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Orginal research article

TO STUDY EFFICACY AND SAFETY OF INTRAVENOUS PALONOSETRON AGAINST ONDANSETRON IN POST SURGICAL PATIENTS UNDERGOING GENERAL ANAESTHESIA

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ABSTRACT :PONV continues to rank as most undesirable surgical outcome despite of multiple advances in recent years with use of nonpharmacological and pharmacological strategies to reduce its incidence to certain extent. Since the inception of general anaesthesia(GA), To assess safety of IV Palonosetron compared to IV ondansetron in relation to adverse effects in post surgical patients undergoing GA .Methods and results: 116 out of 129 patients were recruited for the study based upon inclusion and exclusion criteria and routine investigations and grouped into A and B. **palonosetron and ondansertron given to groups and safty and efficacy assessed.** In the above table it was observed that mean age among Group A and Group B were 33.93± 10.32 and 34.86 ± 11.43 years respectively Conclusion: Palonosetron was more efficacious than ondansetron in controlling PONV in a post-surgical patients undergoing general anaesthesia.In addition, palonosetron was also effective in reducing PONV in first 24 hours of post-operative period. Overall satisfaction was high in palonosetron receivers than patients whom ondansetron was given.Palonosetron was found equally safe as Ondansetron.

Key words : palonosetron , ondansertron , safty , efficacy. PONV(postoperative nausea vomiting)

MAINT TEXT

Inroduction: Post operative nausea vomiting (PONV) is an alarming surgical complication2 with critical clinical consequences leading to delayed recovery in patients undergoing general anaesthesia. PONV continues to rank as most undesirable surgical outcome despite of multiple advances in recent years with use of nonpharmacological and pharmacological strategies to reduce its incidence to certain extent. 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 has described this issue as big "little problem"[2] . It is distressing for patient as well as for the treating physician as it affects post-operative care and recovery substantially. PONV is an unpleasant sensation which patient often

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describes it as worse than post-operative pain. 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 contributing to development of PONV quantification of risk of PONV in individual patient is difficult. Apfel and colleagues[3] mentioned major predictors of PONV that include age, obesity[4] , female patient,[5,6] past history of PONV or motion sickness[7] , use of opioids[8] as an adjunct to anaesthesia and non smoker group [9] . 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[3.6.10]. In general population, incidence of PONV is very high (i.e.30-40%) and which increases further in high risk individuals up to 80%[7] . In addition to such displeasing sensation PONV may have adverse consequences like pulmonary aspiration, Hypovolemia, electrolyte imbalance and wound dehiscence which prolongs post operative as well as total hospital stay and increase hospital cost[11] . The Prevention of above said complications improve quality of life and reduce unexpected hospital admissions and duration of hospital stay leading to overall decrease in financial burden to the patient. Patho-physiological mechanism of PONV is complex due to involvement of different neurotransmitters at different sites. Activation of vomiting centre mainly occurs due to stimulation of chemoreceptor trigger zone (CTZ) situated at the floor of fourth ventricle. CTZ constitutes receptor for dopamine, serotonin, opioids, acetylcholine and neurotransmitter substance P. Each of these receptors innervates the pathway that stimulate vomiting centre. At least three nerves and seven neurotransmitters play role in causation of PONV. There are several classes of drugs that constitute basic of anti-emetic therapy. Several pharmacological agents1 like anti-histaminics, butyrophenones, dopamine receptor antagonist and dexamethasone has been tried for the prevention of PONV but none of them found to be superior. Despite extensive research and introduction of new classes of anti-emetic agents with better safety and efficacy profile, there seems to be little progress in reducing incidence of PONV. As single agent has not been proved to be 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 has its own disadvantages in the form of added side effects and drug interactions. Therefore development of single molecule with prolonged action and lesser side effects is encouraged. Ondansetron, a 5HT3 receptor antagonist is used as antiemetic in patients of malignancy along with chemotherapy[11] and also approved in prevention of PONV. Palonosetron is considered to be second generation latest 5 HT3 receptor antagonist with unique action and much longer half life than other 5HT3 antagonists offering flexibility to use as once a day. It has higher receptor affinity compared to other 5HT3 antagonists and requires much smaller dose (0.075mg I.V) [12] than ondansetron for the prophylaxis of PONV. Safety and efficacy of Palonosetron in comparison to ondansetron has been well established in recent studies in patients undergoing specific surgeries like laparoscopic cholecystectomy, gynaecological laparoscopic surgery, paediatric surgery and lower segment caesarean section but most of the studies are restricted to laparoscopic or gynaecological or thyroid surgeries. 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.

