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Efficacy and Safety of Intravenous Palonosetron against Ondansetron in Preventing Postoperative Nausea Vomiting in Patients Undergoing General Anaesthesia: Double blind Randomized Control Study in Tertiary Care Hospital, Tamil Nadu, India

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Post operative nausea vomiting (PONV) is distressing for patient as well as clinician as it affects post-operative care and recovery substantially. Causes of PONV are multi factorial which are primarily categorized into patient related factors, pre- surgical factors and post-surgical factors. There are several classes of drugs that constitute basic of anti-emetic therapy. Primary objective of the study is to assess the efficacy and safety of intravenous (IV) Palonosetron in preventing post operative nausea vomiting (PONV) in comparison with IV ondansetron. This is a double blinded randomized controlled study conducted during the period of January 2015 to February 2016 in patients with ASA (American Society of Anesthesiologist) grade I category who underwent surgical intervention under general anaesthesia. Both male and female patients in the age range of 15-60 years with ASA grade I status and willing to give written informed consent were recruited for the study. 116 out of 129 patients were recruited for the study based upon inclusion and exclusion criteria. The patients were randomly assigned to two equal groups, Group A, who received palonosetron 0.075 mg intravenously and Group B, who received ondansetron 8 mg intravenously. The efficacy and safety of palonosetron was tested on the use of ondansetron. Statistical analysis was done by Chi-square test and Student t-test. P value less than 0.05 was considered statistically significant. Efficacy of palonosetron was assessed by complete response (CR), use of rescue medication, gratification score and severity of nausea. The P value of all efficacy parameters was <0.05 which was statistically significant. Safety parameters include adverse reactions related to palonosetron or other adverse drug events. Adverse drug reactions were less in group A compared to Group B. Palonosetron was more efficacious than ondansetron in controlling PONV in a post-surgical patient undergoing general anaesthesia. Palonosetron was found equally safe as ondansetron.

Keywords: General Anesthesia; Ondansetron; PONV; Palonosetron; Postsurgical vomiting.

Post-operative nausea vomiting (PONV) is a displeasing sensation. The patient usually expresses it as worse than postoperative pain. Despite the development of new drugs & treatment strategies to reduce its incidence & severity to some extent, it continues to rank as the most undesirable surgical outcome[1]. Since the inception of general anaesthesia, PONV remains an important complication after surgery for which no complete solution is available till date. PONV had gained more attention in 1991 after Kapur described this problem as big "little problem"[2]. It is distressing for both the patient and the clinician as postoperative care and recovery are substantially affected. Causes of PONV are multi factorial which are primarily categorised into patient related factors, pre- surgical factors and post-surgical factors. Due to various factors that contribute to the development of PONV, quantification of the risk of PONV in the individual patient is difficult. Apfel and colleagues mentioned major predictors of PONV that include age, obesity, female patient, past history of PONV or motion sickness, use of opioids as an adjunct to anaesthesia and non-smoker group[3-8]. Other pre-surgical and intra-surgical factors that contribute to PONV are pre-operative anxiety, underlying medical condition, hydration status, use of volatile anaesthetics, type and duration of surgery and type of anaesthesia[3, 5, 9].

The incidence of PONV in the general population is approximately 30-40%, with a further increase in high-risk individuals of up to 80%[6]**.** In addition to this displeasing sensation, PONV may have adverse consequences such as pulmonary aspiration, hypovolemia, electrolyte imbalance, and wound dehiscence that prolongs postoperative and total hospital stay, leading to increased hospital cost[10]. The prevention of the above-mentioned complications improve quality of life, reduces unexpected hospital admissions and duration of hospital stay, and induces reduction in direct & indirect cost to the patient.

