RESEARCH ARTICLE

Comparison of the Prophylactic Effect of Ondansetron, Dexamethasone, and the Combination of These Drugs on Decreasing Nausea and Vomiting in Children Aged 1 to 12 Years Old Undergoing Upper Gastrointestinal Endoscopy

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Background: Endoscopy is a diagnostic and therapeutic method with a high risk of nausea and vomiting. Considering the lack of adequate studies on the prevention of postoperative nausea and vomiting after endoscopy in children, this study was conducted to compare the effects of ondansetron, dexamethasone and a combination of these drugs on the reduction of nausea and vomiting in children aged 1 to 12 years undergoing upper gastrointestinal endoscopy.

Methods: In this double-blind, randomized clinical trial, 146 children aged 1 to 12 years, undergoing upper gastrointestinal endoscopy were randomly allocated to four groups of 36. Before endoscopy, the groups received 0.1 mg / kg of ondansetron, 0.2 mg / kg dexamethasone, a combination of the two drugs and placebo, respectively.

Results: According to the results of our study, children who underwent upper GI endoscopy, administration of ondansetron plus dexamethasone was associated with a significantly lower frequency of nausea in all assessment time points. However, the difference between the groups was significant only on admission to recovery and the 15 minutes after admission to recovery (P<0.001).

Conclusion: The results of our study indicated that in children undergoing endoscopy, the use of ondansetron plus dexamethasone is associated with reduction in the incidence of nausea and vomiting, and the use of the combination does not cause significant side effects compared to ondansetron, dexamethasone or placebo, separately.

Keywords: endoscopy; ondansetron; dexamethasone; nausea; vomiting

Upper gastrointestinal (GI) endoscopy is one of the most prevalent and growing methods used in children especially in the diagnosis of gastrointestinal reflux disease (GERD), esophageal and stomach diseases, foreign body disease and suspicion of malabsorption [1]. One of the most common complications of endoscopy is nausea and vomiting which can cause discomfort for the patient and can increase the length of hospital stay and treatment expenses. Various medications have been used to decrease postoperative nausea and vomiting (PONV), including dopamine antagonists (metoclopramide), steroids (dexamethasone), serotonin (5HT3) receptor antagonist (ondansetron) [2-4]. The use of the combination of two drugs has been proposed in recent studies to prevent nausea and vomiting in such procedures in children [5-7]. In various studies, many different drug combinations have been reviewed for the prevention of nausea and vomiting in children, including a combination of dexamethasone and ondansetron in some procedures with a high risk of nausea and vomiting, such as laparoscopy or strabismus repair surgery [8-9].Considering the lack of sufficient studies on the prevention of nausea and vomiting after endoscopy in children, this study was conducted to compare the effectiveness of prophylactic ondansetron, dexamethasone and a combination of the two drugs in preventing nausea and vomiting after upper GI endoscopy in children aged 1 to 12 years old.

Methods

This study was a double-blind clinical trial with control group and was performed (enrolment period Jun. 2016 to Apr. 2017) in patients referred to Imam Hossein Children's Hospital. A consent form was obtained from the parents for the patients' participation in this study.

Inclusion criteria: Children 1 to 12 years old, ASA class I or II who were scheduled for upper GI endoscopy, parental consent for participation of children in the study.

Non-inclusion criteria: History of allergy to study drug, severe respiratory disease, severe cardiovascular disease and children with an unstable medical condition.

Exclusion criteria: Endoscopy procedure lasting more than 30 minutes, changing of the diagnostic procedure to a

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therapeutic procedure or occurrence of complications related to endoscopy.

