

Efficacy of palonosetron in the management of postoperative nausea vomiting in oral and maxillofacial surgery

ABSTRACT

Objective: The objective is to evaluate the efficacy of prophylactic single intravenous dose of palonosetron in the management of postoperative nausea and vomiting (PONV) following oral and maxillofacial surgical interventions performed through an intraoral approach under general anesthesia (GA).

Materials and Methods: A prospective study was conducted on 100 subjects who underwent intraoral surgical procedures for the management of maxillofacial trauma, pathology, dentofacial anomalies, and deformities under GA. All subjects received a prophylactic single intravenous dose of 0.075 mg palonosetron along with premedication. Predisposing factors for PONV such as patient age, gender, Apfel risk score, history of motion sickness, smoking, type of procedure, and administration of postoperative opioids were taken into consideration. All the patients were monitored for PONV for the 1st 24 h postoperatively (PO). First, at an interval of 30 min for 1st 4 h and then at every 2 h interval for next 8 h followed by monitoring every 6 h interval till 24 h. Time and frequency of rescue medication were noted.

Results: Seventy-nine percentage subjects did not have PONV. 15% subjects had a single episode of vomiting PO which could be attributed to multiple intra oral surgical sites performed as well as longer duration of exposure to anesthetic agents in addition to providing opioid analgesics for the management of postoperative pain. Only 6% subjects needed rescue antiemetic drug. Palonosetron did not show any significant changes in cardiac status and serum profile.

Conclusion: Palonosetron is effective in the management of PONV for maxillofacial surgical procedures performed through an intraoral approach under GA.

Keywords: Antiemetic, nausea and vomiting, palonosetron

INTRODUCTION

It is a well-known fact that postoperative nausea and vomiting (PONV) is a common sequel following surgical intervention in the oral and maxillofacial region under general anesthesia (GA). Previous studies have shown that GA is associated with an 11-fold increased risk of PONV due to the emetic properties of volatile anesthetics and the use of opioids.^[1] In addition to this, an intraoral approach act as an independent risk factor for PONV.^[2] It is considered to be the utmost unpleasant experience associated with surgery and is considered as the most common reason for poor patient satisfaction in the postoperative period.^[3]

Certain predisposing factors are associated with PONV but little evidence exists in the literature regarding their

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magnitude or real effects.^[4] PONV in the immediate postoperative phase can result in aspiration, laryngospasm, dehydration, electrolyte disturbances, gastric bleeding, increased intracranial pressure, increased intraocular pressure, and wound dehiscence in addition to increased unanticipated hospital stay.^[3,5-7] Literature had advocated the use of a wide variety of prophylactic antiemetic regimens for the prevention and management of PONV.^[6] However, they are associated with undesirable side effects and have inadequate efficacy.

Palonosetron a newer 5-hydroxytryptamine 3 (5-HT₃) receptor antagonist has a longer half-life in addition to a better safety profile when compared to the older generation of 5-HT₃ receptor antagonists such as ondansetron.^[8] Around 60% of the drug is bound to plasma proteins with about 50% metabolism by liver cytochrome *P* enzymes.^[9] Palonosetron is considered safe and more effective than ondansetron or Ramosetron in preventing early and late PONV without any effects on the QTc interval.^[10,11] Numerous anti-emetics have been used for the management of PONV. The authors hypothesize that palonosetron when used as a single-dose prophylactically would eliminate the incidence of PONV. Thereby, it eliminates the use of antiemetics in the postoperative period. Hence, this study intended to evaluate the efficacy of palonosetron in the prevention of PONV following maxillofacial surgical interventions performed through intraoral approach under GA.

MATERIALS AND METHODS

A prospective study was conducted to assess the efficacy of palonosetron in the management of PONV following oral and maxillofacial surgical interventions performed through an intraoral approach under GA between December 2017 and May 2019. This study included 100 subjects who underwent intraoral surgical approach for the management of maxillofacial trauma, pathology, and dentofacial anomalies and deformities under GA.

Subjects with the American Society of Anesthesiologists (ASA) Grade I/II patients within the age group of 18–60 years were included. All surgical interventions through an extraoral approach and those with hypersensitivity to Palonosetron, Dexamethasone or Ondansetron, those on Steroid therapy, antiemetics or on treatment with other medication known to produce nausea and vomiting, pregnant and lactating subjects are excluded from this study. Institutional Ethical clearance is obtained from Sri Sai College of Dental Surgery, Vikarabad with reference no 626/SSCDS/IRB-E/2017 on 11/12/2017.