Several pharmacological agents have been tried, such as anti-histamines, butyrophenones, dopamine receptor antagonist and dexamethasone, for the prevention of PONV but none of them was found to be superior[1]. Despite extensive research and introduction of novel anti-emetic agents with better safety and efficacy profile, there seems to be little progress in reducing incidence of PONV. As a single agent has not been proven to be a complete solution to tackle this problem; recent research has advanced the use of combination anti-emetic therapy acting at more than one molecular site to control PONV. Use of more than two anti-emetic drugs offer its own disadvantages with added side effects and drug interactions. Therefore, research was strengthened on development of single molecule with prolonged action and lesser side effects. Ondansetron, a $5HT_3$ receptor antagonist is used as antiemetic in patients of malignancy along with chemotherapy and also approved in prevention of PONV[11]. Palonosetron is considered the latest $5HT_3$ receptor antagonist of the second generation with a unique action and a half-life much longer than other $5HT_3$ antagonists with a comfortable dose frequency option of once a day. It has higher receptor affinity compared to other $5HT_3$ antagonists and requires much smaller dose (0.075mg I.V) than ondansetron for the prophylaxis of PONV[11,12].

Very minimal data is available on efficacy of palonosetron in all different types of surgeries under individual research. Hence palonosetron study was undertaken to compare its safety and efficacy with ondansetron in all adult patients planned for surgical procedures under general anaesthesia.

Aims and Objectives

The primary objective of the study includes the evaluation of the efficacy and safety of IV palonosetron in preventing post-operative nausea vomiting (PONV) compared to IV ondansetron. Secondary objective of the study is to find whether both drugs are comparable with demographic parameters like age, sex, height and weight.

There are few similar studies published on use of Palonosetron in PONV which includes specific group of population undergoing laparoscopic cholecystectomy, day care surgery, thyroidectomy, laparoscopic surgery, but our study aimed to be different from other published studies by selecting a broad group of patients undergoing various types of surgeries under general anesthesia rather than single specific type of surgery.

MATERIALS AND METHODS

The study was initiated after getting approval from the Institutional Ethical committee dated 21.01.2015.

Study Design

Double blinded randomized controlled study.

Study period

January 2015 to February 2016.

Source of Data

All eligible patients of ASA grade I category undergoing surgical intervention under general anaesthesia in Karpaga Vinayaga Institute of Medical Sciences and Research Centre were enrolled.

Sample Size

Sample size was calculated with 5% ($p<0.05$) level of significance and a power of study at 80%. (â error 20%). Sample size required for our study was 50 in each group but 8 more samples in each group were added to improve accuracy of study results.

Inclusion Criteria

Both male and female patients in the age range of 15-60 years with ASA grade I status were recruited for the study.

Exclusion Criteria

Pregnant women, patients with a diagnosed case of acid peptic disease, a history of nausea and vomiting before surgery, a patient taking antiemetics or steroids, a patient with major organ involvement such as liver, kidney, heart, brain, and lungs, chronic alcoholics, a patient with hypersensitivity to any of the study trial drugs, a patient with a history of motion sickness, patients diagnosed with malignancy were excluded from the study.

Subject enrollment

A written informed consent was obtained from all participants in each group prior to surgery. Meticulous care was taken while obtaining demographic data, details of previous illness and retrieving details like past history of motion sickness or PONV.

116 out of 129 patients were recruited for the study based upon inclusion and exclusion criteria. Routine investigations like Hb%, Total Leukocyte Count (TLC), Fasting Blood Sugar Level (FBSL), Postprandial Blood Sugar Level (PPBSL), Blood Urea Level (BUL), Serum Creatinine, Chest X-ray and ECG were recorded for all the study participants.

Patients were randomly assigned into two equal groups.

Group A: Received palonosetron 0.075 mg intravenously.

Group B: Received ondansetron 8 mg intravenously.

Block randomization method was used for assigning equal groups. Four lettered 6 blocks were prepared as: AABB, ABAB, ABBA, BAAB, BABA, BBAA and patients were allocated accordingly. For example, if a randomly selected block would be BAAB then the first patient would go to group B, the second and third patient would go to group A, and the fourth patient would go to group B. In this way there was equal distribution of subjects in each group (Figure 1).

Before induction of anaesthesia vitals like pulse, respiratory rate (RR), systolic and diastolic blood pressure (BP), temperature and oxygen saturation (SPO_2) were recorded. A covered envelope was provided to anaesthetist where name of drug group was mentioned. (Obtained from block randomization) Accordingly either palonosetron or ondansetron was administered 10 minutes before anaesthesia. After premedication with fentanyl 2µg/kg and glycopyrrolate 5µg/kg, patients were induced with IV propofol 2mg/kg and intubated with succinyl choline and muscle relaxation was achieved with vecuronium bromide 0.08mg/kg[13]. Patients were reversed back from general anaesthesia with neostigmine 0.05mg/kg and glycopyrrolate 0.2 mg. All vital parameters like pulse, BP, RR, Temperature, SPO_2 and ECG were monitored intra operatively and post operatively at 0, 6,12,24,48 hrs.

