

# Prevention Role of Metoclopramide, Ondansetron and Granisetron for Postoperative Nausea and Vomiting ( PONV) in Patients Undergoing Tonsillectomy – A Prospective Randomized Study

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## ABSTRACT

**Introduction:** Tonsillectomy with or without adenoidectomy remains one of the most frequently performed pediatric surgical procedures worldwide. Postoperative Nausea and Vomiting (PONV) is one of the most common and significant complications associated with this procedure. Aim of the study was to find an effective antiemetic agent for prevention of PONV in patients undergoing tonsillectomy performed under G.A.

**Material and Methods:** We included 75 patients in the age group of 5-15 years undergoing Tonsillectomy. Patients were randomly divided into 3 groups of 25 patients each. The patients of Group I received Metoclopramide 0.25mg/kg, Group II Ondansetron 100 mcg/kg and group III received Granisetron 40 mcg/kg intravenously just prior to induction of anesthesia. The following parameters were monitored during the study: duration and quality of antiemesis, pulse rate, blood pressure, modified Aldrete's Score and side effects if any.

**Results :** Based on scoring system, it was found that the recovery score was 9. The patients were observed from 0–3 hrs and 3-24 hours following Tonsillectomy for episodes of Nausea and/or Vomiting. Incidence of nausea and/or vomiting during 3-24 hrs after surgery is 44%, 20% and 8% in Groups I, II, and III respectively, with a statistically significant difference between Metoclopramide (Gr.I) and Granisetron (Gr.II).

**Conclusion:** Granisetron in a dose of 40 mg/kg is more effective with very less side effects than Metoclopramide and Ondansetron in the long term prevention of PONV in the children undergoing tonsillectomy under GA.

**Key Words:** PONV, tonsillectomy, GA, antiemetic agents

## INTRODUCTION

Postoperative Nausea and Vomiting (PONV) is one of the most common and significant complications associated with pediatric surgical procedures. Without prophylaxis, more than 70% of children undergoing tonsillectomy will experience at least one episode of vomiting in the postoperative period. PONV has been reported to be the commonest cause of delayed discharge or overnight admission in day- case tonsillectomy. It has also been reported to be associated with an increased risk of bleeding, aspiration of gastric contents, dehydration and electrolyte disturbances.<sup>1,2</sup>

Incidence of PONV are 20- 30% after G A with volatile anesthetics, up to 70% in High Risk patients and moreover pediatric patients have a higher incidence of POV than adults, with a peak incidence of 34- 50% in school children.<sup>3</sup> The lowest

incidence occurs in infants (5%) and preschool children have an incidence of 20%.<sup>4,5</sup> This is associated with Morbidity like Decreased patient satisfaction, Delayed hospital discharge, Unexpected hospital admission, Wound dehiscence, bleeding, pulmonary aspiration, esophageal rupture and Fluid and electrolyte disturbances. So the present study was aimed to compare the effectiveness of anti-emetic agents (Metoclopramide, Ondansetron and Granisetron ) in the prevention of PONV in patients (of age group 5- 15yrs) undergoing tonsillectomy performed under GA.

## MATERIALS AND METHODS

This study was carried out at MNR Medical College and Hospital, Sangareddy, during the June 2012 to December 2012. 75 patients belonging to both sexes in the age group of 5-15 years, ASA physical status I and II, undergoing tonsillectomy were enrolled. The study was approved by the Hospital Ethical Committee and informed consent from parents was obtained. Patients were randomly divided into three groups (Group I, II and III) consisting of 25 patients each. Patients were assessed at the preoperative visit for past and present history. Routine laboratory investigations were done. Patients were weighed prior to the operation. Preoperative vital parameters namely, pulse and blood pressure were noted. Written informed consent of the parents or guardians of the children were obtained. The patients were not given any solid or liquid feeds for 6 – 8 hrs prior to surgery. All patients were premedicated with I V Glycopyrrolate 0.004 mg /kg and Fentanyl 2mcg/kg. Group 1- They were Given I V Metoclopramide in the dose of 0.25 mg/kg diluted, intravenously slowly over 2- 5 minutes just prior to induction of anesthesia.

