

## COMPARISON OF GRANISETRON WITH THE COMBINATION OF GRANISETRON AND DEXAMETHASONE IN THE PROPHYLAXIS OF POST OPERATIVE NAUSEA AND VOMITING

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### Abstract

**Background:** Post Operative Nausea and Vomiting (PONV), despite the advance in anaesthetic care, is still a ‘big little problem’ within the anaesthesia world. The aim of this study is to compare and evaluate the effect of Granisetron and combination of Granisetron with Dexamethasone given prophylactically in the prevention of post operative nausea and vomiting in patients undergoing elective ENT surgeries. **Materials and Methods:** After obtaining approval from our institutional ethics committee and getting prior informed consent, 90 patients were randomly allocated into three different groups (30 in each group). Patients were given in a randomized, double -blind manner, a single dose of normal saline (placebo) 5ml (GROUP –I) or Inj. Granisetron 40mcg/kg (GROUP –II) or Inj. Granisetron 40mcg/kg with Dexamethasone 8mg (GROUP –III) intravenously. Study medications were prepared by personnel not involved in the study in identical 5 ml volume. The study drugs were given just after intravenous cannulation, before Induction of anaesthesia. **Result:** Granisetron plus Dexamethasone combination when given prophylactically was found to significantly reduce the incidence of post operative nausea and vomiting in patients undergoing middle ear surgeries. The effect was greater than when both the drugs given individually. **Conclusion:** Antiemetic prophylaxis should be definitely included in the anaesthetic management of patients with risk of post operative nausea and vomiting while undergoing general anaesthesia. Granisetron is effective in preventing post operative nausea and vomiting in majority of patients. Granisetron plus Dexamethasone combination prophylaxis is highly effective in controlling postoperative nausea and vomiting with few side effects.

## INTRODUCTION

Post Operative Nausea and Vomiting (PONV), despite the advance in anaesthetic care, is still a ‘big little problem’ within the anaesthesia world.<sup>[1]</sup> It is defined as nausea and/or vomiting that occurs within 24hrs after surgery and can occur following general, regional or local anaesthesia. It is their most distressing concern in post operative period. The incidence can be as high as 80% following certain procedures like ENT, Laparoscopic or gynecological surgeries. When severe, post operative nausea and vomiting can lead to wound dehiscence, bleeding, dehydration, electrolyte imbalance, delayed discharge and increased treatment cost.

## MATERIALS AND METHODS

After obtaining approval from our institutional ethics committee and getting prior informed consent, 90 patients of ASA Physical status 1, aged 15 - 50 yrs, with body weight ranging from 40 – 80 kgs scheduled for elective ENT surgeries were studied at Government Mohan Kumaramangalam Medical College, Salem. Patients with cardiovascular, respiratory, renal or hepatic diseases, pregnant, lactating or menstruating women and those taking medications which would affect the study, those who had an H/o of motion sickness and/or previous H/o of post operative nausea and vomiting were excluded from the study.

**Premedication:** Pentazocine 0.5 mg/kg and Glycopyrolate 0.2mg were given intramuscularly half an hour before surgery for all the patients. Patients were randomly allocated into three different

groups (30 in each group). Patients were given in a randomized, double-blind manner, a single dose of normal saline (placebo) 5ml iv, (or) Inj. Granisetron 40mcg/kg iv, (GROUP –II) (or) Inj. Granisetron 40mcg/kg with Dexamethasone 8mg, (GROUP –III) intravenously. Study medications were prepared by personnel not involved in the study in identical 5 ml volume. The study drugs were given just after intravenous cannulation, before induction of anaesthesia. The patients were fasted for eight hours before surgery and on arrival to the operating theatre, routine monitoring devices were attached and basal HR, BP, ECG, SPO2 were observed throughout the study period.