The patients were questioned by trained staff or on duty doctors using a validated questionnaire to assess safety and efficacy. Efficacy was evaluated by complete response, (no episode of nausea or vomiting and no use of rescue medication) severity of nausea, use of rescue medication, and overall satisfaction score by 5-point Likert scale within 48 hrs of surgery[14, 15]. Nausea severity was measured by Verbal Rating Scale (VRS) and patients were graded into: no nausea 0, mild nausea 1-3, moderate nausea 4-6 and severe nausea 7-10. Those who had developed

severe nausea or vomiting, rescue antiemetic IV metoclopramide (10mg) was administered. The presence of rash, itching, hypotension, or any serious adverse event during and after surgery after the administration of the drug was evaluated. Cardiovascular safety was assessed by comparing pre and post-operative ECG by assessing QTc interval.

Statistical analysis

Mean, standard deviations and proportions were calculated among the groups. Data was entered into excel spread sheet and analyzed by using SPSS software. Statistical analysis was done by Chi-square test and Student t-test. P-value less than 0.05 was considered statistically significant.

RESULTS

It is evident from Table 1 that the mean age among Group A and Group B were 33.93± 10.32 and 34.86 ± 11.43 years respectively. This difference was not statistically significant ($p>0.05$). Large numbers of subjects observed in younger age group (18-28years) while small numbers of participants were present in elder age group (48-58years) (Table 1).

Demographic data for both groups is mentioned in Table 2. Mean age observed in both groups were 33.93 and 34.86 years respectively. The average height and weight in Group A and Group B were 152.95, 153.02 cms, and 54.93 and 54.83 kg (Table 2).

About 56.90% were men and 43.10% were women. The distribution of men and women among both the groups were nearly similar and there was no statistically significant difference (Table 3).

In group A, female patients were 20% more compared to group B. In both groups, non-smokers were having almost equal percentage. In group A, surgical time was prolonged for more than 2 hours in 88% of subjects which was higher than group B (65%) (Table 4). There was no difference in mean vital statistics in both groups during the preoperative, preinduction, intraoperative, and postoperative period.

Mean Hb%, TLC values, Blood sugar values and Renal parameters did not show any significant difference among the groups.

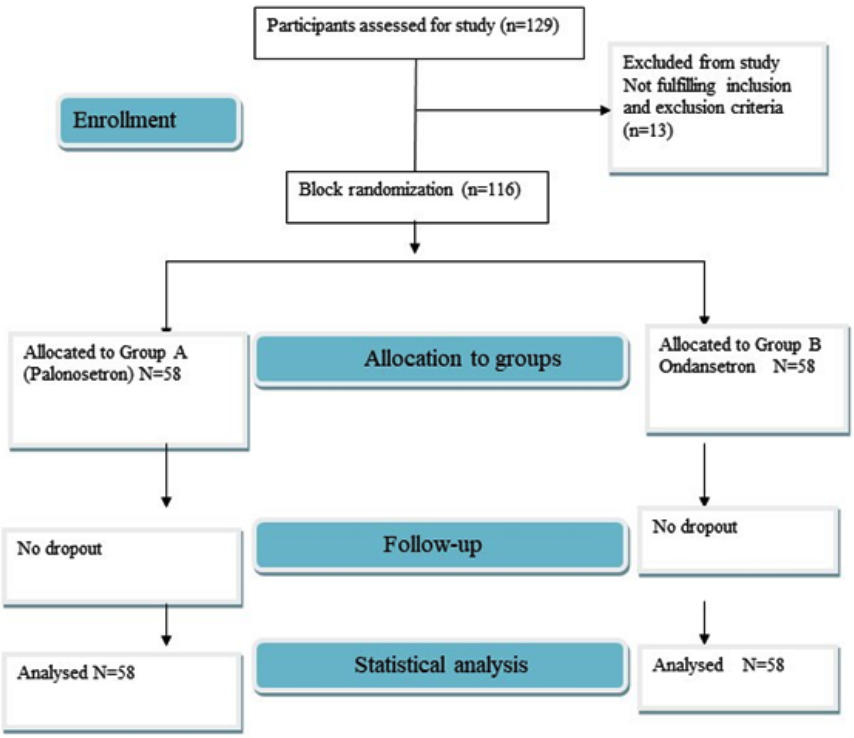

Fig. 1. Randomization procedure of the study

Efficacy of palonosetron was assessed by complete response (CR), number of time rescue medication used, overall gratification and nausea severity score by VRS showed statistically significance (Table 5).

