery. Open Access Maced J Med Sci. 2019 Oct 15; 7(19):3195-3200. https://doi.org/10.3889/oamjms.2019.795

Keywords: Nausea; Vomiting; Strabismus Surgery; Endonestrone; Granisetron

***Correspondence:** Soodeh Kuhestani. Department of Anesthesiology, Bahonar Hospital, Kerman University of Medical Sciences, Kerman, Iran. Tel: 00989131950629. Email: aeghmazi93@gmail.com

Received: 25-Jul-2019; **Revised:** 10-Aug-2019; **Accepted:** 11-Aug-2019; **Online first:** 12-Sep-2019

Funding: This research did not receive any financial support

Competing Interests: The authors have declared that no competing interests exist

Abstract

BACKGROUND: Postoperative nausea and vomiting (PONV) is a common complaint after strabismus surgery that leads to unpleasantness, increased hospitalisation time and increased costs. In severe cases, it can lead to dehydration, electrolyte disturbances, aspiration, pneumonia, and even sutures opening.

AIM: This study was conducted to compare the effects of both ondansetron and granisetron on the reduction of PONV after strabismus surgery.

METHODS: This randomised, and the double-blind clinical study was conducted on patients with ASA I and II undergoing strabismus surgery with age over 3 years old in Shafa Hospital, Kerman University of Medical Sciences during 2017 under general anaesthesia. Patients with inclusion criteria were randomly assigned to one of three groups including Ondansetron (A), Granisetron (B) and control group (C). Matching cases and controls on drugs were fully completed. Furthermore, 100 µg/kg of Ondansetron was intravenously injected, followed by injection of 40 µg/kg Granisetron for another intervention group. All patients underwent the same anaesthetic procedure and intravenous injection of drugs during anaesthesia induction. The severity of nausea and vomiting in recovery, 6 and 18 hours after the operation were verified according to the Verbal Rating Scale (VRS). Our data were analysed by Chi-square, ANOVA and TUKEY tests via SPSS version 18.

RESULTS: There was no significant difference between the three groups in terms of age and sex. The incidence of postoperative nausea in recovery among three groups of A, B and C was determined to be 15, 7.5 and 37.5%, respectively. No significant difference was found between the two groups A and B ($P = 0.68$), although there was a significant difference between these two groups and group C ($P < 0.05$). The incidence of nausea at 6 hours after surgery in groups A, B and C was recorded as 40, 15 and 65% respectively, indicating that the incidence of nausea in group B was significantly lower than the other two groups, while showed a significant difference with group A ($P = 0.039$) and group C ($P < 0.05$). Also, the incident of nausea between groups was not statistically significant 18 hours after surgery ($P < 0.05$). Additionally, no significant difference was found in different groups in terms of vomiting incidence in recovery, 6 and 18 hours after surgery ($P < 0.05$).

CONCLUSION: Our study suggests that Granisetron is more effective in preventing PONV during 6 hours after the surgery in comparison with Ondansetron which makes it a favourable alternative for preventing PONV.

Introduction

Postoperative nausea and vomiting (PONV) are the second most adverse and complicated event following surgery [1], [2]. This usually occurs in the post-anaesthetic phase and ends within 24 hours, which its incidence ranged from 30 to 20% [3]. Risk factors for postoperative nausea and vomiting include females, duration of anaesthesia for more than half an hour, age above 3 years, type of surgery, personal or familial history of postoperative nausea and vomiting, or motion sickness [4], [5].

The type of surgery is not necessarily the most important cause of PONV. The occurrence of PONV following various surgeries is more due to the factors related to the patient and anaesthesia than the self-surgery issue [6], [7]. PONV is an unpleasant experience that patients often find worse than postoperative pain [7]. Prevention of PONV in patients at high risk of this complication improves postoperative satisfaction [8]. Although PONV is self-

limiting, its occurrence following surgery can lead to multiple complications such as aspiration of stomach contents, suture opening, oesophagal rupture, subcutaneous emphysema and pneumothorax [9], [10]. PONV delayed the patient's recovery and prolonged unexpected hospitalisation after an outpatient operation [11]. PONV prolongs the discharge time to 61-47 minutes. The annual impact of PONV on healthcare costs is estimated to be several hundred million dollars in the United States [12]. The reason for the lack of definitive prevention of PONV is the presence of multiple factors associated with this disorder, so the main solution to prevent this complication is still the use of anti-nausea drugs in clinical cases. Ondansetron is a serotonin receptor antagonist that is considered as the most effective anti-vomiting drug for preventing PONV [13], [14]. Granisetron is a serotonin 5-HT_3 receptor antagonist, with a half-life of about two times that of Ondansetron [13], [14].

