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Research Article

A Comparison of Aprepitant and Ondansetron in Prophylaxis of Postoperative Nausea and Vomiting in Laparoscopic Cholecystectomy

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Abstract: Nausea, vomiting and retching are one of the commonest complaints experienced among post operative period. Post operative nausea & vomiting exposes the patient to unusual distress & stress. The aim of study is to compare the efficacy and safety of Aprepitant (NK-1 Antagonist) and Ondansetron (5-HT_3 antagonist) in prophylaxis of post-operative nausea and vomiting in patients undergoing laparoscopic cholecystectomy. In a randomized-double-blinded prospective trial 90 patients of 20-60yrs and ASA (American society of anesthesiologists) I and II were allocated into 3 groups. Group C received placebo tablets orally 3 hrs and 2ml of normal saline intravenous (IV) 10 Min prior to induction. Group O received placebo tablets orally 3 hrs and Ondansetron 4mg IV 10 min prior to induction. Group A received 40 mg Aprepitant oral 3 hrs and 2ml of normal saline IV 10 Min prior to induction. Efficacy of antiemetic was assessed for 0-24 hrs, 24-48 hrs after surgery. Nausea was recorded on 11 point ordinal scale, vomiting episode, doses of rescue antiemetic and adverse effects were noted and statistically analyzed. There were statistically similar nausea scores (Verbal rating scores) in both Group A and Group O at 0-24 hrs (P=0.192). Thereafter also at 24-48 hrs nausea scores remained similar in Group A and Group O (p=0.052). Episodes of vomiting were similar at 0-24 hrs (P=0.267) but at 24-48 hrs, it were less in Group A (P=0.023). In conclusion, prophylactic Ondansetron 4mg IV and Aprepitant 40mg oral are equally effective in early PONV, but Aprepitant because of its long acting effect and delayed vomiting effect can be considered to prevent delayed PONV.
Keywords: Laparoscopic cholecystectomy, PONV, Ondansetron, Aprepitant.

INTRODUCTION

Nausea, retching, vomiting are amongst the most common post operative complaints during recovery from general anesthesia. In absence of peri-operative antiemetic medication 20-30% of adult patients recovering from general anesthesia may experience post-operative emesis and 0.1% may experience severe nausea & vomiting [1]. The patients undergoing general anesthesia for laparoscopic cholecystectomy have high risk for post operative nausea and vomiting (PONV) with incidence up to 75% [2]. Persistence nausea & vomiting may result in dehydration, electrolyte imbalance which may necessitate delayed discharge from the hospital particularly after ambulatory surgery [3], which may persist as post discharge nausea and vomiting (PDNV). Over the last few years several studies have laid an emphasis on the efficacy of a balanced antiemetic approach involving drugs that acts at different sites and receptor [4]. Various drugs like Metoclopramide, Dexamethasone, Ondansetron, Droperidol and Clonidine had been studied (16-19). However currently available antiemetics including 5-HT3 receptor antagonist do not provide complete protection [5] and there is still a medical need for more effective therapies to prevent PONV. Although 5-HT3 receptor antagonist have questionable efficacy against centrally induced emesis, non peptide NK- 1 receptor antagonist have demonstrated activity against both peripheral and central emetic stimuli in animal models [6-10]. The Neurokinin-1(NK-1) receptors which exist in gastrointestinal vagal afferent and central nervous system vomiting reflex pathway generate condition of nausea & vomiting due to activation of substance P [11]. Aprepitant is a novel NK-1 receptor antagonist available for clinical use as an antiemetic. On July 2006 US FDA approved its use for the prevention of PONV [12]. The present study was undertaken to compare the efficacy and safety of NK-1 Antagonist (Aprepitant) and 5-HT3 antagonist (Ondansetron) in prophylaxis of

PONV in patient undergoing laparoscopic cholecystectomy.

MATERIALS AND METHODS

After approval from ethical committee of institution, this prospective randomized double blinded placebo controlled study was conducted on 90 patients of 20 to 60 years of age and American society of anesthesiology (ASA) I and II undergoing laparoscopic cholecystectomy . A written informed consent was taken from all the patients enrolled in study. Patients with high risk for PONV i.e motion sickness were excluded as chances of these patients developing uncontrollable, severe nausea and vomiting if allocated to control group which did not received any prophylaxis. Other excluded were cigarette smokers, known drug allergy and significant systemic disease. The patients were randomized by computer generated random number table into three groups of 30 patients each (Fig. 1). In order to achieve statistical significant result with α =0.05 and power of 80%, sample size of 30 patients was calculated (Fig. 1).

