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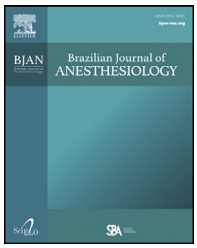

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ORIGINAL INVESTIGATION

Comparison of palonosetron and ondansetron in preventing postoperative nausea and vomiting in renal transplantation recipients: a randomized clinical trial

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PONV intensity scale;
Renal transplantation recipients

Abstract
Background: End-stage renal diseases patients have a high risk of postoperative nausea and vomiting (PONV), which is multifactorial and need acute attention after renal transplantation for a successful outcome in term of an uneventful postoperative period. The study was done to compare the efficacy of palonosetron and ondansetron in preventing early and late-onset PONV in live donor renal transplantation recipients (LDRT).
Methods: The prospective randomized double-blinded study was done on 112 consecutive patients planned for live donor renal transplantation. Patients of both sexes in the age group of 18–60 years were randomly divided into two groups: Group O (Ondansetron) and Group P (Palonosetron) with 56 patients in each group by computer-generated randomization. The study drug was administered intravenously (IV) slowly over 30 seconds, one hour before extubation. Postoperatively, the patients were accessed for PONV at 6, 24, and 72 hours using the Visual Analogue Scale (VAS) nausea score and PONV intensity scale.
Results: The incidence of PONV in the study was found to be 30.35%. There was significant difference in incidence of PONV between Group P and Group O at 6 hours (12.5% vs. 32.1%, $p = 0.013$) and 72 hours (1.8% vs. 33.9%, $p < 0.001$), but insignificant difference at 24 hours (1.8% vs. 10.7%, $p = 0.113$). VAS-nausea score was significantly lower in Group P as compared to Group O at a time point of 24 hours (45.54 ± 12.64 vs. 51.96 ± 14.70, $p = 0.015$) and 72 hours (39.11 ± 10.32 vs. 45.7 ± 15.12, $p = 0.015$).
Conclusion: Palonosetron is clinically superior to ondansetron in preventing early and delayed onset postoperative nausea and vomiting in live-related renal transplant recipients.

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Introduction

Postoperative nausea and vomiting (PONV) are a significant cause of distress in the postoperative period which spoils the otherwise smooth postoperative experience of the patient, resulting in prolonged hospital stay and postoperative complications. The baseline incidence of PONV in general populations is 20–30% and 75–80% in high-risk groups.[1] Gastrointestinal complications are the most common non-renal complaints known to occur in patients with end-stage renal disease (ESRD).[2] Uremia and dialysis increase the risk of lesions in the gastrointestinal tract leading to dyspepsia characterized by nausea, vomiting, early satiety, delayed gastric emptying, upper abdominal pain, and bloating.[3] The anesthesia technique employed like the use of volatile anesthetics, nitrous oxide perioperative opioids use,[4] the prolonged duration of surgery, and the adverse effects of the immunosuppressive regime predispose the patients undergoing renal transplants to high risk for PONV.

Palonosetron is a newer second-generation 5HT-3 receptor antagonist that has a unique allosteric inhibition property that imparts greater binding affinity and a longer plasma half-life than other drugs of the same class.[5] Recent studies have reported the superiority of palonosetron relative to other 5HT-3 receptor antagonists for the prevention of PONV in patients undergoing general anesthesia.[6–8] Palonosetron has also been shown to be a superior drug compared to ondansetron drug in reducing the incidence of emesis and mitigating the clinical impact of nausea and vomiting on patients functional status during the acute (0–24 h) and delayed (24–120 h) phase after chemotherapy and general anesthesia.[7–9] The pharmacological superiority accompanied by previously studied efficacy of palonosetron in preventing chemotherapy-induced nausea and vomiting and PONV prompted us to explore its effects in preventing PONV in renal transplantation recipients assuming the current practice of routine use of shorter-acting agents like ondansetron for PONV is less effective.

