Original Research Article

Evaluation of oral olanzapine versus oral ondansetron in prevention of postoperative nausea and vomiting in patients undergoing laparoscopic surgeries under general anesthesia: A comparative study

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Abstract

Introduction: Nausea and vomiting in the postoperative period occur in 20% to 30% of patients, and together nausea and vomiting are second most common and distressing to patients[1]. The general incidence of vomiting is about 30%, the incidence of nausea is about 50%, and in a subset of high-risk patients, the postoperative nausea and vomiting PONV rate can be high as 80% during the 24hr after emergence[2]. However, the incidence rate of PONV after laparoscopic cholecystectomy (LC) is higher than that after other types of surgery. **Materials and methods:** Data was randomly collected from 120 ASA I and II patients scheduled for surgery under general anesthesia between 18 to 50 yrs. It was a prospective randomized double blinded study. After obtaining informed written consent from parents, the study population was randomly assigned to two groups using a random sequence (Random Sequence Generator, available at www.random.on). Group A: Patients received Tablet Ondansetron 16mg (2 tablets of ondansetron 8mg) 1 hour before surgery with sips of water. Group B: Patient received Tablet Olanzapine 5mg (2 tablets of Olanzapine 2.5mg) 4 hours before surgery with sips of water. Group A received placebo 4hrs before surgery and Group B received placebo 1hour before surgery. Monitoring includes electrocardiography (ECG), oxygen saturation (SpO_2), non-invasive blood pressure (NIBP), end tidal carbon dioxide ($EtCO_2$), respiratory rate (RR), train of four (TOF). **Results:** Mean age of subjects in group A was 38.7 + 9.8 years and in group B was 35.8 + 9.4 years. There was no significant difference in age distribution between two groups. In Group A 55% were females and 45% were males and in group B 50% of them were female and male respectively. There was no significant difference in gender distribution between two groups with p=0.583. In Group A 56.7% had ASA I and 43.3% had ASA II and in group B 50% of them had ASA I and II respectively to significant difference between two groups with p=0.464. **Conclusion:** To conclude, our study demonstrates that premedication with oral olanzapine 5mg provides reduction in the overall incidence of post-operative nausea and vomiting (PONV) which is comparable to ondansetron in patients undergoing general anaesthesia. It also reduced analgesic requirement and causes arousable sedation postoperatively.

Key Words: Nausea and vomiting, ASA, post-operative nausea and vomiting.

Introduction

Nausea and vomiting in the postoperative period occur in 20% to 30% of patients, and together nausea and vomiting are second most common and distressing to patients[1]. The general incidence of vomiting is about 30%, the incidence of nausea is about 50%, and in a subset of high-risk patients, the postoperative nausea and vomiting PONV rate can be high as 80% during the 24hr after emergence[2]. However, the incidence rate of PONV after laparoscopic cholecystectomy (LC) is higher than that after other types of surgery. Although, PONV is rarely fatal, it can result in serious complications such as aspiration pneumonitis, dehydration and disruption of surgical sutures. Unresolved PONV may result in prolonged post anesthesia care unit stay and unanticipated hospital admission that result in a significant increase in overall healthcare costs[3].

Nausea is defined as subjectively unpleasant sensation associated with an urge to vomit. This is felt mainly in the back of the throat and epigastrium, accompanied by loss of gastric tone, duodenal contractions and reflux of the gastric contents into the oesophagus. It is associated with prodromal symptoms such as salivation, swallowing, pallor and tachycardia. Retching is defined as laboured spasmodic rhythmic contractions of the respiratory muscles including the diaphragm and chest wall and abdominal wall muscles without expulsion of gastric contents. Vomiting or emesis is the forceful expulsion of gastric contents from the mouth and is brought about by powerful sustained contraction of the abdominal muscles, descent of the diaphragm and opening of the upper oesophageal sphincter.

PONV is multifactorial origin involving anesthetic, surgical, and individual risk factors. Factors which affect the incidence of PONV includes age, sex, history of previous PONV or motion sickness, smoking, surgical procedures like laparoscopic surgeries, breast surgeries, ophthalmic surgeries, ENT, dental surgeries, duration of surgery and anesthesia and anxiety[4].

Though Laparoscopic surgery alone is a known risk factor for PONV, it has gained popularity among several surgical approaches and has many advantages, including less postoperative pain and hospital stay with early mobilization. Minimal wound size results in early wound healing with lower complication rates. In order to have a enough surgical sight and manipulation pneumoperitoneum is essential in laparoscopic surgery. However, various systemic changes occur dependent to the type of gas used and level of the intraabdominal pressure. Cardiopulmonary effects, systemic carbon dioxide absorption and venous gas embolism are major problems in laparoscopic surgery[5].

Physiological changes occur related to pneumoperitoneum and patient position. Carbon dioxide (CO_2) is the most commonly used gas and several chemical effects of CO_2 may emerge during laparoscopic surgery.

In cardiovascular system increased sympathetic discharge, hypercarbia and decreased venous return lead to tachycardia. Additionally, sympathetic stimulation emerges secondary to decreased venous return and peritoneum stretching. Hypercarbia and acidosis lead to cardiac rhythm disturbances, including premature

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ventricular contractions, ventricular tachycardia and fibrillations. Vagal stimulations may lead to bradyarrhythmia. This vagal stimulation due to pneumoperitoneum, in addition to risk factors related to surgery itself, may cause PONV.

Physiological changes in respiratory system are primarily related with increased intraabdominal pressure. Elevated diaphragm and collapsed lung bases result in decreased functional residual capacity (FRC), ventilation perfusion mismatch and intrapulmonary shunting. Clinical outcomes of these physiological changes are hypoxemia and increased alveolar arterial oxygen gradient[6]. Hence a study was done to compare the effect of oral olanzapine with oral ondansetron for PONV in patients undergoing General Anesthesia.

Aims & objectives

1. To compare the effect of oral olanzapine 5mg and oral ondansetron 16mg for PONV in patients undergoing general anesthesia for Laparoscopic surgeries.
2. To evaluate any side effects associated with the use of olanzapine and ondansetron.

Materials and methodology

Source of data

Data was randomly collected from 120 ASA I and II patients scheduled for surgery under general anesthesia between 18 to 50 yrs.

Inclusion criteria

1) Patients who gave informed written consent.
2) Patients aged between18 and 50years.
3) Patients belonging to ASA Grade I and Grade II.

