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Research Article

A study of comparing single dose granisetron with combination of granisetron with dexamethasone in preventing postoperative nausea vomiting in laparoscopic cholecystectomies

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ABSTRACT

Background: Postoperative nausea and vomiting (PONV) remains a vexing problem despite of advances in anaesthesia care. PONV is distressing adverse effect after anaesthesia and surgery, resulting in significant morbidity due to acute discomfort associated with emetic symptoms and longer stays in the recovery room or unexpected hospital admission in ambulatory settings.
Methods: A prospective, randomized, double blind comparative study was conducted to compare the efficacy and adverse effects of injection granisetron 40µg/kg as a single dose and injection granisetron in two different doses (20µg/kg and 40µg/kg) in combination with dexamethasone 160µg/kg for prevention of postoperative nausea and vomiting in patients undergoing general anaesthesia for elective laparoscopic cholecystectomy.
Results: Nausea and vomiting were observed postoperatively at 0, 1, 2, 4, 8, and 24 consecutive hours after patient responded to verbal commands. Intensity of nausea graded verbally with an eleven point score (0-10) with those patients who scored their nausea as zero were termed nausea free, and 10 being most severe. Nausea scores when patient complains of nausea & if patient demand rescue antiemetic for nausea was noted down along with adverse effects if any. The data was analysed by ANOVA followed by unpaired‘t’ test, Chi-square/Fischer exact test or Kruskal Wallis Test.
Conclusions: Granisetron as a single agent in dose 40µg/kg is effective as prophylactic antiemetic in preventing PONV in laparoscopic cholecystectomy whereas addition of dexamethasone 160µg/kg to granisetron significantly increases antiemetic efficacy of the granisetron in both the doses i.e. 20µg/kg and 40µg/kg without increasing any side effect. Granisetron 40µg//kg+injection dexamethasone 160µg/kg is best for antiemetic prophylaxis in highly emetogenic surgeries like laparoscopic cholecystectomy. Granisetron 20µg/kg + injection dexamethasone can be cost effective alternative for routine antiemetic prophylaxis compared to granisetron 40µg//kg and granisetron 40µg//kg+ injection dexamethasone for all patients undergoing laparoscopic cholecystectomy.

Keywords: PONV, Emetic symptoms, Granisetron, Dexamethasone, Rescue antiemetic

INTRODUCTION

Despite advances in anaesthesia care postoperative nausea and vomiting (PONV) remains a vexing problem. PONV is distressing adverse effect after anaesthesia and surgery, resulting in significant morbidity due to acute discomfort associated with emetic symptoms and longer stays in the recovery room or unexpected hospital admission in ambulatory settings. Patients reports that avoidance of PONV is of greater or equal concern as avoidance of postoperative pain and they are willing to

spend for effective antiemesis. Untreated PONV occurs in 20-30% of the general surgical population and up to 70-80% of high risk surgical patients. Presently incidence of PONV in laparoscopic cholecystectomy is 53-72%.[1-3]

5-Hydroxytryptamine type 3 ($5HT_3$) receptor antagonists are considered as first line therapy for PONV, because of their efficiency and safety compared with other antiemetic drugs. Currently ondansetron, granisetron, dolasetron, polanosetron are 5HT3 receptor antagonists in use. Since 1981 dexamethasone has been reported to be effective in reducing the incidence of emesis in patients undergoing chemotherapy with limited side effects. Recently dexamethasone has also been reported to be effective in reducing incidence of PONV.

In patients who are at high risk for PONV, prophylaxis with combination therapy could be an effective method, perhaps because there is no single stimulus or cause for PONV. Studies evaluating combination therapy in PONV prophylaxis generally have used conventional doses of 5 HT3 receptor antagonists and dexamethasone, but other studies suggest that smaller doses of 5HT3 receptor antagonists with conventional dexamethasone also effective in preventing PONV. Some studies with combination granisetron plus dexamethasone have demonstrated a significantly better clinical efficacy against PONV than granisetron alone but data on granisetron plus dexamethasone combination is limited especially in patients undergoing laparoscopic cholecystectomy.[3,4]

METHODS

This is a prospective, randomized, double blinded, comparative study. A total 90 patients were allocated in to three groups of 30 patients in each. The study was approved by the ethical committee of Institutional Postgraduate Review Board.

