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The Effectiveness of Widely Used Antiemetics and Their Combination in Prevention of PONV in Patient Undergoing Laparoscopic Surgeries

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ABSTRACT

Postoperative Nausea and Vomiting (PONV) are common after general anesthesia. It is a significant cause of morbidity, especially in patients undergoing Laparoscopic cholecystectomy surgery. The most common and distressing symptoms, which follow anesthesia and surgery, are pain and emesis. The syndrome of nausea, retching, and vomiting is known as "sickness" and each part of it can be distinguished as a separate entity. The present research work is carried to compare the efficacy and Patient Acceptance of widely used antiemetic in the prophylaxis of PONV in a patient undergoing laparoscopic surgeries under general anesthesia. This study was carried out after an institutional ethics committee approval and after filling informed consent form by all the patients of ASA I and II (American Society Anesthesiologists) of either sex, aged between 20-60 years randomized selected into the three groups. Group A (n=25), Metoclopramide 10 mg as a single dose was given by slow I .v in. with dilution over 5-10 min, before induction. Group B (n=25), Ondansetron 4 mg as a single dose was given by slow I .v in. with dilution over 5-10 min, before induction. Group-C (n=25) in. Granisetron 3 mg as a single dose was given by slow I .v in. with dilution over 5-10 min, before induction, This study was performed to compare the effectiveness and patient Satisfaction of Granisetron, Ondansetron, and Metoclopramide in the management of PONV. The results of our study revealed that in the management of PONV, Granisetron was more effective than Ondansetron which showed better results than Metoclopramide.

INTRODUCTION

Nausea is defined as the subjectively unpleasant sensation associated with awareness of the urge to vomit. Retching is defined as the labored, spastic, rhythmic contraction of the respiratory muscles without expulsion of the gastric contents and vomiting is defined as the forceful expulsion of gastric contents from the mouth[1]. PONV (Post operative-nausea and vomiting) has been characterized as big “little problem"[2] and has been a common complication for both inpatients and outpatients undergoing virtually all types of surgical procedures[3].

The consequences of PONV are physical, surgical and anesthetic complications for patients as well as financial implications for the hospitals or institutions[4]. Physical consequences include sweating, pallor, tachycardia, stomach, ache, increased chances of esophageal tear, wound dehiscence and electrolyte imbalance. Surgical consequences include disruption of vascular anastomoses and increased intracranial pressure[5]. The anesthetic consequences are aspiration pneumonitis and discomfort in recovery[3]. Sometimes nausea and vomiting may be more distressing especially after minor and ambulatory surgery, delaying the hospital discharge[6]. Several factors are influencing the occurrence of PONV which includes patient factors (age, gender, obesity, anxiety, history of motion sickness or previous PONV and gastroparesis), operative procedures, anesthetic techniques (drugs for general anesthesia, regional anesthesia and monitored anesthesia care) and postoperative factors (pain, dizziness, ambulation, oral intake, and opioids). Laparoscopic surgery is one condition, where the risk of PONV is particularly pronounced. This increased risk of PONV is due to the pneumoperitoneum causing stimulation of mechanoreceptors in the gut[7].

Antemetic drugs available now days include anticholinergic drugs (scopolamine, atropine), dopamine antagonist drugs (Promethazine, prochlorperazine, and metoclopramide), antihistaminic drugs (diphenhydramine, hydroxyzine) $5HT_3$ receptor antagonists (Ondansetron, Granisetron, and Dolasetron) and steroids (dexamethasone). These newly developed 5-HT_3 receptor antagonists have been criticized because of their high cost[8,9]. Thus comparison of the cost-effectiveness of the three drugs (metoclopramide, ondansetron, and Granisetron) was done in the present study.

Metoclopramide

It is a substituted benzamide dopamine antagonist used for nausea and vomiting, gastritis, gastro-oesophageal reflux and diagnostic procedures in gastroenterology. It acts through both dopaminergic & serotonergic receptors. Dopamine (acting through D_2 receptors) is an inhibitory transmitter in the g.i.t (gastrointestinal tract) and normally acts to delay gastric emptying when food is present in the stomach. It also appears to cause gastric dilation & LES (lower esophageal sphincter) relaxation attending causing nausea and vomiting. The D_2 blockade has an opposite effect- hastening gastric emptying and enhancing LES (lower esophageal sphincter) tone by augmenting Acetylcholine release. By 5-HT_4 agonist action, metoclopramide acts in g.i.t to enhance Ach release from the myenteric motor neuron. This results from 5-HT_4 receptor activation on primary afferent neuron (PAN) of the ENS (enteric nervous system) via excitatory interneurons. The gastric hurrying and LES tonic effects are mainly due to this action. At higher concentrations, metoclopramide blocks 5-HT_3 receptors present on inhibitory myenteric interneurons and in NTS (Nucleus tractus solitarius)/CTZ (Chemoreceptor trigger zone). The peripheral action can augment Ach release in the gut but appears to be minor. The central anti-5-HT_3 action appears to be significant only when large doses are used to control chemotherapy-induced vomiting It is rapidly absorbed from the GIT, enters the brain, crosses the placenta and is secreted in milk. It is partly conjugated in the liver and excreted in urine within 24 hours with $t_{1/2}$ 3-6 hours. It has a more prominent effect on upper g.i.t & increases gastric peristalsis while relaxing the pylorus and the first part of duodenum - speeds gastric emptying, especially if it was slow. This action is independent of vagal innervation but is more prominent when the vagus is intact. Lower esophageal sphincter (LES) tone is increased and gastroesophageal reflux is opposed. It also increases intestinal peristalsis to some extent but has no significant action on colonic motility and gastric secretion. In the CNS (central nervous system) metoclopramide is an effective antiemetic acting on the CTZ. The gastrokinetic action may contribute to the antiemetic effect. Metoclopramide is generally well tolerated. Sedation, dizziness, diarrhea muscle dystonias (especially in children) are the main side effect. Long term use can cause parkinsonism, galactorrhoea, and gynaecomastia[7].

Dose 10 mg (children 0.2-0.5 mg /kg) TDS oral or I.M.

For chemotherapy-induced vomiting 0.3 1.0 mg /kg slow I.V / I.M.