Exclusion Criteria

1) Patient refusal to give informed written consent.
2) Patients with preexisting nausea, vomiting or motion sickness.
3) Patient who received opioids or drugs with known antiemetic properties in 24hr before surgery
4) Patients with history of esophageal reflux, opioid abuse or alcohol abuse.
5) Pregnancy.

Methods

It was a prospective randomized double blinded study. After obtaining informed written consent from parents, the study population was randomly assigned to two groups using a random sequence (Random Sequence Generator, available at www.random.on)

Group A: Patients received Tablet Ondansetron 16mg (2 tablets of ondansetron 8mg) 1 hour before surgery with sips of water.

Group B: Patient received Tablet Olanzapine 5mg (2 tablets of Olanzapine 2.5mg) 4 hours before surgery with sips of water.

Group A received placebo 4hrs before surgery and Group B received placebo 1hour before surgery.

Monitoring includes electrocardiography (ECG), oxygen saturation (SpO_2), non-invasive blood pressure (NIBP), end tidal carbon dioxide ($EtCO_2$), respiratory rate (RR), train off our (TOF).

Intravenous (i.v) access was established and an IV infusion of Ringer lactate was started. All the patients were premedicated with Inj.Midazolam0.03 mg/kg, Inj.Glycopyrrolate 0.005 mg/kg and Inj. Fentanyl 2 mcg/kg. Preoxygenated with 100% O_2 for 3 min. Induction of anesthesia is the same for both groups using Inj.Thiopentone 5mg/kg, Inj.Vecuronium 0.1mg/kg for intubation. After endotracheal (ET) intubation with appropriate size ET tube, or gastric tube was introduced and suctioning was done to empty the stomach from air and other contents. Anesthesia was maintained with Oxygen 33%. Nitrous Oxide 66%, Sevoflurane1- 2% and Inj.Vecuronium 0.02mg/kg. Inj.Paracetamol 1gm iv.was given intraoperatively. At the end of surgery patient will be reversed with Inj.Glycopyrrolate 0.01mg/kg iv and Inj.Neostigmine 0.05mg/kg iv. The orogastric tube was suctioned and then removed before tracheal extubation. Post operatively sedation, nausea, vomiting and complete response will be noted. Sedation evaluated using Ramsay Sedation Score.

An emetic episode is defined as one or more instances of vomiting and/or retching or any combination that occurred in rapid sequence of less than 1 min between episodes during postoperative period.

Nausea is defined using a categorical 11-point linear whole number scale for which 0 represented “no nausea” and 10 represented “nausea as bad as possible”. Secondary end point was the complete response (CR) (without nausea and vomiting, no rescue therapy) for acute (0-2hrs) and late (6-24hrs). Nausea and vomiting will be evaluated postoperatively as acute PONV (0- 2hrs) and late PONV(6-24hrs). Inj. Ondansetron 4mg intravenously will be used as rescue antiemetic.

Statistical Methods

With the power of study being 80% and confidence limits at 95% minimum sample size required to detect a difference of 50% in the incidence of nausea and vomiting between two groups is 58 patients in each group. We included 60 patients in each group for better validation of results. Descriptive and inferential statistical analysis has been carried out in the present study. Results on continuous measurements are presented on Mean + SD (Min-Max) and results on categorical measurements are presented in Number (%).

Significance is assessed at 5 % level of significance. **The following assumptions on data were made:**

1. Dependent variables should be normally distributed,
2. Samples drawn from the population should be random, Cases of the samples should be independent.

Categorical data was represented in the form of frequencies and proportions. Chi-square was used as test of significance. Continuous data was represented as mean and standard deviation. Independent t test or Mann Whitney U test was used as test of significance to identify the mean difference between two groups for parametric and non-parametric data respectively. P value <0.05 was considered as statistically significant.

Significant figures: + Suggestive significance (P value: 0.05<P<0.10), * Moderately significant (P value: 0.01<P 0.05), ** Strongly significant (P value: P<0.01).

Statistical software

The Statistical software namely SAS 9.2, SPSS 22, Stata 10.1, MedCalc9.0.1,Systat 12.0 and R environment ver.2.11.1 were used for the analysis of the data and Microsoft word and Excel have been used to generate graphs, tables etc.

Results

It is a prospective randomized controlled double-blind study with 120 patients randomly divided into 2 groups of 60 patients each, using www.random.org.

Group A- receiving Oral Ondansetron 16mg (2 tablets of 8mg) 1 hour before surgery -60 patients.

Group B - receiving Oral Olanzapine 5mg (2 tablets of 2.5mg) 4 hours before surgery- 60patients.

Group A received placebo 4hrs before surgery and Group B received placebo 1hour before surgery. They were evaluated for PONV, side effects of the drugs if any.

Demography

The groups are matched with respect to age and gender.

Table 1: Age distribution of patients studied

	Group				P value
	A		B		
	Mean	SD	Mean	SD	
Age (years)	38.7	9.8	35.8	9.4	0.101

Mean age of subjects in group A was 38.7 + 9.8 years and in group B was 35.8 + 9.4 years.
There was no significant difference in age distribution between two groups.

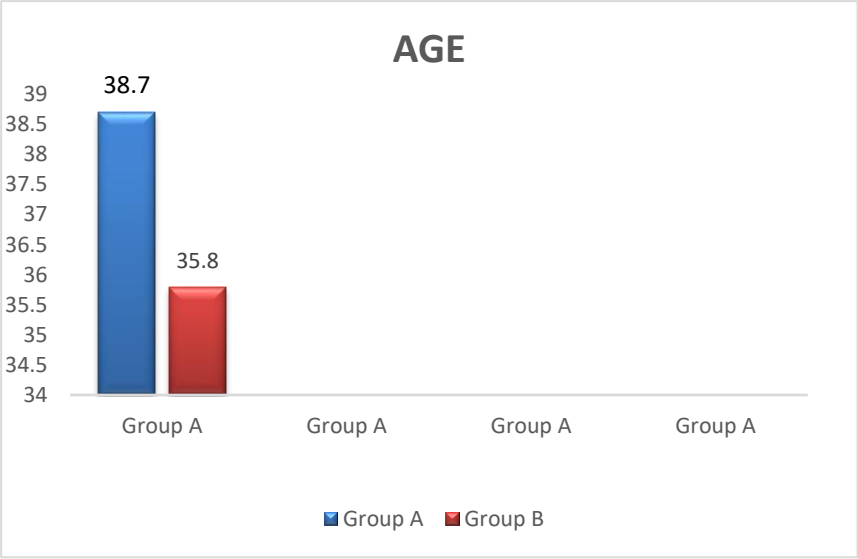

Figure 1: Age distribution of patient studied

Table 2: Gender distribution of patients studied

		Group			
		A		B	
		Number	%	Number	%
Gender	Female	33	55.0%	30	50.0%
	Male	27	45.0%	30	50.0%
	Total	60	100.0%	60	100.0%

