

COMPARATIVE STUDY OF INTRAVENOUS FOSAPREPITANT WITH INTRAVENOUS GRANISETRON AND INTRAVENOUS DEXAMETHASONE FOR PROPHYLAXIS OF POSTOPERATIVE NAUSEA AND VOMITING AFTER LAPAROSCOPIC CHOLECYSTECTOMY: A PROSPECTIVE RANDOMISED DOUBLE BLIND STUDY

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Abstract

Background: Postoperative nausea and vomiting (PONV) are frequent adverse events after general anaesthesia. More common in females undergoing abdominal surgeries. Although it is usually self-limiting and non-fatal, it is unpleasant and leads to considerable post-operative discomfort and dissatisfaction. The aim is to compare the effectiveness of iv Fosaprepitant with iv Granisetron and iv Dexamethasone in prevention of PONV in patients undergoing Laparoscopic cholecystectomy. Setting and design is 114 female patients of ASA grade 1-3, aged 20-50yrs with good mental function planned for elective laparoscopic cholecystectomy were studied for this prospective, double blind, randomized study. **Materials and Methods:** The study comprised of 3 groups of 38 each based on different drugs given. Group F receiving Injection FOSAPREPITANT 150 MG intravenously, Group G receiving Injection GRANISETRON 3 MG intravenously and Group D receiving Injection DEXAMETHASONE 8 MG intravenously. **Result:** No nausea was reported at 0-2hrs and 2-6hrs postoperatively. At 6-24hrs postoperatively, mean Nausea score was least in Group F, followed by Group D and G, being 0 ± 0 , 0.63 ± 1.23 and 1.02 ± 1.44 respectively. A significant difference (p -value <0.05) was observed for both groups D and G. In all groups no vomiting was noticed at 0-2 and 2-6hrs. In Group G, 18.4% had vomiting at 6-24hrs. A significant difference (p -value <0.05) was observed between all three groups with respect to vomiting at 6-24hrs. **Conclusion:** Administration of iv fosaprepitant was better than dexamethasone and granisetron for the prophylaxis of vomiting in the first 24 h postoperatively in females undergoing laparoscopic cholecystectomy.

INTRODUCTION

Post-operative nausea and vomiting (PONV) is a common and distressing complication after anaesthesia and surgery with an incidence of approximately 30%.^[1,2]

Although PONV is usually self-limiting and non-fatal, it is unpleasant and leads to considerable post-operative discomfort and dissatisfaction.^[1,3] For most surgical patients, PONV is a greater concern than is post-operative pain, and patients continue to rank PONV as the most unfavourable complication.^[4,5]

Moreover, PONV can cause, tension in suture lines, wound dehiscence, dehydration, electrolyte imbalance, acid-base disturbances and can increase healthcare costs by increasing patients' stay in the post-anaesthesia care unit (PACU) and hospital. Hence, identifying effective strategies for PONV prophylaxis is crucial.^[1,3]

While several factors conferring increased risk of developing PONV have been identified. Certain procedures such as gynaecological surgeries, laparoscopic surgeries, middle ear surgeries, strabismus surgeries are associated with high incidence of PONV. New guidelines state that

cholecystectomy and laparoscopic surgery are associated with higher PONV incidence.^[6] In these types of cases, the reported incidence rate of PONV has ranged from 40% to 75%. Considering that female patients undergoing Laparoscopic cholecystectomy are at higher risk for developing PONV, increasing attention has been directed towards prophylaxis for PONV in this population.^[7,8] Different pharmacological and non-pharmacological approaches have been used for preventing PONV. Nonetheless, the most effective prophylactic regimen has not been determined, particularly for high-risk patients, and the search for the optimal therapy continues.^[9,10]

Furthermore, to the best of our knowledge, no comparative study has evaluated the effectiveness of IV fosaprepitant with iv dexamethasone and iv granisetron for the prevention of PONV in the patients undergoing laparoscopic cholecystectomy. Fosaprepitant is a Prodrug of aprepitant and accordingly its antiemetic effects are attributed to aprepitant. This drug is a very selective antagonist of the NK-1 receptor and consequently inhibits the action of substance P.