The current study was conducted to evaluate the hypothesis as primary objectives that intravenous Palonosetron provides safe and effective prevention of early and delayed onset PONV as compared to Ondansetron in renal transplantation recipients using the PONV intensity score.[10]

Methods

Trial design

This single-centric study was conducted at government authorized renal transplantation center at SGPGIMS, Lucknow, in North of India. After the approval by the Institutional Ethics Committee (IEC CODE-2019-82-IP-109) the trial was registered with Clinical Trials Registry India Registration No.CTRI/2019/09/021417, accessible online at ctri.nic.in/Clinical trials/pmaindet2.php?trialid=36885). The study was conducted as per the declaration of Helsinki and good clinical practice guidelines for biomedical research in human subjects.

After obtaining written informed consent, 112 ESRD patients planned for live-related donor renal transplantation were recruited for this prospective, randomized, double-blinded study. The study included renal transplantation recipients of either sex between the age of 18–60 years. Exclusion criteria were history of smoking, motion sickness, cognitive impairment, history of allergy to drugs used in the study, usages of medications with known antiemetic effect within 24 hours before surgery, and history of opioid use. Patients who were shifted for postoperative mechanical ventilation were also excluded from the study. After enrollment of patients, they were randomly allotted in a 1:1 ratio to receive either the ondansetron or palonosetron. The group assignment was presented in opaque sealed envelopes to an anesthetist who was not involved in the study. Randomization was performed with a block size of six using a central web-based system by a statistician blinded to the study. Anesthesiologists involved in intraoperative care and investigator collecting data in the postoperative ward were unaware of the group allocation.

All the potential recipients underwent pre-transplantation workup before surgery. Screening and matching of donor and recipient were done before surgery. The immunosuppression induction of the recipient was done as per institutional protocol. Post-hemodialysis hemogram and coagulation profile along with kidney function tests were assessed a day before surgery. Preoperative standard fasting guidelines were followed and no antiemetic was administered before surgery.

After patients arrived in the operating room, standard ASA monitoring was applied (electrocardiography, pulse oximetry, and a noninvasive blood pressure cuff, TOF monitoring). The arteriovenous fistula site was protected and periodically checked for flow. All patients received balanced general anesthesia and a lower thoracic epidural catheter was placed before the induction of anesthesia. Intravenous fentanyl (2 $mcg.kg^{-1}$) was followed by induction with propofol (1.5 $mg.kg^{-1}$) and neuromuscular blockade was achieved by atracurium (0.5 $mg.kg^{-1}$) in all patients. Maintenance of anesthesia was done by desflurane with intermittent boluses of fentanyl (1 $mcg.kg^{-1}$) and neuromuscular blockade was achieved by TOF guided atracurium boluses. An anesthetist who was not involved in the study opened the sealed envelopes and prepared the medications as injectable solutions of either palonosetron 0.075 mg or ondansetron 4 mg. Both of the drugs were diluted in normal saline to make a total volume of 2 mL and loaded in identical-looking syringes. The study drug was administered intravenously (IV) slowly over 30 seconds, 60 minutes before extubation. Tracheal extubation was done at the end of surgery after reversal with neostigmine according to TOF monitoring when appropriate criteria were met and patients were shifted to the postoperative care unit (PACU) for further recovery. All patients received a continuous epidural infusion with 0.1% ropivacaine and 1 $mcg.mL^{-1}$ fentanyl at the rate of 6–8 $mL.h^{-1}$ in the postoperative period.

Sample size calculation and patient randomization

Based on previous studies,[8] there was a reduction of 25% in the incidence of PONV in patients receiving palonosetron (50%) compared to ondansetron (75%). Assuming the same (25%) difference in PONV in our study power of 80%, and a significant level of 5% ($\alpha = 0.05$), the calculated sample size

