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Comparison between Palonosetron and Ondansetron for Prevention of Postoperative Nausea and Vomiting in Patients undergoing ENT Surgery: A Double-blind Randomized Control Study

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Abstract

Post-operative nausea and vomiting (PONV) has an 80% incidence in high-risk patients. Selective serotonin (5HT3) receptor antagonists are considered first line in the prevention of PONV, due to their proven efficacy and favourable side effects. Palonosetron is a selective 5HT3 antagonist, is more potent and longer acting than ondansetron. The aim of this study was to evaluate the antiemetic efficacy of palonosetron in comparison with ondansetron in patients at a high-risk of PONV in ENT surgeries.

After institutional ethical committee approval and informed consent, a prospective randomised double-blind study was conducted in 110 patients belonging to ASA1 & 2, age 15-60yrs with risk factors for PONV were randomised to receive palonosetron 75 mcg (Group P) or ondansetron 8 mg (Group O), 30 min before the end of surgery. The incidence of PONV, severity of nausea and need for rescue antiemetic was recorded over the next 24 h. Primary outcome was the incidence of PONV. Randomised to receive palonosetron 75 mcg (Group P) or ondansetron 8 mg (Group O), 30 min before Secondary outcomes included severity of nausea and need for rescue antiemetic. Student's t test and Chi square test applied, p value <0.05 considered significant. The incidence of PONV was found to be 7% in the

palonosetron group and was 19% in the ondansetron group (P = 0.007). Need for rescue antiemetic was 2% in the palonosetron group and 11% in the ondansetron group (P = 0.008) in the 24 h post-surgery. The study concluded Palonosetron 75 mcg was more effective than ondansetron 8 mg in reducing the incidence of PONV in ENT surgeries

Keywords: Ondansetron, Palonosetron, PONV

Introduction:

Post-operative nausea and vomiting (PONV) is an unpleasant experience with an incidence of 80% in high-risk patients.[1] In fact studies have shown that for postoperative patients, avoidance of PONV is of greater importance than avoidance of post-operative pain.[2] PONV poses several significant problems in our modern anaesthetic practice such as delayed recovery, unexpected hospital admission, delayed return to work after day care anaesthesia, pulmonary aspiration, wound dehiscence, dehydration etc.[3] It is a multifactorial phenomenon that can be triggered by multiple receptor pathways at peripheral, central or both sites. The cause for PONV may be patient related, surgery related or anaesthesia related. High risk factors for PONV are female gender, non-smokers, history of motion sickness or PONV, prolonged surgery and perioperative use of opioids.[4]

Several prophylactic antiemetic agents are available such as metachlopramide, promethazine, droperidol, dexamethasone and ondansetron. Ondansetron is a 5-HT3 receptor antagonist and is effective in prevention of PONV with minimal side effects. Palonosetron, a second generation 5-HT3 receptor antagonist has a longer half-life and a better safety profile compared to ondansetron.[5]However there are few studies comparing the efficacy of palanosetron with ondansetron in prevention of PONV in patients undergoing ear, nose and throat(ENT) procedures which are considered to be high risk for PONV.

We intend to assess and compare the efficacy of palonosetron and ondansetron in patients undergoing ENT procedures.

Subjects and Methods

After ethical committee approval and an informed consent, a prospective randomised double blind study was conducted at Karnataka Institute of Medical Sciences, Hubli from December 2018 to December 2019. 110 patients belonging to ASA physical status 1 and 2, those aged 18-60 years of either sex undergoing elective ENT surgeries under general anaesthesia were included in the study. They were randomized into two groups to receive either palonosetron 75 mcg (Group P) or ondansetron 8 mg (Group O), 30 min before the end of surgery.

Patients posted for emergency surgeries, those having episodes of vomiting or retching within 24h before surgery, those receiving antiemetics or steroids within 24h before surgery and patients with anticipated or actual difficult airway were excluded from the study.

Pre-anaesthetic evaluation of all patients was performed a day before surgery. An informed written and valid consent was taken from the study subjects who satisfied the inclusion criteria and were randomly allocated to one of the two groups according to computer-generated randomized number table. The two groups were group P and group O. Each group comprised of 55 subjects. Patients in Group P received intravenous palonosetron 75 mcg which was diluted to 4ml with normal saline about 30 minutes prior to the end of the procedure. Similarly, patients in Group O received intravenous ondansetron 8mg (i.e. 4 ml) about 30 minutes prior to

the end of the procedure. The study drugs were drawn and diluted in identical syringes to make a volume of 4ml by an anaesthetist who did not take part in the study.The patients and the observer who did the postoperative follow up of the patients were blinded to the study medication.