Following preanesthetic evaluation subjects were explained about the anesthesia technique. Written informed consent was taken. Single dose of intravenous palonosetron 0.075 mg was administered to all individuals as a preanesthetic medication along with other drugs. None were given dexamethasone in the pre- or peri-operative period in the study as it was used as a rescue antiemetic in postoperative period if and when required.

All the subjects were administered GA by standard technique. At the time of induction, glycopyrrolate 0.2 mg, Nalbuphine 0.6 mg/kg, and Propofol 2 mg/kg were administered and nasotracheal intubation was done with help of succinylcholine. Anesthesia maintained with Oxygen, Nitrous oxide and inhalational agent Isoflurane with controlled ventilation. Vecuronium 0.1 mg/kg was given for maintenance. Subsequent anesthetic management was done according to the surgical requirements and reversal was performed with neostigmine 2.5 mg and glycopyrrolate 0.5 mg and extubated following complete recovery.

The duration of anesthesia and surgery were recorded. Subjects were observed in the intensive care unit for 1st 12 h and then shifted to the recovery room for further monitoring up to 24 h. All patients were administered parenteral antibiotics (Amoxycillin + clavulanic acid and metronidazole) and analgesics (diclofenac) in the postoperative period. Primary outcome variables included nausea and vomiting in the 1st 24 h and hemodynamic changes following the administration of palonosetron. Monitoring of PONV was done for 1st 24 h postoperatively (PO), at intervals of 30 min for 1st 4 h, then for every 2 h for next 8 h followed by monitoring every 6 h interval till 24 h. PONV score was recorded.

PONV Score utilized was: No nausea and vomiting-0, Nausea only – 1, Vomiting once – 2, Vomiting more than once - 3. PONV Score 2 or greater were given Dexamethasone 4 mg I.V as a rescue medication. Frequencies and time of rescue medication were noted. Complete response was considered as the absence of nausea and vomiting. In the electrocardiography (ECG), any significant difference among QT interval was evaluated by the anesthetist intraoperatively at intervals of 30 min throughout the procedure from the multichannel monitor and PO for the first 6 h to evaluate the cardiac safety of the drug. Side effects such as headache, constipation, and diarrhea were recorded and observed for serotonergic reactions.

The secondary outcome variables include risk factors associated with PONV along with other complications of palonosetron. Risk factors were categorized as

patient factors, preoperative factors, anesthetic factors, intraoperative factors, and postoperative factors. Statistical analysis: All the data obtained were analyzed using SPSS version 25.0 following Chi-square test and Wilcoxon test to establish any significant differences from any of the tested parameters and their correlation with the primary outcome variable.

RESULTS

This study included 67 males and 33 females of which 62 males (92%) and 15 females (45%) showed complete response to palonosetron. Thus, statistically significant ($P \leq 0.001$) relationship exists between PONV and female gender. Subjects were in the age group of 18–60 years with a mean age of 34 years. The prevalence of PONV was not associated with age of an individual ($P = 0.87$). All the results have been tabulated as shown in Table 1-4.

There is no statistically significant difference between PONV status and ASA criteria in our study as majority of subjects (98%) were in ASA I. With regards to Apfel risk score, 33 females gave history of predisposing factors such as motion sickness, nausea, and vomiting. Fifty six subjects were nonsmokers and 44 were smokers. It was found that 90% patients who had Apfel Score 3 were PONV positive [Figure 1]. Thus, there is statistically significant ($P = 0.001$) increase in PONV status as Apfel score increased.

The results showed that 19 subjects (33.9%) who were nonsmokers had PONV while only 2 subjects (4.5%) who were smokers had PONV [Figure 2]. It was found that PONV is associated with nonsmokers more with smokers ($P \leq 0.001$). Subjects who underwent surgical intervention for the correction of dentofacial deformity revealed a higher incidence (47.36%) of PONV than other surgical intervention due to the prolonged duration of surgery [Figure 3]. Thus, showing strong association ($P = 0.012^*$) between PONV incidence and type of surgical procedure as well as the duration of the procedure [Figure 4].

Postoperative opioids were required in 53 subjects for managing postoperative pain of which 16 subjects (30.18%) developed PONV episodes in first 6–12 h in spite of the administration of palonosetron [Figure 5]. There is a statistically significant association ($P = 0.026$) between PONV with postoperative opioids.