The maximum incidence of PONV in group B was seen in laparoscopic surgeries followed by thyroid surgeries. The incidence of PONV in ENT surgeries in group B was 15% (Table 6). Least incidence was seen in percutaneous nephrolithotomy (PCNL). In group A, incidence of PONV was higher in females as compared to males (3:1) but was equal (1:1) in group B. In the early phase (0-24 hours) the incidence of PONV in group A was less (25%) compared to group B (95%) but in the late phase the incidence of PONV was high (Table 5 & Table 6).

Both groups did not show any serious adverse event. The most common side effect was headache in both groups and the least common side effect was rash or itching. QTc prolongation was observed in the ondansetron group in a single patient, while none in palonosetron receivers (Table 7).

DISCUSSION

The present study was carried out to assess the safety and efficacy of palonosetron versus ondansetron. Two groups with equal number of participants were chosen and total 116 participants were recruited in the study. Efficacy parameters were assessed by complete response (CR), number of rescue anti-emetics used, nausea severity and

Table 1. Distribution of subjects according to age

Age Group	Group A N (%)	Group B N (%)	Total N (%)
18-28	20	23	43 (37.07)
28-38	17	13	30 (25.86)
38-48	16	14	30 (25.86)
48-58	05	08	13 (11.21)
Total	58	58	116 (100)
Mean age	33.93 ±10.32	34.86±11.43	* P> 0.05

*p>0.05 = not statistically significant. There is no statistically significant age difference between the study groups A and B.

Table 2. Demographic data of the study population

Parameters	Group A	Group B	P-value
Mean age	33.93± 10.31	34.86 ± 11.43	0.46
Mean Height	152.95 ± 6.81	153.02± 6.38	0.06
Mean weight	54.93 ± 9.84	54.83 ± 8.72	0.06
Mean BMI	23.54±2.56	23.25±2.45	0.8

p>0.05 = not statistically significant. There is no statistically significant difference in height, weight, BMI between the study groups A and B.

Table 3. Distribution of subjects according to sex

Sex	Group A N (%)	Group B N (%)	Total N (%)
Male	27 (23.27)	39 (33.62)	66 (56.90)
Female	31 (26.73)	19 (16.38)	50 (43.10)
Total	58 (50)	58 (50)	116 (100)

overall satisfaction score. Complete response was evaluated as no nausea, vomiting and no need of rescue anti-emetics.

Of the 116 patients, 88 were complete responders, of which 50 (86%) were in the palonosetron group and 38 (65%) were in the ondansetron group. The difference in numerical value of 12 between the groups was highly significant ($p<0.01$). Similar results were seen in a study published by Musso and colleagues which was prospective study conducted on different types of cancer patients[16] showed 80% CR for chemotherapy induced nausea vomiting (CINV) in palonosetron group and 60% in ondansetron group. Mattiuzzi *et al*. also demonstrated higher CR in the palonosetron arm versus the ondansetron arm[17]. Further, it was concluded that patient receiving palonosetron had less severe nausea from day 1 to day 5 and less impact of CINV. The study conducted by Chattopadhyay and associates where PONV was assessed in post caesarean delivery CR was observed in 85% of subjects using palonosetron and 83% of subjects using ramosetron[18]. In another study for the prevention of CINV, Schwartzberg and colleagues stated overall CR of 51% in the palonosetron group and 40% in the ondansetron, dolasetron, or granisetron group[19]. Our study demonstrated higher CR rates compared to previous studies. This may be due to recruitment of subjects with a smaller number of high-risk populations.