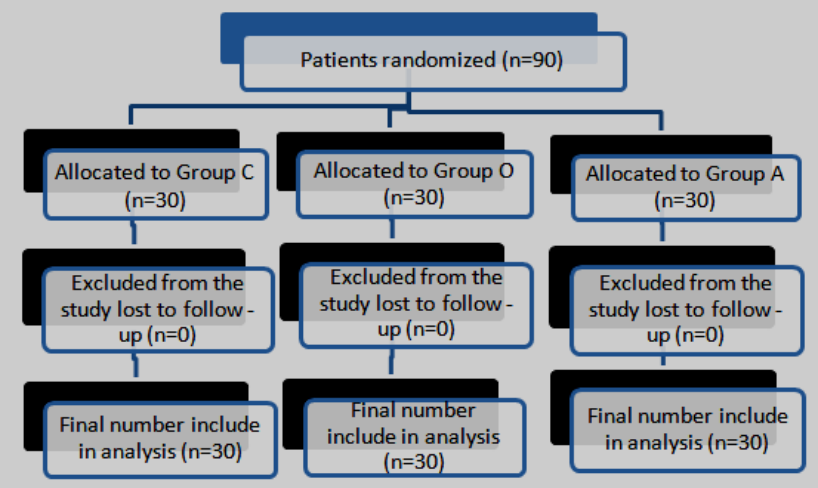

Fig. 1: Consort chart

Group C: Received placebo tablets orally 3 hrs and 2ml of normal saline intravenous (IV) 10Min prior to induction.

Group O: Received placebo tablets orally 3 hrs and Ondansetron 4mg IV 10min prior to induction.

Group A: Received 40 mg Aprepitant oral 3 hrs and 2ml of normal saline IV 10Min prior to induction

Cost of drugs at time of study – Ondansetron 4mg ampoule = 40 INR (0.8USD) and Tablet Aprepitant 40mg = 125 INR (2.5 USD)

The patient concerned as well as data collector was blind to antiemetic used. All patients were asked to fast for 6-8hrs. All patients were given Alprazolam 0.25 mg orally at 10.00 PM the night before surgery and 2hrs prior to surgery with 1-2 sips of water. On arriving in operation theatre, Intravenous line was established using 20G cannula and Ringer lactate started. Peri-operative monitoring included heart rate, oxygen saturation (SpO_2), electrocardiography, noninvasive blood pressure (NIBP) and end-tidal carbon dioxide concentration (E_tCO_2). A standard balanced anesthesia technique was used [13]. Butorphenol 1 mg IV and Glycopyrrolate 0.2 mg IV were given to all patients 10 min prior to induction of anesthesia. All patients were pre-oxygenated with 100% O_2 for 3min. Induction of anesthesia was done with Propofol 2 mg/kg IV. Endotracheal intubation was facilitated with Rocuronium bromide 1.2 mg/kg IV. Ventilation was controlled mechanically and was adjusted to keep E_tCO_2 35 -40 mm of Hg. Anesthesia was maintained using 60% N_2 O in oxygen and (0.5-1%) Isoflurane. Additional increments of Rocuronium 0.02mg/kg IV was given to the patient whenever required. Intraoperative fluid was Ringer lactate. At the end of surgery the neuromuscular blockade was reversed with Neostigmine 0.04mg/kg IV and Glycopyrotate 0.008 mg/kg IV and extubated. The time of last suture/staple was recorded as 0hr.

Efficacy of antiemetic was assessed at 0-24hrs (0, 2, 6, and 24) & 24-48hrs (48) after surgery. The important variables studied in our study were verbal rating scale (VRS) scores for nausea, incidence or episodes of vomiting or retching, use of rescue antiemetic therapy in 48 hrs observation period.

Nausea was defined as a subjective unpleasant sensation associated with awareness of the urge to vomit and usually felt in the back of throat and nausea was recorded on 11 point ordinal scale or VRS, with 0 as no nausea and 10 nausea as bad as possible(1 -3 = mild nausea, 4 -6 =moderate nausea, 7-10 = severe nausea). Retching was defined as spasmodic rhythmic contraction of respiratory muscles without expulsion of gastric contents and vomiting is defined as the forceful expulsion of stomach contents from the mouth. An emetic episode was defined as one or more continuous

episode of vomiting. Complete drug response was defined as no emetic episode and none or mild nausea. Rescue medication was offered if the patient had more than one episode of vomiting or retching, if patient had nausea lasting longer than 15min. Rescue antiemetic was Metoclopramide 10 mg IV slow. Other side effects like headache, constipation, pruritis, excessive sedation, hypersensitivity reactions, pyrexia and dizziness were recorded.