All the patients were kept nil per oral overnight. Intra operative monitoring included pulse oximetry (spo2), non invasive blood pressure (NIBP), pulse rate and electrocardiography (ECG) and end tidal co2 (et CO2). A standard general anaesthesia regimen was followed. All patients were premedicated with midazolam 0.05mg/kg, glycopyrrolate 0.004mg/kg and fentanyl 2mcg/kg. After preoxygenation patients were induced with propofol 2mg/kg and endotracheal intubation was facilitated with succinyl choline 2mg/kg IV. Anaesthesia was maintained with 0.5 – 2% sevoflurane, 33% oxygen in nitrous oxide. Muscle relaxation was maintained with intermittent boluses of vecuronium. Intraoperative analgesia was maintained with intermittent boluses of IV fentanyl. At the end of the surgery, residual neuromuscular blockade was reversed with neostigmine (0.05mg/kg) and glycopyrrolate (0.01mg/kg) IV. Patients received antiemetics 30 min prior to extubation. Postoperative analgesia was provided with inj. Paracetamol or inj. Diclofenac.

The incidence and severity of nausea and the incidence of vomiting was recorded over next 24 hours. The incidence of use of rescue antiemetic was also recorded. This observation period of 24 hours was divided into two intervals i.e. early and late period. First 6 hours after extubation was considered as early period (0-6 hours) and next 18 hours was considered as late period (6-24 hours). Intravenous dexamethasone 8mg was used as rescue antiemetic for PONV.

The severity of nausea was rated on a 4 point scale. Wherein 0 = no nausea, 1 = mild, 2 = moderate and 3 = severe grade. Primary outcome was to determine the incidence of nausea and vomiting during the first 24hrs. Secondary outcome was to assess the severity of nausea and the need for rescue antiemetics.

Sample size was estimated based on the difference in proportion of vomiting between palonosetron and ondansetron groups from the study by Sung Hoon Kim et al.[6] Data was analyzed using SPSS 22 version software, Student's t test was used for quantitative data, Chi square test was used for qualitative data, P value <0.05 was considered as statistically significant

Results

Table 1a: Demographic data

Patient characteristics	Group P (Palonosetron) n=55	Group O (ondansetron) n=55
Age in years	32.7 (13.2)	36.4 (13.0)
Sex (M:F)	30:25	23:32
ASA status I II	 41(74.6%) 14(25.4%)	 44(80.0%) 11(20.0%)
Duration of surgery More than 1 hour Less than 1hour	 34(61.8%) 21(38.2%)	 28(50.9%) 27(49.9%)

Table 1b:Demographic data

Patient characteristics	Group P (Palonosetron) n=55	Group O(ondansetron) n=55
Risk factors		
1. Female	25(45.4%)	32(58.2%)
2. Non smoker	49(89.1%)	50(90.9%)
3. History of motion sickness/PONV	0	0
4. Peri-operative opioids	55(100%)	55(100%)
No of risk factors		
1	6 (10.9%)	7 (12.7%)
2	23 (41.8%)	17 (30.9%)
3	26 (47.3%)	31 (56.4%)

Demographic features in both the groups were comparable.

Table 2: Comparison of incidence of Post-operative nausea and vomiting between the two study groups (n=110)

Incidence of Post-operative Nausea and Vomiting	Group P (n=55)	Group O (n=55)	p-value#
0 – 6 hours	3 (5.5%)	14 (25.5%)	0.004
6 – 24 hours	4 (7.3%)	6 (10.9%)	0.507
0 – 24 hours	7 (12.7%)	19 (34.5%)	0.007

P value Chi-square test

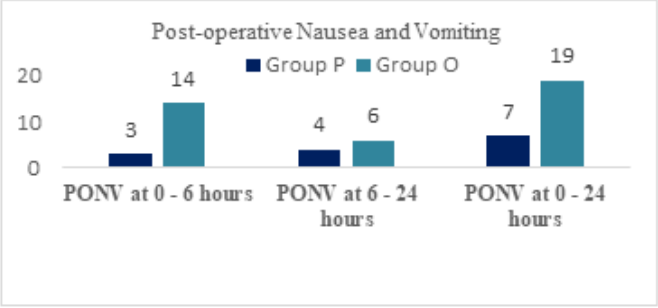

Figure 1: Incidence of PONV between two groups

Overall incidence of PONV in 24 hours postoperatively was higher in group O (34.5%) compared to group P (12.7%) and was statistically significant (p value – 0.007).The incidence of PONV during early period i.e first 6 hours was higher in group O(25.5 %) compared to group P (5.5 %) with P value of 0.004. However during late period i.e 6 - 24 hours there was no significant difference in the incidence of PONV between the two groups (Group P – 7.3% and group O – 10.9%, p – 0.5).

