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RESEARCH ARTICLE

ONDANSETRON AND PALANOSETRON FOR PREVENTION OF POST-OPERATIVE NAUSEA AND VOMITING IN LAPAROSCOPIC CHOLECYSTECTOMY: A COMPARATIVE STUDY

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ABSTRACT

Introduction: The incidence of post-operative nausea and vomiting remains unacceptably high in the first 24 hours without active intervention following laparoscopic cholecystectomy. Post-operative nausea and vomiting like postoperative pain, is a complication that delays recovery, prolongs hospital stays, and increases costs due to additional drug use. The quest for more effective antiemetic drug without sedative or extrapyramidal side effects has led to the recent development of relatively new class of drugs such as Ondansetron and Palanosetron.

Aim: To compare the antiemetic effects of Ondansetron and Palonosetron for prevention of post-operative nausea and vomiting in laparoscopic cholecystectomy.

Material and Methods : In all 100 patients aged 18 to 60 years scheduled for laparoscopic cholecystectomy in Poona Hospital & Research Centre, Pune between December 2014 and November 2015 under general anaesthesia and ready to participate in this prospective, observational double blind randomized study were included. They were randomly divided into two equal groups of 50 each, using computer generated randomization code. Group O patients received 4 mg Ondansetron whereas Group P patients received 0.075 mg Palonosetron. Episodes of post operative nausea & vomiting were determined and recorded after operation at different time intervals. Patients' satisfaction grades were recorded. The comparison of quantitative variables was done using unpaired student's "t" test, whereas comparison of qualitative variables was done by using chi-square test or Fisher's exact test.

Results: Incidence of nausea and vomiting was significantly higher in Ondansetron Group compared to Palonosetron Group during 0 to 6 hours. Incidence of nausea and vomiting did not differ significantly between two groups at 6 to 24 hours and 24 to 72 hours.

Conclusions: Palonosetron is an effective antiemetic than Ondansetron in early post operative period.

INTRODUCTION

The overall incidence of post-operative nausea and vomiting (PONV) can rise to 80% in high-risk patients.[1] The incidence of PONV remains unacceptably high (40-75% in the first 24hours, without active intervention) following laparoscopic cholecystectomy.[2,3] PONV, like postoperative pain, is a complication that delays recovery, prolongs hospital stays, and increases costs due to additional drug use.[4] A previous history of PONV, female gender, non-smoking and postoperative opioid administration are the most important predictors of developing PONV.[5]

Commonly used agents to prevent or treat PONV are dopaminergic, histaminic and muscarinic antagonists. These agents are metoclopramide, droperidol and hyoscine. These are effective to varying degrees and have poor side effect profiles. This restricts their effective use, particularly as prophylactic antiemetic's. Metoclopramide a selective dopaminergic receptor antagonist is often associated with distressing extra pyramidal reactions and sedation. Droperidol is a powerful antidopaminergic agent. Its side effects include extra pyramidal reactions, hypotension, and post-operative sedation. The side effects of commonly used antihistaminic agents include sedation, hypotension, dysphoria, unsteadiness and dry mouth. The side effects of hyoscine are dry mouth, sedation, and occasional disorientation.

The quest for more effective antiemetic drug without sedative or extrapyramidal side effects has led to the recent development of relatively new class of drugs. The 5-Hydroxytryptamine (5-HT_3) receptor antagonist is being commonly used because it is more effective in PONV prevention and treatment than other antiemetics and has few side effects.[6] Among 5-HT_3 receptor antagonists, ondansetron is the most widely used drug. Recently, palonosetron has been reported to be more effective in the prevention of PONV. [7, 8]

Ondansetron was the 1st serotonin antagonist and it's introduction was a milestone in prevention of early

chemotherapy induced nausea and vomiting. It was considerably more effective and had fewer side effects (no extra pyramidal symptoms or sedation) compared with all previous antiemetics. Ondansetron has a plasma half life of 4 hours and is metabolized via CYP2D6 such that select genetic polymorphisms of P450 enzymes can lead to decreased efficacy due to ultra rapid metabolism.