Inclusion criteria

- Patient's age group between 15-60 years.
- American society of anaesthesiologist (ASA) class 1 and 2 patients undergoing elective laparoscopic cholecystectomy, requiring general anaesthesia with endotracheal intubation with expected duration of surgery less than 2 hours.

Exclusion criteria

- Patients on chronic steroid therapy, menstruating, pregnant, & lactating females,
- previous history of motion sickness,
- history of PONV in previous surgical procedures,
- Patients who received antiemetic 24 hours prior to surgery or had emetic episode 24 hour prior to surgery.
- Patients on drugs like tricyclic antidepressants, scopolamine, and phenothiazines.

Thirty patients were assigned to each group. Drug was selected from computer generated random number table and was prepared as study drug (1) and study drug (2). Two syringes prepared for each patient where study drug as follows (1) contained either dexamethasone 160µg/kg or saline and study drug (2) contained either granisetron 20µg/kg or granisetron 40µg/kg with each syringe had fixed volume of 5 ml. Code number were entered on the syringes and on the patient's record sheet. Grouping done as follows group G40 - Inj. granisetron 40 µg/kg; Group G20+D - Inj. granisetron 20 µg/kg+inj. dexamethasone 160µg/kg; Group G20+D - Inj. Granisetron 20 µg/kg+ Inj. dexamethasone 160µg/kg.

Statistical analysis

Patient's demographic data were analyzed with one way analysis of variance (ANOVA) and student's t test. The incidence of postoperative nausea & vomiting and the incidence of adverse events were compared with non-parametric tests (χ^2, Kruskall Wallis tests). A *P* value <0.05 was considered significant. All values were expressed as Mean±SD.

RESULTS

The demographic variables shown in Table 1, which could have modified the incidence of PONV like age, weight, sex, ASA status were randomized properly, and there were no significant differences among these groups. Demographic data of all three groups were comparable. Data expressed in Table 1 is calculated as Mean±SD of total values of their respective findings. A series of one way analyses of variance was conducted to examine differences in these parametric variables among three groups.

Table 2 shows patients attributes like duration of surgery, duration of anaesthesia and total intraoperative dose of propofol. As seen above all these findings have 'p' value >0.05 i.e. all of them are comparable.

Nausea

In early hours i.e. from 0-4 hours, 4 patients in G40 group had nausea while two patients in each G40+D, G20+D group had nausea which did not require antiemetic. The incidence of nausea was not statistically significant between any groups (Table 3).

In late hours i.e. from 4-24 hours, 4 patients in G40 group had nausea while only one patient in each G40+D, G20+D group had nausea which did not require antiemetic. Though clinically significant, the incidence of nausea was not statistically significant between any groups (Table 4).

Table 1: Patients demographic data.

Variables		Groups (Mean±SD)			'P' value
		G40	G20+D	G40+D	
Age (years)		38.8±6.31	40.6±7.50	40.4±8.92	0.498
Weight (kg)		54.4±4.27	53.6±6.22	55.13±4.46	0.505
Sex	Female	20	19	18	>0.05
	Male	10	11	12	>0.05
ASA status	I	28	28	28	>0.05
	Π	2	2	2	>0.05

P <0.05=significant.

Table 2: Other patient related factor (Mean±SD).

Attributes	G40	G20+D	G40+D	'P' value
Duration of surgery (minutes)	90.5±19.76	87.9±15.48	89.73±19.3	0.852
Duration of anaesthesia (minutes)	102.3±20.03	99.16±15.49	102±18.48	0.758
Intraoperative total dose of propofol (milligrams)	238.33±43.83	223.66± 40.56	229±30.44	0.274

P <0.05=significant.

Nausea requiring rescue

Two patients in group G40 had nausea requiring rescue antiemetic, while no patient in group G20+D and G40+D had nausea severe enough to require rescue. There was no statistical significance between the groups. Median nausea score at which patients demand rescue was 5 with range of 4 to 6 (Table 3).

