Original Article

Comparison of equipotent doses of Ramosetron, Ondansetron, and sub-hypnotic dose of Propofol for prevention of postoperative nausea and vomiting in laparoscopic cholecystectomy

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Abstract

Background and Aims: For prevention of Postoperative nausea vomiting (PONV) in laparoscopic surgery, ramosetron is a selective 5-HT3 receptor antagonist with higher receptor affinity and slow dissociation than ondansetron. We compared these 2 drugs with propofol which has also shown antiemetic properties.The aim was to study ondansetron, ramosetron, and propofol with respect to incidence of PONV, its severity and the need for rescue antiemetic along with the side effects. Prospective, randomized, double blind study.

Material and Methods: We compared antiemetic properties of ondansetron (4 mg i.v; n = 40) and ramosetron (0.3 mg i.v; n = 40) with propofol (0.5 mg/kg i.v; n = 40) on 120 ASA I/II patients scheduled for laparoscopic cholecystectomy. The side effects associated with study drugs, time to recovery from anesthesia, readiness for PACU discharge and patient satisfaction was also compared. Qualitative data variables are expressed by using frequency and percentage and quantitative data variables are expressed by using mean and SD. Quantitative data variables were compared using ANOVA test and others were compared by post hoc ANOVA Tukey's test.

Results: Incidence of vomiting and need for rescue antiemetic was lowest with Ramosetron and highest in Propofol group. Time to recovery was more in Propofol group which was statistically significant. Readiness for PACU discharge was comparable in all the three groups.

Conclusion: Subhypnotic dose of propofol requires more rescue antiemetic than Ondansetron and Ramosetron because of its short duration of action. Between Ondansetron and Ramosetron the latter is more effective in PONV prevention.

Keywords: Laparoscopic cholecystectomy, ondansetron, postoperative nausea vomiting, ramosetron, sub-hypnotic propofol

Introduction

In spite of discovery of newer anti-emetics, postoperative nausea vomiting (PONV) still remains the second most common postoperative complication, owing to its multifactorial aetiology. The incidence increases further in laparoscopic surgeries, accounting to almost 40-75%. PONV not only increases hospital stay and cost but can also lead to complications like dyselectrolytemia, bleeding, wound dehiscence and aspiration of gastric contents.[1-3]

Selective 5-HT3 receptor antagonists are the first line drugs in prevention of PONV as they are highly efficacious, with minimal side effects. Ondansetron is a prototype 5-HT3

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antagonist and has established its place over the years. Ramosetron, a relatively newer addition to this class, has a higher affinity to the receptor and a slower dissociation. Hence, it has a longer duration of action.[4,5]

Propofol has been reported to be an effective antiemetic at low doses in patients undergoing anticancer therapy and surgery. Its mechanism of action however remains unclear.[6-8]

We undertook the present study to compare the anti-emetic efficacy of propofol with ondansetron and ramosetron, with primary outcome being the incidence of PONV. The secondary outcomes included severity of PONV, need for rescue antiemetic, times to recovery from anesthesia, and readiness for PACU discharge, complications as well as patient satisfaction.

Material and Methods

We enrolled 120 patients aged between 18 and 60 years, with ASA physical status I and II, and scheduled for laparoscopic cholecystectomy under general anesthesia in this prospective, randomized, double-blind clinical study. Patients who had taken steroids or antiemetics 24 h before surgery, or who had gastrointestinal diseases or motion sickness, and those with history of PONV were excluded. Recruited patients were allocated randomly to groups of 40 each and they received one of the following three drugs at the end of surgery: intravenous (IV) ondansetron (4 mg), ramosetron (0.3 mg) or propofol (0.5 mg/kg). A computerized randomization list was generated, and the study drug was administered by personnel not involved in the study, according to the list. Both, the observer as well as the patient were unaware of the study drug administered [Figure 1].

After explaining the procedure and the nature of safety of the procedure, a written, valid, informed consent was obtained. Patients were kept fasting for 6 hours before surgery. Patients were given tablet ranitidine 150 mg at night and in the morning before surgery.

In the operation theatre (OT), intravenous access was secured and an infusion of lactated Ringer's solution initiated. Monitors were attached and standard anesthesia technique used for induction of general anesthesia. Hemodynamic variables were measured on arrival to the OT and every 5 min thereafter till the end of surgery.