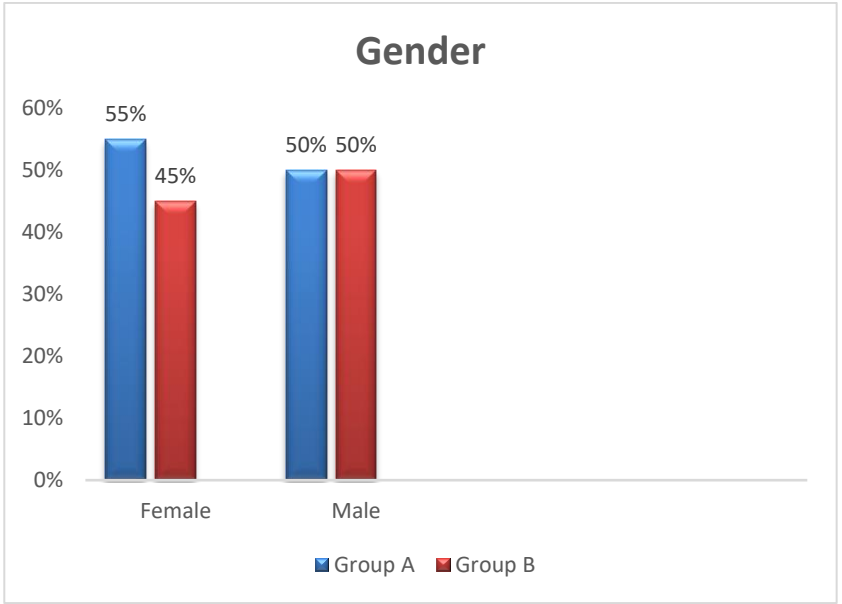

Figure 2: Gender distribution of patients studied

In Group A 55% were females and 45% were males and in group B 50% of them were female and male respectively. There was no significant difference in gender distribution between two groups with p=0.583.

Table3: ASA distribution of patients studied

		Group			
		Group A		Group B	
		Number	%	Number	%
ASA	I	34	56.%	30	50%
	II	26	43.3%	30	50%
	Total	60	100%	60	100%

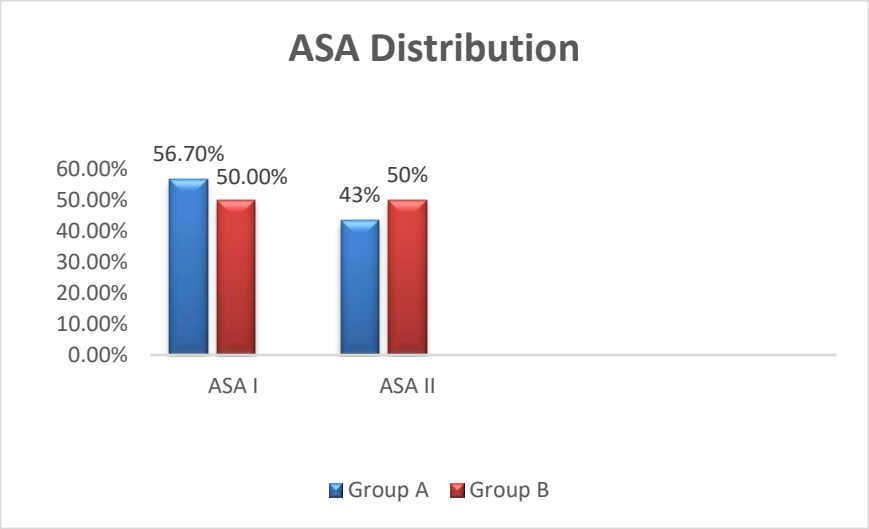

Figure 3: ASA distribution of patients studied

In Group A 56.7% had ASA I and 43.3% had ASA II and in group B 50% of them had ASA I and II respectively to significant difference between two groups with p=0.464.

Table 4: Weight distribution of patients studied

	Group				P Value
	A		B		
	Mean	SD	Mean	SD	
Weight (kg)	54.7	7.4	55.9	8.0	0.392

Mean weight in group A was 54.7 + 7.4 kg and in group B was 55.9 + 8 kg. There was no significant difference in mean weight between two groups with p=0.392.

Table 5: Duration of surgery between two groups studied

	Group				P value
	A		B		
	Mean	SD	Mean	SD	
Duration of surgery (Min)	57.5	13.8	59.5	18.7	0.507

Mean duration of surgery was 57.5 + 13.8 min in group A and 59.5 + 18.7 min in group B. There was no significant difference in mean duration of surgery between two groups with p=0.507.

Table 6: Comparison of Heart rate beats/min between two groups and intra group studied

	Group						P value
	A			B			
	Mean	SD	Intra group P value	Mean	SD	Intra group P value	
Drug given4hr preop(before induction)	89.3	10.7		88.5	12.1		0.697
Drug given 1hr preop(before induction)	89.1	10.1		88.1	12.5		0.652
Baseline	89.7	11.2		87.8	319		0.424
Induction		13.1		85.9	14.6		0.045*
I min	88.0	13.1	0.066	87.2	16.4	0.361	0.754
2 min	87.0		0.003	85.3	15.8	0.803	0.484
5 min	86.1	12.4	0.006	89.0	17.1	0.078	0.293
10min	86.1	13.2	0.008	86.5	15.4	0.481	0.889
15 min	85.7	11.7	0.003	85.3	15.0	0.765	0.844
20 min	85.2	13.1	0.000	85.6	14.0	0.645	0.888
25min	85.2	12.4	0.000	85.6	14.2	0.685	0.870
30 min	85.1	13.8	0.001	85.2	13.5	0.931	0.973
35 min	85.9	13.6	0.020	85.4	14.3	0.786	0.842