All statistical analysis was performed using SPSS package software for windows. The Data are reported as mean± SD or median. Demographic data and clinical data were analyzed using ANOVA (analysis of variance between groups). Severity of nausea VRS scores(ordinal values) were compared using Mann Whitney test , Chi square test applied for calculation of p value in number of episodes of postoperative vomiting (nominal values) , complete drug response and rescue antiemetic therapy.

RESULTS

The patient's characteristics age, weight, sex distribution, duration of surgery, duration of anesthesia, intraoperative vital signs and postoperative vital signs were comparable in all the three groups (Tables 1, 2 & 3).

Table 1: Dermographic data of patient included in study

Data mean ± SD or (n%)	**Group C (n = 30)**	**Group O (n = 30)**	**Group A (n = 30)**	**p value**
Age (years)	46.5 ± 11.2	45.6 ± 9.77	46.9 ± 7.23	0.87
Weight (kg)	61.0 ± 5.8	59.6 ± 6.17	59.5 ± 3.3	0.46
Sex				
Male	6 (20%)	6(20%)	5(16.66%)	>0.05
Female	24(80%)	24(80%)	25(83.33%)	>0.05
ASA status				
I	22 (73.3%)	23(76.6%)	23(76.6%)	>0.05
II	8(26.6%)	7(23.3%)	7(23.3%)	>0.05

No statistically difference between the groups, P values was calculated using ANOVA (analysis Of variance between groups). Where, SD is standard deviation, Group C administered with placebo tablets and normal saline; Group O administered with placebo tablet (3 hours) and Ondansetron 4mg intravenously prior to induction; Group C administered with 40 mg Aprepitant orally (3 hours) and 2ml of normal saline prior to induction.

Table 2: Intra operative data of patients included in study

Data mean ± SD	Group C	Group O	Group A	p value
Duration of Surgery (Minutes)	44.0 ± 8.45	44.5 ± 6.87	44.7 ± 7.65	0.94
Duration of Anesthesia (Minutes)	63.5 ± 8.52	63.7 ± 6.81	64.0 ± 8.21	0.97
Heart Rate (per minute)	85.6 ± 7.03	85.2 ± 6.61	85.0 ± 6.22	0.66
Systolic Blood Pressure(m.m of Hg)	126.5 ± 7.08	125.0 ± 8.67	123.5 ± 7.99	0.36
Diastolic Blood Pressure(m.m of Hg)	85.7 ± 3.75	85.0 ± 3.01	84.5 ± 3.06	0.41

No statistically difference between the groups. Where, SD is standard deviation, Group C administered with placebo tablets and normal saline; Group O administered with placebo tablet (3 hours) and Ondansetron 4mg intravenously prior to induction; Group C administered with 40 mg Aprepitant orally (3 hours) and 2ml of normal saline prior to induction.

Table 3: Post operative recovery room data

Data Mean ± S.D	**Group +C**	**Group O**	**Group A**	**p value**
Heart Rate (per minute)	85.533 ± 6.62	85.300 ± 7.04	83.600 ± 7.63	0.52
Systolic B.P.(mm of Hg)	127.60 ± 6.51	125.93 ± 8.09	125.00 ± 8.42	0.42
Diastolic B.P.(mm of Hg)	86.314 ±2.88	86.316 ±1.91	85.864 ± 3.53	0.41

No statistically difference between the groups.

There was statistically similar nausea scores (VRS scores) in both Group A and Group O upto 24 hrs (2hr, 6hr, 24hr) (P=0.192) but were significantly less than group O. Thereafter also at 48 hrs nausea was similar in Group A and Group O (p=0.052), but group A had less VRS scores as compare to group C (Table 4 & Fig. 2).

Table 4: Verbal rating scale Scores for Nausea (Median and Interquartile range)

Nausea at	Median (Interquartile range)		P value
	Group C vs Group O		
0 hr	32.1(24-59.5)	29(24.5-53)	0.248
2 hr	35.8(16.5-57)	25.2(16.5-46)	0.0091**
6 hr	37.2(16-58.5)	23.8(16-42.5)	0.0014**
24 hr	35.6(16-59)	25.5(16-50.5)	0.0129**
48 hr	31.9(19.5-53)	29.1(19.3-53)	0.26
	Group C vs Group A		
0 hr	32.1(24.5-59.5)	28.9(24.5-53.5)	0.245
2 hr	37.4(19-60)	23.6(19-47)	0.0011**
6 hr	37.3(16-58.5)	23.7(16-43)	0.0014**
24 hr	37(17.5-60)	24(17.5-51)	0.002**
48 hr	35.3(22.5-57)	25.7(22.5-46.5)	0.017**
	Group O vs Group A		
Nausea at 0 hr	30.6(25.5-59)	30.4(25.5-59)	0.492
Nausea at 2 hr	32.2(23-59.5)	28.9(23-59.5)	0.235
Nausea at 6 hr	31.2(19.5-58.5)	29.8(19.5-58.5)	0.385
Nausea at 24 hr	32.5(21-59)	38.5(21-59)	0.192
Nausea at 48 hr	34.2(23.5-58.5)	26.8(23.5-48.5)	0.052