Ondansetron

It is a 5-HT_3 receptor antagonist, used for nausea and vomiting associated with radiation chemotherapy, and PONV. It blocks the depolarizing action of 5-HT through 5-HT_3 receptors on vagal afferents in the g.i.t as well as in NTS/CTZ. Cytotoxic drugs /radiation produce nausea and vomiting by causing cellular damage → release of mediators including 5-HT from intestinal mucosa → activation of vagal afferents in the gut → emetogenic impulses to CNS and CTZ. Ondansetron blocks emetogenic impulses both at their peripheral origin and their central relay. A minor 5-HT_4 antagonistic action has been shown. These agents are absorbed well from the G.I.tract. Ondansetron is extensively metabolized in the liver by CYP1A2, CYP2D6, and CYP3A4, followed by glucuronide or sulfate conjugation, eliminated in urine and feces. $t_{1/2}$ 3-5 hrs and duration of action 4-12 hrs.

Dose For highly emetogenic chemotherapy 8mg by slow I .v. or intramuscular in. immediately before treatment either followed by continuous I .v. infusion of 1mg/hr for up to 24hrs or by a further 2 dose of 8mg 24hrs apart.

For the treatment of PONV a single 4mg dose by intramuscular or slow I .v. the injection is recommended[7].

Granisetron

It is ~ 10 times more potent than ondansetron and the weak 5-HT_4 blockade seen in ondansetron has not been detected in granisetron. It's plasma $t_{1/2}$ is longer (8-12 hr). It is metabolized predominantly by the liver, a process that appears to involve the CYP3A family, which is inhibited by ketoconazole. These drugs are very well tolerated with the most common adverse effect being constipation or diarrhea, headache, and lightheadedness. These agents have been shown experimentally to induce minor ECG (Electrocardiogram) changes but these are not expected to be clinically significant in most cases[9].

Dose Dose equivalent to 3mg of granisetron is diluted in saline up to 10 ml and given intravenously over 5 minutes before the start of the chemotherapy. Alternatively, this dose may be given in 15 ml of infusion solution as a bolus over not less than 30s. The dose may be repeated up to twice in 24 hrs, but should be given at least 10 minutes apart and a total daily dose of 9mg should not be exceeded[7]. The recommended dose for the prophylaxis of PONV is 40 μg/kg slow I .V.

Emesis and Antiemesis

Vomiting occurs due to stimulation of the emetic (vomiting) center situated in the medulla oblongata. The chemoreceptor trigger zone (CTZ) located in the area Postema and the nucleus tractus solitaries (NTS) are the most important relay areas for afferent impulses arising in the g.i.t., throat and viscera. The CTZ is also accessible to blood-borne drugs, mediators, hormones, toxins, etc, because it is unprotected by the blood-brain barrier. Cytotoxic drugs, radiation and other g.i.t irritants release 5-HT from enterochromaffin cells acts on 5-HT_3 receptors present on vagal afferent and sends impulses to NTS and CTZ. Released in large quantities, 5-HT may also spill into circulation and reach CTZ. It may as well be released from platelets by inflammatory mediators. However, 5-HT is not the only mediator of such signals: many peptides and other messengers are also involved. The CTZ and NTS express a variety of receptors e.g. Histamine H_1, dopamine D_2, serotonin, 5-HT_3, cholinergic M and Opioid μ through which the emetic signals are relayed and which could be targets of antiemetic drug action.

The vestibular apparatus generates impulse when the body is rotated or equilibrium is disturbed or when the ototoxic drugs act. These impulses reach the vomiting center mainly relayed from the cerebellum and utilize muscarinic as well as H_1 receptors. Various unpleasant sensory stimuli such as bad odor, ghastly sight, severe pain as well as fear, recall of an obnoxious event, the anticipation of emetic stimulus (repeat dose of Cisplatin) cause nausea and vomiting through higher centers.

Nausea is accompanied by reduced gastric tone and peristalsis. In the emetic response fundus and body of the stomach, esophageal sphincter and esophagus relax, while duodenum and pyloric stomach contract in a retrograde manner. Rhythmic contractions of the diaphragm and abdominal muscles then compress the stomach and evacuate its contents *via* the mouth. Conditions that inhibit gastric emptying predispose to vomiting[7].

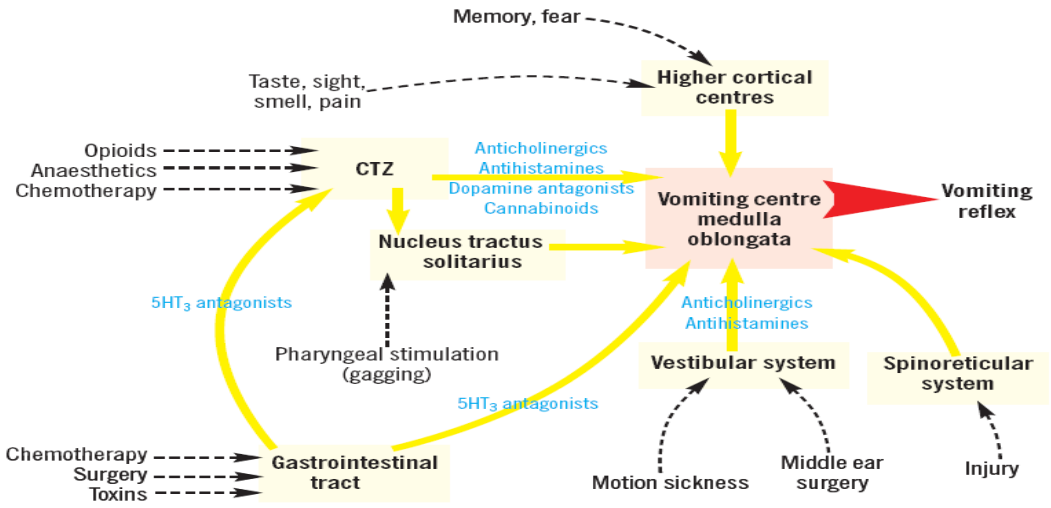


Figure No. 1: Vomiting pathways and drugs commonly used for nausea

The present study was designed to compare the Efficacy, Patient Acceptance of widely used antiemetic in the prophylaxis of PONV in a patient undergoing laparoscopic surgeries under general anesthesia.

MATERIALS AND METHODS

This study was carried out after an institutional ethics committee approval and after filling informed consent form by all the patients of ASA I and II (American Society Anesthesiologists) of either sex, aged between 20-60 years randomized selected into the three groups.

Study site: G.M.C Haldwani.

Duration of study: 3 years

Experimental Protocol

Group A (n=25), Metoclopramide 10 mg as a single dose was given by slow I .v in. with dilution over 5-10 min, before induction.