Strabismus surgery is among the operations with a high prevalence of PONV (75-40%), which causes long recovery, high costs, increased bleeding, increased eye pressure and patient dissatisfaction due to the nature of the strabismus surgery caused by the muscle tightening [15]. Therefore, we compared the effect of two Ondansetron and Granisetron drugs on nausea and vomiting following strabismus surgery.

Material and methods

This randomised, and the double-blind clinical study was conducted on patients undergoing strabismus surgery with age over 3 years old in Shafa Hospital, Kerman University of Medical Sciences during 2017. Sampling was done based on purpose and field information was collected using a questionnaire.

Considering the maximum sample size, the standard deviation in similar studies, alpha coefficient of 5% and power of 80% [16], [17], 120 patients with strabismus surgery were randomly assigned to 3 groups of 40 subjects in the placebo, Ondansetron and Granisetron.

Alpha	=	*0.05*	*(two-sided)*	*Z (1-α/2)*	*1.959964*
power	=	0.8		Z (1-β)	0.841621
m1	=	2		D	1
m2	=	3		s^2	1.69
sd1	=	1.2		sd_1^2	1.44
sd2	=	1.4		sd_2^2	1.96
				n1	26.68619
				n2	26.68619

$$n=\frac{(Z_{(1-\alpha/2)}+Z_{(1-\beta)})^2(sd_1{}^2+sd_2{}^2)}{d^2}$$

Inclusion criteria: 1) Patients undergoing strabismus surgery over the age of 3 years And 2) Class 1 & 2 American Society of Anaesthesiologists' (ASA) classification of Physical Health. Exclusion criteria: 1) History of previous surgery and anaesthesia with postoperative nausea and vomiting; 2) History of Ménière's disease, motion sickness or migraine; 3) Dissatisfaction with surgery; 4) Use of drugs that affect nausea and vomiting within 24 hours of surgery; 5) Pregnancy or breastfeeding.

Patients with inclusion criteria were randomly assigned to one of three groups, including Ondansetron, Granisetron and placebo (normal saline administration). In a randomised clinical trial was blinded, in which neither the patient nor the evaluating person informed the type of drug used. Furthermore, matching cases and controls on drugs were fully completed.

Induction of all three groups was performed with midazolam 1 mg, fentanyl 100-50 micrograms, thiopental 5 mg/kg and atracurium 0.2 mg/kg. Maintenance of anaesthesia was carried out in all three groups with propofol infusion (100 µg/kg/min) and 50% N2O-O2 mixture.

After giving premed to the patient, 100 µg/kg of Ondansetron was intravenously injected, followed by injection of 40 µg/kg Granisetron for another intervention group.

All recovery personnel and section were unaware of the patient groups and the type of drug used. The severity of nausea and vomiting were evaluated by an anesthesiologist at the recovery and after transferring to the section during 6 hours following the operation and then after discharge from the hospital during the next 18 hours. A drug for the treatment of nausea and vomiting was not given to patients during anaesthesia. In case of severe nausea and vomiting, a dose of dimenhydrinate (mg) was administered to the patient. Additionally, patients who suffered from nausea and vomiting in recovery, received metoclopramide 0.1 mg/kg.

Because the two drugs used are both anti-nausea and -vomiting, and only their effect and potency are different, no additional drugs have been given to patients in recovery. Recording the age, height, weight and duration of anaesthesia, the severity of nausea and vomiting in recovery were done by anaesthesia technician. After transferring the patient to the section, the patients were evaluated by the anaesthesia resident within 6 hours after the operation and then after discharge from the hospital within the next 18 hours. The severity of nausea is measured according to the Verbal Rating Scale (VRS). By this method, an individual without nausea is assigned zero, in case of less than two nausea episode, mild nausea was considered, as followed twice or more (moderate nausea). The incidence of vomiting is considered to be the same as severe nausea.

Ethical considerations included: 1. Approval of

the plan by the Research Council of the School of Medicine; 2. Informed consent was obtained from the patient to participate in the study, of mention, obtained by the legal parents for the children; and 3. Both anti-nausea drugs are used routinely without any complications if any unwanted side effects were observed, each treatment was followed by a withdrawal from the study, but no complication was observed.