Anaesthesia was induced with Thiopentone 5 mg/kg intravenously and Succinylcholine 2mg/kg intravenously was used to facilitate tracheal intubation. After tracheal intubation, anaesthesia was maintained with 66% Nitrous oxide, 33% Oxygen with 0.5% Halothane and Pancuronium bromide as non depolarising muscle relaxant. Ventilation was controlled mechanically in all patients. At the completion of surgery, residual neuro muscular blockade was antagonized with intravenous Glycopyrolate 0.01mg/kg and neostigmine 0.04mg/kg. The trachea was extubated when the patient was awake. Patients were shifted to the recovery room.

They were asked to inform whether they had nausea, retching or vomiting during the first 24 hrs and the results were recorded. The results were scored in a manner similar to Belville et al.

Grade 0 - No nausea /retching / vomiting

Grade 1 - Nausea/retching

Grade 2 - Vomiting

Patients were assessed for nausea, retching and vomiting at 1, 2, 4, 12 & 24 hrs post operatively. If two or more episodes of emesis occurred, Inj. Metoclopramide 10mg iv as rescue antiemetic was given. Results were statistically analysed with t test, chi – square test

They were also enquired about adverse effects like headache, sedation, abdominal discomfort, dizziness etc. and noted.

## RESULTS

This was a randomised, double blind placebo controlled study conducted at Government Mohan

Kumaramangalam Medical College, Salem after obtaining informed consent from all the 90 patients subjected to study. They were grouped into three groups and received placebo, Granisetron 40 mcg /Kg and Granisetron 40 mcg/kg with Dexamethasone 8 mg. Age, weight, sex distribution, systolic & Diastolic Blood pressure and Heart rate were not significantly different in these groups as can be seen in [Table 1 and Table 2].

### Incidence & Severity of Nausea

[Table 3(a)] shows the incidence of nausea in 0 - 24 hrs. As shown in [Table 3(a)], 90% of the patients in the group I and 23% in group II had nausea while it fell to 4% in group III.

### Comparison of Nausea between Groups

[Table 3b] compares the incidence of nausea between each group individually i.e. Group I with Group II and Group II with Group III etc. From the below mentioned table one we see that, the incidence of nausea is reduced significantly both in Group II and Group III. Among these two, the grade 0 was in 96% of patients in Group III (P<0.05).

### Incidence of Retching

Similarly the incidence of retching was compared in all the three groups (Table IV). Group I shows an incidence of 80% and group II shows 17% and group III shows only 4%.

### Incidence of Vomiting

As seen in [Table 5(a)] the incidence of vomiting in group I is 80% and in group II it is 20% and in group III is only 3.3%. When numbers of episodes are compared as shown in [Table 5(b)], it was seen that in group I it is 60%, in group II it is 10% and none in group III have multiple episodes and the need for rescue antiemetic.

### Comparison of vomiting between Groups

[Table 5(b)] statistically analyses the differences in the incidence of vomiting when compared with Group I, Group II shows statistically significant but Group III is more effective.

[Table 5(c)], shows a complete response (no post operative nausea and vomiting) occurred 96% in Group III and 77% in Group II and 10% in Group I. Thus a complete response was significantly more common in the patients who had received the drugs Granisetron and Dexamethasone.

[Table 6] shows the Incidence of some side effects which were not statistically significantly among the groups.

**Table 1:**

Parameter	Group I (N = 30)	Group II (N = 30)	Group III (N = 30)	P value	Inference
Age (Years)	29.2 ± 8.04	29.8 ± 9.7	29.1 ± 9.8	0.951	NS
Weight (Kg)	56.3 ± 6.9	59.3 ± 9.89	61.23 ± 10.26	0.1188	NS
Sex (M:F)	14 : 16	15 : 15	16 : 14	0.875	NS

P > 0.05 indicates statistically not significant

**Table 2:**

Parameter	Group I (N = 30)	Group II (N = 30)	Group III (N = 30)	P Value	Inference
BP Systolic	122.4 ± 7.9	119.5 ± 9.38	121.6 ± 10.12	0.4598	NS
BP Diastolic	79 ± 7.12	77.4 ± 8.2	76.4 ± 6.8	0.396	NS
Surgical Duration (mins)	96.7 ± 20.5	93.67 ± 19.8	94.17 ± 18.9	0.817	NS

Pulse Rate	82 ± 4.90	82.2 ± 6.8	79.8 ± 5.1	0.208	NS
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P > 0.05 indicates statically not significant.