Palonosetron is a newly developed 5-HT3 receptor antagonist. Its receptor affinity is more potent than other 5HT3 antagonists. The mean terminal elimination half life, following single intravenous dose, is approximately 40 hours. Therefore, the duration of action exceeds 24 hours and may extend to 48 hours.

AIM: To compare the antiemetic effects of Ondansetron and Palonosetron for prevention of post-operative nausea and vomiting in laparoscopic cholecystectomy.

MATERIAL AND METHODS

All the patients aged 18 to 60 years scheduled for laparoscopic cholecystectomy in Poona Hospital & Research Centre, Pune between December 2014 and November 2015 under general anaesthesia and ready to participate in this prospective, observational double blind randomized study were included. Permission was obtained from Institutional Ethics Committee and Scientific Advisory Committee of the institution. The study was carried out on 100 indoor patients undergoing laparoscopic cholecystectomy under general anesthesia.

Inclusion criteria: Patients age 18 yrs to 60 yrs, American Society of Anaesthesiologist (ASA) grade I and II

Exclusion criteria: Absence or withdrawal of written informed consent, pregnant or lactating women, patients with history drug intake with a potential anti-emetic effect within 24 hours prior to the administration of anesthesia, patients with history of vomiting, retching, or nausea in the 24 hours preceding the administration of anesthesia, patients converted to open cholecystectomy, and known hypersensitivity to study medications.

Based on previously published studies [9], and setting alpha error at 0.05, and power at 80%, the required sample size of 50 in each group was calculated by formula. [10] In all 100 ASA grade I and II patients scheduled for laparoscopic cholecystectomy under general anaesthesia were included in the study. They were randomly divided into two equal groups of 50 each, using computer generated randomization code.

Group O– Patients received 4 mg Ondansetron
Group P –Patients received 0.075 mg Palonosetron

The randomization code was provided to operation theatre nurse who prepared the study medication (Ondansetron or Palonosetron) in 5 ml volume in identical syringes under the supervision of senior anaesthetist. Researcher and the patients were blind as to group assignment.

Written informed consent for surgery and for participation in the study was taken from all the patients. Detailed pre-anesthetic checkup was done for anesthetic fitness for the surgery. Patients were asked to remain NBM for six hours before surgery. During the pre-operative visit day before surgery, all patients were thoroughly explained about PONV. All patients were instructed to report episodes of PONV.

In OT, adequate IV access was confirmed. Standard monitors were attached. All patients were premedicated with IV Glycopyrolate 0.2 mg and Inj. Ranitidine 50 mg. Inj. Ondansetron 4mg, or Palonosetron 0.075mg, in 5 ml volume in identical syringes, was given according to group assignment, as described above. The pulse, arterial blood pressure (both systolic and diastolic), saturation and electrocardiogram were recorded immediately after injecting the drug in all the patients.

After pre-oxygenation for three minutes, induction was carried out with IV Propofol 2 mg/kg. Intubation was facilitated by using Inj. Succinylcholine 2 mg/kg. Patients were intubated orally with portex endotracheal tube (ETT) of appropriate size. ETT placement was confirmed. 16 F orogastric tube was placed for deflating the stomach. This was removed at the end of surgery. Anesthesia was maintained with N_2O: O_2 70:30, Sevoflurane 1.5- 2.5 % (adjusted according to clinical signs) with controlled ventilation. End Tidal CO_2 (ET CO_2) was maintained between 30-35 mmHg. Supplemental doses of Atracurium were 0.1mg / kg. Half of the preoperative fluid deficit was corrected within the first hour and the remaining half subsequently.

The operating table was tilted to 15-20° Trendelenburg position and CO_2 gas was insufflated into the abdominal cavity through a Veress needle inserted into the incision below the umbilicus. After creating a state of pneumoperitoneum, the operation was done with the patient in an inverse Trendelenburg position with a right-side-up tilt. To minimize hemodynamic and respiratory effects, the abdominal pressure was maintained at 12 mm of Hg. All patients received diclofenac sodium 75 mg IM approximately 20 minutes before the end of surgery. All patients received local anesthetic infiltration of four trocar sites by using 5 ml for each port and a total of 20 ml solution of Bupivacaine 0.25% at the end of operation before closure of the wound.