Group B (n=25), Ondansetron 4 mg as a single dose was given by slow I .v in. with dilution over 5-10 min, before induction.

Group-C (n=25) in. Granisetron 3 mg as a single dose was given by slow I .v in. with dilution over 5-10 min, before induction.

Inclusion Criteria

- Patients posted for laparoscopic cholecystectomy surgery under GA
- Patient in the age group of 20 to 60 years
- Belonging to ASA grade of I & II

Exclusion Criteria

- A patient suffering from severe medical illness, ASA grade III & IV
- Patient with the previous history of a drug reaction to any of the drug used in the present study
- History of PONV
- History of motion sickness
- History of jaundice within last one month or common bile duct (CBD) stones
- The patient who have received anti-emetics in the previous 24 hrs
- Pregnant and lactating women

In whom the operative procedure was complicated.

- Dense adhesions
- Prolonged surgery > 1 hr
- Significant intraoperative bleeding
- Menstruating women

Preoperative assessment was done & routine investigations were noted. On the day of surgery, the patient was examined carefully and vitals were noted throughout the surgery period. Using single-blind randomization techniques patients were assigned to three groups *viz*. Group A (Metoclopramide), Group B (Ondansetron), Group C (Granisetron).

Premedication

Injection Midazolam (0.03 mg/kg) and Pentazocine (0.3 mg/kg) was used as a premedication. The study drugs were administered by slow I.V injection immediately before the induction of anesthesia.

General Anaesthesia

Standard general anesthesia was given using Thiopentone sodium (5-7 mg/kg) and Suxamethonium (1mg/kg) injection. Anesthesia was maintained with N_20: O_2 in the ratio of 60:40 and Halothane 0.6% and muscle relaxation maintained within. Vecuronium 0.04 -0.08 mg/kg. All patients have received the insertion of a nasogastric tube (NG) for gastric decompression before induction & port placement. The NG tubes shall be removed immediately after the reversal of anesthesia in all patients. Patients were reversed by in. Neostigmine 0.04 mg/kg and in Atropine (0.02 mg/kg). Intraoperatively vitals were recorded, fluid replaced as per requirements.

Assessment of PONV

Episodes of nausea and vomiting were recorded in the first 24 hours postoperatively at the intervals of 0-1, 1-2, 2-4, 4-6, 6-12, 12-24 hr. PONV was evaluated by using a numeric scoring system 0: no nausea or vomiting, 1: nausea alone 2: vomiting once 3: vomiting two or more times in 30 minutes[10]. A PONV score of 3 or persistent nausea (>2 hours) is defined as severe PONV[10] and treated with 10mg I .v. Metoclopramide as a rescue anti-emetic. Retching was not considered a separate entity and patient reporting retching was classified as nauseous.

Assessment of Patient Satisfaction

Patient satisfaction with the study medication was assessed using a five-point scale, 24 hours after the end of drug administration as 1: Very satisfied, 2: Quite satisfied, 3: Neither satisfied nor unsatisfied, 4: Rather unsatisfied and 5:Very unsatisfied[11].

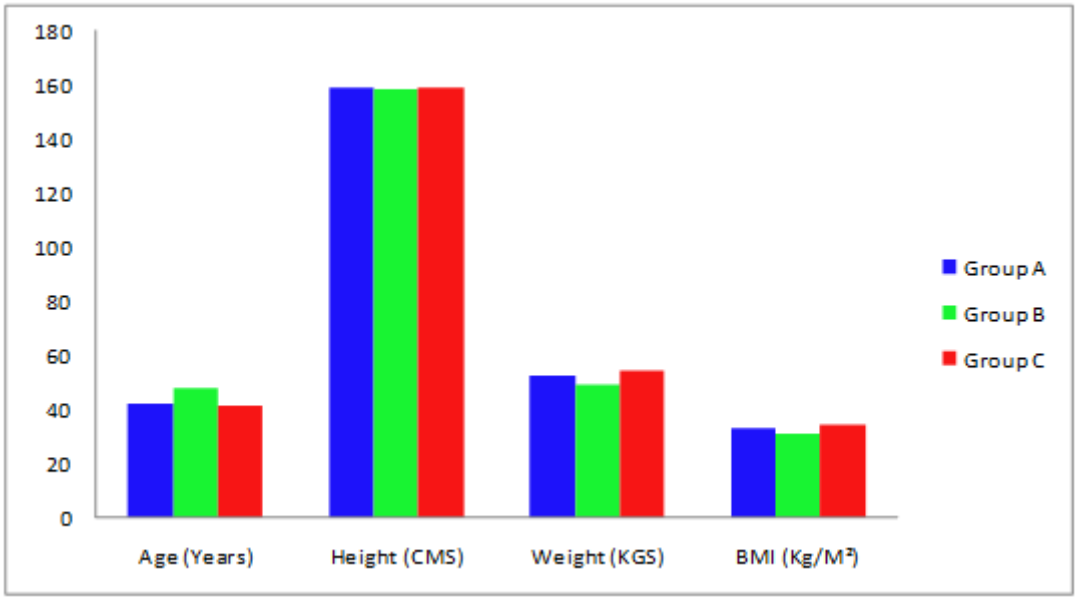
Statistical Analysis

All the observations were compiled and statistically analyzed using one way-ANOVA, chi-square test (SPSS 16.0, *Significant when $P \leq 0.05$, **Highly Significant when $P \leq 0.001$).