Primary objectives:

To assess the efficacy of IV Palonosetron in preventing post operative nausea vomiting (PONV) in comparison with IV ondansetron .

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To assess safety of IV Palonosetron compared to IV ondansetron in relation to adverse effects in post surgical patients undergoing GA

Methodology:

A. Study design: Prospective randomized control study

B. Study period: 1.5 years (Nov 2019- May 2021)

C. .Place of study and source : Patients of ASA grade I category undergoing surgeries under general anesthesia in hospitals attached to Bangalore medical college and research institute.

D. Sample Size: Sample size required for our study was 50 in each group but 8 more samples in each group were added to improve accuracy of results.

Inclusion Criteria:

1. Patients of either sex between age group 15-60 yrs with ASA grade I status

2. Patient willing to give written informed consent .

Exclusion Criteria:

1. Pregnancy

2. Patients with diagnosed case of Acid Peptic Disease

3. Patient with history of nausea and vomiting pre-operatively

4. Patient taking anti-emetics or steroids

5. Patient having major organ involvement like liver, kidney, heart, brain and lungs

6. Chronic alcoholic

7. Patient with known hypersensitivity to any of the study trial drug

8. Patient participated in other study trial

9. Patient with history of motion sickness

10. Patients of Malignancy

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

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116 out of 129 patients were recruited for the study based upon inclusion and exclusion criteria and routine investigations like Hb %, TLC, FBSL, PPBSL, BUL, S. Creatinine, Chest X-ray and ECG were recorded. Enrollment Participants assessed for study (n=129) Excluded from study Not fulfilling inclusion and exclusion criteria (n=13) Block randomization (n=116) Allocated to Group A (Palonosetron) N=58 Allocated to Group B Ondansetron N=58 Allocation to groups No dropout No dropout Follow-up Analysed N=58 Statistical analysis Analysed N=58 48 | P a g e 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 letter blocks were prepared as: AABB, ABAB, ABBA, BAAB, BABA, BBAA and patients were allocated accordingly. For example, if randomly selected block would be BAAB then first patient would go to group B, second and third patient would go to group A and fourth patient would go to group B. In this way there was equal distribution of subjects in each group. Before induction of anaesthesia vitals like pulse, respiratory rate, systolic and diastolic blood pressure, temperature and oxygen saturation (SPO2) 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/kg14 and glycopyrrolate14 5µg/kg, patients were induced with IV propofol 2mg/kg and intubated with succinyl choline14 and muscle relaxation was achieved by vecuronium bromide 0.08mg/kg. Patients were reversed back from general anaesthesia with neostigmine 0.05mg/kg and glycopyrolate 0.2 mg. All vital parameters like pulse, BP, RR, Temperature, SPO2 and ECG were monitored intra operatively and post operatively at 0, 6,12,24,48 hrs. Patients were questioned by trained staff or on duty CRRI by using validated questionnaire for assessment of safety and efficacy. Efficacy was evaluated by complete response,80,98 (no episode of nausea or vomiting and no use of rescue medication) severity of nausea,80, 98 use of rescue medication, and overall satisfaction score by 5 point Likert scale within 48 hrs of surgery98. Nausea severity was measured by Verbal Rating Scale 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. Safety was evaluated for presence of rash, itching or hypotension or any serious adverse event during and after surgery. 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 analysed by using SPSS software. Statistical analysis was done by Chi-square test and Student t-test. P value less than 0.05 was considered as statistically significant.