Granisetron is a selective 5-hydroxy tryptamine - 3(5HT₃) receptor antagonist.

Dexamethasone is a low price corticosteroid which has anti-inflammatory effects, and some studies have also evaluated its effect on nausea and vomiting prophylaxis after chemotherapy.^[11]

Although a number of therapies are available for the management of PONV, none is entirely effective. Most of the published trials indicate an improved antiemetic prophylaxis when using a cation of agents acting at different receptor sites, compared with monotherapy. So we decided to study the efficacy of iv Fosaprepitant with iv Granisetron and iv Dexamethasone for prophylaxis of PONV after laparoscopic Cholecystectomy.

MATERIALS AND METHODS

After approval from ethical committee and taking written informed consent, 114 female patients of ASA physical status 1-3, aged 20-50 yrs, posted for elective laparoscopic cholecystectomy were enrolled for this prospective, double blind, randomized study. Patients with previous history of PONV, not willing to enroll, having Cardiac, Renal or Hepatic dysfunction, motion sickness, allergic to experimental drugs, who received chemotherapy within 4 weeks or radiotherapy within 8 weeks prior to study and patient with ongoing vomiting from organic disease were excluded from the study.

They were randomly allocated into three equally sized Groups of 38 each using computer generated random numbers. Patients of GROUP F: received Injection FOSAPREPITANT 150 MG intravenously, GROUP G: received Injection GRANISETRON 3 MG intravenously and patients of GROUP D:

Patients received Injection DEXAMETHASONE 8 MG intravenously.

A day before surgery, patients were instructed ethically on how to rate the severity of their Nausea using the Nausea score:

0 Absence of Nausea

1. Mild Nausea
2. Moderate Nausea
3. Severe Nausea

All patients were fasted 8 hours for solid food before surgery and advised to take tablet Alprazolam (0.25 mg), tablet Ranitidine (150 mg), tablet metoclopramide (10 mg) on the evening before surgery and 2 hour before the scheduled procedure.

On arrival of the patient in the operative room, ASA standard monitors including pulse oximetry, non-invasive blood pressure, electrocardiography, were connected to the patient and baseline parameters were noted. Venous access was established and pre-medicated with slow iv anti-emetic study drug in 100 ml NS over 20-30 minutes. Any adverse effect like rashes, pain, itching were noted.

All the patients received general anesthesia using the same protocol. As for pre-medication, all received injection Midazolam (30 mcg/kg) iv, injection Fentanyl (2 mcg/kg). Induction was done with 1% of injection Propofol (2mg/kg). Injection Vecuronium (0.1 mg/kg) was given after confirmation of adequate mask ventilation with 100% oxygen for 3 minutes, an appropriate size I-gel was placed as supra-glottic device. Anesthesia was maintained with Isoflurane, 50% oxygen in medical air. Muscle relaxation was maintained by vecuronium bromide 0.01mg/kg intermittently thereafter. Injection paracetamol (15mg/kg) was given after induction as iv infusion for intra-operative Analgesia. Positive Pressure Ventilation was delivered with Tidal Volume & Respiratory Rate adjusted to maintain End-Tidal CO₂ between 30-40.

Intra-operative all the patients received maintenance fluid at the rate of 3ml/kg/hour of ringer lactate. Injection Diclofenac Sodium (1mg/kg) iv and Bupivacaine 0.5% infiltration at each surgical port site before skin closure for post-operative analgesia was given.

At the end of surgery residual neuromuscular block was reversed by injection neostigmine (0.05mg/kg) and injection glycopyrrolate (0.01mg/kg) intravenously and patient was extubated after complete reversal of neuromuscular blockade. BP, HR, SPO₂ at every 15 minutes interval after infusion of Anti-Emetic drug till extubation, was recorded. Also total dose of additional fentanyl given intra-operatively was recorded.