40 min	87.5	12.9	0.169	82.1	16.0	0239	0.052
45 min	89.2	10.5	0.795	85.2	11.9	800	0.074
50 min	88.8	12.0	0.748	86.2	12.8	0.259	0.336
55 min	91.4	13.9	0.258	85.6	11.5	0.426	0.054
60 min	96.9	13.8	0.005	90.4	13.9	0.008	0.053
65 min	93.1	11.4	0.112	92.2	13.8	0.015	0.813
70 min	98.5	14.0	0.013	90.5	14.4	0.057	0.157
75 min	990	7.7	0.009	87.7	16.6	0.364	0.119
80 min	98.0	7.0	0.112	75.2	7.1	0.133	0.001*
85 min	.00.5	2.1	0.475	78.2	10.4	0.404	0.029*
90 min	10.5	13.4	0.028	80.5	15.4	0.729	0.051
Post Operative period							
30 min	88 2	9 9		91.5	12.8		0.128
60 min	88.3	7.7		90.3	11.6		0.272
2 hr	85.2	8.9		88.2	11.3		0.107
4 hr	85 1	7 4		86.6	11.1		0.380
6 hr	84.1	7.1		85.8	11.3		0.337
12 hr	84.0	7.3		85.6	10.2		0.318
18 hr	85.4	8.2		85.4	11.0		0.997
24 hr	86.2	7.6		84.5	10.1		0.332

Mean Heart rate between two groups showed no significant difference clinically. But intraoperative, at intervals of induction, 80 min and 85 min, group A had statistically significant higher values when compared to group B.

Table 7: Comparison of SBP (mmHg) between two groups and intra group studied

	Group						P value
	A			B			
	Mean	SD	Intra group P value	Mean	SD	Intra group P value	
Drug given preop 4hr (before induction)	125.8	11.9		128.4	12.5		0.256
Drug given pre op 1hr (before induction)	121.6	11.4		122.4	11.1		0.806
Baseline	121.9	11.2		122.4	10.8		0.804
Induction	124.7	13.1		117.4	13.4		0.003*
1 min	120.7	14.3	0.031	116.8	18.0	0.710	0.197
2 min	119.0	14.5	0.001	113.9	16.6	0.094	0.076
5 min	119.7	14.7	0.015	119.3	20.8	0.392	0.915
10 min	120.6	17.1	0.085	116.0	16.9	0.595	0.144
15 min	120.9	16.1	0.101	118.9	14.0	0.453	0.466
20 min	119.7	14.1	0.012	120.9	15.6	0.148	0.673
25 min	120.8	14.1	0.074	121.4	13.4	0.070	0.822
30 min	123.3	14.7	0.592	122.4	14.1	0.027	0.737
35 min	124.4	14.6	0.989	120.2	14.8	0.191	0.133
40 min	127.7	11.7	0.216	121.3	14.6	0.166	0.012*
45min	129.2	12.2	0.091	121.0	13.2	0.250	0.002*
50 min	128.4	14.6	0.411	124.1	12.6	0.029	0.154
55 min	126.4	16.6	0.820	123.3	13.3	0.080	0.387
60 min	131.7	11.3	0.090	124.8	12.5	0.028	0.021*
65 min	131.4	13.5	0.531	124.2	13.8	0.224	0.099
70 min	134.4	13.2	0.344	123.5	18.2	0.617	0.086
75 min	131.0	18.8	0.673	117.0	16.5	0.636	0.151
80 min	125.5	16.4	0.511	123.2	23.6	0.918	0.869
85 min	130.7	9.0	0.913	116.3	18.3	0.607	0.250
90 min	133.5	14.8	0.324	114.2	18.1	0.477	0.227
Post Operative period							
30 min	125.8	11.0		125.8	10.2		0.986
60 min	124.4	11.5		121.6	9.6		0.150
2 hr	121.8	11.7		122.6	10.4		0.683
4 hr	121.9	12.9		119.0	10.5		0.184
6 hr	118.9	12.1		117.1	12.3		0.399
12 hr	118.6	13.5		114.4	15.3		0.116
18hr	121.5	15.0		116.5	14.5		0.071
24hr	122.1	13.6		114.8	10.8		0.002*

Mean SBP between two groups showed that there was no significant difference clinically. But intraoperative, at intervals of induction, 40 min, 45 min, 60 min and at 24 hour of postoperative period, Group A had statistically significant higher values when compared to group B.

Table 8: Comparison of DBP (mmHg) between two groups and intra group studied

	Group						P value
	A			B			
	Mean	SD	Intra group P value	Mean	SD	Intra group P value	
Drug given (preop 4hr induction)	78.2	9.1		78.1	10.3		0.963
Drug given (preop l hr Before induction)	76.5	11.1		76	12.8		0.246
Baseline	75.6	8.5		76.0	9.0		0.763
Induction	75.2	11.4		72.6	10.2		0.191
1 min	76.5	11.4	0.031	73.5	13.0	0.710	0.181
2 min	75.3	10.0	0.001	71.7	12.5	0.094	0.090
5 min	75.1	11.4	0.015	73.9	13.0	0.392	0.596
10 min	76.9	14.9	0.085	71.9	12.2	0.595	0.046*
15 min	79.1	13.1	0.101	75.6	13.6	0.453	0.154
20 min	78.6	12.2	0.012	75.9	12.9	0.148	0.246
25 min	77.3	12.7	0.074	73.1	12.1	0.070	0.066
30 min	75.9	11.1	0.592	75.4	12.9	0.027	0.809
35 min	78.2	10.0	0.989	74.5	13.5	0.191	0.102
40 min	80.7	8.8	0.216	72.0	13.2	0.166	<0.001*
45 min	81.9	10.6	0.091	74.8	12.0	0.250	0.002*
50 min	81.6	10.0	0.411	77.3	l 1.3	0.029	0.069
55 min	81.8	8.6	0.820	78.2	9.9	0.080	0.102
60 min	84.2	6.5	0.090	77.9	11.7	0.028	0.008*
65 min	85.5	7.0	0.531	77.2	12.1	0.224	0.01*
70 min	85.7	7.8	0.344	77.7	8.7	0.617	0.018*
75 min	81.5	11.8	0.673	77.6	10.7	0.636	0.507
80 min	79.5	6.7	0.511	76.8	8.3	0.918	0.607
85 min	86.0	5.7	0.913	72.5	7.0	0.607	0.050
90 min	86.5	7.8	0.324	73.5	4.9	0.477	0.027*
Post Operative period							
30 min	76.4	10.0		75.6	8.8		0.648
60 min	76.9	10.8		73.4	11.6		0.094
2 hr	74.9	11.7		72.9	9.5		0.308
4 hr	76.6	10.7		72.1	8.7		0.015*
6 hr	74.5	10.8		70.6	8.8		0.034*
12 hr	72.d	10.4		68.2	13.3		0.048*
18hr	77.5	12.8		72.4	12.6		0.03
24hr	78.2	10.9		71.2	10.5		<0.001*

Mean DBP between two groups shows that there was no significant difference clinically but intraoperative at intervals 10min, 40min, 45 min, 60min, 65min, 70min, 90min and from 4hr to 24hr of postoperative period, Group A had statistically significant higher values when compared to group B.