*** Significant p values, p values were calculated using Mann-Whitney test.Where, Group C administered with placebo tablets and normal saline; Group O administered with placebo tablet (3 hours) and Ondansetron 4mg intravenously prior to induction; Group C administered with 40 mg Aprepitant orally (3 hours) and 2ml of normal saline prior to induction.**

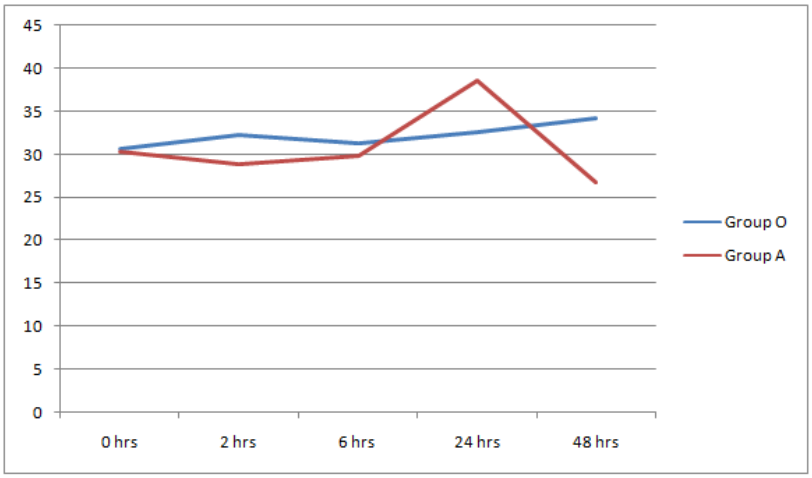

Fig. 2: Verbal rating scale Scores for Nausea (Median and Interquartile range) Group O vs Group A calculated using Mann- Whitney test, p values non significant

The incidence of vomiting in 0 -24 hrs observation period was significantly high in Group C (33.3%) as compared with group O (20%)(p=0.008) and group A (10%) (p=0.001) but in group O & group A it remained comparable (p=0.278). There was significant reduction in incidence of vomiting in 24 -48 hrs observation period in Group A (3.33%) as compared with Group C (33.3%) (P=0.03) & Group O (23.3%) (p=0.023), whereas Group C and Group O remained comparable (Table 5 & Fig. 3).

Table 5: Incidence/ Episodes of Vomiting

	Group C (n=30)		Group O (n=30)		Group A (n=30)		P Values		
	N	%	N	%	N	%	C vs O	C vs A	O vs A
Vomiting 0-24 hrs	11	33.6	6	20	3	10	0.008*	0.001*	0.278
Vomiting 24-48 hrs	10	33.3	7	23.3	1	3.3	0.39	0.03*	0.023*

*** Significant P values, P values were calculated using Chi square test. Where, Group C administered with placebo tablets and normal saline; Group O administered with placebo tablet (3 hours) and Ondansetron 4mg intravenously prior to induction; Group C administered with 40 mg Aprepitant orally (3 hours) and 2ml of normal saline prior to induction.**

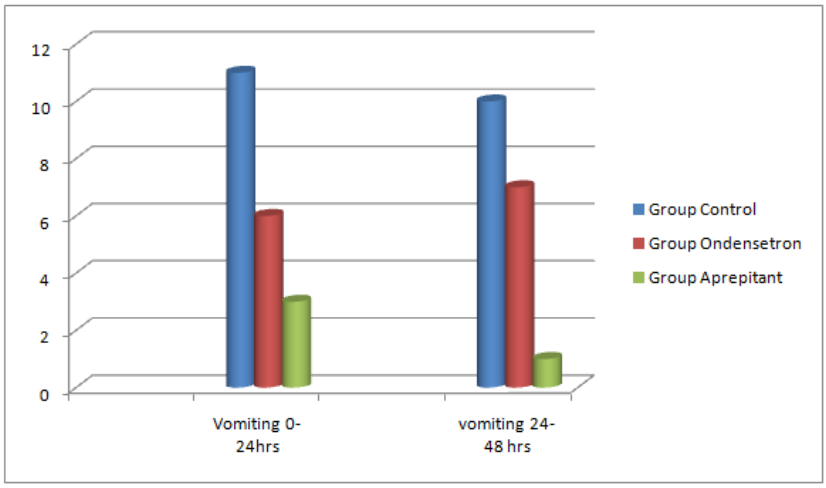

Fig. 3: Incidence/ Episodes of post operative vomiting, Significant p value (<0.05) at 24-48 hrs in vomiting in Group Aprepitant