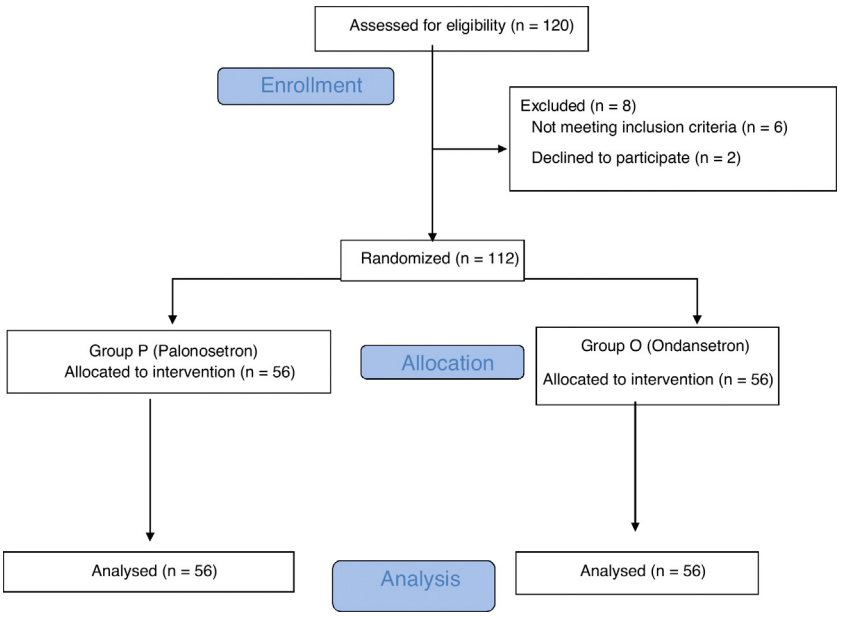

Figure 1 Consort diagram of the study.

was 56 patients in each group (a total of 112 patients). After considering the dropouts, we decided to take 60 patients in each group. The sample size was estimated using the software G Power version – 3.1.9.2 (Düsseldorf University, Germany).

Data collection tool

Patient's demographic data were collected and they were interviewed by one of the investigators at 6, 24, and 72 hours postoperatively about vomiting, antiemetic medication, or complications related to PONV-by-PONV intensity scale and VAS nausea scale (Fig. 1).

PONV intensity scale and VAS nausea score

The PONV intensity Scale (Appendix-1) and VAS scale for nausea were applied at regular intervals. Patients were asked to score postoperative pain on a 10-point verbal numerical rating scale (NRS), and nausea on a 100-mm Visual Analogue Scale (VAS-nausea). The limits of the nausea VAS were ''no nausea'' to ''nausea as bad as it possibly could be''. A score greater than 70 was the cut-off for severe nausea. Vomiting was objectively measured as the total number of patients who had emesis and the number of episodes of vomiting. A score was calculated for each patient and a PONV intensity Scale score of $\geq$ 50 was defined as clinically significant PONV.[10]

Statistical analysis

The normality of the continuous variables was assessed using the Z score of the skewness and a variable was considered normally distributed when the Z score was within the range of 3.29. Normally distributed variables were presented in mean $\pm$ standard deviation and compared by independent samples *t*-test. Ranking data presented in median (interquartile range ''IQR'') and compared by Mann-Whitney U test. Categorical variables were presented in frequency (%) and tests of the association between study groups and categorical variables (including the incidence of nausea, vomiting) were assessed by the Chi-square test/ Fisher exact test as applicable. *P*-value < 0.05 was considered, as statistically significant. Data were analyzed using Statistical Package for social sciences, version-23 (SPSS-23, IBM, Chicago, USA).

Results

A total of 120 renal transplant recipients were included in the study. Two patients did not consent to participate in the study. Three patients did not meet the inclusion criteria and two patients were shifted to PACU on mechanical ventilation and one patient was re-explored 12 hours after surgery and was excluded from the study. Thus, the study included 112 kidney transplant recipients (56 in Group P and 56 in Group O). The mean age of the patients was 34.71 years (median, 35, IQR [19–55]) with a higher proportion of males (84.8%). There was no significant difference in mean age and gender between the two study groups. The mean duration of the surgery was 5.42 hours with no significant difference between the groups (p = 0.268) (Table 1). The incidence of postoperative nausea and vomiting in patients was compared between the two study groups (P and O). There was a significant difference in incidence of PONV between groups P and O at 6 hours (12.5% vs. 32.1%, p = 0.013) and 72 hours (1.8% vs. 33.9%, p < 0.001) but no difference at 24 hours (1.8% vs. 10.7%, p = 0.113). The use of rescue antiemetic (metoclopramide 10 mg slow IV) was compared between the groups. Group P showed decreased requirement of metoclopramide, [7/56 (12.5%) vs. 25/56) (44.6%), p < 0.001] at 72 hours significantly as compared to the Ondansetron, (Group O) in the postoperative period (Table 2, Fig. 2). There