Table 9: Comparison of MAP (mmHg) between two groups and intra group studied

	Group						P value
	A			B			
	Mean	SD	Intra Group P value	Mean	SD	Intra group P value	
Drug given (preop 4hr Before induction)	93.3	11.4		95.9	10.5		0.197
Drug Given(preop 1hr before induction	93.8	12.4		89.9	13.1		0.095
Baseline	91.9	10.7		91.2	8.4		0.677
Induction	88.7	15.5		86.0	9.2		0.242
l min	90.9	11.9	0.752	87.7	13.4	0.523	0.164
2 min	90.1	11.7	0.925	84.7	12.4	0.534	0.016*
5 min	90.6	12.7	0.318	88.4	14.8	0.357	0.376
10 min	90.8	15.1	0.039	86.5	16.3	0.792	0.139
15 min	92.7	14.8	0.193	90.1	12.8	0.117	0.306
20 min	92.1	13.4	0.494	90.7	13.0	0.054	0.552
25 min	90.4	12.7	0.021	90.4	12.8	0.622	0.994
30 min	91.5	12.4	0.005	90.4	12.2	0.107	0.636
35 min	93.8	12.4	0.004	89.9	13.1	0.282	0.095
40 min	95.9	9.9	0.017	89.8	12.4	0.742	0.005*
45 min	96.2	12.2	0.035	89.8	12.6	0.208	0.01I*
50 min	96.2	11.9	0.004	93.1	12.0	0.028	0.235
55 min	96.8	12.2	0.072	91.3	10.1	0.021	0.038*

60 min	99.4	10.7	0.081	93.0	11.9	0.054	0.023*
65 min	100.7	10.8	0.956	89.4	10.9	0.344	0.002*
70 min	99.5	9.1	0.081	91.0	9.2	0.512	0.023*
75 min	97.3	10.0	0.956	90.6	10.2	0.727	0.218
80 min	92.3	10.2	0.895	88.3	13.9	0.920	0.645
85 min	97.7	4.5	0.054	91.5	10.6	0214	0.378
90 min	96.5	16.3	0.500	89.2	7.9	0.168	0.396
Post Op period							
30 min	90.0	13.5		92.0	11.6		0.397
60 min	88.3	12.2		88.0	10.2		0.902
2 hr	86.1	16.4		89.3	10.4		0.198
4 hf.	89.3	11.9		86.2	7.8		0.100
6 hr	85.5	13.7		85.4	9.2		0.937
12 hr	84.6	13.3		84.7	14.4		0.995
18hr	88.5	14.9		86.4	13.0		0.402
24 hr	89.0	14.6		85.2	10.8		0.110

Mean MAP between two groups showed there was no significant difference clinically. But intraoperative, at intervals of 2 min, 40 min, 45 min, 55 min, 60 min, 65 min and 70 min, Group A had statistically significant higher values when compared to group B.

Table 10: Comparison of SPo2 (%) between two groups studied

	Group A		Group B		P value
	Mean	SD	Mean	SD	
Drug given (preop 4 hr)	98.3	2.0	99.3	1.0	0.001*
Drug given (preop l hr)	99.5	1.0	99.2	.9	0.195
Baseline	99.4	.5	99.0	1.2	0.028*
lnduction	99.8	.6	99.6	.6	0.097
1 min	99.7	.7	99.7	.6	0.572
2 min	99.6	.7	99.8	.4	0.024*
5min	99.6	.7	99.6	.5	1.000
10min	99.5	.7	99.5	.7	0.895
15 min	99.6	.7	99.5	.7	0.340
20min	99.6	.8	99.5	.7	0.804
25min	99.6	.9	99.3	.9	0.192
30 min	99.5	.9	99.4	.7	0.746
35 min	99.5	1.0	99.2	.9	0.195
40min	99.2	.8	99.2	1.0	0.985
45 min	98.9	1.0	99.4	.9	0.005*
50 min	99.0	.7	99.1	.8	0.775
55 min	98.4	.8	99.1	1.0	0.001*
60 min	98.8	1.0	99.2	.8	0.056
65 min	98.9	1.4	99.0	.8	0.777
70 min	98.6	1.0	97.2	7.8	0.529
75 min	98.6	1.0	98.9	.6	0.435
80 min	99.5	.6	99.0	.9	0.356
85 min	99.3	.6	98.7	1.2	0.407
90 min	98.3	.6	99.5	.5	0.021*
95 min			99.2	1.1	
Post Op period					
30 min	99.2	.5	99.5	.7	0.001*
60 min	98.2	.4	99.3	.8	<0.001*
2 hr	98.5	1.1	99.0	1.0	0.01*
4 hr	98.1	.9	99.1	1.0	<0.00 l *
6hr	98.7	.9	99.1	1.0	0.019*
12 hr	98.1	1.3	98.9	1.0	<0.001*
18 hr	98.6	.6	98.8	.9	0.164
24 hr	98.9	.8	99.1	.8	0.315

Mean Spo2 between two groups showed that there was no significant difference clinically. But intraoperative, at intervals of initiation, 2min, 45 min, 55 min, 90 min and postoperatively from 30 min to 12 hr, group A had statistically significant higher values when compared to group B.

Table: 11 Comparison of Pre-operative nausea and vomiting between two groups studied

		Group			
		A (Ondansetron)		B (Olanzapine)	
		Count	%	Count	%
Nausea	No	60	100.0%	60	100.0%
Vomiting	No	60	100.0%	60	100.0%

In preoperative period none of them in both groups had nausea and vomiting.