RESULTS

Table No. 1: Demographic Data in three groups

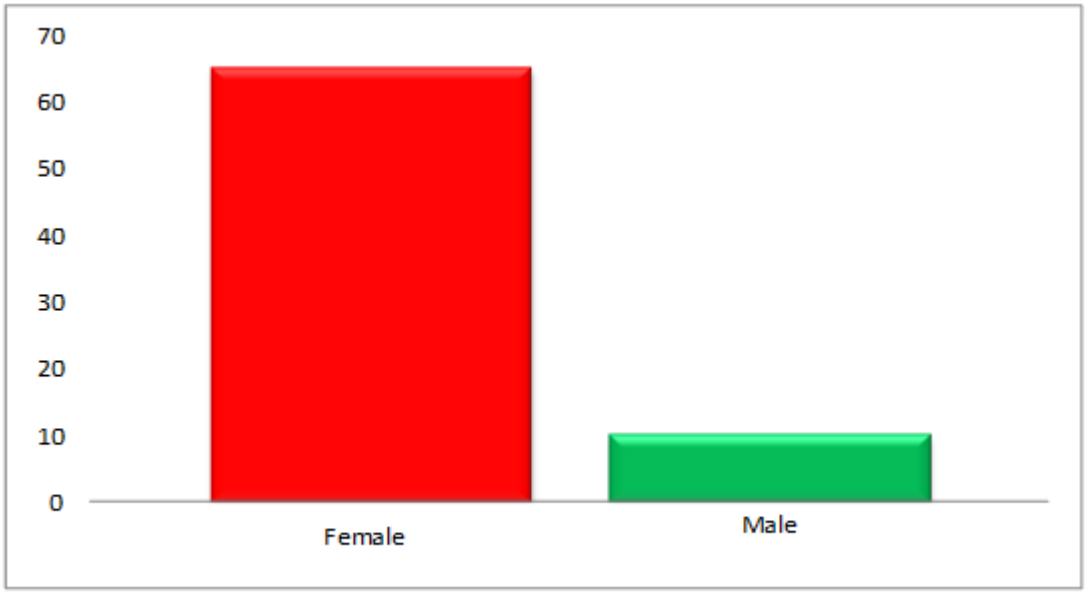
	Group A (n=25)	**Group B** (n=25)	**Group C** (n=25)
Age (yrs)	42.48±	48±	41.44±
Mean ± SD	11.09	14.77	11.66
Height (cms)	159.16±	158.80±	159.36±
Mean ± SD	4.68	4.16	3.80
Weight (kg)	52.36±	49.08±	54.72±
Mean ± SD	9.74	5.85	10.11
BMI (kg^{-2})	32.93±	30.92±	34.38±
Mean ± SD	6.23	3.75	6.56



Graph No. 1: Demographic Data in three groups

Table No. 2: Gender-wise Distribution of Patients

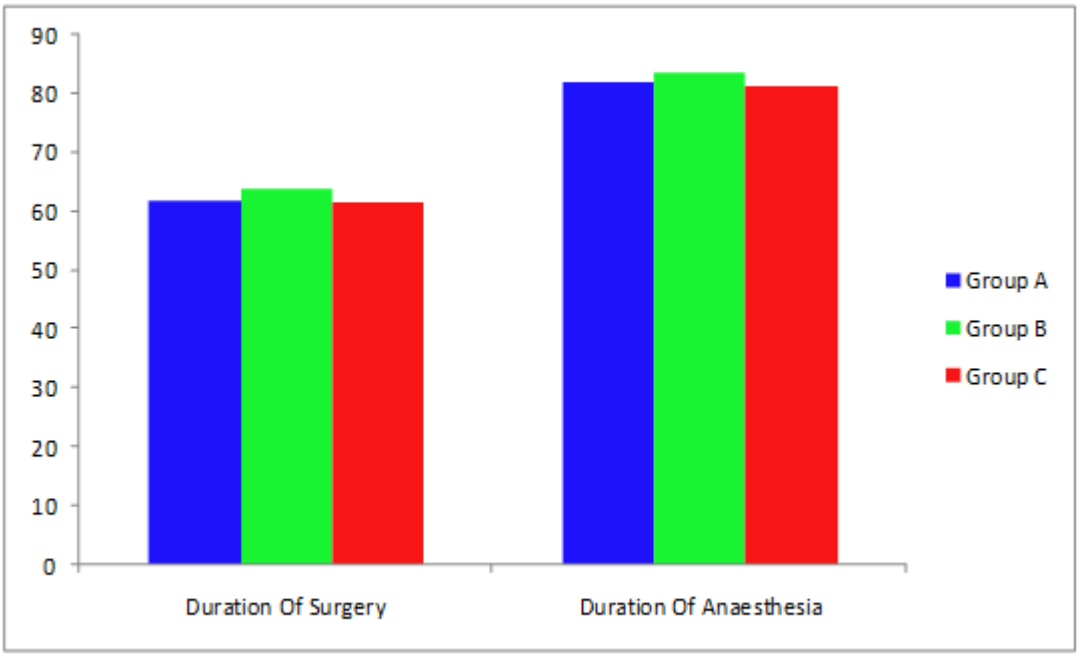
Female	**65**
Male	**10**
Total	**75**



Graph No. 2: Gender-wise Distribution of Patients

Table No. 3: Mean duration of Surgery and Anaesthesia (mins)

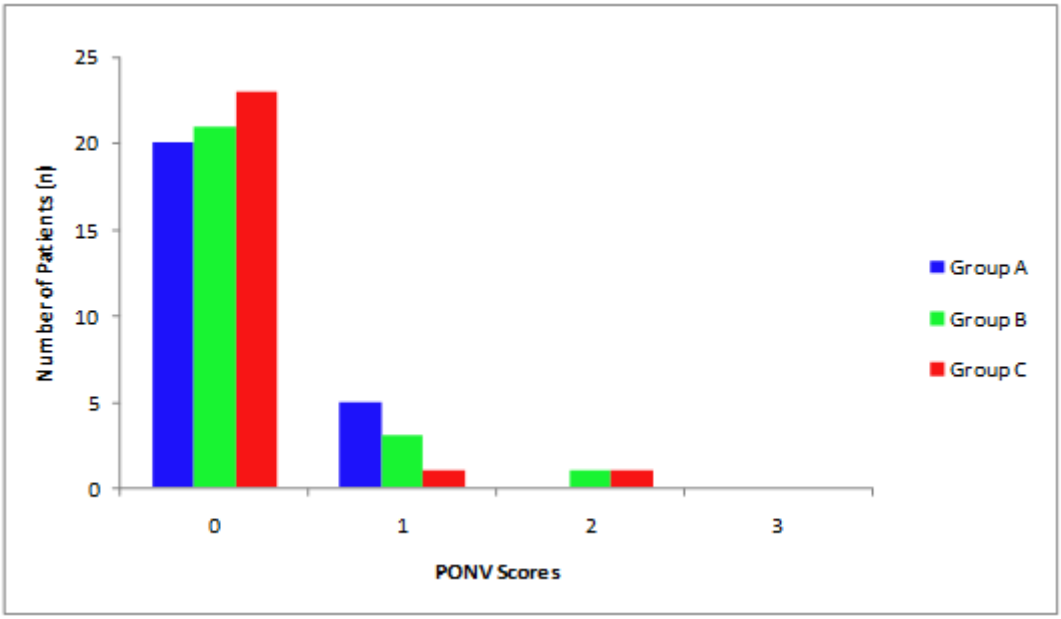
	Group A (n=25)	Group B (n=25)	Group C (n=25)
Duration of Surgery (mins) Mean ± SD	62± 11.99	63.80± 9.38	61.40± 10.85
Duration of Anesthesia (mins) Mean ± SD	82± 11.99	83.80± 9.38	81.40± 10.85