One patient each in group G40, G20+D had nausea severe enough to require rescue antiemetic, while no patient in group G40+D had nausea severe enough to require rescue. There was no statistical significance between the groups. The mean nausea score at which patients demanded rescue was 5 with range of 4-6 in both G40 and G20+D groups (Table 4).

Vomiting

There were 2 emetic episodes in group G40, 2 emetic episodes in group G20+D while none of the patient had emetic episodes in group G40+D and required rescue antiemetic for it. None of group showed statistically significant difference in emetic episode (Table 3).

There were 3 emetic episodes in group G40, 2 emetic episodes in group G20+D and 1 emetic episodes in group G40+D & required rescue antiemetic for it (Table 4). None of group showed statistically significant difference in emetic episode.

Rescue antiemetic

Four patients in group G40, 2 patients in group G20+D but none of the patient in group G40+D required rescue antiemetic in early hours postoperatively. Difference between the groups G40+D & G40 was statistically significant but there was no statistical significance between other groups. No patient required twice rescue antiemetic medication during 0 to 4 hours (Table 3).

Four patients in group G40, 3 patients in group G20+D and 1 patient in group G40+D required rescue antiemetic between 4-24 hours. Though difference between groups G40+D and G40 looks clinically significant, none of the group reached statistical significance. No patient required twice rescue antiemetic medication during late hours i.e. between 4 to 24 hours (Table 4).

Complete response

In early hours in group G40+D 93.34% patients had complete response as compared to 86.67% patients in group G20+D and 73.33% patients of group G40 in first four hours. In first four hours, we found G40+D combination worked best. This implies that addition of dexamethasone has made a significant improvement in antiemetic effect of granisetron in both the doses in early hours postoperatively (Table 3).

In group G40+D, 93.33% patients had complete response as compared to 86.67% patients in group G20+D and 73.33% patients of group G40 in late hours i.e. from 4-24 hours. In this study we had statistically significance difference between G40+D & G40 groups for complete response. Even group G20+D had clinically improved response as compared to group G40 (Table 4).

This implies that addition of dexamethasone has made significant improvement in antiemetic effect of granisetron in both the doses in late hours.

The incidence of PONV during the first 24 hours after anaesthesia was significantly more in the patients who had received granisetron alone than those who had received granisetron plus dexamethasone combination ($p<0.05$). The overall cumulative incidences (0-24 h) of PONV were 4 (13.33%) in group G40+D; 8 (26.67%) in group G20+D and 11 (36.66%) in group G40 groups. Difference in groups G40+D verses G40 was statistically significant (p value<0.05) but differences in groups G40+D verses G20+D and groups G20+D verses G40 though clinically significant did not reach statistical significance (Table 5).

Cumulative frequencies of rescue antiemetic required in first 24 hours were found to be 1 (3.33%) in G40+D and 5 (16.67%) in group G20+D while in group G40 it was 8 (26.67%). Thus there was statistically significant difference between group G40+D and group G40 p value <0.05, but difference in groups G40+D verses G20+D and groups G20+D verses G40 did not reach statistical significance & none of the group required rescue twice.

The incidence of total emetic episodes in first 24 hours were 1 (3.33%) in G40+D group and 4 (13.33%) G20+D while 5 (16.67%) in group G40. Difference between groups G40+D and group G40 was clinically significant but none of the values reached statistical significance.

All the above results suggest that addition of dexamethasone has definitely improved antiemetic efficacy of granisetron.

Table 3: Incidence of postoperative nausea and vomiting in 0-4 hours.

0-4 hours	Number (%) of patients			'P' value		
	G40 (n=30)	G20+D (n=30)	G40+D (n=30)	G40+D versus G40	G20+D versus G40	G40+D versus G20+D
Nausea	4 (13.33%)	2 (6.6%)	2 (6.6%)	>0.05	>0.05	>0.05
Nausea requiring rescue	2 (6.6%)	0	0	>0.05	>0.05	>0.05
Vomiting	2 (6.6%)	2 (6.6%)	0	>0.05	>0.05	>0.05
Rescue	4 (13.33%)	2 (6.6%)	0	0.03*	>0.05	>0.05
Complete response	22 (73.33%)	26 (86.67%)	28 (93.34%)	0.03*	>0.05	>0.05
Median nausea score requiring rescue	5 (4 to 6)	-	-			

P <0.05=significant.