This study was registered in the Iranian Registry of Clinical Trials (IRCT) at www.irct.ir with an identification registration code: IRCT20160307026950N7. The sample size was calculated using the sample size formula for means, as being 144 patients. Sampling was done using simple randomization and patients were allocated into 4 groups of 36 patients using a randomization chart. The medications were prepared in 1 ml volumes by the anesthesiologist and placed in uniform syringes. 5 minutes before endoscopy, the nurse injected 0.1 mg/kg ondansetron to the first group (O), 0.2 mg/kg dexamethasone to the second group (D) and a combination of the two drugs to the third group (OD). The fourth group was injected the same volume of normal saline used as a placebo(C). The nurse and the patient were unaware of the contents of each syringe. The patient was then premedicated with 0.1 mg/kg midazolam plus 1 mg/ kg ketamine and transferred to the endoscopy room and placed under sedation using 2 mg/ kg of fentanyl and 2 mg/ kg of propofol 2%. Mean arterial pressure (MAP), heart rate (HR) and peripheral oxygen saturation (SpO2) were measured every 5 minutes after endoscopy. The patient was transferred to the recovery room and the severity of nausea and vomiting was assessed using the Bexter Retching Face Nausea Scale every 15 minutes in the recovery room and at 2,4, 6 hours after endoscopy in the ward. The duration of recovery was assessed using the Modified Aldrete Score. If there was a need for antiemetic drugs, 0.1 mg/ kg ondansetron was used in the recovery room. The initial time of antiemetic drug request and the administered dose were recorded for analysis. For data analysis, the data were entered into the SPSS software version 24 and analysed using one-way variance analysis, Chi-square and variance analysis of repeated measurements.

Results

Characteristics of the patients

140 children who were scheduled for diagnostic endoscopy were entered into the study. They were allocated into 4 groups, one group receiving ondansetron, the second group dexamethasone, the third group, a combination of ondansetron plus dexamethasone and a fourth control group, receiving normal saline as placebo.

According to (Table 1), there were no significant differences in terms of age, weight, gender or duration of endoscopy ($p< 0.05$).

Table 1- Distribution of age, weight, gender or duration of endoscopy between four groups

		Frequency (%)				Total	P-Value*
		Group O	Group D	Group OD	Group C		
Gender	F	(48.6%)17	(37.1%)13	(27.7%)9	(34.3%)12	(36.4%)51	0.26
	M	(51.4%)18	(62.9%)22	(65.7%)23	(74.3%)26	(63.6%)89	
Age (y)		5.3±3.3	6.3±3.2	5.3±5.4	5.3±7.6	5.55±4.9	0.66
Weight (Kg)		19.9±7.9	23.3±9.0	19.9±8.7	20.9±6.0	20.9±7.9	0.44
duration of endoscopy(min)		28.3±2.3	27.3±3.9	27.5±1.2	28.3±1.6	27.85±2.25	0.59
*Independent t-test							

*F, Female; M, Male; O, Ondansetron; D, Dexamethasone; OD, Ondansetron- Dexamethasone; C, Placebo.

Hemodynamic changes

Evaluation of hemodynamic parameters which is shown in table 2, illustrated that SpO2 among the 4 groups had a significant difference at all times, with the control group having the lowest SpO2, but the other three groups had no significant difference amongst each other. The mean HR at all times had a significant difference between the three groups with the control group. Moreover, HR had a significant difference between the ondansetron group with the ondansetron plus dexamethasone group, but not in the dexamethasone group with the ondansetron group. Analysis of MAP also showed a significant difference between the placebo group and the other three groups. (Table 2).

Furthermore, MAP between the ondansetron group and the dexamethasone plus ondansetron group at minutes; 20, 25 and 30 and in recovery and in the ward had significant differences. The analysis of variance with repeated measurements showed that the changing trend of the aforementioned parameters (MAP, HR, and O_2 Sat) had a significant difference between the 4 groups, with the Group OD showing the highest hemodynamic stability. In addition, using the same analysis method for age, gender, weight and the duration of endoscopy, they appeared to have no significant effect on the changing trend of the parameters. (Table 3).

Nausea variables

According to the results, the severity of nausea at all times had a significant difference between the four groups. The Group OD had the least severe nausea while the control group had the most severe nausea ($p<0.001$). The severity of nausea in the ondansetron, dexamethasone, ondansetron plus dexamethasone and control group at entry to the recovery room were 4.9± 2.1, 5.2±1.6, 2.3 ±0.8 and 6.8±2.4, respectively ($p<0.001$). At 15 minutes after recovery it was 2.8±1.7, 3.1±1.8, 2.0±0.01 and 4.8± 2.6, respectively ($p<0.037$). At 30 minutes it was 2±1.5, 2±0.1, 1.5±0.7 and 3.1±6.5, respectively ($p=0.054$), while it was 2±0.1, 2 ±0.1, 1±0.01 and 2.9±2.4, respectively, at 45 minutes ($p=0.8$). Therefore, the severity of nausea had a significant difference until the 15th minute but not at 30 and 45 minutes. (Figure 1).