Results :

In the above table it was observed that mean age among Group A and Group B were 33.93± 10.32 and 34.86 ± 11.43 years respectively.

In our study 66 (56.90%) were males and 50 (43.10%) were females. The distribution of men and women among both the groups were nearly similar and there was no statistically significant difference.

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Table1: EFFICACY PARAMETERS

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			
DG	2	9	
NGNDG	8	22	
GR	43	26	0.0001*
HGR	5	1	
4. Severity of nausea			
Nil	50	38	0.03*
Mild	4	12	
Moderate	4	08	

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

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Table 2: Incidence of PONV (%) in various surgeries in Palonosetron group

Type of surgery	Percentage
ENT surgery	37.50%
Laparoscopic surgery	25%
Oro-maxillary Surgery	25%
Thyroidectomy	12.50%

Table3 : Incidence of PONV (%) in various surgeries in ondansetron group

Type of surgery	Percentage
ENT	15%
Thyroidectomy	20%
Orthopaedic surgery	10%
Laparoscopic surgery	30%
Gynaecologic surgery	10%
Oro-maxillary-surgery	10%
PCNL	5%

Both the groups did not show any serious adverse event. Most common side effect was headache in both groups and least common side effect was rash or itching. QTc prolongation was seen in ondansetron group in single patient while none in palonosetron receivers.

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. **Discussion ;**

This study was undertaken to assess 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. The most commonly performed surgeries in both the groups were laparoscopic abdominal surgery followed by ENT and Oro-maxillary surgeries. There was no statistical significance between group A and group B in relation to types of surgery. Efficacy parameters were assessed by complete response, number of rescue anti-emetics used, nausea severity and overall satisfaction score.

Complete response was evaluated as no nausea, vomiting and no need of rescue anti-emetics. Out of 116 patients, 88 were complete responders among which 50 (86%) were from palonosetron group and 38(65%) were from ondansetron group. The difference of numerical value of 12 among the groups was highly ` colleagues which was prospective study conducted on different types of cancer patients. It showed 80% CR for CINV in palonosetron group and 60% in ondansetron group. palonosetron and 83% of subjects using ramosetron. In another study for prevention of CINV, Schwartzberg and colleagues[14] stated overall CR 51% in palonosetron group and 40% in ondansetron, dolasetron or granisetron group. Our study demonstrated higher CR rates compared to previous study. This may be due to recruitment of subjects with less number of high risk population in ourstudy.

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In our study, number of times rescue medications used in palonosetron group and ondansetron group were 8 and 20 respectively. In ondansetron group, more number of patients required rescue anti-emetics as compared to palonosetron group and the difference was statistically significant. Sharma and colleagues[15] study also showed higher (20%) use of rescue medication in ondansetron group as compared to palonosetron group

Out of 116 patients, only 28 had nausea among which 8 belonged to palonosetron group and 20 belonged to ondansetron group. Of 8 patients from palonosetron receivers, 4 had mild nausea and remainder had moderate nausea while in ondansetron group, 12 had mild nausea and rest had moderate nausea. None had severe nausea in both the groups. Severity of nausea among the group was statistically significant. Similar results were observed by Bajwa[16] et al study where 6.66% had nausea and 3.33% had vomiting in palonosetron group while 20% observed nausea and 13.33% observed vomiting in ondansetron group and the difference was statistically significant.

PONV episodes during first 48 hrs were 8 (13.76%) in palonosetron group and 20 (34.4%) in ondansetron group which was highly significant. Consistent results were also observed in previous study conducted by Kim[17] and associates where PONV incidence in palonosetron group was 22.2% and 77% in ondansetron group. Lower values observed in our study were due to patient related and surgery related factors. Higher incidence was because of recruitment of more high risk predictors of PONV in other stu

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In spite higher number of females in our study group, PONV incidence was (14%) as compared to ondansetron group (34.48%). Palonosetron proved its utility not only in normal patients but also in high risk individuals[18,19,20,21] in controlling episodes of PONV.. From above mentioned findings we can conclude that palonosetron is also equally competent to other 5 HT_3 antagonist in controlling early phase PONV.