Group 2-They were given I V ondansetron 100 mcg/kg prior to induction of anesthesia

Group 3-They were given I V Granisetron in the dose of 40 mcg/ kg diluted to 10ml with normal saline, I V slowly over

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2- 5 minutes immediately prior to induction of anesthesia

The pulse and arterial pressure (both systolic and diastolic) were recorded at 1, 5 and 10 min intervals in all the patients. The mean arterial pressure of each patient was derived using the equation.

Induction was carried out with an I V Propofol 2 mg/kg. Intubation was facilitated by using I V suxamethonium (2mg /kg). Patients were intubated orally with portex endotracheal tube of appropriate size. The throat was packed. Anesthesia was maintained with nitrous oxide in oxygen (60:40) by controlled ventilation using either a Bain's circuit or a Jackson Rees' circuit according to the weight of the patient. Atracurium (0.5 mg/kg) was the non- depolarizing muscle relaxant used in all the patients.

Intravenous fluid used was Isolyte P or Ringer's Lactate with 50 ml of 25% dextrose added to it. Half of the preoperative fluid deficit was corrected within the first hour and the remaining half subsequently, the neuromuscular blockade was reversed with a combination of anticholinesterase, Neostigmine (0.04- 0.06) diluted to 10ml with distilled water administered I V slowly.

Patients were extubated when widely awake after thorough suctioning of the oropharynx and confirming the absence of any active bleeding from the tonsillar fossae. The patients were shifted to the recovery room.

Each episode of nausea and/ or vomiting was recorded. Scoring was done. Repeat vomiting occurring within 1- 2 min of the previous episode was recorded as a single episode of vomiting. Any side effects were also noted. Postoperatively, the recovery time was noted, as the time from the end of surgery till the recovery score was 9. Post-anesthesia Aldrete Recovery Score was calculated based on G. E Morgan et al (2006). The patient should be discharged when the total score is 10, but minimum of 9 is required.

### Statistical methods

Data obtained were analyzed using Statistical Package for Social Sciences (SPSS Inc., Chicago, USA) 15.0 for windows. Kruskal – Wallis test used for comparison of the occurrence of PONV across the groups, Bonferroni test used for listing the significant treatment groups, Chi –square test used for Gender distribution and ANOVA test used for comparing Age, Weight, Pulse rate, MAP, Duration of anesthesia across the treatment groups.  $P < 0.05$  was considered statistically significant

### RESULTS

The patients were randomly divided into 3 groups of 25 patients each. Group I received Metoclopramide 0.25 mg/kg, Group II received Ondansetron 100 mcg/kg and Group III received Granisetron 40 mcg/kg slowly Intravenously.

With reference to age between three groups, significance was measured using analysis of variance (two tailed,  $\alpha = 0.05$ ) across the treatment groups. As p-values (.8791, 0.4006 and 0.4285) are  $>0.05$ , we concluded that the age difference is not significant across treatment groups (Table 1). Regarding the weight across three groups, significance was measured using analysis of variance (two tailed,  $\alpha = 0.05$ ) across the treatment groups. As p-values (0.99, 0.20, 0.61 and 0.82) are  $>0.05$ , it was concluded that the weight difference is not significant across treatment groups.

There was no significant change in the pulse rate (beats/min) values at pre-operative, 1 min, 5 min and 10 min across treatment groups ( p-values (0.9305, 0.3222, 0.5908 and 0.6554) are  $>0.05$ ) which is based on significance measured using analysis of variance (two tailed,  $\alpha = 0.05$ ) across the treatment groups (Figure 1).

There was no significant change in the MAP values at pre-operative, 1 min, 5 min and 10 min across treatment group's p-values (0.31, 0.71, 0.26 and 0.14) are  $>0.05$ , which is based on

Gender	Statistics	Metoclopramide (n = 25)	Ondansetron (n = 25)	Granisetron (n = 25)	p-value*
Male	n (%)	11(44)	14(56)	13(52)	0.8791
	Mean	8.5	8	8	
	SD	3.7	2.4	2.9	
	Median	8	8	8	
	95% CI for Mean	(6,11)	(6.6,9.4)	(6.3,9.7)	
	Range (Min, Max)	(5,15)	(5,13)	(5,13)	
Female	n (%)	14(56)	11(44)	12(48)	0.4006
	Mean	10.1	10.2	8.5	
	SD	3.3	3.6	3.4	
	Median	10	10	7.5	
	95% CI for Mean	(8.2,12.1)	(7.8,12.6)	(6.3,10.7)	
	Range (Min, Max)	(5,15)	(5,15)	(5,15)	
Overall	n (%)	25(100)	25(100)	25(100)	0.4285
	Mean	9.4	9	8.2	
	SD	3.5	3.1	3.1	
	Median	10	9	8	
	95% CI for Mean	(8,10.9)	(7.7,10.3)	(7,9.5)	
	Range (Min, Max)	(5,15)	(5,15)	(5,15)	