Table 2- Mean heart rate, arterial blood pressure and oxygen saturation in four groups at minutes; 5, 30

	Time	GRD	GRO (MD±SD)	GR OD	GR C	P-Value*	P-Value**
SpO2	5th min	99.3±5.7	99.0±1.89	99.0±2.8	97.1±8.7	0.005	
	10th min	98.1±9.1	99.1±1.0	99.0±2.8	97.1±7.7	0.001	
	15th min	98.1±9.0	98.1±9.1	99.0±2.9	97.1±5.9	0.001	0.001
	20th min	99.9±0.0	99.0±9.5	99.0±4.7	97.1±6.8	0.001	
	25th min	99.0±1.8	99.0±2.9	99.0±4.7	97.1±7.7	0.001	
	30th min	99.0±1.9	99.0±2.8	99.0±4.7	97.1±7.6	0.001	
HR	5th min	123.8±4.4	119.1±3.9	113.1±9.3	133.1±9.6	0.001	
	10th min	123.8±6.0	112.9±5.7	112.9±5.8	134.1±4.0	0.001	
	15th min	123.8±6.0	118.1±5.0	111.9±9.6	135.1±3.4	0.001	
	20th min	123.6±7.0	117.1±4.3	111.9±3.5	136.1±2.9	0.001	0.001
	25th min	119.1±8.1	117.9±3.9	110.9±7.3	136.1±2.9	0.001	
	30th min	120.1±2.5	117.9±5.8	110.9±7.6	134.1±4.5	0.001	
MAP	5th min	62.3±2.8	60.4±6.6	58.4±4.3	68.9±7.3	0.001	
	10th min	61.3±8.6	60.1±4.0	57.4±9.2	68.9±7.2	0.001	
	15th min	61.3±9.6	60.0±4.0	57.4±8.2	68.9±8.1	0.001	
	20th min	61.3±8.3	60.2±4.0	57.4±9.0	68.9±9.1	0.001	0.001
	25th min	61.3±8.4	60.3±4.0	57.4±9.2	69.8±8.0	0.001	
	30th min	61.3±7.4	60.4±1.4	57.4±7.1	68.8±9.8	0.001	
	*Independent t-test						

*SpO2, Peripheral Oxygen Saturation; HR, Heart Rate; MAP, Mean Arterial Pressure; O, Ondansetron;
**D, Dexamethasone; OD Ondansetron- Dexamethasone; C, Placebo.

Figure 1- Mean of nausea severity between four groups in recovery times.