All patients rated their Nausea using Nausea score immediately; 0-2 hour, 2-6 hours & 6-24 hours after surgery. An anesthesiology resident who was blinded to the study groups assessed the Nausea intensity for each patient. Post-operatively, those patients who had Nausea score >2/ Vomiting, received rescue anti-emetic drug Metoclopramide 10 mg intravenously. Time for first dose along with total dose of rescue

anti-emetic drug in 24 hours was recorded by a blinded investigator with relative at the patient bedside by telephone or in person. Any adverse reaction was also monitored. Post-operative analgesia was covered with 1 gm injection Paracetamol intravenously six hourly.

Statistical Evaluation

Variables were tested about normal distribution with Kolmogorov-Smirnov test and Q-Q plots. For intragroup comparison of various size and symptoms Wilcoxon signed rank test was applied whereas for intergroup comparison chi square test was applied. For intragroup comparison of clinical continuous variables paired t test was applied whereas one way ANOVA test was applied for intergroup comparison. $P < 0.05$ was considered statistically significant.

RESULTS

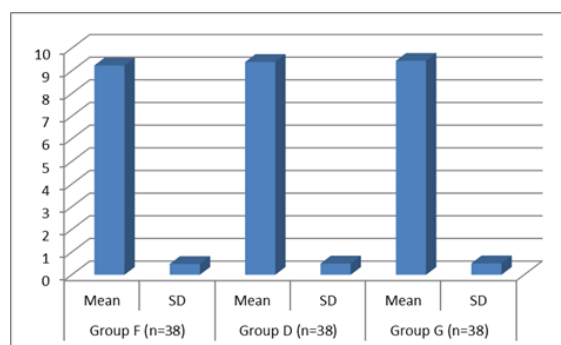
A total of 114 female patients scheduled to undergo laparoscopic cholecystectomy and fulfilling the inclusion criteria were enrolled in the study and were randomly divided into one of the three groups F, D and G ($n = 38$).

[Table 1] shows no nausea was reported at 0-2 and 2-6hrs. At 6-24hrs, mean Nausea score was least in Group F, followed by Group D and G, being 0 ± 0 , 0.63 ± 1.23 and 1.02 ± 1.44 respectively. A significant difference (p -value < 0.05) was observed between the various time intervals for both groups D and G.

[Table 2] shows no vomiting was noticed at 0-2 and 2-6hrs. In Group G, 18.4% had vomiting at 6-24hrs. A significant difference (p -value < 0.05) was observed between all three groups with respect to vomiting at 6-24hrs.

[Table 3] shows no rescue anti-emetic drug was required at 0-2 and 2-6hrs. At 6-24hrs, Group F didn't required any anti-emetic rescue drug, whereas 21.05% subjects of Group D and 34.21% subjects of Group G required 1 dose of Injection Metoclopramide 10 mg intravenous as a rescue antiemetic drug. A significant difference (p -value < 0.05) was observed between all three groups at 6-24 hrs.

[Table 4] shows both in Group D and G, no adverse reactions were noticed, whereas in Group F, 5.3% had rashes and pain at injection site and 2.6% had dizziness and rash. A significant difference (p -value < 0.05) was observed between all three groups with respect to adverse reactions.



[Table 5] shows the Mean ALDRETE SCORE in all groups at 2hrs. Mean ALDRETE SCORE was least in Group F, followed by Group D and G, being 9.23 ± 0.48 , 9.39 ± 0.49 and 9.45 ± 0.50 respectively. ANOVA statistical analysis was done to assess the intergroup comparison between three groups, and an insignificant difference (p -value > 0.05) was observed between all three groups.