Data analysis

Information for each group was coded as 1, 2 and 3, and the recorded in the checklist for each drug or placebo, followed by statistical analysis through the SPSS version 18 software. Data analysis Information for each of the 3 groups, coded 1, 2 and 3, was recorded in the checklist for each drug or placebo, and then entered the SPSS version 18 software. Using the Kolmogorov-Smirnov test, the data were analysed for normal distribution. Depending on the distribution of data and quantitative or qualitative values, quantitative data such as age were analysed using one-way ANOVA test regarding their normalisation, while Non-parametric Kruskal-Wallis H test was used for data with skewed distribution. If parametric or parametric tests showed significant values, Dunn's multiple comparisons test and Tukey tests were employed to compare the groups. Chi-square test was applied to evaluate the qualitative variables. Regarding the lack of time assessment, repeated tests such as repeated measures ANOVA were not used. In all tests, a significant level of 0.05 was considered.

Results

Our study was conducted on 120 patients who referred to the operating room of the hospital for strabismus surgery and randomly divided into three groups: A (Ondansetron), B (Granisetron) and C (Placebo). Study population consisted of 76 male patients (63.3%) and 44 (36.7%) female. Among them, 26 patients received A, 21 drug B and 29 C, respectively. Among the female patients, 14 received A, 19 B and 11 C, respectively. Forty people were considered for each group A, B and C, without regarding gender.

The results of the chi-square test showed no significant relationship between nausea rate in all three groups and sex (P = 0.175). The mean age and standard deviation in each of groups A, B, C were determined as 43.68 ± 19.3, 22.78 ± 16.1 and 97.74 ± 13.1.

The mean age of patients in Ondansetron, Granisetron and control groups was 19.43, 16.22 and 13.97, respectively. The mean age of the subjects was 16.49 years. Based on the ANOVA test, no significant difference was found between the groups in terms of age (P = 0.332).

Table 1 shows the magnitude and severity of nausea and vomiting in recovery. Of the 120 participants, 15% had a feeling of nausea in group A, followed by group B (7.5%) and group C (37.5%). The best possible status for lack of nausea episode was in group B with 92.5%, followed by group A (85%) and group C (62.5%). The highest vomiting (3 cases) was recorded in group C, followed by group A (one person) and group B (none), (Table 1).

Table 1: The rate and severity of nausea and vomiting in recovery among three groups (A, B, C)

Variable		An (Endonestrone)		B (Granisetron)		C (control)		Total	
		Frequency	Percent	Frequency	Percent	Frequency	Percent	Frequency	Percent
Recovery	No nausea	34	85	37	92.5	25	62.5	96	80
	Mild nausea	4	10	3	7.5	7	17.5	14	11.7
	Moderate nausea	1	2.5	0	0	5	12.5	6	5
	Severity Nausea (Vomit)	1	2.5	0	0	3	7.5	4	3.3

Table 2 indicates the measurement of nausea episodes and severity in 6 hours after surgery. Of the 120 patients, 60% of the subjects did not feel nauseous, while 23.3% had mild nausea, followed by moderate nausea (7.5%) and severe nausea (vomiting: 9.2%).

The most common nausea episodes were observed in group C (placebo) with 65%, while episodes were 40% in group A and 15% in group B. In other words, the best possible situation was seen in Group B (85% without nausea). Vomiting in groups A, B and C was 7.5, 2.5 and 17.5%, with the lowest vomiting in group B and the highest in group C (Table 2).

Table 2: The rate and severity of nausea and vomiting in the first 6 hours after surgery in the three groups (A, B, C)

Variable		An (Endonestrone)		B (Granisetron)		C (control)		Total	
		Frequency	Percent	Frequency	Percent	Frequency	Percent	Frequency	Percent
6h after	No nausea	24	60	34	85	14	35	72	60
	Mild nausea	10	25	4	10	14	35	28	23.3
	Moderate nausea	3	7.5	1	2.5	5	12.5	9	7.5
	Severity Nausea (Vomit)	3	7.5	1	2.5	7	17.5	11	9.2

The incidence rate and severity of nausea and vomiting in 18 hours after surgery are listed in Table 2. After 18 hours of operation, 96.7% of the patients had no nausea episode One in group A, one in group B and two in group C patients, expressed the feeling, while vomiting was seen only in the group C (Table 3).