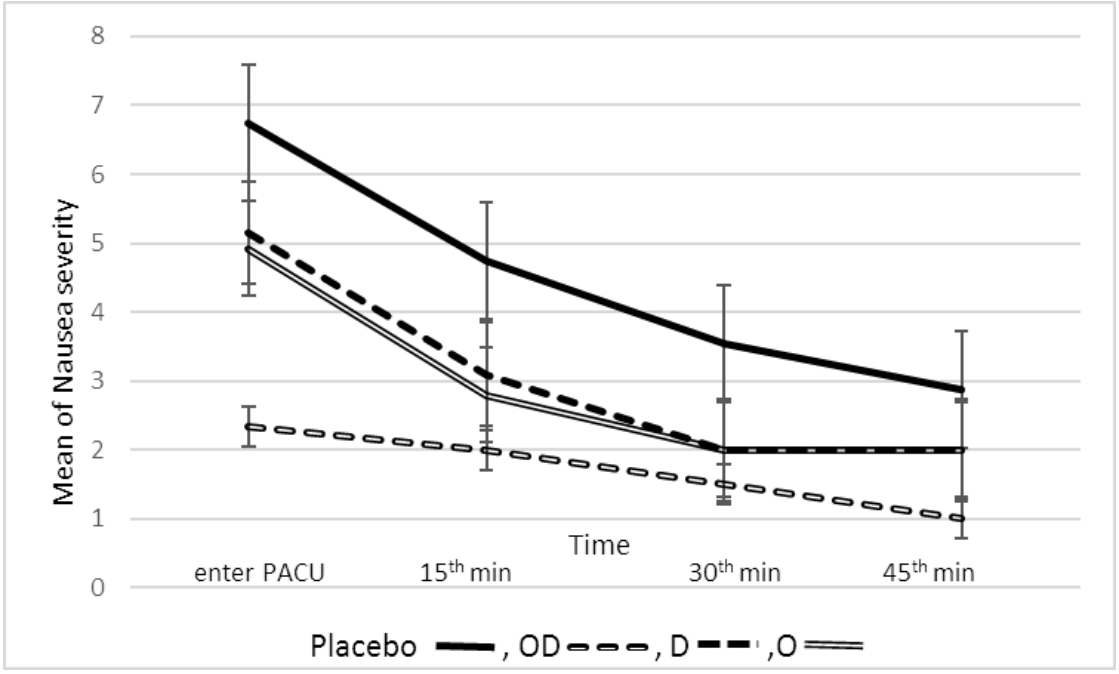

Table3- Mean heart rate, arterial blood pressure and oxygen saturation since recovery after 6 hours between the 4 groups.

	Time	GRD	GRO (MD±SD)	GR OD	GR C	P-Value*	P-Value**
SpO2	enter PACU	99.0±4.7	99.0±5.8	99.0±6.6	98.1±5.5	0.001	
	15th min	99.0±4.8	99.0±6.6	99.0±7.6	98.1±7.2	0.001	
	30th min	99.0±2.9	99.0±7.6	99.0±7.5	99.1±1.0	0.001	
	45th min	99.0±3.8	99.0±7.6	98.0±8.4	99.0±2.9	0.001	0.001
	60th min	99.0±3.8	99.0±8.5	99.0±8.5	99.0±2.9	0.001	
	2th hr	99.0±5.7	99.0±8.5	99.0±8.5	99.0±3.8	0.001	
	4th hr	99.0±5.7	99.0±8.5	99.0±8.4	99.0±4.8	0.003	
	6th hr	99.0±5.8	99.0±8.5	99.0±9.4	99.0±4.8	0.01	
HR	enter PACU	119.7±7.2	115.7±1.0	107.9±9.3	131.1±5.8	0.001	
	15th min	117.7±7.4	114.1±4.8	107.9±2.7	113.1±5.6	0.001	
	30th min	117.7±2.7	114.1±1.6	106.9±4.8	128.9±5.4	0.001	
	45th min	117.7±2.7	114.1±1.6	106.9±4.8	128.9±5.4	0.001	0.001
	60th min	116.7±6.2	112.1±7.6	104.9±7.1	127.1±3.8	0.001	
	2th hr	115.7±2.8	110.7±1.0	104.8±5.9	120.1±9.1	0.001	
	4th hr	114.8±9.6	109.1±1.1	104.9±4.1	120.1±6.1	0.001	
	6th hr	112.1±7.1	109.1±1.4	102.1±8.7	119.1±5.8	0.001	
MAP	enter PACU	61.8±6.0	61.1±1.3	56.3±7.5	67.1±3.2	0.001	
	15th min	60.2±3.0	58.4±8.2	56.4±5.0	65.8±8.0	0.001	
	30th min	59.3±7.1	58.4±7.3	56.3±2.9	65.7±4.8	0.001	
	45th min	59.2±4.8	58.4±7.1	56.4±4.0	64.7±1.8	0.001	
	60th min	57.4±5.6	60.6±9.4	56.3±1.9	63.7±4.3	0.001	
	2th hr	59.2±5.4	58.3±1.4	56.4±6.0	62.7±2.3	0.001	0.001
	4th hr	59.2±6.3	58.3±3.7	56.3±5.9	61.7±5.3	0.001	
	6th hr	59.2±7.7	58.3±4.5	56.4±4.7	61.7±3.0	0.001	
	*Independent t-test						

*SpO2, peripheral oxygen saturation; HR, Heart rate; MAP, Mean arterial pressure; O, Ondansetron;

**D, Dexamethasone; OD Ondansetron- Dexamethasone; C, Placebo; PACU, Post Anesthesia Care Unit.

During recovery time in the 4 groups of ondansetron, dexamethasone, ondansetron plus dexamethasone and placebo, 3 patients (8.6%), 0 patients (0%), 2 patients (5.7%) and 14 patients (40%) had vomiting, respectively. The mean number of episodes of vomiting between the four groups was 0.5±0.1, 1.2±0.01, 0.8±0.01 and 2.5±1.5 respectively, which was significantly different (p=0.002). In the four mentioned groups 5 patients (14.3%), 6 patients (17.1%), 2 patients (5.7%) and 13 patients (37.1%) received ondansetron, respectively, with the difference being significant (p= 0.006). The mean dosage of administered ondansetron was 0.11 mg/kg in the control group and 0.15 mg/kg in the other 3 groups.