Table 3: Comparison of Post-operative Nausea scale between the two study groups (n=110)

	Group P (n=55)	Group O (n=55)	p-value#
0 – 6 hours			
Grade 0	52 (94.5%)	42 (76.4%)	0.043
Grade 1	0	4 (7.3%)	
Grade 2	2 (3. 6%)	7 (12.7%)	
Grade 3	1 (1.8%)	2 (3.6%)	
6 – 24 hours			
Grade 0	51 (92.7%)	49 (89.1%)	0.564
Grade 1	4 (7.3%)	4 (7.3%)	
Grade 2	0	1 (1.8%)	
Grade 3	0	1 (1.8%)	
0 – 24 hours			
Grade 0	48 (87.3%)	37 (67.3%)	0.082
Grade 1	4 (7.3%)	8 (14.5%)	
Grade 2	2 (3.6%)	8 (14.5%)	
Grade 3	1 (1.8%)	2 (3.6%)	

#All p-value were calculated using Chi-square test

Analysis of severity of nausea in the two groups revealed that incidence of nausea of moderate severity is higher in group O compared to group P during the early period. However there is no difference during late period.

Table 4: Comparison of need for rescue anti-emetic between the two study groups (n=110)

Need for rescue anti-emetic	Group P (n=55)	Group O (n=55)	p-value[#]
0 – 6 hours	2 (3.6%)	7 (12.7%)	0.082
6 – 24 hours	0	4 (7.3%)	**0.042**
0 – 24 hours	2 (3.6%)	11 (20.0%)	**0.008**

#Chi-square test was done

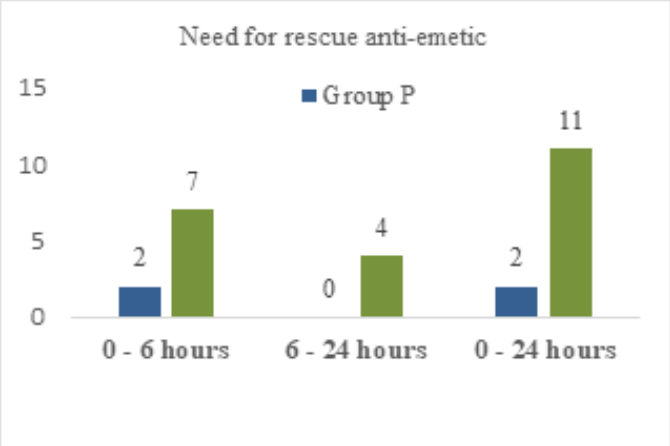

Figure 02: Need for rescue anti-emetics between two groups

The number of patients who needed rescue antiemetic during both early and late period was higher in group O (7 and 4 patients respectively) compared to those in group P (2 and 0 patients respectively) with overall p value of 0.008 which is statistically significant.

Discussion

Postoperative nausea and vomiting (PONV) is one of the most common and distressing adverse effects of anaesthesia and surgery and may lead to serious postoperative complications. The overall incidence of PONV has been reported to be between 20% and 30%, but can increase up to 80% in high-risk patients.[7] This is despite the availability of different classes of antiemetic drugs.

Selective serotonin (5HT3) receptor antagonists are considered first line in the prevention of PONV, due to their proven efficacy and favourable safety profile. Ondansetron is considered as the gold standard in preventing and managing PONV. Its half-life is 3-5 hours. Palanosetron has been traditionally being used for treatment of chemotherapy induced nausea and vomiting in patients with cancer. Because of its long t½ (40 hrs) it has been suggested as better alternative choice to ondansetron by the consensus guidelines published in 2020.[8] The meta-analysis by **Tramèr et al** suggested 8 mg as the optimal dose of ondansetron.[9] **Kovac et al** in a study conducted on patients undergoing laparoscopic surgeries suggested that 75mcg of palanosetron was the effective dose in preventing PONV.[10] **Rao et al** reported that palonosetron was superior (1.5 mcg/kg) to ondansetron (4mg) in middle ear surgeries.[11] **Sun *et al*** observed that ondansetron (4 mg IV) was more effective in reducing the need for rescue antiemetics in the recovery room when administered at the end versus prior to the start of otolaryngologic surgery.[12] Considering the observations of above authors, we decided to use ondansetron at 8mg dosage and palanosetron at 75mcg dosage and the study drugs were administered towards the end of the surgery.

Patients undergoing laparoscopic surgeries, gynaecological surgeries, ENT surgeries, abdominal surgeries and strabismus surgeries are more prone for PONV. Our study was conducted in ENT surgeries. The likely causes for PONV in tympanoplasties and mastoid explorations are vestibular stimulation caused by drilling and irrigating the bone adjacent to the inner ear and those in adenotonsillectomies and FESS are emetogenic impact of swallowed blood in the stomach acting on vagal innervations.[13] Other precipitating causes of PONV

in general include inhaled anesthetics, opioid analgesics and use of nitrous oxide.[14]

In our study baseline demographics between the two groups were comparable and did not show any statistical significance with respect to age, gender, height, weight, BMI, ASA grading and type of surgery(p value > 0.05).