**Table 3a:**

0 – 24 Hours	Group I	Group II	Group III
Incidence of nausea	90%	23%	4%

**Table 3b:**

Comparison of Nausea	P Value	Inference
Group I vs Group II	< 0.001	S
Group I vs Group III	< 0.001	S
Group II vs Group III	< 0.02	S

**Table 4:**

Retching	Group I		Group II		Group III	
	No.	%	No.	%	No.	%
Presence	24	80	5	16.7	1	3.3
Absence	6	20	25	83.3	29	96.7
Total	30	100	30	100	30	100

P value < 0.001

**Table 5a:**

Vomiting	Group I		Group II		Group III	
	No.	%	No.	%	No.	%
Presence	24	80	6	20	1	3.3
Absence	6	20	24	80	29	96.7
Total	30	100	30	100	30	100

P value < 0.001

**Table 5b: Distribution of Incidence of vomiting according to Groups**

Vomiting episodes	Group I		Group II		Group III	
	No.	%	No.	%	No.	%
None	6	20	24	80	29	96.7
Single	6	20	3	10	1	3.3
Multiple	18	60	3	10	0	
Total	30	100	30	100	30	100

### Comparison of vomiting

Comparison of Vomiting	P Value	Inference
Group I vs Group II	< 0.001	S
Group I vs Group III	< 0.001	S
Group II vs Group III	< 0.05	S

### Distribution of Patients according to Nausea score

Grade 0	Grade 1	Grade 2
No Nausea/Vomiting	Nausea/Retching	Vomiting
No Rescues		

**Table 5(c):**

Grade	Group I		Group II		Group III	
	No.	%	No.	%	No.	%
0	3	10	23	76.7	29	96.7
1	3	10	1	3.3	0	
2	24	80	6	20	1	3.3
Total	30	100	30	100	30	100

**Table 6: Group wise distribution of side effects**

Side effects	Group I		Group II		Group III		P Value
	No.	%	No.	%	No.	%	
Headache	3	10	3	10	2	6.7	0.87
Sedation	1	3.3	1	3.3	2	6.7	0.76
Abdominal discomfort	1	3.3	1	3.3	1	3.3	1
Dizziness	2	6.7	1	6.7	2	6.7	0.80

## DISCUSSION

Post Operative Nausea and Vomiting is distressing and sometimes the patients dread it more than the post operative pain. There are various factors that predispose a patient to post operative nausea and vomiting. It is more frequent in women, in non-smokers, in patients with a past history of motion sickness, morning sickness or post operative nausea and vomiting and with perioperative use of opioid.

The frequency of nausea and vomiting following middle ear surgery can be as high as 62%-80%. If the prophylactic anti emetic is not given as in the control group in our study, the incidence is a little bit higher at about 90%. Prophylactic administration of scopolamine, prochlorperazine, droperidol, 5HT3 antagonists and combination of anti emetics have been advocated for post operative nausea and vomiting in middle ear surgery and in ENT surgeries in various studies. Ondansetron has been less effective in preventing post operative nausea and vomiting in middle ear surgery patients.<sup>[3]</sup>

Granisetron alone or in combination with Dexamethasone has been shown to be highly effective in patients undergoing middle ear surgery as concluded by Fujii et al in various studies.<sup>[4-6]</sup> In high risk population, the current mode of preventing post operative nausea and vomiting is by multimodal therapy and commonly used combinations are 5HT3 receptor antagonist & Dexamethasone.<sup>[6]</sup>

So in our present study we tried to compare the efficacy of Granisetron 40 mcg/kg with Granisetron 40 mcg/kg plus Dexamethasone 8mg and found statistically significant decrease in the incidence of nausea and vomiting between Group I, Group II and Group III. All factors which predisposed to increase post operative nausea and vomiting like age, obesity, gender, duration, type of surgery, anaesthetic technique are equally distributed among the groups and hence the difference in the incidence of complete response between groups and the requirement of rescue anti emetics between groups can be attributed to the difference in the anti emetics tested.