Patients were premedicated with midazolam 0.02 mg/kg, glycopyrrolate 5 mcg/kg and fentanyl 2 mcg/kg. Anaesthesia was induced with propofol 2 mg/kg and tracheal intubation was done under muscle relaxation of vecuronium bromide 0.08 mg/kg. Anesthesia was maintained by O2 + N2O (50-50%) with Isoflurane. End-tidal CO2 was maintained between 35 and 40 mm of Hg. Pulse rate, electrocardiogram, NIBP, and oxygen saturation were monitored continuously throughout the procedure.

Patients in Group I were administered intravenous ondansetron 4 mg, those in Group II were given intravenous ramosetron 0.3 mg and those in Group III received intravenous propofol 0.5 mg/kg, just before the removal of the umbilical port. The person who administered the drug was not included in any part of the study observation thereafter. The observer who monitored the patient for incidence of PONV was hence unaware of the study drug received by the patient. At the end of procedure, neuromuscular blockade was reversed with neostigmine 50 mcg/kg and glycopyrrolate 10 mcg/kg. After extubation, patients were shifted to recovery room for further observation. Duration of surgery and time to recovery i.e., stopping of isoflurane to time of extubation were noted.

Postoperatively patients received diclofenac sodium 75 mg intramuscularly 8 hourly. Paracetamol 1 gm intravenously was given as a rescue analgesic. Patients were observed postoperatively by an anesthetist, unaware of which group the patient belonged to. All patients were observed at three time intervals of 0-1, 1-6, and 6-24 hrs for nausea and vomiting score. No nausea or vomiting was assigned a PONV score of 0, the score was 1 if patient had only nausea without vomiting, 2 if both nausea and vomiting were present and the score was 3 if patient had more than 2 episodes of vomiting within 30 minutes.

If the events of vomiting or retching were separated by more than 2 mins, they were considered as separate events. Patients with PONV score of 2 or more were given rescue antiemetic metoclopramide 0.15 mg/kg. Patients were asked to rate the nausea (0- no nausea to 10-worst imaginable nausea). Patient satisfaction was graded as a subjective criteria by the patient, (0-no satisfactions to 10- complete satisfaction) with respect to their overall postoperative experience. Complete response was studied as a separate criteria to emphasize on the complete efficacy of the drug/s studied. It indicated a total absence of nausea &/or vomiting during the entire study period of 24 hours. It was compared among all the study groups. Time to readiness for discharge from PACU (time to achieve Aldrete score 9) was also recorded.

Data analysis was done by using SPSS version 20:0. Qualitative data variables are expressed by using frequency and percentage while quantitative data variables were expressed by using mean and SD. The quantitative data variables within the three groups were compared using ANOVA test. The

incidence of post-operative nausea and vomiting at different time intervals was compared amongst the groups, in pairs, using the Mann Whitney U test. Qualitative data variables were compared using Chi-square test. A *P* value of <0.05 was considered as statistically significant.

The sample size was calculated considering 80% power by using 2 sample proportion formula. We have calculated 2 sample sizes for comparison of group I Vs group II and group I and group III. We considered the maximum sample size amongst these, for comparing three groups in our study.

Proportion of occurrence of PONV was considered by using previous hospital data as well as previous studies which quote an incidence as high as up to 75%.[1-3]

Results

Demographic parameters, as well as duration of surgery, duration of anesthesia, and patient satisfaction score were comparable in all the three groups. Time to recovery was prolonged in group III as compared to other two groups. ($p < 0.001$) [Table 1].

Incidence of vomiting was 17.5%, 7%, 7% in 0-1 hour interval ($p = 0.359$); 7.5%, 4%, 4% in 1-6 hour interval in groups I, II and III respectively ($p = 0.105$). This difference was not statistically significant. However, in the 6- to 24-hour interval, no patient in Group I and II had vomiting while 20% patients in Group III had vomiting out of which 7.5% had grade III PONV ($p < 0.001$). [Figure 2].

Incidence of nausea was 60%, 66.6%, and 70% in 0-1 hour interval; 43%, 45.5%, 56% in 1-6 hours interval; 26%, 4%, 63% in 6-24 hours interval. The difference was not statistically significant [Figure 3]. Median nausea score in group I was 3,1,0; in group II was 2,0,0 and in group III was 2,2,4 in 0-1, 1-6, and 6-24 hour interval, respectively [Table 2]. In the first post operative hour the scores were comparable, in 1-6 hr interval the score was significantly higher in group III whereas in 6-24 hr interval the score was significantly lower in group II.