After the surgery was completed, the operating surgeon pressed on the patient's abdomen by hand to remove the remaining CO_2 within the abdominal cavity before inserting closing stitches. After surgery was over and spontaneous respiratory efforts appeared, residual muscle relaxation was reversed with Inj. Neostigmine 50mcg / kg and Inj. Glycopyrolate 40 mcg / kg. After confirming adequate reversal and return of consciousness patients were extubated and shifted to post anesthesia care unit. The operative time for each procedure was noted.

Each episode of nausea, retching and/ or vomiting was recorded. For the purpose of the study, an episode of PONV denoted either a distinct spell of nausea, retching (an involuntary attempt to vomit but not actually productive of stomach contents) or vomiting (actual expulsion of stomach contents). The primary effectiveness measure was the total number of PONV episodes in the 72 hrs period following conclusion of laparoscopic surgery. The secondary efficacy variables were:

- Frequency of nausea and emetic episode (one or more instances of vomiting and/ or retching separated by no more than one minute of respite) in the 72 hours period following the surgical procedure.
- Use of rescue antiemetic medication (metoclopramide 10 mg orally).

- Overall satisfaction with the nausea-vomiting experience on a four-point Linkert scale (dissatisfied, neutral, satisfied, and highly satisfied) at 24 hrs after surgery completion.

Episodes of Post operative nausea & vomiting were determined and recorded after operation at different time interval of 0,2, 6, 24,48,72 hours. Rescue medicine Inj. Metoclopramide 10 mg was given to all patients who had two or more episodes of PONV or on patients demand. Patients' satisfaction grades were also recorded.

Data collected were entered in the Excel 2007 and analysis of data was done using Statistical Package for Social Sciences (SPSS) version 20. The comparison of quantitative variables between the groups such as mean age, mean duration of anesthesia, mean duration of surgery, mean pulse rate, mean systolic blood pressure, mean diastolic blood pressure was done using unpaired student's "t" test, whereas comparison of qualitative variables such as gender, age groups, weight, ASA grade , patients satisfaction, rescue analgesia, post operative nausea and vomiting was done by using chi-square test or Fisher's exact test . The confidence limit for significance was fixed at 95% level with p-value < 0.05

RESULTS

Between December 2014 and November 2015, 50 patients in each group were recruited for the study.

Table 1 Demographic profile

Demographic characteristic	Ondansetron Group (N = 50)	Palonosetron Group (N = 50)	p value
Mean age in years (SD)	43.2(± 11.0)	42.5(± 11.5)	
Age group, no (%)			
20-30 years	8 (16.0)	9 (18.0)	
31-40 years	11 (22.0)	12 (24.0)	
41-50 years	17 (34.0)	13 (26.0)	0.857
51-60 years	14 (28.0)	16 (32.0)	
Gender, no (%)			
Male	26 (52.0)	26 (52.00)	0.689
Female	24 (48.0)	24 (48.00)	
Weight in Kgms, no (%)			
40-49	11 (22.0)	13 (26.0)	
50-59	24 (48.0)	19 (38.0)	
60-69	14 (28.0)	14 (28.0)	0.467
≥ 70	1 (2.0)	4 (8.0)	
ASA Grade (%)			
I	22(44.0)	28(56.0)	

As shown in Table 1, the two groups were demographically comparable. There was no statistically significant differences with respect to mean age, age groups, sex distribution, weight and ASA distribution between the two groups.

As depicted in Table 2, there was no statistically significant differences in mean duration of surgery, mean duration of anaesthesia, pre-operative mean pulse rate, mean systolic blood pressure, mean diastolic blood pressure, after giving drug mean pulse rate, mean systolic blood pressure, mean diastolic blood pressure, patient satisfaction, administration of rescue analgesia between the two groups.