In our study, there was statistically significance on use of rescue medication between palonosetron & ondansetron group ($p<0.01$). Sharma and colleagues study also showed higher (20%) use of rescue medication in ondansetron group as compared to palonosetron group (4%)[20]. Kim and associates found less use of rescue anti-emetics in palonosetron group than ondansetron or ramosetron group[21].

A non-inferiority randomized controlled trial for prophylaxis of PONV conducted by Davolos FJC *et al* concluded high incidence of PONV in ondansetron (43.4%) group compared to palonosetron (36.8 %) group. The calculated risk difference between palonosetron and ondansetron

Table 4. Risk factors among study groups

Risk factor	Group A	Group B	P-value
Female Gender	31/58 (53%)	19/58(33%)	0.02
Non smokers	52/58 (89%)	49/58 (84%)	0.4
Duration of surgery > 2 hrs	7/8(88%)	13/20 (65%)	0.23

p>0.05= not statistically significant. There is no statistically significant difference in risk factors studied in Group A and Group B.

Table 5. Efficacy parameters tested

Efficacy parameters	Group A (n=58)	Group B (n=58)	P-value
1.Complete response	50	38	0.009**
2. Use of rescue medication	8	20	0.009**
3.Gratification score		0.0001***	
Disgratified (DG)	2	9	
Not Gratified Not Disgratified (NGNDG)	8	22	
Gratified (GR)	43	26	
Highly Gratified (HGR)	5	1	
4. Severity of nausea	0.03*		
Nil	50	38	
Mild	4	12	
Moderate	4	08	

*p<0.05 = statistically significant, **p<0.01 =highly significant, ***p<0.001 =very highly significant.

was 0 for initial 2 hours and 6.6 at 2-6 hours. The statistically significant results were observed on use of rescue medication between palonosetron and ondansetron.[22]

While considering severity of nausea among the groups, results were statistically significant in our study. ($p< 0.01$) Similar results were observed in the prospective double-blind study by Bajwa *et al*. where 6.66% had nausea and 3.33% had vomiting in the palonosetron group, while 20% observed nausea and 13.33% observed vomiting in the ondansetron group and the difference was statistically significant[14].

Schwartzberg and associates demonstrated no significant difference between palonosetron and other $5HT_3$ antagonists during early post-chemotherapy period but significant difference was observed in delayed chemotherapy period[19].

PONV episodes during the first 48 hours were 8 (13.76%) in the palonosetron group and 20 (34.4%) in the ondansetron group, which was highly significant. Consistent results were also observed in a previous study conducted by Kim and associates, where the incidence of PONV was 22.2% and 77% in the palonosetron and ondansetron group, respectively[23]. The lower values observed in our study were due to factors related to the patient and surgery. The higher incidence was due to the recruitment of more high-risk predictors of PONV in another study. The study conducted by Choudhary A and Parashkar V concluded that palonosetron is more effective in treating long term PONV in patients undergoing laparoscopic surgery under general anesthesia[24].

The total satisfaction score in palonosetron group was high (82.75 %) as compared to ondansetron group (46.55%) which was very highly significant ($p< 0.001$). An analogous results were observed in a double-blind active control study done by Emad E Mansour. In three different groups, palonosetron, saline, or metoclopramide along with dexamethasone had a total satisfaction score of 88%, 48%, and 62%, respectively[25].

Table 6. Distribution of various surgeries in study groups

Type of surgery	Group A	Group B	Chi-square test	P-value
Oromaxillary	08/58 (14%)	07/58 (12%)	0.07	0.7
Laparoscopic abdominal	14/58 (25%)	17/58 (29%)	0.39	0.5
LSCS	Nil	01/58 (2%)	-	-
Gynaecological Surgeries	04/58 (7%)	04/58 (7%)	-	-
Orthopaedic surgeries	04/58 (7%)	05/58 (9%)	0.12	0.7
ENT surgeries	10/58 (17%)	10/58 (17%)	-	-
Thyroid surgery	02/58 (3%)	04/58 (7%)	0.7	0.4
Spine Surgery	03/58 (5%)	nil	-	-
Dental surgery	02/58 (3%)	nil	-	-
General surgery excluding thyroid and laparoscopic procedures	03/58 (5%)	05/58 (9%)	0.54	0.4
Radical Neck Dissection	07/58 (12%)	02/58 (3%)	3.01	0.08
PCNL	01/58 (2%)	03/58 (5%)	1.04	0.3
Total	58/58	58/58	-	-

$p>0.05$ = not significant. There is no statistically significant difference in the various surgeries carried out in Group A and Group B.