The mean recovery time in the four ondansetron, dexamethasone, ondansetron plus dexamethasone group and control group was respectively, 44.9±9, 43.1±5.1, and 38.9±1 and 54.2±10 minutes, with a significant difference among the four groups. The recovery time was longer in the placebo group compared to the other three groups. Additionally, the two ondansetron and ondansetron plus dexamethasone groups had a significant difference (p=0.038), but not between the ondansetron and dexamethasone groups (p=0.14).

Discussion

Nausea and vomiting is one of the most common complications after endoscopy, which can cause discomfort to patients and create complications for patients. Since, children have a lower tolerance for nausea and vomiting, it is important to control nausea and vomiting in this age group. On the other hand, there are limitations in using various medications in children, therefore, it has been attempted to use drugs with the lowest side effects in controlling such complications in children, but no consensus has been reached yet. In this study, the effects of prophylactic ondansetron, dexamethasone and a combination of these two drugs have been studied in the prevention of nausea and vomiting in children aged 1 to 12 years old

undergoing diagnostic upper GI endoscopy.

4 groups of patients who participated in the study were all under 12 years old and showed no significant difference in terms of age, gender, weight and endoscopy duration, therefore, no confounding effects were seen from these factors. Thus, the differences in the results among the groups were more likely due to the effects of the medications used in each group.

Assessment of the hemodynamic parameters including BP, HR, and O_2 sat during endoscopy and recovery showed that the patients who received ondansetron plus dexamethasone had higher hemodynamic stability compared to the other groups, particularly the placebo group. Although these patients had fluctuations during endoscopy and recovery, the range of such fluctuations was lower in the ondansetron plus dexamethasone group. In general, patients in this group showed a more favorable condition. In addition, the results of this study demonstrated that the combination of dexamethasone and ondansetron had no particular side effects in children.

In two studies performed by De Orange and Shen on children undergoing laparoscopy and strabismus repair surgery, the combination of ondansetron and dexamethasone showed no specific hemodynamic complications [8-9].

According to our results, children who were given prophylactic ondansetron plus dexamethasone showed low nausea and vomiting severity during all times assessed, but statistically there was only a difference between using combination therapy and the other groups at the time of entry to the recovery room and at minute 15 afterwards. In the studies by De Orange and Shen, there was a significant decrease in nausea and vomiting in children under laparoscopy and strabismus surgery [8-9]. Moreover, in our findings the frequency of vomiting and need for antiemetic therapy was significantly different in the 4 groups, with the patients receiving a prophylactic combination of dexamethasone and ondansetron having a lower frequency of vomiting and lower levels of administered rescue ondansetron, which was in accordance with the research conducted by De Orange and Shen [8-9].

Many studies have emphasized the prophylactic administration of a drug combination for reducing nausea and vomiting [10-11].

In a study conducted by Bakri et al, on women undergoing laparoscopy, a combination of lactated ringer's solution plus dexamethasone decreased nausea and vomiting more significantly than using dexamethasone alone [12].

In the study by Fournier et al, on children undergoing adenotonsillectomy, adding ondansetron to dexamethasone was more effective than adding droperidol to dexamethasone in reducing post-operative nausea and vomiting [13].

In another study performed by Oluwole et al, it was demonstrated that using combination therapy with ondansetron, dexamethasone and prochlorperazine was related to lower post-operative nausea and vomiting, reduce length of stay in the recovery room and reduced hospitalization after surgery [14].

Conclusion

Our study showed that preventative use of ondansetron plus dexamethasone in children undergoing upper GI endoscopy reduced nausea and vomiting and reduced the use of antiemetic drugs postoperatively. Moreover, the combination of these drugs was not related to any particular side effects. Meanwhile, because of the importance of controlling nausea and vomiting in children after diagnostic and therapeutic procedures, it is suggested that more studies be performed in this area.

Ethical Issues

Ethics committee approval was received for this study from the Ethics Committee of Isfahan University of Medical Sciences (2015/05). In addition, written informed consent was obtained from parental patients who participated in this study.

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