Graph No. 3: Mean duration of Surgery and Anaesthesia

Table No. 4: Postoperative Nausea and Vomiting in three groups in 0-1 hrs time interval

	PONV Score	Group A (n=25)	Group B (n=25)	Group C (n=25)	P-Value (Chi-Square test)
0-1 hrs	0	20	21	23	0.422
	1	5	3	1	
	2	0	1	1	
	3	0	0	0	



Graph No. 4: Postoperative Nausea & Vomiting in three groups in the 0-1hrs time interval

0: NO NAUSEA OR VOMITING

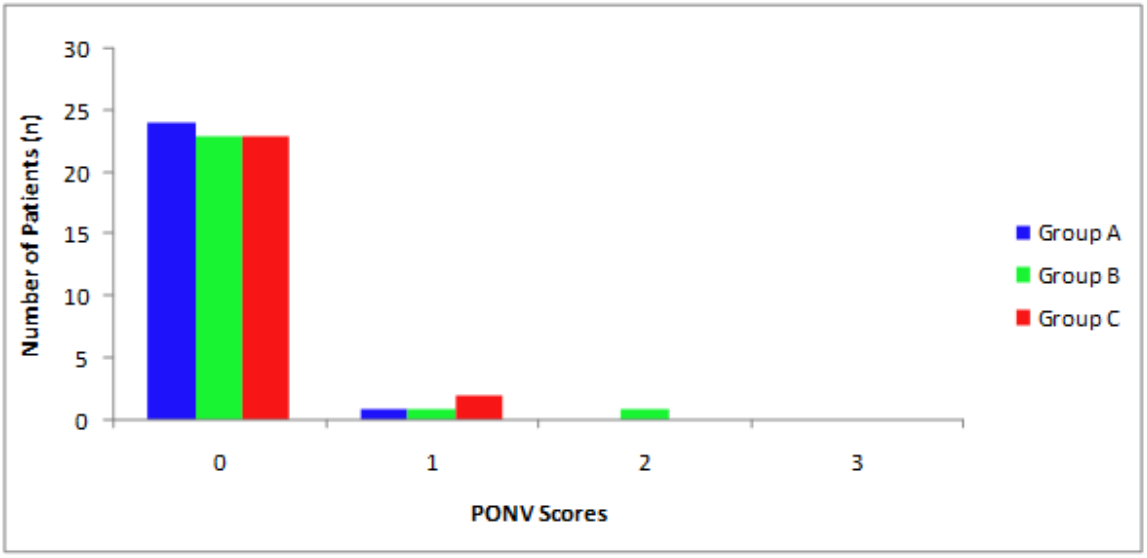
1: NAUSEA ALONE.

2: VOMITING ONCE.

3: VOMITING TWO OR MORE.

Table No. 5: Postoperative Nausea and Vomiting in three groups in 1-2 hrs time interval

	PONV Score	Group A (n=25)	Group B (n=25)	Group C (n=25)	P-Value (Chi-Square test)
1-2hrs	0	24	23	23	0.640
	1	1	1	2	
	2	0	1	0	
	3	0	0	0	

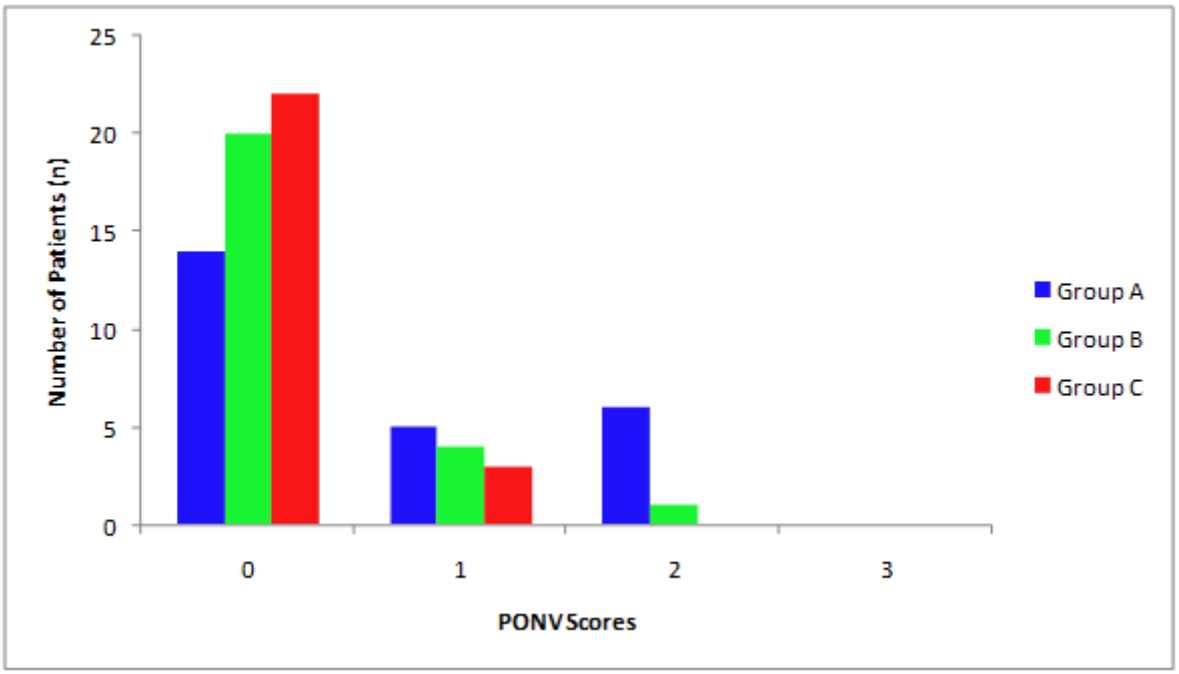


Graph No. 5: Postoperative Nausea & Vomiting in three groups in 1-2 hrs time interval

Table No. 6: Post-operative Nausea and Vomiting in three groups in 2-4 hrs time interval

	PONV Score	Group A (n=25)	Group B (n=25)	Group C (n=25)	P-Value (Chi-Square test)
2-4 hrs	0	14	20	22	0.024*
	1	5	4	3	
	2	6	1	0	
	3	0	0	0	