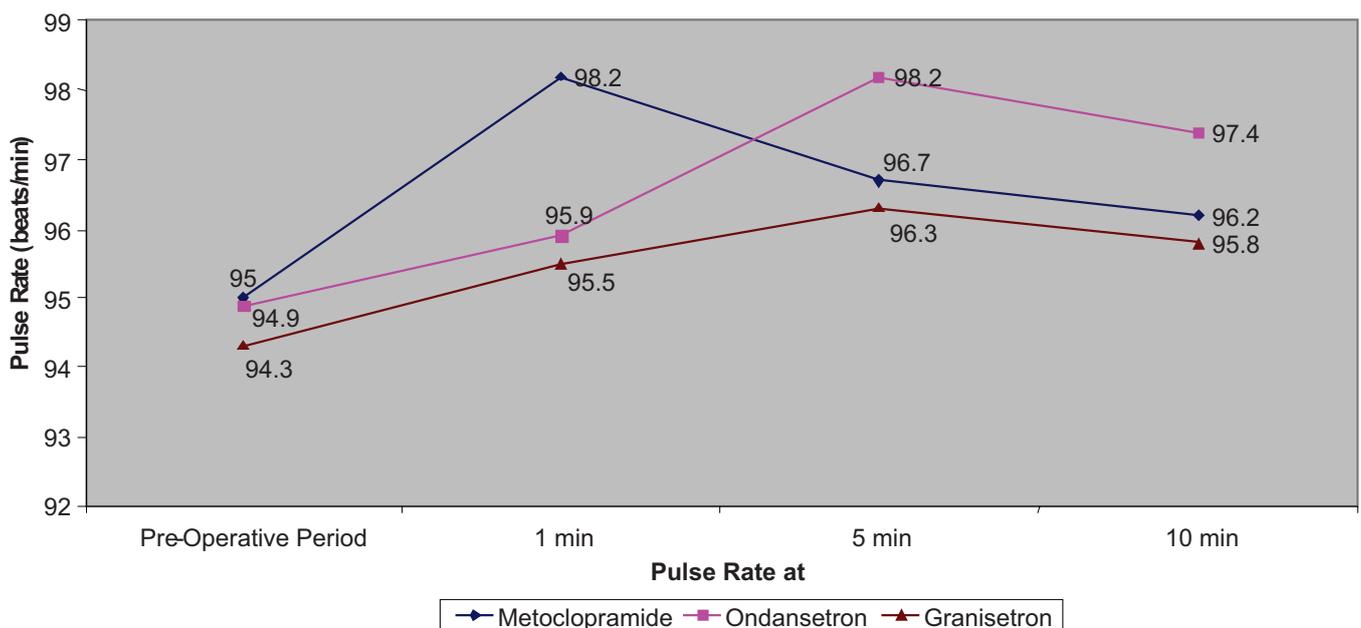
\* p-value obtained using ANOVA (two tailed,  $\alpha = 0.05$ ).

**Table-1:** Summary of Age (yrs) across Treatment Groups by Gender( N = 75)

Nausea & Vomiting at	Statistics	Metoclopramide (n = xx) n (%)	Ondansetron (n = xx) n (%)	Granisetron (n = xx) n (%)	p-value*
0 – 3 hrs	n (%)	25(100)	25(100)	25(100)	
	Mean	0.32	0.2	0.2	0.4770
	Median	0	0	0	
3 - 24 hrs	n (%)	25(100)	25(100)	25(100)	
	Mean	0.56	0.28	0.08	<b>0.0110</b>
	Median	0	0	0	
0 - 24 hrs	n (%)	25(100)	25(100)	25(100)	
	Mean	0.64	0.44	0.24	0.0760
	Median	0	0	0	

\* p-value obtained using Kruskal-waliis test (two tailed,  $\alpha = 0.05$ ).