Table 7. Safety parameters tested in the study population

Adverse effects	Group A (n=58)	Group B (n=58)
Headache	2	4
Constipation	1	1
Dizziness	1	2
Fatigue	1	1
Itching	0	0
Insomnia	1	1
QT_C prolongation	0	1

In our study, patients from palonosetron group had higher CR, lesser nausea, lesser vomiting and higher satisfaction score as compared to ondansetron group. Even though both drugs belong to same structural group, palonosetron was much superior in controlling PONV. Few studies conducted[26-29] among two groups have shown domination of palonosetron as antiemetic agent. palonosetron has ranked one in anti-emetic property than other $5HT_3$ antagonists like ramosetron and granisetron[23]. The study conducted by S H Kim and associates observed incidence of nausea, vomiting & retching lower in palonosetron as compared to ondansetron & ramosetron groups[23]. Even with combination chemotherapy palonosetron appears to be effective in controlling PONV. Sharma A N & associate concluded a study on PONV in palonosetron with dexamethasone and ondansetron with dexamethasone. In their study, combination of palonosetron and dexamethasone was more effective in controlling early & late phases of PONV in patients of laparoscopic hysterectomies[20].

Although there was a higher number of women in our study group, the incidence of PONV was less (14%) compared to the ondansetron group (34.48%). Palonosetron proved its utility not only in normal patients but also in high risk individuals[29-32] in controlling episodes of PONV. Superior efficacy of palonosetron could be due to its higher receptor affinity, due to allosteric site[30,33] and longer half life[11,26]. Palonosetron was not only effective in reducing overall incidence of PONV but in controlling PONV episodes during early post-operative period (0-24hrs). This cardinal finding has more value when a previous study has demonstrated the efficacy of another $5HT_3$ antagonist to palonosetron in decreasing early episodes of PONV[34]. Study conducted by Elrashidy AA *et al* also showed that palonosetron group had less nausea, vomiting, retching as compared to ondansetron group in first 4-12 hours. Also, total episodes of nausea, vomiting and retching were significantly less in palonosetron group[32]. From the above-mentioned findings, we can conclude that palonosetron is also equally competent to the other 5 HT_3 antagonists in controlling early phase PONV.

Various clinical trials had been supporting the safety of palonosetron[36,37]. In our study, palonosetron was well tolerated and was equally safe as ondansetron because both groups had mild and less side effects. The side effects in both groups were similar to those of previous studies. The common side effects observed were headache, constipation, fatigue, and insomnia. The most common side effect in each group was headache. Mattiuzzi *et al,* demonstrated most frequent adverse effect as headache and constipation[17]. A study by Sadaba *et al,* also listed headache, constipation, and diarrhoea as frequent adverse events[38]. No one in either group developed rash, itching, or diarrhoea. A single participant had QT prolongation in the ondansetron group but no one had it from the palonosetron group. Very few studies have demonstrated cardiac safety of palonosetron with increasing dose[36]. In our study, no effect was observed on the electrocardiogram measured by QT prolongation. Mean QTc for palonosetron group before and after surgery was 0.391 and 0.396 milli second while mean QTc for ondansetron group before and after surgery was 0.393 and 0.396 milli second respectively.

In our study, there was no loss of follow-up, as patients were monitored from 0 to 48 hours after surgery with regular intervals. Additionally, no deaths were observed in either group.

CONCLUSION

Ondansetron is most frequently used anti-emetic agent prescribed 8mg every 8 hourly. It has serious adverse effect of QTc interval prolongation. Palonosetron is having high receptor binding as compared to ondansetron is preferred with smaller dose (0.075mg) and once a day frequency. Also, QTc prolongation with use of palonosetron is associated with increase in dose. From the present study findings, it can be concluded that, palonosetron was more efficacious than ondansetron in controlling PONV in a post-surgical patient undergoing general anaesthesia. In addition, palonosetron was also effective in reducing PONV in first 24 hours of post-operative period. Overall satisfaction was higher in palonosetron recipients than in patients given ondansetron. Palonosetron was found equally safe as Ondansetron.

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