Table 1 Distribution of demographic and clinical values in study groups.

Variables	Total (n = 112)	Group P (n = 56)	Group O (n = 56)
Age (years)	34.71 ± 8.30	34.20 ± 8.92	35.21 ± 7.70
Sex (male)	95 (84.8%)	49 (87.5%)	46 (82.1%)
Duration of Surgery (hours)	5.42 ± 0.60	5.48 ± 0.69	5.36 ± 0.49

Mean ± SD, compared by independent samples *t*-test.
Frequency (%), compared with the Chi-square test used.

Table 2 Association between PONV intensity scale, VAS Nausea score, and effect of rescue antiemetic.

	Total			With rescue			Without rescue		
	P (n = 56)	O (n = 56)	*p*	P (n = 7)	O (n = 25)	*p*	P (n = 49)	O (n = 31)	*p*
PONV: Frequency (%)[a]									
6 h	7 (12.5)	18 (32.1)	0.013	7 (100)	18 (60)	0.069	0 (0)	3 (9.7)	0.055
24 h	1 (1.8)	6 (10.7)	0.113	1 (14.3)	6 (24)	0.099	0 (0)	0 (0)	-
72 h	1 (1.8)	19 (33.9)	0.001	1 (14.3)	19 (76)	0.006	0 (0)	0 (0)	-
VAS: Median (IQR) [Mean][b]									
	P (n = 56)	O (n = 56)	*p*	P (n = 7)	O (n = 25)	*p*	P (n = 49)	O (n = 31)	*p*
6 h	2 (2-3) [2.48]	2.5 (2-3) [2.51]	0.7812	(2-3) [2.29]	2 (2-3) [2.48]	0.442	3 (2-3) [2.51]	3 (2-3) [2.55]	0.741
24 h	3 (2-4) [2.86]	3 (2-3) [2.77]	0.607	4 (2-4) [3.29]	2 (2-3) [2.68]	0.116	3 (2-3) [2.80]	3 (2-3) [2.84]	0.710
72 h	3 (2-3) [2.77]	2.5 (2-3.8) [2.75]	0.792	3 (2-4) [3.00]	2 (2-3.5) [2.72]	0.390	3 (2-3) [2.74]	3 (2-4) [2.77]	0.919
VAS-nausea score: Mean ± SD [Median][c]									
	P (n = 56)	O (n = 56)	*p*	P (n = 7)	O (n = 25)	*p*	P (n = 49)	O (n = 31)	*p*
6 h	41.43 ± 6.99 [40]	43.21 ± 9.93 [50]	0.273	44.29 ± 7.87 [70]	44.80 ± 12.95 [70]	0.922	41.02 ± 6.85 [40]	41.94 ± 6.54 [40]	0.555
24 h	45.54 ± 12.64 [40]	51.96 ± 14.70 [40]	0.015	65.71 ± 16.18 [50]	61.20 ± 17.40 [40]	0.543	42.65 ± 9.08 [40]	44.52 ± 5.06 [40]	0.300
72 h	39.11 ± 10.32 [40]	45.7 ± 15.12 [40]	0.008	51.43 ± 18.64 [50]	56.00 ± 15.81 [50]	0.520	37.35 ± 7.30 [40]	37.42 ± 7.73 [40]	0.966

$p < 0.05$ significant.
[a] Compared by the Chi-square test/Fisher exact test used.
[b] Median (IQR) [Mean], compared by Mann Whitney U test.
[c] Independent samples t-test used.