Table 4: Incidence of postoperative nausea and vomiting in 4-24 hours.

4-24hrs	Number (%) of patients			'P' value		
	G40 (n=30)	G20+D (n=30)	G40+D (n=30)	G40+D versus G40	G20+D versus G40	G40+D versus G20+D
Nausea	4(13.33%)	1 (3.3%)	1 (3.3%)	>0.05	>0.05	>0.05
Nausea requiring rescue	1 (3.3%)	1 (3.3%)	0	>0.05	>0.05	>0.05
Vomiting	3 (10%)	2 (6.6%)	1 (3.3%)	>0.05	>0.05	>0.05
Rescue	4 (13.33%)	3 (10%)	1 (3.3%)	0.16	>0.05	>0.05
Complete response	22 (73.33%)	26 (86.67%)	28 (93.34%)	0.03*	0.19	0.38
Median nausea score requiring rescue	5 (4 to 6)	5 (4 to 6)	-			

P<0.05=significant.

Adverse effects

There were no significant differences in incidence of adverse effects between the groups and overall incidence of adverse effects was found to be low. One patient in group G20+D had one episode of bradycardia intraoperatively this may be because patient was already having heart rate towards lower side and additive effect

of injection propofol. Bradycardia is not a known side effect of either granisetron or dexamethasone and bradycardia did not follow administration of study drug. Addition of dexamethasone improved antiemetic efficacy of granisetron, as granisetron 40 µg/kg+injection dexamethasone worked best of all three groups and results of G20+D group were clinically better than G40 group though could not be proven statistically. Addition of dexamethasone did not increase incidence of side effects compared to granisetron alone group (Table 6).

All patients were monitored intra and postoperatively for heart rate and blood pressure, but no patient developed significant bradycardia or hypotension in all three groups and all patients were hemodynamically stable.

Table 5: Cumulative frequencies of PONV, rescue, and emetic episodes in 24 hours.

0-24 hours	Number (%) of patients			'P' value		
	G40 (n=30)	G20+D (n=30)	G40+D (n=30)	G40+D versus G40	G20+D Versus G40	G40+D Versus G20+D
PONV 24 hours	11 (36.66%)	8 (26.67%)	4 (13.33%)	0.03*	0.40	0.19
Rescue 24 hours	8 (26.67%)	5 (16.67%)	1 (3.3%)	0.03*	0.34	0.08
Emetic episode in 24 hours	5 (16.67%)	4 (13.33%)	1 (3.3%)	>0.05	0.19	0.16

P<0.05=significant.

Table 6: Adverse effects.

0-24 h	G40+D	G20+D	G40
Headache	1 (3.3%)	1 (3.3%)	1 (3.3%)
Dizziness	1 (3.3%)	0	1 (3.3%)
Constipation	0	0	0
Myalgia	0	0	0
Bradycardia	0	1 (3.3%)	0

DISCUSSION

PONV are frequent and unpleasant symptoms following general anaesthesia. Some patients view PONV as being more debilitating than operative procedure itself.[5] Persistent PONV can cause tension on suture line, venous hypertension, increase bleeding under skin flaps, esophageal rupture and even expose patient to increase risk of pulmonary aspiration of vomitus if airway reflexes are depressed due to residual anaesthetic dosage in body.[6]

Propofol has been shown to reduce incidence of emesis in patients undergoing general anaesthesia but the exact mechanism for this action is unknown.[7]

Steroids (like dexamethasone methylprednisolone), cannabinoids (nabilone) and NK1 receptor antagonists (like aprepitant) are other drugs used for prevention and treatment of chemotherapy induced nausea/vomiting.[8] Granisetron is shown to be effective in preventing chemotherapy induced nausea and vomiting.[9]

Studies done by Fujii Y et al demonstrated that granisetron is superior to metoclopramide in prevention of PONV after general anaesthesia and optimum antiemetic dose is 40µg/kg intravenously.[10-13]

Mikawa K studied antiemetic efficacy of prophylactic granisetron in patients posted for gynaecologic surgery. They demonstrated 83%, 78%, and 20% complete response in granisetron 20µg/kg and 40µg/kg and placebo groups respectively and granisetron treated patients experienced significantly fewer emetic episodes as compared to saline treated patients.[14]

Wilson AJ studied the antiemetic effects of granisetron in abdominal and gynaecological surgeries with different doses.[15] They demonstrated that granisetron in 1.0 and 3.0 mg doses provide effective prophylaxis against vomiting as compared to placebo.

