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Prospective randomized trial with Palonosetron verses ondensetron for postoperative nausea and vomitting in general surgical population

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Abstract: *Background:* Postoperative nausea and vomiting (PONV) is distressing complication of anesthesia and surgery. It has been suggested that this may increase patients' discomfort, increase costs and other unwarranted side effects and complications. *Aim and objectives:* To study incidence of PONV, in Indian scenario and association of PONV with various factors and efficacy of palonosetron verses ondensetron in this prospective randomized control trial. *Materials and Methods:* Prospectively preoperative and ICU - related data of 170 patients, who underwent laparoscopic surgical procedures under general anesthesia, were collected. Preoperative variables included age, sex, obesity, history of diabetes, and previous PONV and/or motion sickness. ICU - related data included number of episodes of PONV, need for rescue medication, and QTc interval procedures. Patients were extubated after surgery and were shifted to either ICU or wards for further post operative care. Patients who developed PONV were randomized by computer generated random number table to receive intravenous injection palonosetron 0.075mg or injection ondensetron 4 mg. *Results: Out of* 170 patients, PONV was documented in 52 i.e. 30.50 % of cases. Previous history of PONV, diabetic status, female sex and opiod was found to be significantly associated with PONV with p values of 0.042, 0.0513, 0.002, and 0.0038 respectively. Among 52 cases of PONV, after randomization 27 patients received palonosetron while 25 received Ondensetron. Successful treatment from PONV was observed in 26 cases of palonosetron while 22 cases of ondensetron. This difference did not culminate into statistically significant levels with p value of 0.3499 indicating both drugs were similar in efficacy for PONV. *Conclusion:* Data on PONV in general surgical patients is limited in Indian scenario with the incidence is as high as around 30%.
Incidence of PONV is high with risk factors like female sex, diabetic status,use of opiods and previous history of PONV. Newer 5HT3 antagonist palonosetron is equally effective for PONV treatment as ondensetron.
Keywords: Palonosetron, Ondensetron, Post operative nausea, Vomitting

Introduction

Post operative nausea and vomiting (PONV) is common and distressing complication after surgeries undergoing general anesthesia. The prevalence of PONV in reported series is between 20-30%and can increase up to 80% in certain high risk cases [1], and various authors have suggested as incidence as high as 20 to 50 % from western population [2-3].

The presence of PONV can lead to multiple complications such as wound dehiscence, bleeding, dehydration, electrolyte imbalance, pulmonary aspiration, and delayed hospital discharge, all have special relevance to surgical cases [2, 4]. As any complication listed above can lead to increased morbidity in general surgical setting [4]. There is very little data in Indian population, the study done in Saint John hospital Bangalore, quoted incidence around 20% even after premedication with ondensetron [5].

Different class of antiemetic are available for the treatment of PONV [6]. among these ondensetron , 5 hydroxytryptamine type 3 receptor antagonist is most frequently used drug over last 15 years.[7] However, palonosetron is latest addition with greater receptor binding affinity and longer half life and provides a long term PONV control [8]. Palonosetron, due to its allostearic interactions trigger receptor internalization and leads to long term inhibition of receptor function [8-9].

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It was approved by USFDA in 2008. We tried to study incidence of postoperative nausea and vomiting, in Indian scenario and association of PONV with various factors and efficacy of palonosetron verses ondensetron in this prospective randomized control trial.

Material and Methods

After obtaining institutional ethics committee approval and patients' consent, we prospectively studied all patients undergoing laparoscopic surgical procedures like laparoscopic cholecystectomy, appendicectomy, orchidopexy, herniotomy, diagnostic laparoscopy and laparoscopic adhesionolysis. After surgery, patients were extubated and were shifted to either ICU or post operative wards for further postoperative care. Patients who had received anti emetic medication before surgery were excluded. Preoperative and ICU-related data were collected. Preoperative variables included age, sex and obesity, history of diabetes, and previous PONV and/or motion sickness. ICU-related data included numbered of episodes of PONV, need for rescue medication and QTc interval.