Table 3: Incidence and severity of nausea and vomiting 18 hours after operation in three groups (A, B, C)

Variable		An (Endonestrone)		B (Granisetron)		C (control)		Total	
		Frequency	Percent	Frequency	Percent	Frequency	Percent	Frequency	Percent
18h after	No nausea	39	97.5	39	97.5	38	95	116	96.7
	Mild nausea	1	2.5	1	2.5	1	2.5	3	2.5
	Moderate nausea	0	0	0	0	0	0	0	0
	Severity Nausea (Vomit)	0	0	0	0	1	2.5	1	0.8

The incidence of postoperative nausea in recovery in the three groups of Ondansetron, Granisetron and control was determined to be 15, 7.5 and 37.5%, respectively (Table 4). The result of the test demonstrated a significant general relationship between the groups. Based on the results of Tukey test, we found that despite the low nausea rate in the Granisetron group compared to the Ondansetron group, no significant difference was found between the two groups in terms of nausea (P = 0.658), although there was a significant difference between the two groups and the control group (P < 0.05) (Table 4).

Table 4: Comparison of the three groups in terms of postoperative nausea in recovery

Variable	An (Endonestrone)		B (Granisetron)		C (control)		Total		Results of the Chi-Square Test
	Frequency	Percent	Frequency	Percent	Frequency	Percent	Frequency	Percent	
Recovery Nausea	6	15	3	7.5	15	37.5	24	20	0.002

Regarding the incidence of vomiting in recovery, although it was relatively reduced in the Granisetron group in comparison with Ondansetron and placebo, but no statistically significant difference was observed between the groups (P = 0.164) (Table 5).

Table 5: Comparison of the three groups in terms of postoperative vomiting in recovery

Variable	An (Endonestrone)		B (Granisetron)		C (control)		Total		Results of the Chi-Square Test
	Frequency	Percent	Frequency	Percent	Frequency	Percent	Frequency	Percent	
Recovery Vomiting	1	2.5	0	0	3	7.5	4	3.3	0.164

The incidence of nausea in the 6 hours after strabismus surgery in the Ondansetron, Granisetron and control groups was 40, 15 and 65% respectively, indicating that the incidence of nausea was significantly lower in the Granisetron group when compared with the other two groups.

Table 6: Comparison of the three groups in terms of postoperative nausea in 6 hours after surgery

Variable	An (Endonestrone)		B (Granisetron)		C (control)		Total		Results of the Chi-Square Test
	Frequency	Percent	Frequency	Percent	Frequency	Percent	Frequency	Percent	
6H after Nausea	16	40	6	15	26	65	48	40	0.0001

Although the incidence of vomiting demonstrated a decreasing trend in the granitic group at 6 hours after the operation as compared to placebo and indomethacin, there was no statistically significant difference between the groups (P = 0.061; Table 6 and 7).

Table 7: Comparison of the three groups in terms of vomiting in 6 hours after surgery

Variable	An (Endonestrone)		B (Granisetron)		C (control)		Total		Results of the Chi-Square Test
	Frequency	Percent	Frequency	Percent	Frequency	Percent	Frequency	Percent	
6h after Vomiting	3	7.5	1	2.5	7	17.5	11	9.2	0.061

The incidence of nausea was not significantly different between the groups 18 hours after surgery (P = 0.772).

Table 8: Comparison of the three groups in terms of nausea 18 hours after surgery

Variable	An (Endonestrone)		B (Granisetron)		C (control)		Total		Results of the Chi-Square Test
	Frequency	Percent	Frequency	Percent	Frequency	Percent	Frequency	Percent	
18h after Nausea	1	2.5	1	2.5	2	5	4	3.3	0.772

Also, there was no significant difference between the groups in terms of vomiting incidence 18 hours after the operation (P = 0.336; P < 0.05; Table 8 and 9).

Table 9: Comparison of the three groups in terms of vomiting 18 hours after surgery

Variable	An (Endonestrone)		B (Granisetron)		C (control)		Total		Results of the Chi-Square Test
	Frequency	Percent	Frequency	Percent	Frequency	Percent	Frequency	Percent	
18 h after Vomiting	0	0	0	0	1	0.52	1	0.8	0.365

Discussion

Today, the increasing number of surgeries has increased the desire for early release of patients from recovery. Decreasing the incidence of PONV has accelerated the discharge of patients, reduces the length of hospitalisation or re-admission, and leads to patient satisfaction [18], [19]. In this regard, we aimed to compare the effect of both Ondansetron, and Granisetron on nausea and vomiting following strabismus surgery.