Table 2 Post-operative characteristics

Characteristic	Ondansetron Group (N = 50)	Palonosetron Group (N = 50)	p value
Mean Duration of surgery in min (SD)	59.0 (± 6.3)	58.6(± 8.2)	0.785
Mean Duration of anaesthesia in min (SD)	74.8 (± 7.1)	75.2(± 9.8)	0.817
Pre-op findings(SD)			
Mean Pulse rate (Per min)	77.7 (± 10.0)	78.8(± 9.2)	0.569
Mean Systolic BP (mmHg)	121.4(± 7.9)	123.5(± 5.8)	0.127
Mean Diastolic BP (mmHg)	78.2(± 6.6)	80.4 (± 6. 9)	0.101
After giving drug(SD)			
Mean Pulse rate (Per min)	79.0 (± 10.5)	80.3(± 8.9)	0.525
Mean Systolic BP (mmHg)	123.4(± 8.4)	124.4(± 8.1)	0.516
Mean Diastolic BP (mmHg)	78.1(± 6.0)	76.0 (± 6. 4)	0.107
Patient Satisfaction, no (%)			
Highly satisfied	12 (24.0)	16 (32.0)	
Satisfied	15 (30.0)	18 (36.0)	0.525
Neutral	13 (26.0)	10 (20.0)	
Dissatisfied	10 (20.0)	6 (12.0)	
Rescue analgesia no (%)			
Not given	40 (80.0)	44 (88.0)	0.275
Given	10 (20.0)	6 (12.0)	

Table 3 Post operative nausea and vomiting

Characteristic	Ondansetron Group (N = 50)	Palonosetron Group (N = 50)	p value
Nausea (%)			
0-6 hours	26 (52.0)	9(18.0)	0.001
6 – 24 hours	11(22.0)	15(30.0)	0.362
24- 72 hours	16(32.0)	13 (26. 0)	0.509
Mean vomiting episodes (SD)			
1-6 hours	0.20 (0.53)	0.04(0.19)	0.050
6 – 24 hours	0.08(0.27)	0.06(0.31)	0.735
24- 72 hours	0.00	0.00	0.999

As depicted in Table 3, there was statistically significant differences in incidence of nausea and vomiting between the two groups. Incidence of nausea and vomiting was significantly higher in Ondansetron Group compared to Palonosetron Group during 0 to 6 hours. Incidence of nausea and vomiting did not differ significantly between two groups at 6 to 24 hours and 24 to 72 hours.

DISCUSSION

Today laparoscopic cholecystectomy is one of the most commonly performed procedures in general surgery. It is considered the "gold standard" for the surgical treatment of gallstone disease, with more than 5,00,000 procedures performed annually in the world.[11] Various studies reported that post-operative period was associated with variable incidence of nausea and vomiting depending on the duration of surgery[12,13], the type of anesthetic agents used (dose, inhalational drugs, opioids) [14,15], smoking habit [16] etc. The incidence of PONV was 20- 30% after general anesthesia with volatile anesthetics and up to 70% to 80% in high risk patients such as abdominal, gynaecologic, eye, ear, nose and throat and breast surgery, any surgery lasting over 30 minutes[13,17],female, young age, history of motion sickness, history of prior postoperative nausea and vomiting, non-smoker, family history of PONV.[16,18]

There are several types of antiemetic used in the management of PONV currently. In 1930's promethazine was introduced into anaesthetic practice and its significant effects on PONV has been reported. Its side effects includes mainly sedation and hypotension and limits its use as an antiemetic.

Prochlorperazine was introduced in anesthetic practice in 1950's .[19] It's side effects include sedation and extrapyramidal reactions. Droperidol an butyrophenone derivative was introduced in 1950's to decrease incidence of PONV. It's side effects include extrapyramidal reactions, sedation and increases hospital stay. Metoclopramide a gastrointestinal prokinetic (benzamide) drug was developed in the early 1960's. It's side effects include sedation, extra pyramidal reaction. Other benzamides include Cisapride, Alizapride, Clebopride.