General anaesthesia with endotracheal intubationand controlled ventilation was standardized. Patients were premedicated with glycopyrolate 4mcg kg^{-1} and midazolam 0.02-0.04 mg kg^{-1} Anaesthesia was induced with propofol 2mg kg^{-1}, fentanyl 2-4 µg kg^{-1} and Atracurium bromide 0.7mg kg^{-1} was administered to facilitate tracheal intubation. A gastric tube was inserted in all patients at the induction. The lungs were ventilated with an oxygen/air mixture (FI_{O2}0.5–0.6) with a tidal volume of 8-10 ml kg^{-1} to maintain normocapnia. Anaesthesia was maintained with isoflurane, fentanyl and intermittent doses of muscle relaxant. After completion of surgery, weaning from the ventilator and extubation were performed according to the protocol.

Patients were transferred to either ICU or Post operative wards, where they were treated with warm air heaters to ensure normothermia. Inotropic drugs were continued when needed. Analgesia was provided by IV paracetamol injections. Incidence of PONV is recorded by simplified PONV impact scale (table no.1) and scale above 5 was considered having PONV. patients who developed PONV were randomized by computer generated random number table to receive intravenous injection palonosetron 0.075mg or ondensetron 4 mg. ICU staff and duty resident were blinded for the study drug who collected the data regarding PONV episodes. Primary investigator who knew regarding drugs did not participate in data collection for PONV. Patients were again assessed by simplified PONV impact scale, every 6th hourly till discharge from ICU. The second line rescue medication was given if there is still PONV score above 5 after 2 hours. Rescue medication was from different class.

Table-1 : The PONV Impact scale
Q1. Have you vomited or had dry-retching*?
0 - No
1 - Once
2 - Twice
3 -Three or more times
Q2. Have you experienced a feeling of nausea ("an unsettled feeling in the stomach and slight urge to vomit")? If yes, has your feeling of nausea interfered with activities of daily living, such as being able to get out of bed, being able to move about freely in bed, being able to walk normally or eating and drinking?
0 - Not at all
1 - Sometimes
2 - Often or most of the time
3 - All of the time
To calculate the PONV Impact Scale score, add the numerical responses to questions 1 and 2. A PONV Impact Scale score of > 5 defines clinically important PONV.
Note - *Count distinct episodes: several vomits or retching events occurring over a short time frame, say 5 min, should be counted as one vomiting/ dry-retching episode: multiple episodes require distinct time periods without vomiting/dry-retching.

Statistical tests: Initially data was presented as percentage of total numbers. Univariate analysis was initially performed to identify risk factors associated with PONV using $\chi 2$ analyses. $P<0.05$ was considered statistically significant. Power of the study considering various previous incidence of PONV was 80% considering alpha of 0.05.statistical analysis was performed using SPSS 17. Power of the

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study considering various previous incidence of PONV was 80% considering alpha error of 0.05.

Results

A total of 170 patients were included in the study which was done in our institute from December 2015 to April 2016. Demographic data of the patients are present in Table 2. Nearly 49% of the patients were above 40 years of age. 34% were females and nearly 50% were diabetic. Previous history of PONV was present in 22% of the cases. In our study 170 laparoscopic procedure were conducted under general anaesthesia, among these 66(38.8%) were laparoscopic cholecystectomy, 52(30.5%) were laparoscopic appendicectomy 20(11.7%) were laparoscopic orchidopexy, 10(5.8%) were laparoscopic herniotomy, 20(11.7%) were diagnostic laparoscopy and 2(1.17%) were laparoscopic adhesionolysis. PONV was documented in 52 (30.50%) cases.

Table-2: Patient characteristics

Patient characteristics	Total number of cases	Percentage
Age		
10-20	20	11.83
20-40	67	39.64
Above 40	82	48.52
Female sex	58	34.31
Diabetes	84	49.70
Renal insufficiency	8	04.10
Previous history of PONV motion sickness	38	22.48
Type of surgery- Laparoscopic procedures		
a. Laparoscopic cholecystectomy	66	38.8
b. Laparoscopic appendicectomy	52	30.5
c. Laparoscopic orchidopexy	20	11.7
d. Laparoscopic herniotomy	10	05.8
e. Dignostic Laparoscopy	20	11.7
Emergency surgery-.Laparoscopic adhesinolysis	2	1.17
Incidence of PONV	52/170	30.50

Risk factors of PONV are presented in table 3. Chi square test was used to calculate significance level. History of PONV, diabetic status, female sex and opiod use was found to be significantly associated with PONV with p values of0.0422, 0.0513, 0.002 and 0.0038 respectively.