The findings of the statistical tests showed that there was no significant difference between the level of nausea in all three groups and gender (p = 0.175). Furthermore, the mean age of patients in the three groups revealed no significant difference between the groups in terms of age (P = 0.332). The best possible status for lack of nausea was observed in group B (92.5%), followed by group A (85%) and group C (62.5%). Despite the low nausea rate in the Granisetron group in comparison with Ondansetron, there was no significant difference between them (P = 0.658);

The highest vomiting (3 cases) was recorded in group C, followed by group A (one person) and group B (none), (Table 1). However, there was a significant difference between the two intervention groups and the control group (P < 0.05).

The highest vomiting (3 cases) was recorded in group C, followed by group A (one person) and group B (none). Although recovery vomiting was relatively reduced in the Granisetron group as compared to Ondansetron and placebo, but no

statistically significant difference was found between the groups (P = 0.164).

Based on the results presented herein, 60% of the subjects did not feel nauseous, while 23.3% had mild nausea, followed by moderate nausea (7.5%) and severe nausea (vomiting: 9.2%).

The most common nausea episode was observed in group C (placebo) with 65%, while the episode was 40% in group A and 15% in group B. The best possible situation was seen in Group B (85% without nausea); Statistically, the incidence of nausea in the Granisetron group was significantly less than the other two groups, and this difference was significant in comparison with the Ondansetron group (P = 0.039) and the control group (P < 0.05).

In addition, vomiting in groups A, B and C was determined as 7.5, 2.5 and 17.5%, where the lowest vomiting was observed in group B and the highest in group C. Although, relative reduction of vomiting was observed in the Granisetron group as compared to placebo and Ondansetron, but no statistically significant difference was found between the groups (P = 0.061).

The incidence rate and severity of nausea and vomiting in 18 hours after surgery are listed in Table 2. After 18 hours of operation, 96.7% of the patients had no nausea episode. One in group A, one in group B and two in group C expressed episodes while vomiting was seen only in the group C.

The incidence of nausea was not statistically significant among the groups 18 hours after surgery (P = 0.772). Moreover, there was no significant difference between the groups in terms of vomiting18 hours after surgery (P = 0.365), (P < 0.05).

Very limited studies have been conducted on the effects of both Granisetron and Ondansetron on reducing the incidence of PONV in strabismus surgery, although more studies are available for other surgeries such as laparoscopy. Most studies have shown that Granisetron is more effective than Ondansetron which is consistent with our study, although some studies have also shown contradictory results.

A study assessed the effect of Granisetron, Ondansetron, Midazolam combination with Dexamethasone for reduction of PONV after strabismus surgery among 100 children ASA class I and II, where findings did not show significant differences between different groups [20].

Another study evaluated antiemetic effects of Ondansetron and Granisetron in preventing postoperative nausea and vomiting in subjects undergoing daycare laparoscopic tubal ligation where minimal emetic episodes in patients receiving intravenous granisetron when comparing with those receiving ondansetron and placebo. The study mentioned above indicated that emetic episodes were attributed to 7% of patients receiving intravenous granisetron, followed by 20% in the ondansetron group and 50% in placebo group C [21].

In a randomized double-blind investigation, 100 female patients were assessed for effect of Ondansetron and Granisetron in preventing PONV (intervals of 6-0, 12-6, 18-12 and 24-18 after surgery) in subjects undergoing elective laparoscopic cholecystectomy, where a significant was found in the incidence of PONV among two groups after 6 hours to 24 hours [16].

Gauchan et al. evaluated the antiemetic efficacy of Ondansetron and Granisetron in patients undergoing laparoscopic cholecystectomy during the first 24 hours after anaesthesia. They indicated that Granisetron was effectively capable of increasing incidence of PONV as compared to Ondansetron in the first 24 hours [17].

In another study by Savant et al., the effects of ondansetron (4 mg, 2 mL) and granisetron (2 mg, 2 mL) was assessed in preventing PONV in subjects undergoing oral and maxillofacial surgery.

Except for the headache side effect, it has been shown that the incidence of nausea and vomiting in the Granisetron group was significantly lower than that of Ondansetron [22].

In conclusion, our study suggests that Granisetron is more effective in preventing PONV for 6 hours after the surgery in comparison with Ondansetron which makes it a favourable alternative.

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