The complete drug response (no emetic episode) during 0 -24 hrs of observation period was achieved in 20 patients in Group A (66.6%), 19 patients in Group O (63.3%) and 10 patients in Group C (33.3%). On comparing there was no statistically significant difference between Ondansetron and Aprepitant (p - 0.787).The complete response achieved during 24 -48 hrs observation period was comparable in Group O and Group A (p =0.067) (Table 6 & Fig. 4).

Total number of patients receiving the rescue antiemetic therapy was high in Group C 12(40%) as compared with Group O 5(16.66%) and Group A 3(10%) patients. There was no statistically significant difference between Ondansetron and Aprepitant group (p=0.448) (Table 6 & Fig. 5).

Table 6: Drug Response and Rescue antiemetic therapy

Complete response	Group C (n=30)	Group O (n=30)	Group A (n=30)	P Values		
				C vs O	C vs A	O vs A
0-24 hrs	10	19	20	0.02*	0.01*	0.787
24-48 hrs	9	20	26	0.004*	0.001*	0.067
Rescue antiemetic therapy	12	5	3	0.045*	0.007*	0.448

*** Significant P values, P values were calculated using Chi square test. Where, Group C administered with placebo tablets and normal saline; Group O administered with placebo tablet (3 hours) and Ondansetron 4mg intravenously prior to induction; Group C administered with 40 mg Aprepitant orally (3 hours) and 2ml of normal saline prior to induction.**

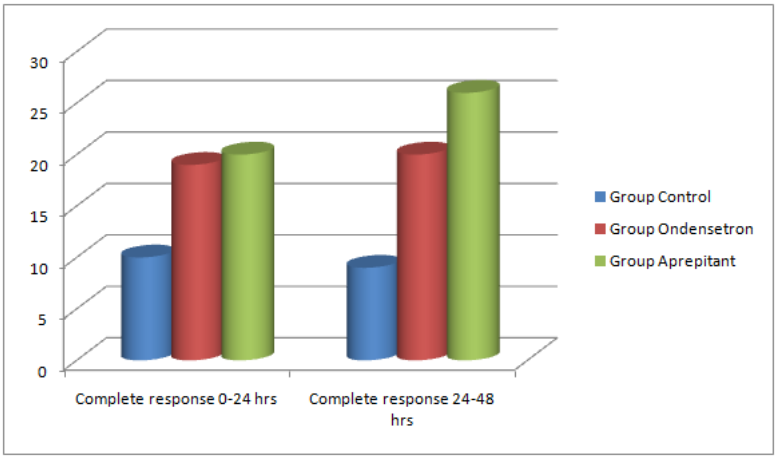

Fig. 4: Complete drug response, no difference in Group Ondansetron and Aprepitant (P > 0.05), but significant (p <0.05) as compared to Control group.

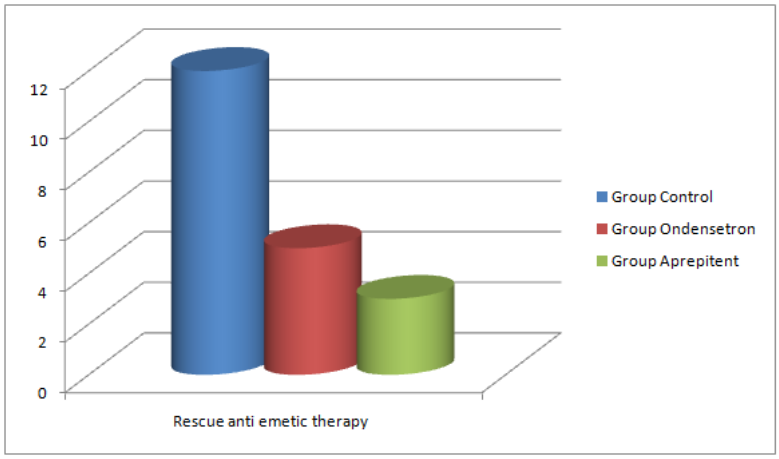

Fig. 5: Rescue anti emetic therapy: Inj. Metocpramide 10 mg IV slow was administed as rescue drug, no difference in Group Ondensetron and Aprepitant (P > 0.05), but significant (p <0.05)as compared to Control group.