Various clinical trials had been supporting about safety[22,23] of palonosetron. In our study palonosetron was well tolerated and was equally safe as ondansetron because both group had mild and lesser side effects. Side effects in both the groups were similar to previous studies. The common side effects observed were headache, constipation, fatigue and insomnia. Most common side effect in both group was headache. Mattiuzzi et al[24]demonstrated most frequent adverse effect as headache and constipation. A study carried out by Sadaba et al[25] also stated headache, constipation and diarrhoea as frequent adverse events. No one from either group developed rash or itching or diarrhoea.. In our study, no effect was observed on electrocardiogram measured by QT prolongation. Mean QTc for palonosetron group before and after surgery was 0.391 and 0.396 ms while mean QTc for ondansetron group before and after surgery was 0.393 and 0.396 ms respectively. with above inadequate data. To prove cardiac safety of palonosetron over ondansetron more number of subjects will be required. Hence we can draw inference that palonosetron is not superior to ondansetron in terms of safety but equally safe as far as side effects are concerned. There is definite scope to explore cardiac safety profile of palonosetron over ondansetron in large sample size population to affirm higher safety of palonosetron.

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Our study has few limitations…

First, non-inclusion of placebo group to evaluate baseline incidence but withholding antiemetic therapy in post-operative patients would be like denying treatment to them.Second, propofol containing regimen used for induction of anaesthesia may interfere with incidence of PONV.

Third, Patient satisfaction score cannot be considered as end point because subjective feeling may show wide variation in groups.

Conclusion;

Thus from the current study we conclude that…

Palonosetron was more efficacious than ondansetron in controlling PONV in a post-surgical patients undergoing general anaesthesia.In addition, palonosetron was also effective in reducing PONV in first 24hours of post-operative period. Overall satisfaction was high in palonosetron receivers than patients whom ondansetron was given.Palonosetron was found equally safe as Ondansetron.

References :

Watcha M.F, White P.F. Postoperative nausea and vomiting. Its etiology, treatment and prevention. Anesthesiology 1992; 77:162-184.

2. Kapur PA. The big "little problem". Anesth Analg 1991; 73: 243-245.

3. Apfel CC, Laara E, Koivuranta M, Greim CA, Roewer N. A simplified risk score for predicting postoperative nausea and vomiting: conclusions from cross-validations between two centers. Anesthesiology 1999; 91: 693-700.

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4. Gan TJ, Meyer T, Apfel CC, Chung F, Davis PJ, Eubanks S, et al. Consensus guidelines for managing postoperative nausea and vomiting. Anesth Analg. 2003; 97: 62–71.

5. Burtles R, Peckett BW. Postoperative vomiting; some factors affecting its incidence. Br J Anaesth. 1957; 29:114–123.

6. Kenny GN. Risk factors for postoperative nausea and vomiting. Anesthesia. 1994 ; 9: 6–10.

7. Islam S, Jain PN. Postoperative nausea and vomiting (PONV): A review article. Indian J Anaesth. 2004; 48: 253-258.

8. Tramèr MR. Treatment of postoperative nausea and vomiting. BMJ. 2003; 327: 762–763.

9. Muchatuta NA, Paech MJ. Management of postoperative nausea vomiting: focus on palonosetron. Ther clin Risk Manag 2009; 5: 21-34.

10.. Chatterjee S, Rudra A, Sengupta S. Current Concepts in the Management of Postoperative Nausea and Vomiting. Anesthesiology Research and Practice. 2011;2011:748031. doi:10.1155/2011/748031.

11. Golan David E, Tashjian Jr Armen H, Armstrong Ehrin J, Armstrong April W. Principles of Pharmacology . 3rd edition. New Delhi: wolters kluwer India Pvt Ltd; 2012.

12. Candiotti KA, Kovac AL, Melson TI. A randomized, double- blind study to evaluate the efficacy and safety of three different doses of palonosetron versus

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placebo for preventing postoperative nausea and vomiting. Anesth Analg 2008;107: 445-451.