Twenty-one of our subjects developed incomplete response to palonosetron in 12–24 h of this only 6 subjects had more than 2 episodes of PONV within 12–24 h and were given a rescue antiemetic in the form of intravenous dexamethasone

Table 1: Age group of subjects

Age group	PONV		Total	X	df	P
	Present	Absent				
18-30	13	49	62	0.70	3	0.87
31-40	4	15	19			
41-50	1	9	10			
51-60	2	7	9			
Total	20	80	100			

PONV: Postoperative nausea and vomiting

Table 2: Gender of the sample size

Gender	PONV		Total	Fisher's exact test P value
	Positive	Negative		
Male	5	62	67	<0.001*(S)
Female	16	17	33	
Total	21	79	100	

S: Significance, PONV: Postoperative nausea and vomiting

Table 3: Blood serum profile changes

Variable	n	Preoperative		Postoperative		Z	P
		Mean	SD	Mean	SD		
Na	100	137.4	5.41	135.47	4.48	-2.36	0.018
K	100	5.21	0.65	21.84	84.15	-2.85	0.004
Total proteins	100	6.55	0.57	5.96	0.49	-8.49	<0.001
Serum bilirubin	100	0.82	0.12	1.03	0.72	-6.53	<0.001
SGOT	100	30.37	6.16	36.14	27.26	-7.44	<0.001
SGPT	100	22.88	5.63	29.06	5.17	-8.66	<0.001
Alkaline phosphatase	100	73.2	16.32	84.51	18.71	-7.95	<0.001

SD: Standard deviation, SGOT: Serum glutamic oxaloacetic transaminase, SGPT: Serum glutamic pyruvic transaminase

Table 4: Adverse effects of palonosetron

Adverse effect	Incidence
Headache	20
Constipation	2
Dizziness	0
Increase in QTc intervals in ECG	0

ECG: Electrocardiogram

4 mg and there was no requirement of rescue antiemetic for 15 subjects as they showed complete response to drug in later hours. The results of this study showed that only 6% of patients needed rescue antiemetic and 94% patients had complete response to palonosetron [Figure 6].

Changes in the serum profile and ECG were evaluated in the pre- and post-operative period to assess the effects of drug on variables such as serum sodium, serum potassium, total serum proteins, and liver function test. The results showed no statistically significant difference among serum electrolytes sodium, serum potassium, total proteins, and liver enzymes.

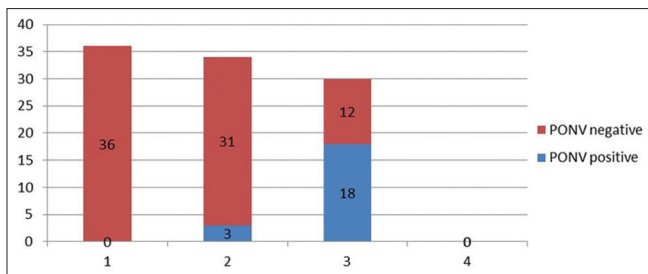


Figure 1: Graph showing the Apfel risk scores

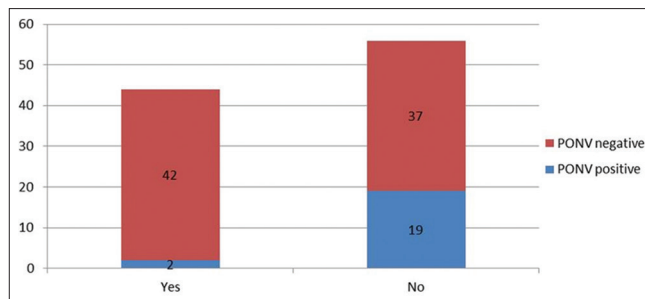


Figure 2: Graph showing the relationship between smoking and postoperative nausea and vomiting

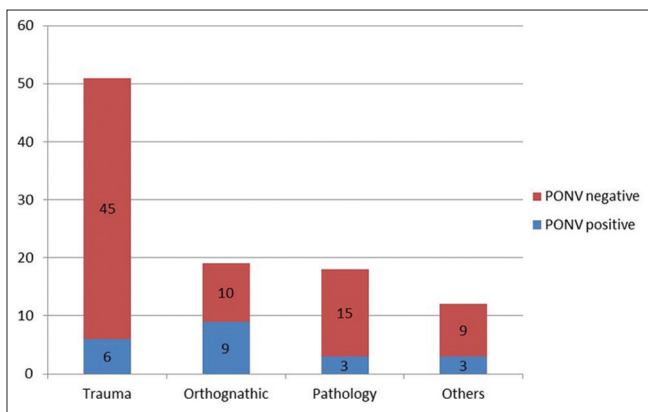


Figure 3: Graph showing the relationship between different surgical interventions and postoperative nausea and vomiting