Side effects noted were in Control group 1(3%) patient had pyrexia, in Ondansetron group 1(3%) patient had headache and in Aprepitant group 1(3%) patient had constipation (Table 7).

Table 7: Side effects

Side effect	Group C (n=30)	Group O (n=30)	Group A (n=30)
Headache	-	1	-
Constipation	-	-	1
Pruritis	-	-	-
Excessive sedation	-	-	-
Hypersensitivity reaction	-	-	-
Pyrexia	1	-	-
Dizziness	-	-	-

No statistically difference between the groups (p > 0.05).

DISCUSSION

PONV is still a common complication of anesthesia and number one cause of unanticipated admission after surgery [14, 15]. Serotonin receptor antagonist have been widely used for prevention and treatment of PONV and CINV (Chemotherapy induced nausea and vomiting) because there is low risk of side effects as compared with other antiemetics [14]. The total incidence of postoperative nausea and vomiting within 24 hrs after laparoscopic cholecystectomy was 31% in Ondansetron group and 56% in Metoclopramide group [16]. Studies comparing Ondansetron and Granisetron, used singly or in combination with Dexamethasone have yielded mixed results with respect to efficacy as well as cost effectiveness [17-19]. Aprepitant has recently been studied in the role of prevention of PONV. Aprepitant is a selective antagonist of neurokinin-I (NK-I) receptors, blocking the emetic effects of substance P in the gastrointestinal tract and brains nucleus tractus solitaries [20]. Aprepitant has long half life and has demonstrated efficacy against nausea and vomiting according to studies focused on chemotherapy CINV in combination with other antiemetic drugs [21]. On literature review and extensive Medline search we did not come across any study in patients undergoing laparoscopic cholecystectomy where efficacy of Neurokinin -1 receptor antagonist, Aprepitant and 5-HT3 receptor antagonist, Ondansetron have been compared. We therefore designed a prospective double blinded randomized placebo controlled trial to detect the difference in antiemetic efficacy of these two drugs. Laparoscopic cholecystotomy is commonly performed surgery in our institute and incidence of postoperative nausea & vomiting is high in laparoscopic cholecystectomy [16]. The etiology of PONV is multifactorial and depends upon a variety of factors including patients demographic characteristics, type of surgery, anesthesia technique, duration of anesthesia and post operative care [22]. All the patients in the study were considered at risk of PONV with risk factors including laparoscopic cholecystectomy (70%) more female patients (there is two times greater risk of gallstones in women than in men) [23], non smokers and intraoperative use of opioids and N_2O and volatile anesthetics.

Severity of nausea at 24hrs observation period in our study was comparable in Ondansetron group (median=34.23) vs Aprepitant group (median=38.5) p=0.192, it also remained comparable at 48 hrs Ondansetron group (median=34.2) vs Aprepitant group (median=26.8) p=0.052. Similar observations were made by Habib *et al.* [24], Vallgio MC *et al.* [25] and

Gan TJ *et al*. [26] (p nausea>0.05). Episodes of vomiting at 24 hrs, Ondansetron group (20%) and Aprepitant group (16.6%) p=0.267 were compariable. There was significant reduction in incidence and episodes of vomiting in 48hrs observation period in Aprepitant group (3.3%) as compared to Ondansetron group (23.3%)(P=0.023). Habib *et al*. [24] conclusion is similar to our study cumulative incidence of vomiting at 48hrs was 16% in Aprepitant group and 38% in Ondansetron group (P = 0.0149). Gan TJ *et al*. [26] concluded Aprepitant was superior to Ondansetron for prevention of vomiting in the first 24hrs and 48hrs. In our study, the complete drugs response (no nausea, vomiting or need for rescue therapy) was similiar in both Ondansetron and Aprepitant group in 0-24hrs (P=0.787) & 24hrs-48hrs (P=0.067). The rescue antiemetic therapy recieved was similiar between Ondansetron (16.66%) and Aprepitant (10%) group (p=0.448). Habib *et al*. [24] and Gan TJ *et al*. [26] also found similar results of complete drug response and rescue antiemetic therapy in Aprepitant and Ondansetron groups (p>0.05). Metanalysis conducted by Wilhelm SM *et al*. [27] showed complete response was achieved in 37.9% of the Aprepitant slight better compared with 31.2% of the Ondansetron. There was no statistically significant difference seen between groups as for side effects are concerned (p>0.05) which is comparable with above studies. Other major studies include Diemunsch *et al*. [28], they found that in patients with established PONV, Aprepitant significant controlled nausea & Vomiting compared with placebo (p<0.05) for up to 24hrs after major gynecological surgery. Aprepitant is superior in preventing delayed vomiting up to 48hrs. Neurorkinin-1 receptor antagonist effectively lowered PONV, increased pain tolerance and expedited recovery in patients undergoing laparoscopic gynecological surgery [29]. In a report of combined data from two large trials, oral Aprepitant 40mg was superior to intravenous Ondansetron 4mg for prevention of PONV [30].