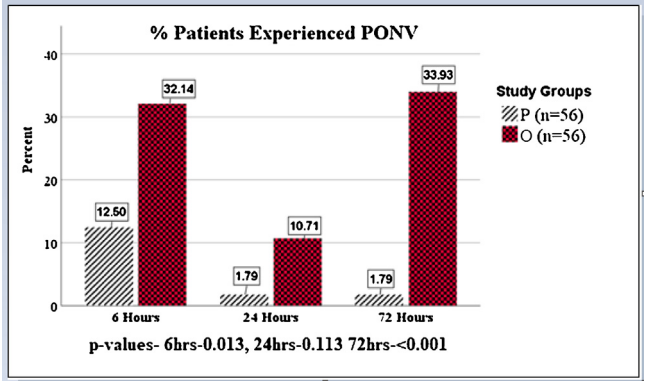

Figure 2 Distribution of PONV incidences in Group P and Group O.

was no difference in the administration of rescue antiemetics at the 6 and 12 hours between the two groups.

NRS used to assess postoperative pain was comparable between the two study groups (Table 2).

Similarly, the VAS-NAUSEA score of patients was compared between the two study groups. VAS-NAUSEA score was significantly lower in Group P as compared to Group O at a time point of 24 hours (45.54 ± 12.64 vs. 51.96 ± 14.70,

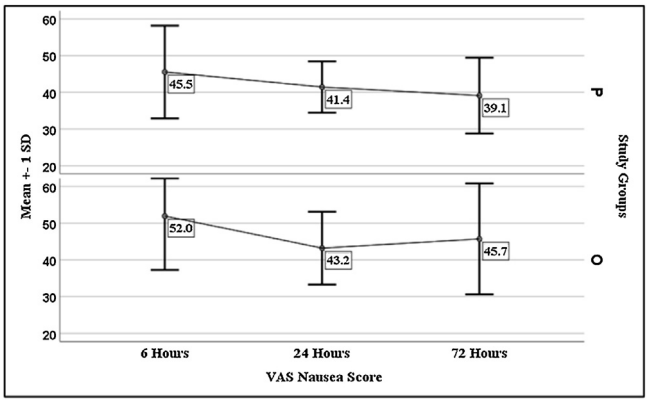

Figure 3 Distribution of VAS-Nausea score in Group P and Group O (p-value 6 h = 0.273, 24 h = 0.015, 72 h = 0.008).

p = 0.015) and 72 hours (39.11 ± 10.32 vs. 45.7 ± 15.12, p = 0.015) but not significant at the time of 6 hours (p > 0.05) (Table 2, Fig. 3).

Discussion

In this prospective randomized trial, we compared a single dose of ondansetron (4 mg) and palonosetron (0.075 mg) to determine the most effective prophylactic antiemetic agent for early and late-onset PONV in renal transplantation recipients.

Patients with ESRD are at high risk for gastrointestinal complications of renal failure like uremic gastropathy, dyspepsia, constipation, diarrhea, and delayed gastric emptying. Dyspepsia is highly prevalent in patients with chronic kidney disease and is characterized by nausea, vomiting, bloating, and early satiety. The prevalence of dyspepsia among HD patients varies between 48% and 70%,[11] predisposing these patients to high risk for perioperative nausea and vomiting. Other factors that increase the risk of PONV include the use of opioids perioperatively, the immunosuppression regime,[12] prolonged duration of surgery, use of volatile anesthetic agents.[13]