On comparing the grade of PONV during the first postoperative hour there was no statistically significant difference between the three groups. None of the patients in any of the study group had PONV score of 3.

During 6-24 hours postoperatively, all patients in group II had PONV score 0. The difference in the score was statistically significant in the 1-6 and 6-24 hour intervals. [Figure 4] The incidence of 'Complete response' was 32.5% in group I, 40% in group II and 22.5% in group III ($p = 0.002$). It was highly significant statistically. Rescue antiemetic requirement was comparable in all the three groups ($p = 0.199$) during the study period of 0-24 hrs. [Figure 5] Rescue analgesic requirement was comparable in all three groups. ($p = 0.493$).

Patient satisfaction score was better in group II as compared to group I and III but the difference was not statistically significant. One patient in group I had headache and 2 patients developed rash after injection. No patient in group II and III had any side effects.

Discussion

One of the commonest and distressing side effects after laparoscopic cholecystectomy is Postoperative nausea and vomiting (PONV), the incidence approaching to the tune of 46–72% in the absence of any prophylaxis.[9-11] A few studies have compared ramosetron and ondansetron to prevent postoperative nausea and vomiting in high risk surgeries. There are studies comparing antiemetic effects of ramosetron and granisetron for preventing vomiting associated with cisplatin chemotherapy.[12-15]

Celik *et al.* have compared subhypnotic doses of propofol with dexamethasone for prevention of PONV in patients undergoing laparoscopic cholecystectomy.[16] There is no study in literature, comparing subhypnotic doses of propofol with the 5HT3 antagonists for prevention of PONV in high-risk surgeries. Hence, we designed this unique study which compares the incidence of early as well as late PONV following laparoscopic cholecystectomy associated with the use of ondansetron, ramosetron, and subhypnotic doses of propofol.

Our study shows that ondansetron, ramosetron, and propofol are comparable in 0-1 and 1-6 hours interval with respect to the incidence of postoperative nausea as well as vomiting but after 6 hours, propofol group showed increased incidence of nausea and vomiting which is statistically significant ($p < 0.05$). When compared pair-wise, we found that ondansetron and ramosetron groups had comparable incidence of PONV up to 6 hours however in the 6-24 hours interval ramosetron had significantly lower incidence. Kim *et al.* concluded that ramosetron was as effective as ondansetron in decreasing the incidence of PONV and reducing nausea severity in female patients during the first 24 h after gynecological surgery.

In contrast to our study, they concluded that the incidence of nausea and vomiting was lower in both the ramosetron and the ondansetron groups than in the placebo group during the first 24 h after surgery. This difference in results could be because the dose of ondansetron studied by Kim at al was

Table 1: Demographic parameters, surgery and anaesthesia duration, time to recovery, time to PACU discharge, patient satisfaction. Values are mean (SD) except for sex distribution and ASA status.(* statistically significant)

Parameter	Group I	Group II	Group III	*P*
Age (years)	36.1 (11.12)	41.3 (9.6)	39.5 (10.8)	0.108
Sex (M: F)	19:21	20:20	23:17	0.647
BMI (kg/m^2)	21.54 (3.43)	23.80 (2.44)	23.04 (3.21)	0.796
ASA (I: II)	18:22	25:15	22:18	0.564
Surgery duration (min)	120.3 (9.4)	123.0 (6.3)	119.2 (5.7)	0.131
Anesthesia duration (min)	133.1 (9.1)	135.8 (5.6)	133.7 (4.6)	0.274
Time to recovery (min)	9.8 (1.8)	10.1 (1.0)	14.6 (1.3)	<0.001*
Patient satisfaction score at 24 hrs	7.1 (2.2)	8.0 (2.1)	7.3 (2.0)	0.258
Readiness for PACU discharge (min)	19.9 (2.4)	18.3 (1.9)	20.5 (2.8)	0.171