**Table-2:** Comparison of Occurrence of Nausea & Vomiting across Treatment Groups



**Figure-1:** Figure 1 Comparison of Mean Pulse Rate (beats/min) of Subjects among the Three Groups

significance measured using analysis of variance (two tailed,  $\alpha = 0.05$ ) across the treatment groups (Figure 2).

Incidence of nausea and/or vomiting during 0-3 hrs after surgery is 24%, 12% and 12% in Groups I, II, and III respectively, with a P value of 0.47 (Table 2). The incidence of nausea and/or vomiting during 3-24 hrs after surgery is 44%, 20% and 8% in Groups I, II, and III respectively, with a statistically significant P value ( 0.01) by Kruskal Waliis Test. The only statistically significant result of the present study, which is the difference in occurrence of PONV between Group I (Metoclopramide) and Group III (Granisetron ) with a P value of 0.026 ( statistically significant) by Bonferroni Test.

Overall incidence of nausea and/or vomiting during 0-24 hrs after surgery is 48%, 28% and 16% amongst Groups I, II, and III respectively, with a P value of 0.07.

Postoperatively the recovery score was noted. From table 3, it is found that the recovery score of 9, which was considered to be adequate for discharge from the PACU was achieved by majority of the patients at the end of 40 minutes. So it is concluded the all the three antiemetic agents in the study have no significant effect on the recovery from anesthesia.

Out of 25 subjects in metoclopramide group, 6(24%) subjects reported with at least one side effect. 4 (16%) subjects reported headache, 1 (4%) subject reported dizziness, 2 (8%) subjects reported drowsiness and 2 (8%) subjects reported extra pyramidal (Table 4).

## DISCUSSION

The incidence of PONV in children undergoing tonsillectomy is sufficiently high (up to 70%) to warrant the use of effective antiemetic prophylaxis.<sup>2</sup>

The most extensively used antiemetic for the last thirty years for the treatment of PONV is Metoclopramide. Recently many investigators have demonstrated the effectiveness of Ondansetron, a selective 5-HT<sub>3</sub> antagonist, for PONV with less side effects. Granisetron is a new 5-HT<sub>3</sub> antagonist with higher selectivity and is 5-10 times more potent antiemetic agent than Ondansetron.

The present study compared the properties of the above three drugs in patients undergoing tonsillectomy under GA.

The selected 75 patients belonged to either sex in the age

PARS (min)	Score	Metoclopramide (n = 25) n (%)	Ondansetron (n = 25) n (%)	Granisetron (n = 25) n (%)
0 min	6	6(24)	5(20)	3(12)
	7	14(56)	13(52)	13(52)
	8	5(20)	7(28)	9(36)
	9	0(0)	0(0)	0(0)
	10	0(0)	0(0)	0(0)
20 min	6	0(0)	0(0)	0(0)
	7	2(8)	2(8)	0(0)
	8	13(52)	12(48)	14(56)
	9	10(40)	11(44)	11(44)
	10	0(0)	0(0)	0(0)
40 min	6	0(0)	0(0)	0(0)
	7	0(0)	0(0)	0(0)
	8	4(16)	3(12)	3(12)
	9	16(64)	17(68)	16(64)
	10	5(20)	5(20)	6(24)
60 min	6	0(0)	0(0)	0(0)
	7	0(0)	0(0)	0(0)
	8	0(0)	0(0)	0(0)
	9	11(44)	9(36)	7(28)
	10	14(56)	16(64)	18(72)

**Table-3:** Summary of Post Anesthesia Recovery Score (PARS) across the Treatment Groups

Side Effects/Complications	Metoclopramide (n = 25) n (%)	Ondansetron (n = 25) n (%)	Granisetron (n = 25) n (%)
No. of Side Effects	4	3	1
No. of Subjects with at least One Side Effect	6(24)	5(20)	2(8)
Headache	4(16)	4(16)	2(8)
Dizziness	1(4)	1(4)	0(0)
Drowsiness	2(8)	1(4)	0(0)
Extra Pyramidal	2(8)	0(0)	0(0)

**Table-4:** Summary of Adverse Effects/Complications by Treatment Group

group of 5-15 years with a physical status I and II. The patients were divided randomly into 3 groups of 25 patients each. All patients received GA.