Table: 12 Comparison of PONV between two groups studied

		Group				P value
		A		B		
		Number	%	Number	%	
Immediate	No	60	100.0%‹	59	98.3%	0.315
	Yes	0	0.0%	1	1.7%	
15 min	No	60	100.0%	59	98.3%	0.3 15
	Yes	0	0.0%	1	1.7%	
30 min	No	60	100.0%	60	100.0%	
1st hr	No	60	100.0%	56	93.3%	0.042*
	Yes	0	0.0%	4	6.7%	
2nd hr	No	51	85.0%	57	95.0%	0.068
	Yes	9	15.0%	3	5.0%	
6th hr	No	56	93.3%	58	96.7%	0.402
	Yes	4	6.7%	2	3.3%	
12"' hr	No	57	95.0%	59	98. %	0.309
	Yes	3	5.0%	l	1.7%	
18" hr	No	60	100.0%	58	96.7%	0.154
	Yes	0	0.0%	2	3.3%	
24thhr	No	60	100.0%	60	100.0%	

In group A till 1st hr there was no incidence of nausea or vomiting, whereas at 2hr, 6th hr, 12th hr, 15%, 6.7% and 5% had nausea or vomiting.

In group B incidence of nausea and vomiting was at 1st hr- 6.7%, 2nd hr- 5%, 6th hr- 3.3%,12th hr - 1.7%,18th hr - 3.3%respectively.

Significant difference in Nausea and vomiting was observed between two groups at 1st hr and was statistically significant p=0.042. where as in 1-24th hr incidence of nausea and vomiting was not significant statistically but was clinically significant.

Table13: Comparison of PONV score at 1hr and 1-24 hr between two groups

	Group						
	Group A			Group B			P value
	Mean	Median	SD	Mean	Median	SD	
PONV SCORE at 1hr	0.0	0	0.1	0.4	0	1.1	<0.001*
PONV SCORE 1-24 hr	1.7	1	2.0	0.9	0	2.2	<0.001*

Mean PONV score was lower in Group A compared to Group B at 1hr, p<0.001 and higher in Group A than Group B from 1to 24 hr, p<0.001. This difference in PONV score was significant between two groups. Initially Group B had higher score and later Group A had higher score for PONV.

Table14: Comparison of complete response (no nausea, no vomiting) between two groups studied

		Group				P value
		A		B		
		Number	%	Number	%	
Acute (0-2hr)	No	2	3.3%	9	15.0%	0.027*
	Yes	58	96.7%	51	85.0%	
Late (2-24 hr)	No	15	25.0%	5	8.3%	0.014*
	Yes	45	75.0%	55	91.7%	

Complete response at acute period (0-2hr) was seen in 96.7% of subjects in group A and in85% of subjects in group B that was statistically significant pm 0.027. During late period (2- 24hr) complete response was seen in 75% and in 91.7% of subjects in Group A and B respectively. This difference in complete response rate was statistically significant with p<0.014.

Table15: Comparison of rescue antiemetic required between two groups

		Group				P value
		A		B		
		Number	%	Number	%	
Rescue Antiemetic	No	43	71.7%	49	81.7%	0.195
	Yes	17	28.3%	11	18. %	

In group A 28.3% of subjects and in Group B 18.3% of subjects required rescue antiemetic. There was no significant difference in rescue antiemetic given between two groups.

Table16: Comparison of time of rescue antiemetic between two groups

	Group						P value
	A			B			
	Mean	Median	SD	Mean	Median	SD	
Time of Rescue Antiemetic	1.6	0	3.1	2.6	0	8.2	0.451

Mean time of rescue antiemetic in group A was 1.6 + 3.1 hr and in group B was 2.6 + 8.2 hrs. No difference in time of rescue antiemetic was observed between two groups.

Table 19: Comparison of time of rescue analgesic required between two groups

	Group						P value
	A			B			
	Mean	Median	SD	Mean	Median	SD	
Rescue Analgesic Time	6.0	6	1.8	8.2	8	2.0	<0.001*

Mean time of rescue analgesic in group A was 6+1.8hr and in group B was 8.2+2hr Group A required rescue analgesia at a shorter duration compared to Group B. This difference between two groups was statistically significant with p<0.001.

Table 20: Comparison of post-operative VAS score between two groups

	Group						P value
	A			B			
	Mean	Median	SD	Mean	Median	SD	
Immediate	2.0	2	0.0	2.0	2	0.1	0.317
15 min	2.0	2	0.0	2.0	2	0.1	0.317
30 min	2.0	2	0.0	2.0	2	0.0	1.000
45 min	2.0	2	0.0	2.0	2	0.0	1.000
1st hr	2.1	2	0.5	2.0	2	0.2	0.381
2nd hr	2.4	2	0.9	2.2	2	0.6	0.1 29
6th hr	4.1	4	1.8	3.1	3	1.2	0.002*
12th hr	3.4	2	1.9	3.1	2	1.6	0.664
18th hr	2.3	2	1.1	2.4	2	10	0.954
24th hr	2.4	2	1.1	2.1	2	0.3	0.016*

In the study there was no significant difference in Mean or Median VAS score between two groups at all the interval except at 6th hr and 24th hr. At 6th hr Median VAS score was 4 in group A and 3 in Group B, at 24th hr median VAS score was 2 in group A and group B respectively. This difference was statistically significant between two groups.

Table 21: Comparison of RSS score between the two groups

	Group						P value
	A			B			
	Mean	Median	SD	Mean	Median	SD	
Drug given 4hr Preop	1.0	1	0.4	1.1	1		
Drug given 1hr preop	1.0	1	0.0	2.3	2		<0.00 1 *
Baseline	1.0	1	0.0	2.7	3	0.5	<0.001*
Immediate Post op	0	1	0.2	2.9	3	0.5	<0.001*
15 min	1.1	1	0.3	2.4	2	0.5	<0.001*
30min	1.1	1	0.	2.3	2	0.4	<0.001*
45 min	1.2	1	0.4	2.1	2	0.2	<0.001*
1st hr	1.	1	0.5	2.0	2	0.0	<0.001*
2nd hr	1.5	2	0.5	2.0	2	0.0	<0.001*
6th hr	1.5	1	0.5	1.7	2	0.4	0.005*
12th hr	1.4	1	0.5	1.9	2	0.	<0.001*
18th hr	1.5	1	0.5	2.0	2	0.0	<0.001"
24th hr	1.4	1	0.5	2.0	2	0.0	<0.001*

Median RSS score was significantly high in group B compared to group A at all the interval from Preop to post op 24hrs.