In present study incidence of nausea was 4 (13%), 2 (6.6%) and 2 (6.6%) in first 4 hours and 4 (13%), 1 (3.3%) and 1 (3.3%) in next 20 hours in G40, G20+D, G40+D groups respectively. The incidence between monotherapy group and combination groups though look clinically significant did not reach statistical significance between any groups.

Similarly in present study it was found that for moderate to severe nausea, 2 (6.6%), 0 (0%), 0 (0%) patients in first 4 hour and 1 (3.3%), 1 (3.3%), 0 (0%) in next 20 hours demanded rescue in G40, G20+D and G40+D group respectively and mean nausea score at time of rescue was 5 with a range of 4 to 6.

These results were comparable with incidence of nausea in studies done by Fujii Y in middle ear surgery i.e. 4 (10%), 1 (3%) in first 0-3 hour and 4 (10%), 1 (3%) in next 24 hour for granisetron 40µg/kg and granisetron

40µg/kg+dexamethasone 160µg/kg respectively.[16] Fujii Y did another study in women undergoing gynaecological surgery and found similar incidence for nausea in 24 hour, 13% and 4% in group G40 and G40+D respectively.[17] Similar incidence of nausea was found in study done by Biswas & Rudra i.e. 6 (10%), 1 (3%) in first 4 hour and 5 (8%), 2 (3%) in next 24 hours for granisetron 40µg/kg and granisetron 40µg/kg+ dexamethasone 8mg combination respectively.[18]

In our study 2 (6.6%), 2 (6.6%), 0 (0%) patient in first 4 hour and 3 (10%), 2 (6.6%), 1 (3.3%) patient in next 20 hour developed vomiting in G40, G20+D & G40+D groups respectively. There was no statistical significance between any groups for incidence of vomiting, both in early as well as late hours postoperatively.

In our study, we found no statistically significant difference between any group and clinically best results was seen with combination of dexamethasone with granisetron 40µg/kg. Granisetron even in reduced dose i.e. 20µg/kg in combination with dexamethasone had clinically better anti-vomiting effect compared to granisetron 40µg/kg alone. This suggests that combination of dexamethasone increases efficacy of granisetron in both the doses.

The present results were comparable with study done by Fujii Y in which incidence of vomiting was 3 (8%), 1 (3%) in first 3 hour and 3 (8%), 1 (3%) in next 21 hour, in G40 and G40+D groups respectively.[16] In present study results were also comparable with study done by Biswas et al, who had incidence of vomiting as, 4 (7%), 1 (2%) in first 4 hour and 5 (8%), 2 (3%) in next 20 hour in G40 and G40+D groups respectively.[18]

CONCLUSION

Granisetron as a single agent in dose 40µg/kg is effective as prophylactic antiemetic in preventing PONV in laparoscopic cholecystectomy which is supposed to be highly emetogenic surgery. Addition of dexamethasone 160µg/kg to granisetron significantly increases antiemetic efficacy of the granisetron in both the doses i.e. 20µg/kg and 40µg/kg without increasing side effect profile. Granisetron 40µg//kg+injection dexamethasone 160µg/kg is best for antiemetic prophylaxis in highly emetogenic surgeries like laparoscopic cholecystectomy, in patients with high risk factors like history of motion sickness, previous history of PONV and especially in day care surgeries, even though it is more costly than G40 and G20+D groups. Granisetron 20µg/kg+injection dexamethasone can be cost effective alternative for routine antiemetic prophylaxis compared to granisetron 40µg//kg and granisetron 40µg//kg+injection dexamethasone for all patients undergoing laparoscopic cholecystectomy.

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