The possible mechanism of Dexamethasone action might be to decrease the level of prostaglandins in the central nervous system. They regulate neurotransmitter concentrations, receptor densities, signal transduction and neuronal configuration.<sup>[6,7]</sup> As concluded in many studies, the Granisetron plus Dexamethasone significantly reduces the post operative nausea and vomiting when given prophylactically.<sup>[4,5,8]</sup> It is usually recommended that an anti emetic be given prophylactically before surgery or chemotherapy to improve the efficacy of the drug. Hence, the study agents were administered intravenously before the commencement of surgery. The dose of Granisetron used in this study was based on the previous studies by Fujii et al.<sup>[9]</sup> They have suggested that 40 mcg/kg was the minimum effective dose for prevention of post operative nausea and vomiting following surgery. The dose of

Dexamethasone used (8 mg) 10 was based on the studies previously shown to decrease emesis when added as an anti emetic regimen. In the present study, therefore, the same dose of Dexamethasone was added to Granisetron. The precise mechanism by which Dexamethasone increase the effectiveness of Granisetron is not known. Granisetron produces antiemesis by blocking 5HT3 receptors. Dexamethasone may inhibit stimulation of 5HT3 receptors and may also potentiate the other pharmacological receptors.<sup>[10,11]</sup>

Ali SZ et al studied the effects of pre-op fluid on the post operative nausea and vomiting and found a considerable decrease in the incidence of post operative nausea and vomiting.<sup>[12]</sup> Apfel cc et al concluded that volatile anaesthetics,<sup>[13]</sup> were the leading cause of early post operative vomiting. The pro emetic effect was larger than other risk factor. In patients who are at high risk for post operative nausea and vomiting, it would therefore be better to avoid inhalation anaesthesia.

Adeno -tonsillectomy is also associated with a high post operative nausea and vomiting rate (36 -76%) Patel R. Rouley. This is thought to be due to the irritant effects of blood on oesophago gastric chemo receptors, irritation of trigeminal afferents during surgery. In our study the incidence of post operative nausea and vomiting is high among female patients. Obesity increases the incidence of vomiting. In our study patients who weighed more than 60 kg had increased incidence. Gigilo at al,<sup>[3]</sup> in their study to prevent nausea and vomiting following cancer chemotherapy concluded that both Ondansetron and Granisetron have similar anti emetic efficacy but dose of Granisetron is much less than Ondansetron iv. Moreover Ondansetron has a shorter half-life of 3 hrs, whereas Granisetron has a half life of 8-9 hrs, for which it is more effective in preventing nausea and vomiting. Granisetron is also a more selective 5HT3 receptor antagonist than Ondansetron.<sup>[14,15]</sup>

In our study the need for rescue antiemetic in Group I is 60%, Group II is 10% where as in Group III is nil. The safety of intravenous and oral Granisetron has been evaluated in more than 7,000 patients in clinical trial, which have shown the drug to be well tolerated, with mild and transient side effects. There have been no reports of extra pyramidal side effects with either intravenous or oral Granisetron for the prevention and treatment of chemotherapy-induced emesis and post operative nausea and vomiting. In our study also the patients tolerated the drug well with few side effects. In our study, patients receiving placebo had stayed in the hospital more than patients receiving Granisetron with Dexamethasone.<sup>[16-20]</sup>

## CONCLUSION

Antiemetic prophylactic should be definitely included in the anaesthetic management of patients with risk of post operative nausea and vomiting undergoing general anaesthesia. Granisetron is

effective in preventing post operative nausea and vomiting in majority of patients. Granisetron plus Dexamethasone combination prophylaxis is highly effective in controlling postoperative nausea and vomiting with few side effects.

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