None of the above alone or in combination have been entirely successful in mitigating the distressing occurrence of emesis and its potential sequel. All the compounds available for prevention or treatment of emesis had significant side effects. This limited their use for the treatment of emesis rather than prophylactic use. Recently a study has reported the effectiveness of Ondansetron , a selective 5-HT3 antagonist, for PONV with fewer side effects.[20] Palonosetron is a newer selective serotonin subtypes3 (5-HT3) receptor antagonists. It is a novel 5-HT_3 receptor antagonist first approved for the prevention of chemotherapy induced nausea and vomiting.[21] It has greater binding affinity and longer biological half-life than older 5-HT_3 receptor antagonists.[22] The mechanism of its action in PONV prophylaxis is also to be confirmed but the primary mechanism is possibly similar to ondansetron. Any differences between the drugs could stem from differences in pharmacokinetics or receptor binding profiles. It is 100 times more potent than ondansetron.

Joslyn A [23] conducted a study for determining ondansetron and its clinical development for PONV and stated that large multicenter studies have demonstrated the efficacy of Ondansetron in the prevention and treatment of postoperative nausea and vomiting. Based on the studies of Candiotti K A ***et al.,*** the minimum effective dose of palonosetron in the prophylaxis of PONV was 0.075 mg, and this has been approved by the Food and Drug Administration(FDA). They used palonosetron 0.025 mg, 0.05 mg, and 0.075 mg groups, and the incidence of early emesis was lower in the palonosetron 0.075 mg group compared with placebo.[8] These finding were similar to present research.

According to Candiotti *et al*., patients with Apfel score >2, undergoing day care laparoscopy, received prophylaxis against PONV with palonosetron 0.025 mg, 0.05 mg, 0.075 mg, or placebo. Nitrous oxide was used but no other prophylactic antiemetics were administered. A dose-dependent increase in complete response was observed, with rates in the 0 to 24 hour period for the placebo, palonosetron 0.025 mg, 0.05 mg, and 0.075 mg groups of 26%, 33%, 39%, and 44%, respectively. The incidence of early emesis was lower in the palonosetron 0.075 mg group compared with placebo (26 % vs 44%), as was the severity of nausea.[8]

Y E Moon *et al* reported that palonosetron was more effective than ondansetron for high-risk patients especially 2-24 hours after surgery. They compared the effects of IV ondansetron and palonosetron administered at the end of Thyroid surgery in preventing PONV. A total of 100 female non-smoking subjects were randomly assigned into a palonosetron group or an ondansetron group. [24] Kim Y Y *et al* conducted a comparative study between palonosetron and ondansetron for prevention of PONV in patients receiving Intravenous Patient Controlled Analgesia (IV PCA)after gynecological laparoscopic surgery and concluded that, the effects of palonosetron and ondansetron in preventing PONV were similar in high risk patients undergoing gynecological laparoscopic surgery and receiving opioid based IV PCA.[9] Baisakhi Laha *et al* performed an RCT and evaluated anti emetic effects of IV palonosetron vs. IV ondansetron in laparoscopic cholecystectomy and reported that there was no statistically significant difference between the groups in primary outcome and concluded that, Palonosetron was comparable to Ondansetron for PONV prophylaxis in elective laparoscopic cholecystectomy when administered as single pre-induction dose.[1] Our results were comparable to YE Moon *et al*.

Limitations: For this study equipotent doses of the two drugs were not used; instead optimal doses were used for comparisons. Some degree of subjectivity is inevitable in the assessment of patient satisfaction profile and although we excluded patients receiving drugs that obviously can influence emesis, such as psychotropic medication, we did not exclude patients taking concomitant medication like antihypertensive and antidiabetics.

CONCLUSIONS

1. Incidence of nausea and vomiting was significantly higher in Ondansetron Group compared to Palonosetron Group during 0 to 6 hours. Incidence of nausea and vomiting did not differ significantly between two groups at 6 to 24 hours and 24 to 72 hours.
2. Palonosetron is an effective antiemetic than Ondansetron in early post operative hours i.e. 0-6 hours.

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