Table 1: Mean Nausea SCORE in all groups at different time intervals

	Group F (n=38)		Group D (n=38)		Group G (n=38)		Statistical analysis	
	Mean	SD	Mean	SD	Mean	SD	F-statistics	p-value
0-2hrs	.0000	.00000	.0000	.00000	.0000	.00000	-	-
2-6hrs	.0000	.00000	.0000	.00000	.0000	.00000	-	-
6-24hrs	.0000	.00000	.63	1.23	1.02	1.44	2.10	0.021*
F-statistics	-	-	0.998	-	0.980	-	-	-
p-value	-	-	0.01*	-	0.011*	-	-	-

*p-value < 0.05 is significant

Table 2: Presence of Vomiting in all groups at different time intervals

	Group F (n=38)		Group D (n=38)		Group G (n=38)		Statistical analysis	
	Frequency	Percentage	Frequency	Percentage	Frequency	Percentage	Chi square	p-value
0-2hrs	0	0	0	0	0	0	-	-
2-6hrs	0	0	0	0	0	0	-	-
6-24hrs	0	0	0	0	7	18.4	2.019	0.04*

*p-value < 0.05 is significant

Table 3: Post operative RESCUE ANTI-EMETIC DRUG given in all groups at various time intervals

Rescue Anti-Emetic Drug	Group F (n=38)		Group D (n=38)		Group G (n=38)		Statistical analysis	
	Frequency	Percentage	Frequency	Percentage	Frequency	Percentage	Chi square	p-value
0-2hrs	0	0	0	0	0	0	-	-

2-6hrs	0	0	0	0	0	0	-	-
6-24hrs	0	0	8	21.05	13	34.21	1.918	0.01*

*p-value<0.05 is significant

Table 4: Presence of adverse reactions in all groups.

Adverse reactions	Group F (n=38)		Group D (n=38)		Group G (n=38)		Statistical analysis	
	Frequency	Percentage	Frequency	Percentage	Frequency	Percentage	Chi square	p-value
Dizziness, Rash	1	2.6	0	0	0	0	0.998	0.0002*
Rash, Pain at Injection Site	2	5.3	0	0	0	0	0.878	0.011*
Negative	35	92.1	38	100	38	100	1.617	1.890

*p-value<0.05 is significant

Table 5: Mean ALDRETE SCORE in all groups at 2hrs

	Group F (n=38)		Group D (n=38)		Group G (n=38)		Statistical analysis	
	Mean	SD	Mean	SD	Mean	SD	F-statistics	p-value
	9.2397	.47786	9.3947	.49536	9.4474	.50390	2.991	0.908

*p-value>0.05 is insignificant.

DISCUSSION

Postoperative nausea and vomiting (PONV) is one of the most distressing symptoms that commonly seen after surgeries under general anesthesia, the incidence being around 30% in adults.⁷⁸In laparoscopic methods the tissue injury is less than open surgeries but still post-operative nausea and vomiting (PONV) are among common complications, and its prevalence has been reported in different studies about 44%-83%.^[12]

Different medications have been evaluated in PONV prophylaxis and patient satisfaction after cholecystectomy. Previously, anti-cholinergics, anti-histamines and phenothiazines were used to prevent PONV; but reduced effect of these medications and their complications led to drug shifts. Recent studies have shown that serotonin receptor antagonists are more effective than previous medications in PONV prophylaxis. It has been proved that Granisetron and Ondansetron are effective medications in this field.^[13]

Dexamethasone is a low price corticosteroid which has anti-inflammatory effects, and some studies have also evaluated its effect on nausea and vomiting prophylaxis after chemotherapy.^[11]

Authors have revealed that the antiemetic neurokinin-1 receptor antagonist fosaprepitant is a safe and effective drug.^[14] Aprepitant is an NK-1 receptor inhibitor that is capable of blocking the action of substance P at its action sites.^[15]

The present study was conducted in the Department of Anaesthesiology, Institute of Medical Sciences, BHU, Varanasi after approval from the ethical committee. The total of 114 female patients (38 in each group) of > 18years old were enrolled for the study to prospectively evaluate the efficacy of iv Fosaprepitant with iv Granisetron and iv Dexamethasone for the prophylaxis of PONV in patients undergoing Laparoscopic Cholecystectomy.