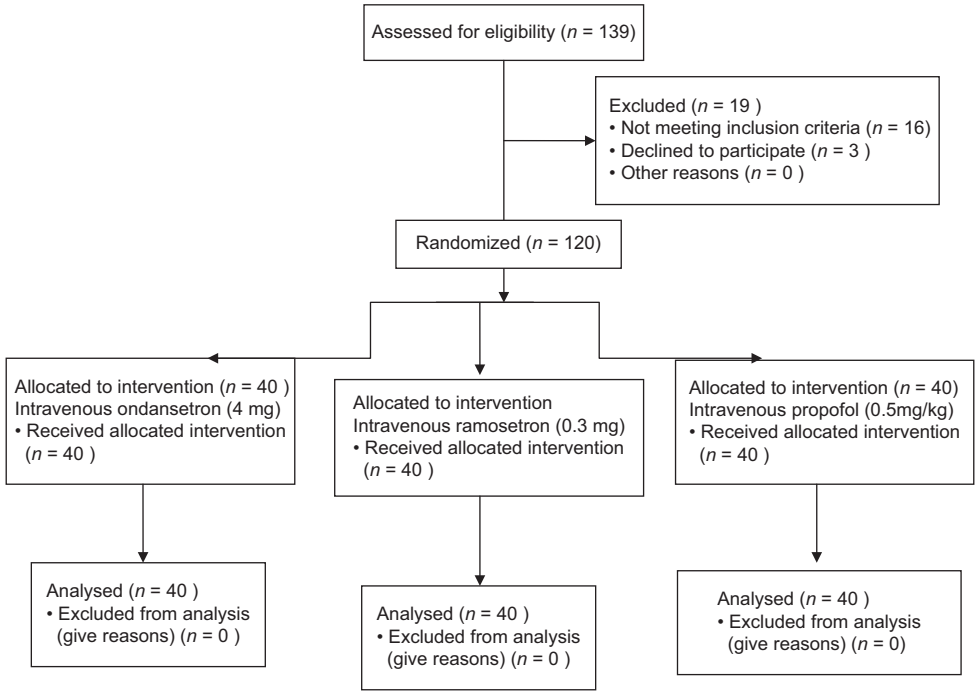

Figure 1: Consort Flow

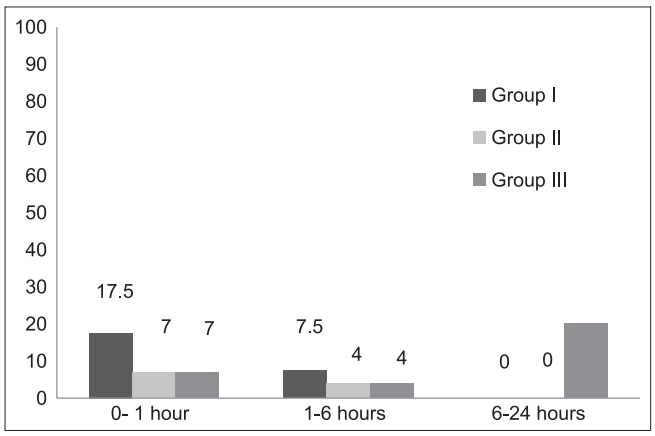

Figure 2: Incidence of postoperative vomiting at 0-1 hour, 1-6 hours and 6-24 hours

8 mg whereas we used ondansetron 4 mg for comparison considering the equipotency.[17,18]

Our study shows statistically significant prolonged time to recovery in propofol group; however, the time to achieve an Aldrete of 9 was comparable in the three groups. Similar results were obtained by Song *et al.* in their study which proved that 0.5 mg/kg propofol is an effective antiemetic after laparoscopic cholecystectomy; it prolongs time to awakening but not time to discharge.[19] Kim *et al.* also studied propofol 0.5 and 1 mg/kg and showed decreased incidence of PONV and slightly longer emergence time in propofol group as compared to placebo.[6]

Khosrou N. *et al.* did a placebo-controlled study comparing two doses (10 and 30 mg) of propofol and metoclopramide. They found a trend towards increased complete response in 30 mg propofol dose in 0-6 hour interval. The result is similar to our study.[20] The PONV score were comparable in all 3 groups in the first postoperative hour and no patient

Table 2: Pair wise comparison of incidence of PONV (*P*)