LIMITATIONS

We did not include all patients at high risk of postoperative nausea &vomiting .We did not follow patients once discharged from the hospital. Post discharge nausea and vomiting (PDNV) was not studied.

Further research is needed to study the efficacy, safety profile and optimum dosage in different age groups in Indian population.

CONCLUSION

We observed that prophylactic Ondansteron 4 mg IV and Aprepitant 40 mg oral are equally effective in early PONV, however Aprepitant because of its long acting effect and delayed vomiting effect than Ondansetron can be considered to prevent delayed vomiting.

REFERENCES

1. Gold BS, Kitz DS,Lecky JH, Neuhaus JM; Unanticipated admission to the hospital following ambulatory surgery. JAMA, 1989; 262(21): 3008-3010.
2. Ryu JH, Jeon YT, Hwang JW, Oh AY, Moon JY, Ro YJ *et al*.; Intravenous , oral ,and the combination of intravenous and oral Ramosetron for the prevention of nausea and vomiting after laparoscopic cholecystectomy :a randomized, double blind ,controlled trial. Clin Ther., 2011; 33(9):1162 -1172.
3. White PF, Shafer A; Nausea and vomiting: Causes and prophylaxis. Semin Anesth, 1988; 6: 300-308.
4. Hafferman AM, Rowbotham DJ; Postoperative nausea and vomiting -time for balanced antiemesis? Br J Anaesth., 2000; 85: 678-688.
5. Apfel CC, Korttila K, Abdalla M, Kerger H, Turan A, Vedder I *et al*.; IMPACT Investigators. A factorial trial of six interventions for the prevention of postoperative nausea and vomiting. N Engl J Med., 2004; 350(24): 2441-2451
6. Gonsalves S, Watson J, Ashton C; Broad spectrum antiemetic effects of CP -122,721, A tachykinin NK1 receptor antagonist, in ferrets. Eur J Pharmacol., 1996; 305(1-3): 181-185.
7. Tattersall FD, Rycroft W, Francis B, Pearce D, Merchant K, MacLeod AM *et al*.; Tachykinin NK_1 receptor antagnonists act centrally to inhibit emesis induced by the chemotherapeutic agent cisplatin in ferrets. Neuropharamacology, 1996; 35(8):1121-1129.
8. Tattersal FD, Rycort W, Hill RG, Hargreaves RJ; Enantioselective inhibition of Apomorphine – induced emesis in the ferret by the neurokinin$_1$ receptor antagonist CP -99994. Neuropharmacology, 1994; 33(2): 259-260.
9. Tattersall FD, Rycroft W, Cumberbatch M, Mason G, Tye S, Williamson DJ *et al*.; The novel N K1 receptor antagonist M K –0869 (L -754,030) and its water soluble phosphoryl prodrug, L – 758,298, inhibit acute and delayed cisplatin - induced emesis in ferrets. Neuropharmacology, 2000; 39(4); 652-663.
10. Leslie RA; Neuroactive substances in the dorsal vagal complex of the medulla oblongata: nucleus of the tractus solitarius, area postrema, and dorsal motor nucleus of the vagus. Neurochem Int., 1985; 7: 191–211.
11. Hesketh PJ, Van Belle S, Aapro M, Tattersall FD, Naylor RJ, Hargreaves R *et al*.; Diffferential involvement of neurotransmitters through the time course of Cisplatin – induced emesis as revealed by therapy with specific receptor antagonists. Eur J Cancer, 2003; 39(8): 1074-1080.
12. Aprepitant; Available from; http://www.drugs.com/ppa/aprepitant.html
13. Sung YF, Weinstein MS, Ghani GA; Balanced anaesthesia: A comparison of Butorphenol and Morphine. South med J., 1984; 77(2):180-182.