13. Musso M, Scalone R, Bonanno V, Crescimanno A, Polizzi V, Porretto F et al. Palonosetron (Aloxi) and dexamethasone for the prevention of acute and delayed nausea and vomiting in patients receiving multiple-day chemotherapy. Support Care Cancer. 2009 ; 17(2): 205-209.
14. Schwartzberg L, Barbour SY, Morrow GR, Ballinari G, Thorn MD, Cox D. Pooled analysis of phase III clinical studies of palonosetron versus ondansetron, dolasetron, and granisetron in the prevention of chemotherapy-induced nausea and vomiting (CINV). Support Care Cancer. 2014; 22(2):469-477.

15. Sharma AN, Shankaranarayana P. Postoperative Nausea and Vomiting: Palonosetron with Dexamethasone vs. Ondansetron with Dexamethasone in Laparoscopic Hysterectomies. Oman Med J. 2015; 30(4): 252-256

16. Bajwa SS, Bajwa SK, Kaur J, Sharma V, Singh A, Singh A, Goraya S, Parmar S, Singh K. Palonosetron: A novel approach to control postoperative nausea and vomiting in day care surgery. Saudi J Anaesth. 2011; 5(1): 19-24.
17. Kim SH, Hong JY, Kim WO, Kil HK, Karm MH, Hwang JH. Palonosetron has superior prophylactic antiemetic efficacy compared with ondansetron or ramosetron in high-risk patients undergoing laparoscopic surgery: a

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prospective,randomized, double-blinded study. Korean J Anesthesiol. 2013; 64(6): 517-523.

18. De Leon A. Palonosetron (Aloxi): a second-generation 5-HT_3 receptor antagonist for chemotherapy-induced nausea and vomiting. Proc (Bayl Univ Med Cent). 2006; 19(4): 413-416.

19. Del Cadia M, De Rienzo F, Weston DA, Thompson AJ, Menziani MC, Lummis SC. Exploring a potential palonosetron allosteric binding site in the 5-HT(3) receptor. Bioorg Med Chem. 2013; 21(23): 7523-7528.

20. Moon YE, Joo J, Kim JE, Lee Y. Anti-emetic effect of ondansetron and palonosetron in thyroidectomy: a prospective, randomized, double-blind study. Br J Anaesth. 2012; 108(3): 417-422.

21. Bhattacharjee DP, Dawn S, Nayak S, Roy PR, Acharya A, Dey R. A comparative study between palonosetron and granisetron to prevent postoperative nausea and vomiting after laparoscopic cholecystectomy. J Anaesthesiol Clin Pharmacol. 2010; 26: 480-483.

22. Morganroth J, Flaharty KK, Parisi S, Moresino C. Effect of single doses of IV palonosetron, up to 2.25 mg, on the QTc interval duration: a double-blind, randomized, parallel group study in healthy volunteers. Support Care Cancer. 2016; 24(2): 621-627.

23. Aapro MS, Grunberg SM, Manikhas GM, Olivares G, Suarez T, Tjulandin SA et al. A phase III, double-blind, randomized trial of palonosetron

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compared with ondansetron in preventing chemotherapy-induced nausea and vomiting following highly emetogenic chemotherapy.Ann Oncol. 2006; 17(9): 1441- 1449.

24. Mattiuzzi GN, Cortes JE, Blamble DA, Bekele BN, Xiao L, Cabanillas M, Borthakur G, O'Brien S, Kantarjian H. Daily palonosetron is superior to ondansetron in the prevention of delayed chemotherapy-induced nausea and vomiting in patients with acute myelogenous leukemia. Cancer. 2010 ; 116(24): 5659-5666.
25. Sadaba B, del Barrio A, Campanero MA, Azanza JR, Gomez-Guiu A, Lopez-Picazo JM et al. Randomized pharmacokinetic study comparing subcutaneous and intravenous palonosetron in cancer patients treated with platinum based chemotherapy. PLoS One. 2014; 9(2): e89747. doi: 10.1371/journal.pone.0089747. [Last accessed on 19 March 2015].

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