PONV can lead to significant morbidity and complication post-transplantation surgery. It can lead to prolonged intensive care stay, increased infections in already immunocompromised patients, and increase the cost of treatment, therefore effective preventive strategies are required to prevent PONV in these high-risk groups.[14] Palonosetron is the new 5-HT_3 (serotonin) receptor, antagonist. Unlike other drugs in this class, it exhibits simple bimolecular binding and positive co-operatively in binding to its receptors this differential interaction triggers a receptor alteration or internalization resulting in a long-lived inhibition of receptor function. Due to the unique interaction palonosetron is substantially longer acting and it has a plasma half-life is 40 hours. Palonosetron also causes prolonged inhibition of serotonin-induced calcium-ion influx that triggers functional effects that persist beyond its immediate binding to 5-HT3 receptors.[5] The molecular interaction leads to increase the effectiveness in preventing and treating both early and delayed onset nausea and vomiting. Previous clinical trials have reported a beneficial role of palonosetron when compared to placebo or other 5-HT3 receptor antagonists for the prevention of PONV.[15,16] Two very recent meta-analyses showed reductions in the incidence of PONV when palonosetron was compared with ondansetron in patients who underwent surgery under general anesthesia.[6,7]

None of the studies have compared palonosetron and ondansetron in ESRD patients undergoing renal transplantation under general anesthesia. In the study, we used the PONV intensity score as developed by Wengritzky et al.[10] It is a validated score to access clinically significant PONV and also helps distinguish early and late PONV. The PONV Intensity scale describes PONV based on its intensity and clinical importance. The key features of the scale include the intensity, pattern, and duration of nausea.[17]

We found the incidence of PONV of 30.35 % in our study in renal transplantation recipients. Patients who received palonosetron (Group P) showed an incidence of 12.5% PONV as compared to 48.21% in patients that received ondansetron. Xiong et al.[7] evaluated 9 randomized control trials including 741 patients undergoing elective surgery under general anesthesia and found that Palonosetron provides more effective prophylaxis against early (RR-0.51) and late postoperative nausea (RR-0.53) and late postoperative vomiting (RR-0.41) compared with ondansetron. In another meta-analysis by Singh et al.[6] included 22 trials comparing palonosetron with first-generation 5-HT3 receptor antagonist or placebo to prevent PONV, the significant statistical difference in favor of palonosetron in the prevention of PONV (acute and delayed) was found, while side effects were comparable between palonosetron and control groups. In this study, palonosetron significantly reduced the incidence of PONV during 0–6 hours and 24–72 hours postoperative period, but not during the 6–24 hours post-transplant surgery, even though palonosetron significantly reduced the overall incidence of PONV during the 0–72 hours postoperative period this was in agreement with Candiotti and colleagues.[16] Thus suggesting a superior prophylactic effect of palonosetron in preventing both early and late-onset PONV in the high-risk group. The use of rescue medication for episodes of vomiting was less in patients who received palonosetron 12.5% as compared to the ondansetron group.

During the 6 to 24 hours and 24 to 72 hours interval, our study showed that significantly fewer patients treated with palonosetron 0.075 mg experienced nausea compared with patients who received ondansetron. The mean at 24 h (45.54 ± 12.64 vs. 51.96 ± 14.70, p = 0.015) and 72 hours (39.11 ± 10.32 vs. 45.7 ± 15.12, p = 0.015) were consistent with the reduction in nausea as reported by Kovac and colleagues[15] in a previous study. No major side effects were encountered in either group of patients. In our experience, palonosetron is effective in preventing both episodes of nausea and postoperative vomiting in the early and late postoperative periods. A single dose of the drug has a prolonged duration of action, thus preventing repeated administration of drugs with minimal side effects. It provides greater patient satisfaction during recovery.

One possible limitation of this study was the modest population size for a dose-response trial, with few patients in each treatment arm for a robust evaluation of the treatment effect on all endpoints and all-time intervals for statisti-

cal analyses. Furthermore, patients' satisfaction was not included in the study. A comparative evaluation with various dosages of the two antiemetics used in the study was not done and a fixed dose of the drug was used in both groups. New multicenter randomized controlled trials with a larger population of renal transplantation recipients are required for further evaluation of these antiemetics on PONV.

Conflicts of interest

The authors declare no conflicts of interest.

Acknowledgments

The authors are grateful to P. S. Myles and the team for permission to use the PONV intensity scale for this study. We also thanks Dr. Prabhakar Mishra, Associate Professor, Department of Biostatistics and Health Informatics, SGPGIMS, Lucknow, India for helping in statistical analysis.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.bjane.2021.07.027.

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