14. Gan TJ, Meyer T, Apfel CC, Chung F, Davis PJ, Eubanks S *et al*.; Consesus guidelines for managing postoperative nausea and vomiting. Anesth Analg., 2003, 97(1): 62 -71.
15. Fortier J, Chung F, Su J; Unanticipated admission after ambulatory surgery: a prospective study. Canadian J Anaesth., 1998; 45(7): 612-619.
16. Wu SJ, Xiong XZ, Cheng TY, Lin YX, Cheng NS; Efficacy of Ondensetron vs Metoclopramide in prophylaxis of postoperative nausea and vomiting after laproscopic cholecystectomy: A Systematic Review and Meta-analysis Hepatogastroenterology, 2012; 59(119): 2064-2074.
17. Granisetron TM; New insights into its use for the treatment of chemotherapy induced nausea and vomiting. Expert Opin Pharmacotherapy. 2003; 4(9):1563-1571.
18. Fujii Y, Tanaka H, Kawasaki T; Effects of Granisetron in the treatment of nausea and vomiting after laparoscopic cholecystectomy: a dose ranging study. Clin Ther., 2004; 26(7):1055-60: 1055-1060.
19. Dua N, Bhatanagar S, Mishra S, Singhal AK; Granisetron and Ondansetron for the prevention of nausea and vomiting in patients undergoing modified radical mastectomy. Anaesth Intensive Care, 2004; 32(6): 761-764.
20. Green MS, Green P, Malayaman SN, Hepler M, Neubert LJ, Horrow JC; A Randomized, Double – blind comparison of oral Aprepitant alone vs oral Aprepitant and transdermal Scopolamine for preventing postoperative nausea and vomiting. Br J Anaesth., 2012;109(5): 716-722.
21. Longo F, Mansueto G, Lapadula V, De Sanctis R, Quadrini S, Grande R *et al*.; Palonosetron plus 3-day Aprepitant and Dexamethasone to prevent nausea and vomiting in patients receiving highly emetogenic chemotherapy. Support Care Cancer, 2011; 19(8): 1159–1164.
22. Fujii Y, Tanaka H, Somekawa Y; Granisetron, Droperidol and Metoclopramide for the treatment of established postoperative nausea and vomiting in women undergoing gynecologic surgery. Am J Obstet Gynecol., 2000; 182(1 Pt 1): 13-16.
23. Shiffer SW, Buttaro TM; Cholelithiasis and cholecystitis. In Primary Care: A Collaborative Practice. Buttaro TM, Trybulski J, Bailey PP, Cook JS ediorss; St. Louis: Mosby, 1999: 486.
24. Habib AS, Keifer JC, Borel CO, White WD, Gan TJ; A comparison of the combination of Aprepitant and Dexamethasone versus the combination of Ondansetron and Dexamethasone for the prevention of postoperative nausea and vomiting in patients undergoing craniotomy. Anaesth Analg., 2011; 112(4): 813-818.
25. Vallejo MC, Phelps AL, Ibinson JW, Barnes LR, Milord PJ, Romeo RC *et al*.; Aprepitant plus Ondansetron compared with Ondansetron alone in reducing postoperative nausea and vomiting in ambulatory patients undergoing plastic surgery. Plast Reconstr Surg., 2012; 129(2): 519-526.
26. Gan TJ, Apfel CC, KovacA, PhilipBK, Singla N, Minkowitz H *et al*.; Aprepitant-PONV Study Group. A randomized, double blind comparison of the NK1 antagonist, Aprepitant versus Ondansetron for the prevention of postoperative nausea and vomiting. Anesthesia and Analgesia, 2007; 104(5): 1082-1089.
27. Wilhelm SM, Dehoorne-Smith ML, Kale-Pradhan PB; Prevention of postoperative nausea and vomiting. The annals of Pharmacotherapy, 2007; 41(1): 68-78.
28. Diemunsch P1, Schoeffler P, Bryssine B, Cheli-Muller LE, Lees J, McQuade BA *et al*.; Antiemetic activity of the NK1 receptor antagonist GR205171 in the treatment of established postoperative nausea and vomiting after major gynaecological surgery. Br J Anaesth., 1999; 82: 274-276.
29. Kakuta N, Tsutsumi YM, Horikawa YT, Kawano H, Kinoshita M, Tanaka K *et al*.; Neurokinin – 1 receptor antagonism ,Aprepitant, effectively diminishes postoperative nausea and vomiting while increasing analgesic tolerance in laparoscopic gynecological procedures. J Med Invest., 2011; 58(3-4): 246-251.
30. Diemuncsh PA, Apfel C, Phillip B, Gan TJ, Reiss TR; NK1 antagonist Aprepitant vs Ondansetron for prevention of PONV: combined data from 2 large trials (abstract A125). Presented at: American Society of Anesthesiologists 2006, Annual Meeting, Chicago, IL, October 14-18, 2006.