We observed that during first 6 hours (early period) incidence of PONV was significantly higher in ondansetron group (25.5%) compared to palonosetron group (5.5%). In the next 6-24 hours (late period) incidence of PONV in both the groups was comparable i.e 10.9% and 7.3% respectively. Hence palonosetron was found to be more effective than ondansetron in the prevention of PONV during the early (0-6hrs) period while there was no difference between the groups during the late period (6-24 hrs) period.

We observed that the need for rescue anti emetic (dexamethasone 8mg) was more in ondansetron group (20%) than in palonosetron group (3.6%) over 24 hours with p value of 0.008 which is statistically significant.

In our study nausea was graded into grade 0 – no nausea, grade 1 – mild, grade 2 - moderate, grade 3 - severe nausea.[15] The incidence of nausea of moderate severity was higher in group O compared to group P during the early period. However there was no difference during late period.

Sharma et al in 2019 conducted a study comparing ondansetron and palonosetron for prevention of PONV in middle ear surgeries and they observed that incidence of vomiting in ondansetron group was higher than palonosetron group (28% vs 6%) during 2-12 hrs postoperatively.[14] The results of our study also showed that palonosetron was more efficient in preventing PONV during early period (0-6 hrs).

Moon et al. in 2012 conducted a study comparing ondansetron 8mg and palonosetron 75mcg in patients undergoing thyroidectomies. They observed that palonosetron was more effective than ondansetron in preventing PONV during 24-hour postoperatively.[5]

SK Park and EJ Cho conducted a study in 2011 comparing ondansetron 8mg and palonosetron 75mcg in patients undergoing gynaecological laparoscopic surgeries. They concluded that palonosetron was more effective than ondansetron in preventing PONV during 24-hour postoperatively.[16]

Palonosetron was evaluated and found to be favorable for prevention of PONV in middle ear surgeries by **Mohamed and Michel** in a double-blind placebo-controlled study.[17]

In our study 17 patients had PONV in early period and 10 patients had PONV in late period. Increased incidence of PONV during early period in our study maybe because of persistent effect of emetogenic factors like volatile anaesthetics, nitrous oxide and opioids like fentanyl. **Apfel et al** reported that early PONV was caused by intraoperative use of volatile anaesthetics, nitrous oxide, opioids as their effect lasts for 2 to 3 hrs and late PONV was caused by postoperative opioids.[15]

When you compare the efficacy of the two drugs in preventing vomiting, palonosetron scores over ondansetron during early period(1.8 % vs 10.9 %, p value = 0.050). However we did not observe any difference between the 2 groups during the late period. In a study conducted by **Parathoduvil et al** the incidence of vomiting was more in ondansetron group (34.9%) than in palonosetron group (17.9 %).[18]

Apfel et al identified four risk factors (female gender, history of PONV or motion sickness, non smoker and predicted opioid use) that form the basis of apfel scoring

system.[4] In our study the incidence of PONVin patients with more than 3 risk factors was 11.5 % in group P and 35.5 % in group O with a p value of 0.03 which is statistically significant. This proves that increase in number of risk factors increases the risk of PONV.

Shaikh **et al** mentioned that for every 30 min increase in duration of surgery the risk of PONV increase by 60%.[3]

In our study incidence of PONV in patient whose duration of surgery was more than 1 hour was 17.7% and 50% in group P and group O respectively. Whereas that in patients whose duration of surgery was less than 1 hour was 4.8 % and 18.5 % in group P and group O respectively. This proves that increase in duration of surgery increases the risk for PONV. However, we could not find any association between PONV and intraoperative or postoperative usage of opioids.

5-HT_3 antagonists are known to prolong QT_C interval and predispose to arrhythmias.[18]However palanosetron is the safest in this class of drugs in this aspect**. Kim** *et al* studied the effect of palonosetron on the QT interval in patients undergoing sevoflurane anaesthesia and they concluded that palonosetron was safe in terms of QT interval prolongation.[20]

There was no adverse events like headache, constipation, dizziness and prolonged QT interval observed in our study.

Conclusion

Thus we conclude that palanosetron when compared to ondansetron is more effective in preventing PONV in patients undergoing various ENT surgeries. However both ondansetron and palonosetron are safe antiemetic agents.

Limitations

1. Our study population is limited to ENT surgeries and ASA 1 and ASA 2 patients.

2. Incidence of PONV beyond 24 hours could not be studied because of our study design.

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