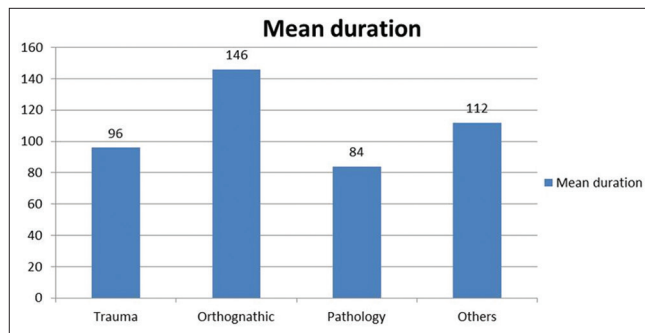


Figure 4: Graph showing the relationship between duration of the surgical intervention and postoperative nausea and vomiting

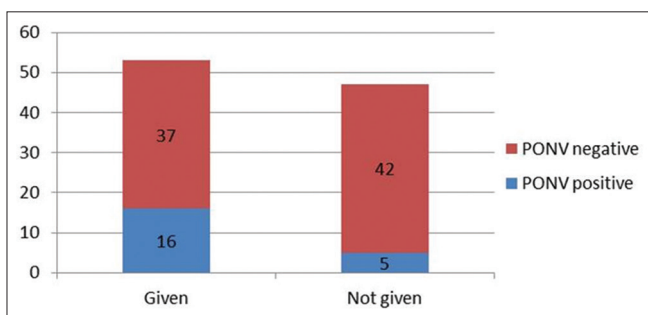


Figure 5: Graph showing the relationship between use of postoperative opioids and postoperative nausea and vomiting

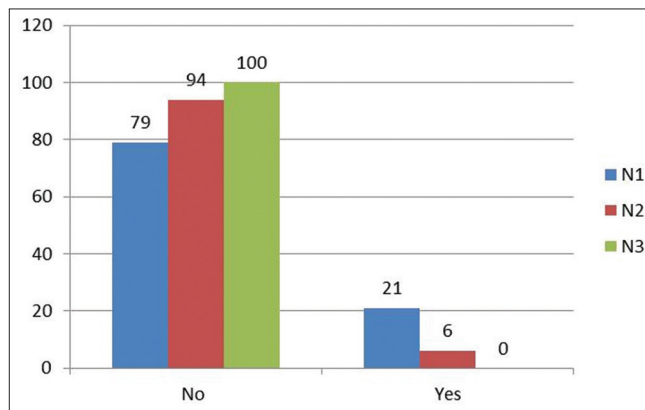


Figure 6: Graph showing the efficacy of Palonosetron in managing postoperative nausea and vomiting

In the ECG, there was no significant difference among QT interval implying that palonosetron did not show any significant changes in cardiac status. Among 100 patients who received palonosetron, 20 patients (16 females and 4 males) developed headache as a complication in immediate postoperative period which subsided spontaneously after couple of hours. They had given positive history of migraine which could be a predisposing factor for PONV.

DISCUSSION

The incidence of PONV accounts to around 8% to 92% and varies based on the type and duration of the surgical procedure, age, gender, and smoking status of the patient, use of opioids, and anesthetic technique.^[12] It is considered

to be one among the ten most frequently occurring complications following surgery under GA.^[13] Since the available antiemetics work on different receptor classes, it is advocated that in high-risk patients, multiple antiemetics can be safely and effectively combined to reduce the risk of PONV.^[12,13]

Metoclopramide shows poor efficacy while drugs such as promethazine, Dimenhydrinate, Prochlorperazine and Cyclizine though effective, clinical utility is limited due to their sedative effects. Scopolamine can only be useful as an adjunct to other antiemetic due to its slow action and side effects such as dry mouth, visual disturbances, dizziness, and

agitation.^[6,7,13] Droperidol is cost effective drug but is cardio toxic. Haloperidol carries a risk of QTc prolongation and thus it is not recommended as first line therapy for PONV.^[14] Efficacy of dexamethasone for PONV prophylaxis seems to be similar to that of ondansetron and droperidol.^[15,16] Literature suggests that the use only a single antiemetic for PONV prophylaxis is not effective.^[3]