	Grp I Vs II	Grp I Vs III	Grp II Vs III
Nausea 0-1 hr	0.981	0.067	0.120
Nausea 1-6 hrs	0.781	0.002	0.003
Nausea 6-24 hrs	0.014	0.001	<0.001
Vomiting 0-1 hr	0.974	0.856	0.862
Vomiting 1-6 hrs	0.709	0.058	0.081
Vomiting 6-24 hrs	0.001	0.002	0.006

had score of 3. However, in the 1-6 hour and 6-24 hour the score was significantly higher in ondansetron and propofol group as compared to ramosetron. This can be explained by the pharmacokinetic profiles of the drugs and attributed to longer duration of action of ramosetron as compared to propofol and ondansetron.[5,6,15]

In our study we found that the patient satisfaction was better with ramosetron which could be attributable to lower incidence of nausea and vomiting in 6-24 hours interval. However, it was not statistically significant. The requirement of rescue antiemetic was comparable in all three groups during the study period. This was because we gave rescue antiemetic only in patients with PONV score 2 or more.

Since our study compares anti-emetic efficacy of different drugs, a single anti-emetic had to be used even though the surgery is laparoscopic cholecystectomy which is associated with high risk of PONV. Various previous studies have also used single anti-emetic agents to compare their efficacy, when used in laparoscopic and other surgeries associated with similar risk of PONV.[6,16,19,21] In our study design we have excluded all the other factors that are associated with increased PONV risk such as patients with previous history of nausea, vomiting, or motion sickness. Also, we have not used postoperative opioids.

There are a few limitations of our study. This is not a placebo-controlled study. Ramosetron is a costlier drug as compared to ondansetron and hence further studies are required to quantify the cost effectiveness of the drug. We have used nitrous oxide and inhalational agents for maintenance and hence their effect on incidence of PONV, though minimal, could not be negated.

We hereby conclude that Propofol is not effective as a sole antiemetic agent for laparoscopic cholecystectomy. Amongst ondansetron and ramosetron latter provides effective and prolonged antiemesis at equipotent doses.

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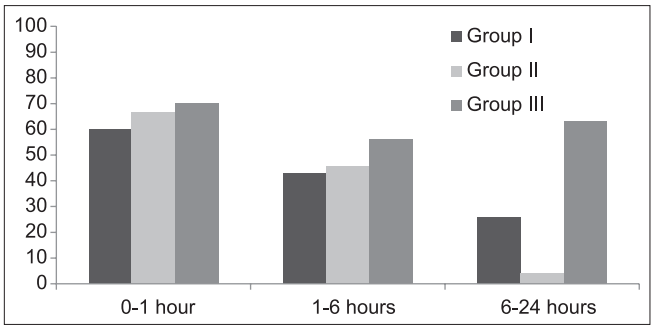

Figure 3: Incidence of postoperative nausea at 0-1 hour, 1-6 hours and 6-24 hours

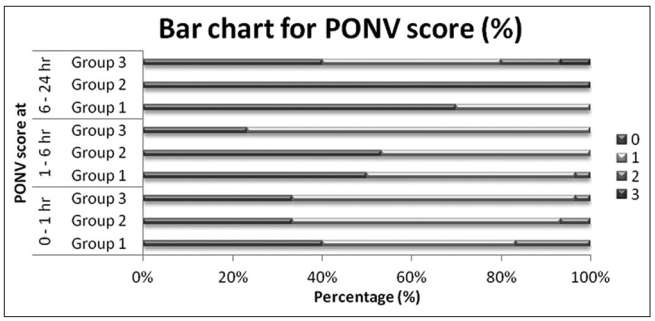

Figure 4: Comparison of PONV score

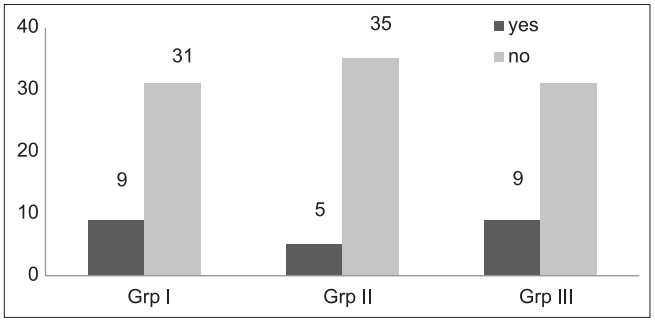

Figure 5: Comparison of the requirement of rescue anti-emetic

Conflicts of interest

There are no conflicts of interest.

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