Group I patients received Metoclopramide, Group II patients Ondansetron and Group III patients received Granisetron i.v. in the doses of 0.25mg/kg, 100mcg/kg and 40mcg/kg respectively, prior to the induction of anesthesia, which were shown to be the effective antiemetic doses based on previous studies.<sup>6,7</sup>

The use of volatile anesthetic agents has been purposefully avoided because in one study by Apfel et al., they suggested that Volatile agents may be the main cause of early PONV.<sup>8</sup> The present study has shown that the pulse rate, MAP, and the post anesthesia recovery are not significantly affected by any of the antiemetic agents used.

The P values for pulse rate at preoperative period, 1min, 5min,

10min are 0.93, 0.32, 0.59, 0.65 respectively, all of which are statistically insignificant.

The P values for MAP at preoperative period, 1min, 5min and 10min are 0.31, 0.71, 0.26, 0.14 respectively, all of which are statistically insignificant.

The Post Anesthesia Recovery Score of 9, which was considered as adequate for discharge of the patient from PACU, was achieved by majority of the patients in all the 3 groups at the end of 40 minutes postoperatively. The above results concur the finding of previous studies.<sup>9,10</sup>

Previous studies suggest that Risk of POV increases with duration of surgery and anesthesia, possibly because of greater accumulation of emetogenic anesthetic agents.<sup>5</sup> In the present study the mean duration of anesthesia for Group I, II and III was 40.4, 42.8 and 41.6 minutes respectively and the difference amongst the 3 Groups was insignificant.

The common side effects of the traditional antiemetic agents like Headache, Dizziness, Drowsiness, Extrapyramidal effects, diarrhea, constipation etc. have been compared amongst the 3 Groups.

We found that the number of patients with at least 1 side effect were 24%, 20%, and 8% amongst the Gr I, II and III respectively.

The incidence of Headache was seen in 16% of patients from Gr I and II each as compared to 8% from Gr III. Dizziness was observed in 1 (4%) patient from Gr I and II as compared to 0% in Gr III. Drowsiness was seen in 8% patients from Gr I as compared to 4% in Gr II & 0% in Gr III. Extrapyramidal effects in the form of Dystonia were found in 2 (8%) patients only from Gr I.

This concludes that Granisetron causes much less side effects as compared to both metoclopramide and Ondansetron and the Extrapyramidal side effects can occur with Metoclopramide.

The monitoring of nausea and vomiting during 0-3 hrs and 3-24 hrs after tonsillectomy and its scoring (0=no nausea and vomiting, 1= only nausea and 2= vomiting) in the present study is similar as in a study by Fujii et al.<sup>11</sup>

In a study conducted by Fujii et al (1996)<sup>12</sup> using Granisetron 40 mcg/kg i.v. in children undergoing strabismus surgery and Tonsillectomy, incidence of PONV was 12% in 24 hrs after the surgery which can be compared with the incidence of 16% in our study.

As per Matti Aapro,<sup>13</sup> Granisetron is a potent and highly selective 5-HT<sub>3</sub> antagonist that has little or no affinity for other receptors, characteristic that is thought to underly the favorable side effect and the safety profiles of this agent. In our study also Granisetron caused the least side effects as compared to Metoclopramide and Ondansetron.

Thus, the present study indicates that Granisetron in a dose of 40 mcg/kg is more effective than Metoclopramide in the long term prevention of PONV in the children undergoing tonsillectomy under GA. This result is similar to the one obtained in a study conducted by Fujii et al<sup>11</sup> in patients undergoing major gynecological surgeries.

## CONCLUSION

Metoclopramide, Ondansetron and Granisetron when admin-

istered intravenously in the doses of 0.25 mg/kg, 100 mg/kg and 40 mg/kg, do not have significant effect on the vital parameters like pulse rate and MAP in children undergoing tonsillectomy under General anesthesia. Our study showed that Granisetron is highly effective in the long term prevention of PONV in children undergoing Tonsillectomy as compared to Metoclopramide and is associated with minimum side effects and higher patient satisfaction as compared to both Metoclopramide and Ondansetron.

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