Palonosetron is a second-generation 5HT₃ receptor antagonist with a half-life of 40 h. The most effective dose of 0.075 mg is considered more effective than granisetron 1 mg and ondansetron 4 mg in preventing PONV.^[11,17] The dosage of the drug to be administered is 0.1 microgram/kg body weight.^[11,17] It is used for prophylaxis against acute as well as delayed chemotherapy induced nausea vomiting (CINV).^[18] Previous study showed that palonosetron 0.25 mg and dexamethasone 8 mg produced no incidence of emesis even in delayed CINV from 0 to 5 days.^[15] Hence, dexamethasone is used as a rescue antiemetic in our study since it is effective in managing immediate episodes of nausea and vomiting.

Palonosetron is metabolized in liver by cytochrome P450 enzymes. Nearly 40% of the administered dose is excreted unchanged.^[10] This slow elimination is considered to be the cause for its half-life being approximately 40 h. Its adverse effects are headache, constipation, and dizziness. Palonosetron slightly increases QTc intervals from 1 to 3 cm, however, it can be safely used in patients with cardiac impairment.^[18] A meta-analysis revealed that palonosetron is safe and more effective than ondansetron or ramosetron in preventing early and late PONV.^[19]

Surgical interventions in the maxillofacial region performed through an intraoral approach harbors blood, saliva and saline in the surgical field some of which may eventually go into the stomach during and after surgery. Blood is an emetogenic substance that causes discomfort when present in the stomach, often triggering emetic pathways and causing occurrence of PONV.^[7,12] It is advocated that in majority of the cases PONV occurs in the 1st 2 h of the postoperative period leading to deleterious effects.^[3]

Females have increased risk of PONV with probable reason of fluctuation of hormonal levels and younger the individual, greater the incidence of PONV.^[3,4,11,13] The results of our study are in agreement with previous studies. ASA classification did not show any significant relation with PONV but few studies observed that there was decreased incidence of PONV as the ASA classification increased.^[2-4]

Apfel risk score was assessed preoperatively and it was found that subjects with higher Apfel score had increased PONV

episodes when compared to subjects with low Apfel score. This constitutes a significant correlation between incidence of PONV and Apfel risk score for PONV. Nonsmokers are associated with increased incidence of PONV. It is observed that smoking has an effect on the dopaminergic system, thereby diminishing the incidence of PONV. Inhibition of emetic events caused by smoking could be the reason for decreased occurrence of PONV.^[4]

The incidence of PONV is higher in subjects who were on inhalational agent nitrous oxide for longer duration to maintain GA. We observed higher prevalence of PONV among patients who have been administered with volatile anesthetics compared to intravenous anesthetics.^[3,4] Propofol has antiemetic properties limited to 1st 2 h of surgery and inhalational anesthetics are main cause of early PONV but have no impact on later phase in postoperative period. We found PONV incidence is statistically significant in subjects who received nitrous oxide for longer duration as maintenance of GA.^[3,4]

Among the various maxillofacial surgical procedures, the incidence of PONV was higher for orthognathic surgeries due to longer duration of surgical procedure and multiple intraoral surgical sites.^[20] Results of this study show a significant relation between of duration of the procedure and incidence of PONV.

Those who received postoperative opioids have shown emetic episodes in postoperative period despite the administration of palonosetron prophylactically. Postoperative opioids sensitize the otic and vestibular areas to motion and cause emesis with movement. The results of our study are in agreement with previous studies.^[2,21] This study revealed that the drug has minimal or no changes with reference to serum electrolytes, serum proteins, and liver enzymes. It has no clinical effects on QTc interval and no significant effects on cardiovascular activity. Palonosetron can result in mild asymptomatic increase in serum bilirubin levels, ALT and AST but these are seen in patients receiving highly emetogenic chemotherapy where 0.25 mg of palonosetron was administered.^[2]

Palonosetron was well tolerated by all the subjects but headache was reported in 20 subjects which subsided within few hours without intervention. The clinical efficacy of palonosetron in preventing PONV was 94% in early postoperative period ensuring that it is a first choice of drug for management of PONV following maxillofacial surgical procedures.

CONCLUSION

The results of this study reveal that 0.075 mg palonosetron is a safe drug with good patient compliance with long duration of action sufficient enough till complete recovery of the patient. It can be advocated that palonosetron is an effective antiemetic in the management of PONV for maxillofacial surgical procedures performed through an intraoral approach under GA.

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Conflicts of interest

There are no conflicts of interest.

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