*****Significant (P≤0.05)

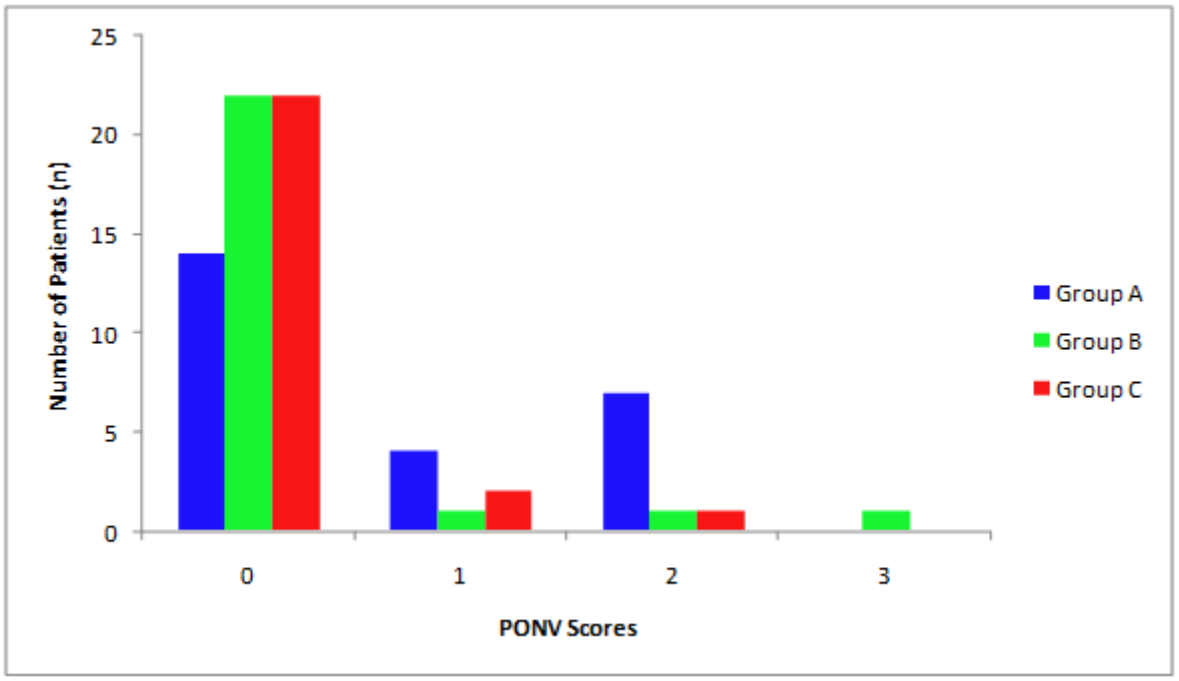


Graph No. 6: Postoperative Nausea & Vomiting in three groups in the 2-4hrs time interval

Table No. 7: Postoperative Nausea and Vomiting in three groups in 4-6 hrs time interval

	PONV Score	Group A (n=25)	Group B (n=25)	Group C (n=25)	P-Value (Chi-Square test)
4-6 hrs	0	14	22	22	0.027*
	1	4	1	2	
	2	7	1	1	
	3	0	1	0	

*Significant (P≤0.05)

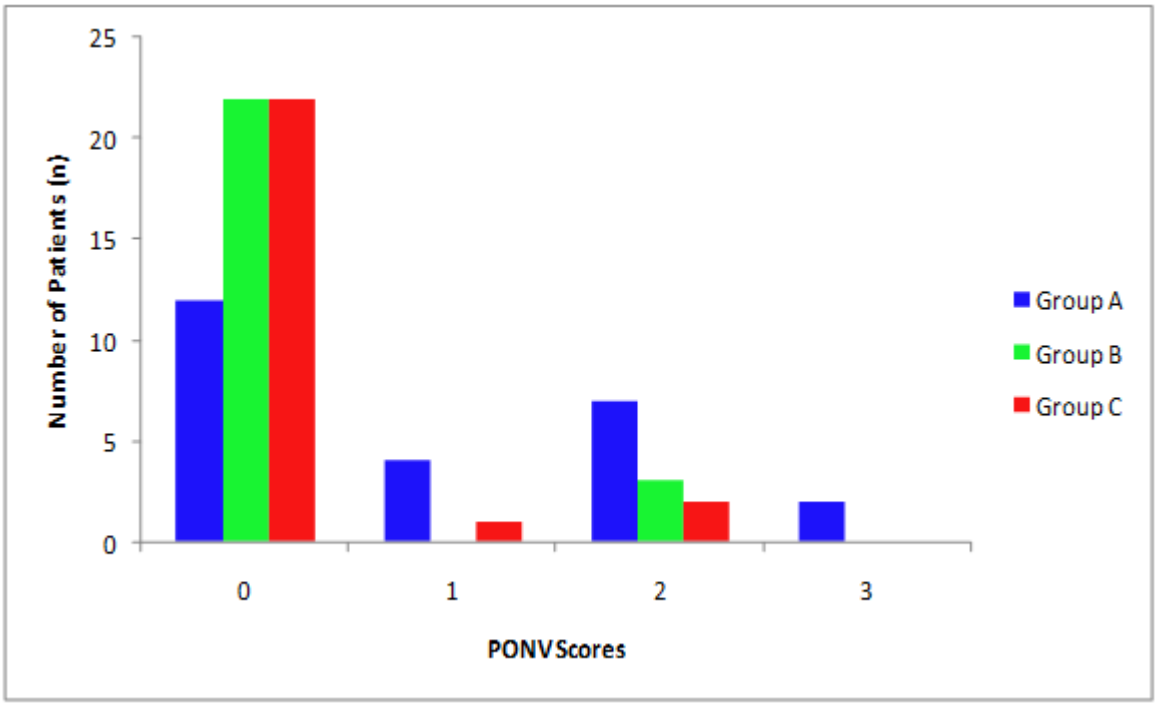


Graph No. 7: Postoperative Nausea & Vomiting in three groups in 4-6 hrs time interval

Table No. 8: Postoperative Nausea and Vomiting in three groups in 6-12 hrs time interval

	PONV Score	Group A (n=25)	Group B (n=25)	Group C (n=25)	P-Value (Chi-Square test)
6-12 hrs	0	12	22	22	0.012*
	1	4	0	1	
	2	7	3	2	
	3	2	0	0	