Table-3: Risk factors for PONV

Risk factors for PONV	Occurrence	Significance level
Age less than 60 years	13/52	>0.999
History of PONV	21/52	0.0422
Diabetes	20/52	0.0513
Female sex	22/52	0.002
Use of Opiods	24/52	0.0038

Table-4: Comparison of palonosetron verses ondensetron for PONV and QTc interval

	Group palonosetron	Group ondensetron	P value
Number of cases	27	25	
Complete recovery (ponv impact scale less than 2)	26	22	0.3499
Qtc interval	427 msec+_14	436 msec+_12	

Out of total 52 cases which developed PONV, 27 cases were randomized to receive palonosetron while 25 received ondensetron.

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Complete recovery from PONV were seen in 26 cases of palonosetron and 22 cases of ondensetron. This difference did not culminate into statistically significant levels with p value of 0.3499 indicating both drugs were similar in efficacy for PONV. Both drugs did not show elevation in QTc interval. This data is presented in table-4.

Discussion

Incidence of PONV in our study is nearly 30% this incidence is low compared to western population, but much higher than recorded in one Indian study [2-3].Though our study cannot be compared directly with previous Indian study by sanjay OP [10] as incidence in their study is after giving one prophylactic antiemetic drug. We did not give prophyla drug, as we wanted to know exact incidence in our population. A latest guideline set published by ambulatory society of anesthesia also recommands wait and watch policy for low risk cases. [11] PONV thought to be multifactorial involving anaesthetic , surgical and individual risk factors or different definition used to define PONV.[11-12] Though whatever scales were used, one fact is clear that incidence is definitely higher in Indian population and there is a need to give prophylactic antiemetic in general laparoscopic surgery as the complications of PONV can affect patient outcome.

When we assessed risk factors, previous history of PONV, diabetic status, female sex and opiod use were identified as statistically important risk factors for PONV. In this first 3 have already been studied and proven to be risk factors for PONV [1-2, 4]. We have included opiod use as predictor in the analyses because the use of narcotics in daily practice is often foreseeable and depends very much on the institutional analgesic policy as well as on the duration and type of operation [4, 13]. A modification or change of the anesthetic technique might be considered if two or more risk factors are present. One approach would be prophylactic antiemetic treatment, because recent metaanalysis implies that the efficiency (in terms of the number needed to treat) may only be reasonable in high-risk [3].

Palonosetron is a second generation 5HT3 receptor antagonist with a half-life of 40 hours [9]. The dose given is 0.075mg for 24 hours control of PONV control [14-15].Lara B et al in their controlled trial study concluded that palonosetrone may be effective and superior as rescue therapy for PONV in patients for whom preoperative prophylaxis with ondensetrone had been unsuccessful [16]. Hereby study done by Dhurjoti Prosad Bhattacharjee et al, in Calcutta National medical college on 60 patients compared long term efficacy of palonosetrone versus granesetrone [17].

However, we compared palonosetron with ondensetron for control of PONV and found both drugs equally effective for PONV control. Though number of patients those who got PONV control with palonosetron (96% vs 86%) was more compared to ondensetrone, but this was not statistically significant (p value of 0.349).So it can be concluded that palonosetron is equally effective for PONV control as ondensetron in general surgical population in Indian scenario. QTc interval was not prolonged with both of the drugs and was not a problem for postoperative care.

Conclusion

Data on PONV in general surgical patients is limited in Indian scenario, the incidence is high and is around 30%. In addition to classic risk factors, opiod use is another risk factor for PONV. Newer 5HT3 antagonist palonosetron is equally effecitive for PONV treatment as ondensetron.

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