No nausea was reported at 0-2 and 2-6hrs. At 6-24hrs, mean Nausea score was least in Group F, followed by Group D and G, being 0 ± 0 , 0.63 ± 1.23 and 1.02 ± 1.44 respectively and a significant difference (p-value<0.05) was observed between all three groups at 6-24hr. In all groups no vomiting was noticed at 0-2 and 2-6hrs. In Group G, 18.4% had vomiting at 6-24hrs. a significant difference (p-value<0.05) was observed between all three groups with respect to vomiting at 6-24hrs. Similar to Nami Kukuta et al,^[16] who compared the incidence of vomiting in 38 patients who underwent lower limb surgery where 19 patients received intravenous fosaprepitant 150mg and 19 patients received intravenous ondansetron 4mg and they found the incidence of vomiting was 0% in fosaprepitant group vs 26% in ondansetron group (p value <0.046).

Likewise Yasuo M. Tsutsum et al,^[17] compared the incidence of PONV in 68 neurosurgical patients undergoing craniotomy where 34 patients received intravenous fosaprepitant 150mg and 34 patients received intravenous ondansetron 4mg and they found the incidence of PONV was 38% in fosaprepitant group vs 56% in ondansetron group (p value<0.001). Hessami MA et al.^[18] observed that intravenous injection of 8 mg Dexamethasone, or 3 mg Granisetron have similar effects on PONV prophylaxis in laparoscopic cholecystectomy.

But our study showed 8 mg Dexamethasone iv was more effective (differences were statistically significant) than 3 mg Granisetron similar to Erhan et al.^[19]

We observed that in all groups no rescue anti-emetic drug was required at 0-2 and 2-6hrs. At 6-24hrs, Group F didn't required any anti-emetic rescue drug, whereas 21.05% subjects of Group D and 34.21% subjects of Group G required 1 dose of injection metoclopramide 10mg iv as a rescue antiemetic drug. Chi-square statistical analysis was done to assess the intergroup comparison between three groups at all three time periods, and a significant difference (p-

value<0.05) was observed between all three groups at 6-24 hrs. In all groups no post operative adverse reactions were noticed at all time intervals.

International guidelines recommend an antiemetic prophylaxis with corticosteroids, 5-HT₃ R-antagonists and NK₁R-antagonists. The NK₁ R-antagonist fosaprepitant has shown favorable results in pediatric and adult patients.^[14] Adverse reactions were assessed at various time periods. In both Group D and G, no adverse reactions were noticed, whereas in Group F, 5.3% had rashes and pain at injection site and 2.6% had dizziness and rash following administration of drug. A significant difference was observed between all three groups with respect to adverse reactions. But Cabanillas Stanchi KM et al,^[14] observed in their study that there was insignificant difference among fosaprepitant and granisetron with or without dexamethasone. The drugs were well tolerated, safe and effective in pediatric and adult patients.

In 1970, Aldrete and Kroulik developed a postanesthesia scoring system to monitor recovery from anesthesia. The original Aldrete score assigned a number of 0, 1, or 2 to 5 variables: activity, circulation, pain, surgical bleeding, nausea & vomiting. A score of 9 out of 10 was considered adequate for discharge from the PACU. The Aldrete score has been successful in addressing the early phase 1 recovery.^[20]

Post-operative effect of drugs was assessed at 2 hrs, 2-6 hrs and 6-24 hrs. At 2hrs, mean ALDRETE SCORE was least in Group F, followed by Group D and G, being 9.23±0.48, 9.39±0.49 and 9.45±0.50 respectively. ANOVA statistical analysis was done to assess the intergroup comparison between three groups, and an insignificant difference (p-value>0.05) was observed between all three groups. Sinha R et al,^[21] found insignificant difference (p-value>0.05) was observed between Granisetron versus Granisetron-Dexamethasone with respect to ALDRETE SCORE.

CONCLUSION

The study indicated that fosaprepitant was more effective than Dexamethasone and Granisetron injection, showing minimum incidence of nausea and vomiting after laparoscopic cholecystectomy, which led us to conclude that the administration of fosaprepitant was as effective and better than the administration of dexamethasone and granisetron for the prophylaxis of vomiting in the first 24 h postoperatively in women undergoing laparoscopic cholecystectomy.

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