Discussion

Post-operative nausea and vomiting (PONV) is a common problem and distressing symptom in surgical patient population. Many surgeries are associated with high incidence of PONV. This has led to many hypothesized causal mechanisms of PONV in various types of surgeries. General anaesthesia with inhalational agents is associated with an average PONV incidence of 20-30% in surgical patients[4]. The incidence largely depends on pre-operative patient characteristics, operation, type of anaesthesia, gender, intensity of pain and its postoperative management. Postoperative vomiting will harm skin flaps, abdominal wall sutures, vascular anastomoses, and other areas recently operated on[8]. It increases intra-ocular, intra-cranial pressure and may also cause tachycardia, electrolyte imbalance, wound dehiscence, oesophageal tears and aspiration pneumonitis. PONV after minor and ambulatory surgery delays the hospital discharge. Antiemetics drugs including antihistamines, butyrophenones, dopamine receptor antagonists were used a few years ago. These antiemetics had undesirable side effects like excessive sedation, hypotension, dry mouth, dysphasia, hallucinations and extra-pyramidal symptoms and they are now rarely used[7].

In 1981, Dexamethasone was found to be an effective antiemetic in patients undergoing chemotherapy with limited side effects and its use in prophylaxis for PONV was started two years later. In 1990, 5-HT3 antagonists were introduced. Gregory et al, reported the effectiveness of 5-HT3 antagonists in prevention of chemotherapy induced nausea and vomiting. Combinations of antiemetic drugs with different mechanisms of action are known to be effective and have been studied for the prophylaxis of PONV with variable results. In CINV, combination of olanzapine with dexamethasone or granisetron or ondansetron was used. In our study we compared 5HT3antagonist Ondansetron and Olanzapine (which also as action on 5 HT3 receptors) for prevention of PONV in patients undergoing surgery under general anaesthesia[8].

Selection of study population

The general incidence of nausea and vomiting can be 30% to 50%, with further increase in high risk patients. Apfelet al, described female gender, previous history of PONV or motion sickness, non-smoking status and postoperative use of opioids as important risk factors for PONV. Scinclairet al, described female gender, previous history of PONV or motion sickness, non- smoking status and postoperative duration, type of anaesthesia and surgery as the important risk factors for PONV. Patients with history of motion sickness, migraine, nausea

and vomiting in preoperative period and patients with renal, gastro-intestinal disorders and liver disorders were excluded[9].

Type of anaesthesia

In regional anaesthesia, spinal and epidural anaesthesia is the most popular and most frequently used technique for abdominal and pelvic surgeries in adults. Sinclair et al, found the risk for PONV is nine times less among patients receiving regional anaesthesia than those receiving general anaesthesia[10].

The incidence of PONV is high in general anaesthesia. Use of volatile anaesthetics, nitrous oxide, large-dose neostigmine (>2.5mg) and use of intraoperative or postoperative opioids in general anaesthesia are associated with high incidence of PONV. Propofol is known to reduce the incidence of PONV and is also used in the treatment of refractory vomiting and hence was avoided in the present study. Thiopentone was used in our study as it has no antiemetic effect and it will not interfere with the study findings[11].

Inhalational anaesthetic agent

Nitrous oxide is known to increase PONV by direct CNS stimulation of vomiting center, interaction with opioid receptors, stimulation of the sympathetic nervous system with catecholamines release, changes in middle ear pressure and distension of air containing spaces. The newer inhalational agents namely desflurane and sevoflurane have a lower incidence of PONV.

Trameret al, reported a 59%incidence of PONV in patients treated with a volatile anaesthetic or nitrous oxide. Apfelet al, suggested that avoiding nitrous oxide reduced PONV risk by12%. In our study nitrous oxide and isoflurane were used as per institutional protocol. Nitrous oxide and isoflurane were used in all cases as we wanted to test the efficacy of the Olanzapine chosen in the present study in prevention of PONV with standard anaesthesia protocol employed in the institute.

Perioperative analgesics

Perioperative use of opioids increases the risk of PONV. Elia et al in a randomized study suggested that use of NSAIDS reduced the risk of PONV. In our study, pain was managed in a multi modal way in the perioperative period, using Inj. Fentanyl 2µg / kg iv as premedication and Inj. Paracetamol 1gm IV was administered for post-operative analgesia.

Reversal of neuromuscular blockade

Meta-analysis by Trainer et al, demonstrated that high-dose neostigmine is associated with increased PONV and that reducing the dose can decrease PONV risk. However, Cheng et al, in their study questioned the clinical importance of neostigmine in PONV. Residual neuromuscular blockade is associated with dangerous complications than a questionable raise in incidence of PONV. Therefore, in our study neostigmine was used in total dose of 0.05mg/kg for reversal of residual neuromuscular blockade[12].

Type of surgery

The incidence of emesis after general anaesthesia is influenced also by the type of surgical procedure, irrespective of the anaesthetic technique used.The highest incidence is noted in women undergoing laparoscopic ovum retrieval procedures (54%).

Selection of antiemetic drugs

5-HT_3receptor antagonists:

5-HT_3antagonists were introduced in 1990. The 5HT_3receptor antagonists suppress nausea and vomiting by inhibiting serotonin binding to the 5-HT_3receptors. The 5-HT_3receptors are present in several critical sites involved in emesis, including vagal afferents, the nucleustractus solitarius (NTS), and 5- HT_3antagonists suppress nausea and vomiting by acting at these sites.

Selective serotonin type 3 receptor antagonists are considered first line of therapy when therapeutic intervention to prevent PONV is considered. The 5-HT_3antagonists have a favourable side effect profile and are considered equally safe. Here we selected Ondansetron, a protypical drug of 5-HT_3antagonist[13].

Olanzapine

Olanzapine, an atypical antipsychotic agent of thiobenzodiazepine class, blocks multiple neurotransmitter, receptors including dopaminergic (D_1, D_2, D_3, D_4), serotonergic (5-HT_{2A}, 5- HT_{2c}, 5-HT_3, 5-HT_6), adrenergic(alpha1), histaminic(H_1) and muscarinic(m_1,m_2,m_3,m_4) receptor. Because of its action on number of receptors site, it has an advantage over combination of various antiemetics by improving compliance and reducing drug interactions[7]. Hence a study was done to the compare the efficacy of oral olanzapine with oral ondansetron for post-operative nausea and vomiting.