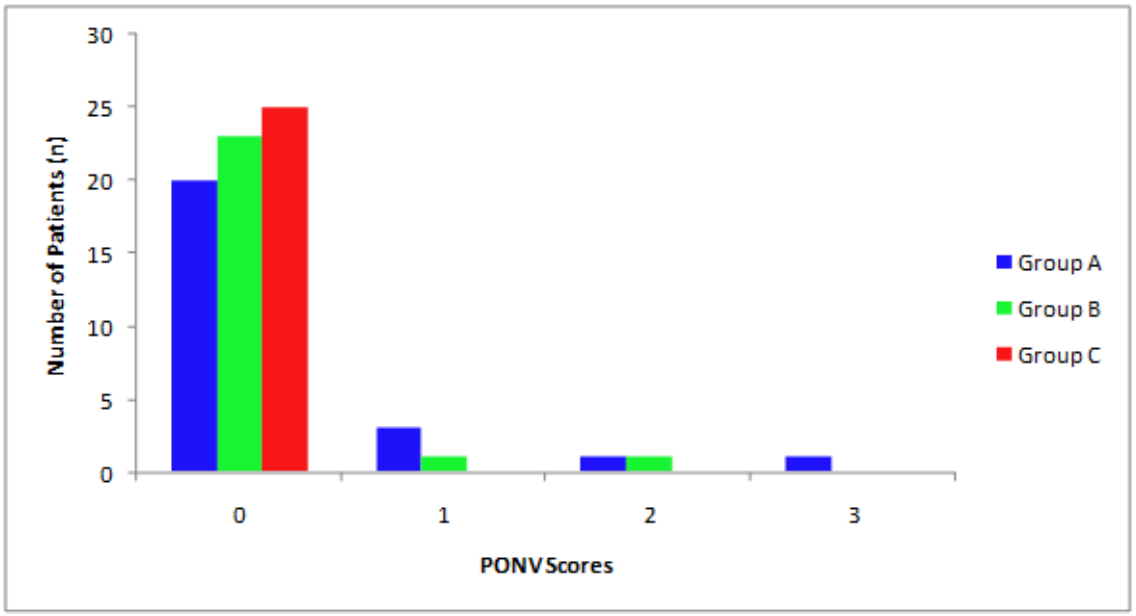
*****Significant (P≤0.05)



Graph No. 8: Postoperative Nausea & Vomiting in three groups in 6-12 hrs time interval

Table No. 9: Postoperative Nausea and Vomiting in three groups in 12-24 hrs time interval

	PONV Score	Group A (n=25)	Group B (n=25)	Group C (n=25)	P-Value (Chi-Square test)
12-24 hrs	0	20	23	25	0.315
	1	3	1	0	
	2	1	1	0	
	3	1	0	0	

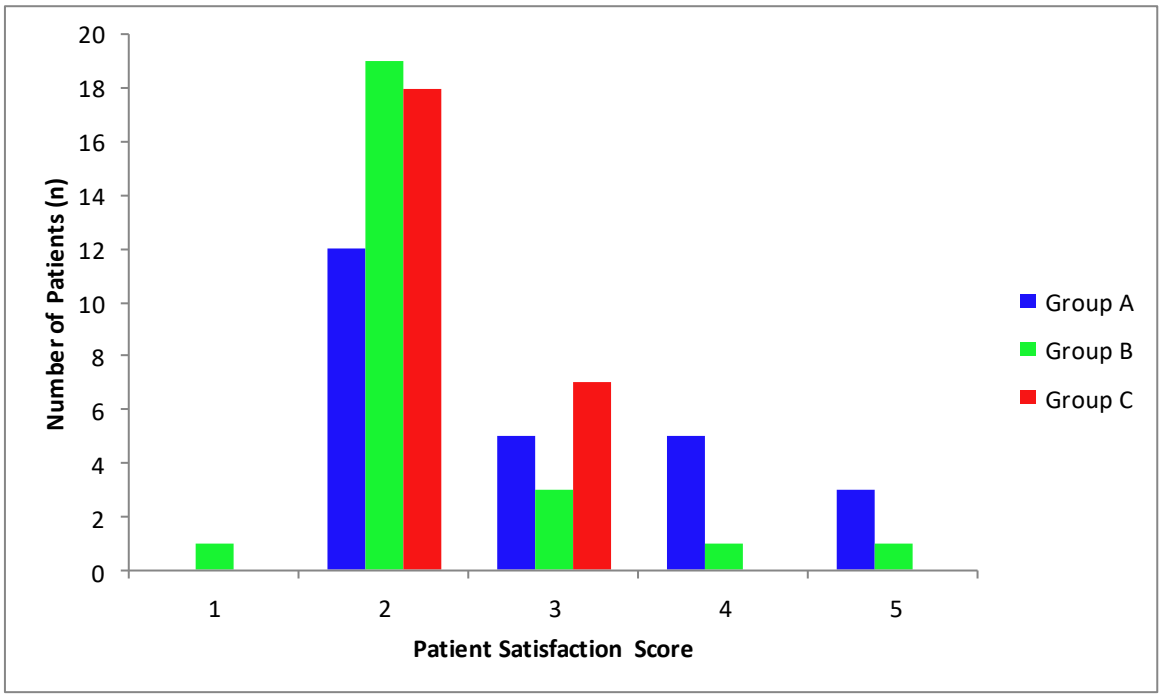


Graph No. 9: Postoperative Nausea & Vomiting in three groups in 12-24 hrs time interval

*Significant (P≤0.05)

Table No. 10: Patient Satisfaction Score (12hrs)

Patient Satisfaction Score	Group A (n=25)	Group B (n=25)	Group C (n=25)	P-value (Chi-Square test)
1	0	1	0	
2	12	19	18	
3	5	3	7	0.045*
4	5	1	0	
5	3	1	0	



Graph No. 10: Patient Satisfaction Score in three groups in 12 hrs

1: VERY SATISFIED.

2: QUITE SATISFIED.