By keeping confidence interval at 95%» and power at 80%. We presumed a general incidence of nausea and vomiting to be 50% and hypothesized that olanzapine would reduce the incidence of PONV. A minimum sample size required to detect a difference of 50% in the incidence of nausea and vomiting between two group is 58 patients in each group. We included 60 patients in each group for better validation of results.

Demographic data

Demographic data comparing age, sex, weight, height, ASA grade, duration of surgery shows no statistically significant difference among both the groups.

Hemodynamic variations

In our study, mean heart rate between two groups, intraoperatively at intervals of induction, 80min, and 85min, group A had statistically significant higher values when compared to group B and there was no significant increase in heart rate clinically.

Mean arterial pressure between two groups, intraoperatively at intervals of induction, 40min, 45min, 55min, 60min, 65min and 70min, group A had statistically significant higher values when compared to group B and there was no significant increase in mean arterial pressure clinically not more than 20% from baseline.

In a study by Mohamed Ibrahim et al, they found that better pain tolerance in olanzapine receiving patients, they concluded that olanzapine may reduce opioid requirements. In our study heart rate and mean arterial pressure was maintained in olanzapine group compared to ondansetron group might be due to analgesic action of olanzapine.

In a study by Mohamed Ibrahim et al, they found no significant differences between olanzapine and ondansetron groups regarding mean vital signs recorded intraoperative and postoperatively which was similar to our study clinically.

In preoperative period none of them in both groups had nausea and vomiting.

PONV

In our study, we observed in the 1st hr that group A had no incidence of nausea or vomiting where as 6.7% of subjects in group B had nausea and vomiting. Mean PONV score at 1sthrwas lower in group A compared to group B ($p< 0.001$).

At intervals of 2hr, 6th hr, 12th hr, group A had15%, 6.7% and 5% nausea and vomiting but in group B we noted incidence of 5%, 3.3%, 1.7% respectively.

At18th hr group A did not have any episode of nausea and vomiting but group B had 3.3%. Mean PONV score was higher in Group A than Group B at 1 to 24 hr.

In a study by Mohamed Ibrahim et al[23] 48%, 38% of patients who received olanzapine 5mg, ondansetron 16mg had vomiting and received rescue antiemetic in 24hr observation period. In our study we observed that Complete response(CR) at acute period was seen in 96.7%subjects in group A and in 85% subjects in group B with p=0.027.During late period complete response was seen in 75% and in 91.7% of subjects in Group A and B respectively with p=0.014.

Overall incidence of PONV during 1-24hr postop period was 17 patients in group A (28.3%)compared to 14 patients in group B (23.3%) which was statistically not significant with p=0.62 This was similar to study conducted by Mohammed Ibrahim et al.

Mohammed Ibrahim et al in their study noted that CR at acute period for ondansetron was90 %(p= 0.04) and olanzapine 5mg was 73%(p=0.48) and for late period CR rates for ondansetron and olanzapine5mg (p>0.005). For acute period, ondansetron 16mg was better but was not significant whereas in late period olanzapine 5mg was found to be better but was not significant.

Navari RM, Jung SH,.et al in their Phase II study in 2005, the regimen consisted of 5mg/day of oral olanzapine on the 2 days prior to chemotherapy, 10 mg on the day of chemotherapy, day 1,(added to i.vgranisetron,10µg/kg and dexamethasone 20mg),and 10mg/day on days 2-4 after chemotherapy(added to dexamethasone, 8mg p.o. BID days 2 and 3,and 4rng p.o. BID day 4).Thirty patients were included in their study.

Complete response (no emesis, no rescue) was 100% for the acute period (24hr post chemotherapy), 80% for the delayed period (days 2-5 post chemotherapy), and 80% for the overall period (0-120 h chemotherapy) in ten patients receiving highly emetogenic chemotherapy.

They concluded that olanzapine is safe and highly effective in controlling acute and delayed CINV in patients receiving highly and moderately emetogenic chemotherapy. In our study too, we found that ondansetron had complete response in acute period and olanzapine had CR for late period.

Rescue antiemetic given and the time required between two groups-It was seen in our study that group A 28.3% of subjects and in group B 18.3% of subjects required rescue antiemetic. Mean time of rescue antiemetic in group A was 1.6 + 3.1 hrs and in group B was2.6+8.2 hrs. There was no significant difference in time of rescue antiemetic given and the time between two groups.

In a study by Mohamed Ibrahim et al 48%, and 36% patients receiving olanzapine 5 mg and ondansetron 16 mg respectively required antiemetics.

Time of Rescue analgesia and postoperative VAS score between two groups

It was seen in our study that mean time of rescue analgesic in group A was 6 + 1.8 hrs and in group B was 8.2+2 hrs. i.e. Group A required rescue analgesia at a shorter duration compared to group B which, there was no significant difference in Mean or Median VASscore between two groups except at 6th hr and 24th hr. At 6thhr Median VAS score was 4 in group A and 3 in group B, at 24thhr median VAS score was 2 in group A and group B respectively. In group A, rescue analgesic was received at 3rdhr, 5thhr, 6thhr was 16.6%, 16.6%, 33.3% respectively whereas in group B rescue analgesia was received only by 6thhr which was 30%.

In a study by Mohamed Ibrahim et al, they found that better pain tolerance in olanzapine receiving patients, they concluded that olanzapine may reduce opioid requirements.

Mohammed Ibrahim et al in their study, 45% of patients received rescue analgesia's with a better tolerance in olanzapine patients. They concluded that olanzapine may reduce opioid requirements. This was similar to our study[14].

RSS Score comparison between two groups-

Median RSS score was significantly high in group B compared to group A at all the interval from Pre op to post op 24hrs with p<0.05. This was statistically significant. In a study by Mohamed Ibrahim et al Olanzapine 5mg and 10mg were not associated with significant sedation. But in our study, we found arousable sedation in olanzapine group[15].

In our study we did not find any significant side effects like headache, restlessness, abnormal movements, arrhythmias. In a study by Mohamed Ibrahim et al, headache was seen in ondansetron group (6%) which was insignificant, when compared to olanzapine group. This was similar to our study results.

Conclusion

To conclude, our study demonstrates that premedication with oral olanzapine 5mg provides reduction in the overall incidence of post-operative nausea and vomiting (PONV) which is comparable to ondansetron in patients undergoing general anaesthesia. It also reduced analgesic requirement and causes arousable sedation postoperatively.

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