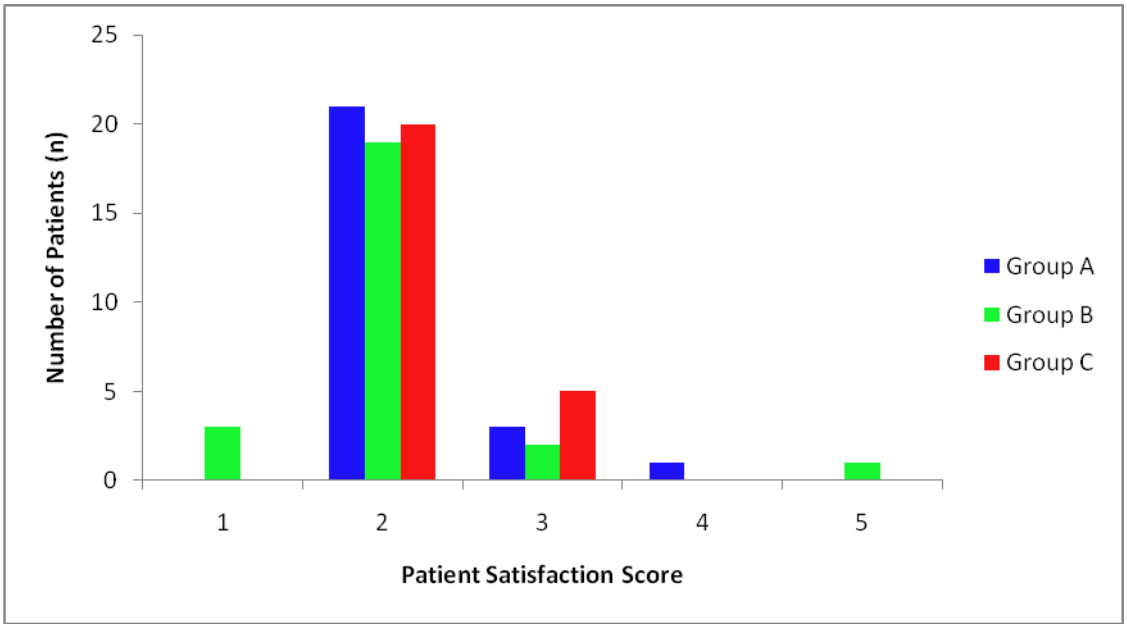
3: NEITHER SATISFIED NOR UNSATISFIED.

4: RATHER UNSATISFIED.

5: VERY -UNSATISFIED

Table No. 11: Patient Satisfaction Score (24 hrs)

Patient Satisfactions Score	Group A (n=25)	Group B (n=25)	Group C (n=25)	P-value (Chi-Square test)
1	0	3	0	
2	21	19	20	
3	3	2	5	0.175
4	1	0	0	
5	0	1	0	



Graph No. 11: Patient Satisfaction Score in three groups at 24 hrs

1: VERY SATISFIED.

2: QUITE SATISFIED.

3: NEITHER SATISFIED NOR UNSATISFIED.

4: RATHER UNSATISFIED.

5: VERY -UNSATISFIED

A total of 80 laparoscopic surgeries patients within the age range of 20-60 year was enrolled in this study. Five patients were excluded from the study because they did not follow the inclusion criteria. Before enrollment in this study patients were informed verbally about this study and written consent form was signed by each subject. The patients were randomly divided into three groups.

Group A patients received Metoclopramide 10 mg as a single dose while group B patients & group C patients received Ondansetron 4 mg and Granisetron 3 mg as a single dose respectively.

Among 75 patients, 65 were female and 10 were male (Table:2). The data showed that laparoscopic cholecystectomy surgery was more common in females. Patients in all three

groups were statistically comparable about age, body means index (BMI), duration of surgery and duration of anesthesia. (Table:1,3, P≤0.05).

Comparative Efficacy

In all three groups, at 0-2 hrs duration, the PONV difference was not significant (Table: 4, 5). The difference was statistically significant in all three groups between 2-12 hrs (Table: 6, 7, 8) but not beyond that (Table: 9). The order of performance was as follows group C > group B > group A.

Patient Acceptance / Satisfaction

Patients were asked to indicate their satisfaction score from 1 to 5 for the medicine/therapy at 12 and 24 hrs (1: Very satisfied, 2: Quite satisfied, 3: Neither satisfied nor unsatisfied, 4: Rather unsatisfied and 5: Very unsatisfied). The statistical comparison showed a significant difference among the three groups at 12 hrs (Table:10).

The performance of group C was better than groups B & A and order of performance was group C then group B and group A. There was no significant difference at 24 hrs. (Table:11).

DISCUSSION

PONV is amongst the most common complications following anesthesia and surgery with a selectively high incidence after laparoscopic cholecystectomy. The etiology behind the PONV following laparoscopic cholecystectomy is complex and multifactorial and is dependent on a variety of factors including patient demographic data, type of surgery, anesthetic technique and post-operative care. Patient-related factors are age, sex, obesity history of motion sickness, menstruation and history of PONV[6]. There are four main classes of drugs used in the management of PONV, Anticholinergic, Antihistaminics, D_2 antagonists and 5- HT_3 antagonists.

All patients were anesthetized and operated by the same team of anesthesiologists and surgeons. The duration of surgery and agents used for anesthesia were also similar. The introduction of 5-HT_3 (Serotonin) receptor antagonists has heralded a major advance in the treatment of PONV because of the absence of adverse reaction that was commonly observed with used antiemetic drugs. The current 5-HT_3 receptor antagonist is Granisetron, Tropisetron, Ondansetron, Alosetron, and Dolasetron.

Among 75 patients, 65 were female and 10 were male. The data showed that laparoscopic cholecystectomy surgery was more common in females. This suggests hormonal influence as a possible cause.

The results of our study revealed that in the management of PONV Granisetron was more effective than Ondansetron which is considered better than Metoclopramide. The findings of our study have a resemblance to the other two studies where Ondansteron was more effective than Metoclopramide & placebo[12,13]. One other study revealed that minimal emetic episodes were observed in the early postoperative period (1-12 hrs) in patients who had received Granisetron (I.V.) in comparison to Ondansetron and Metoclopramide[14].

Patients in both Granisetron and Ondansetron groups showed better satisfaction (patient satisfaction scores 2 and 3) in the first 12 hrs postoperatively as compared to Metoclopramide.

CONCLUSION

This study was performed to compare the effectiveness of Granisetron, Ondansetron, and Metoclopramide in the management of PONV. The results of our study revealed that in the management of PONV, Granisetron was more effective than Ondansetron which showed better results than Metoclopramide. The patient satisfaction is also better for Granisetron in comparison with Ondansetron and Metoclopramide. The results showed that Granisetron is a better choice for the treatment of postoperative nausea and vomiting. Some other advanced studies are needed to establish these findings.

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