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COMPARISON OF ANTIEMETIC EFFECT OF GRANISETRON AND PALONOSETRON IN PATIENTS UNDERGOING THYROIDECTOMY: A PROSPECTIVE, RANDOMIZED, DOUBLE-BLIND STUDY.

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ABSTRACT

Background: Postoperative nausea and vomiting (PONV) is the second most frequent postoperative complaint after pain. The 5-hydroxytryptamine type-3 antagonists have proven a particularly valuable addition to the armamentarium against PONV. Granisetron has been very popular drug in this class for its efficacy and patient tolerability. Palonosetron is a second-generation 5-HT_3 antagonist that has recently been approved for prophylaxis against PONV. It has unique structural, pharmacological and clinical properties that distinguish it from other agents in its class. This study compared the effects of intravenous granisetron and palonosetron administered five minutes before induction of anaesthesia in preventing postoperative nausea and vomiting (PONV) in patients undergoing thyroidectomy. **Methods:** 120 female patients of physical status ASA-I & ASA-II, 25-50 years of age, posted for elective thyroidectomy were enrolled in the study and randomly divided into two groups (group-G and group-P). Patients in group-G received 2.5 mg of granisetron and group-P received 0.075 mg of palonosetron intravenously five minutes before induction of anesthesia according to group assignment by an anesthesiologist not involved in the study. Incidence of nausea and vomiting, severity of nausea and vomiting, need for rescue anti emetics and side effects if any were evaluated at 0-2 hours, 2-24 hours and 24-48 hours after surgery. **Results:** The incidence of PONV during 24-48 hours postoperative period was lower in palonosetron group than in granisetron group (8.33% vs 31.66%, p-value=0.001) and was statistically significant however no differences were observed between the two groups at 0-2 hours and 2-24 hours. The severity of nausea and vomiting was significantly lower in the palonosetron group as compared to granisetron group at all study intervals. The number of patients requiring anti-emetics was statistically insignificant between the two groups at 0-2 hours and 2-24 hours postoperatively. However, the difference was statistically significant (p-value=0.025) at 24-48 hours postoperatively with 11 patients (18.33%) requiring rescue anti-emetics in group-G (Granisetron) and 2 patients (3.33%) in group-P (Palonosetron). Total number of rescue anti-emetics used in both the groups during 0-48 hours was 28, out of which 22(78.57%) were used in group-G (Granisetron) and 6 (21.43%) used in group-P (Palonosetron). **Conclusions:** From our study, we concluded that palonosetron is more effective than granisetron for antiemetic prophylaxis in patients undergoing thyroidectomy under general anesthesia.

KEYWORDS: anti-emetics, granisetron; anti-emetics, palonosetron; postoperative nausea and vomiting; thyroidectomy.

INTRODUCTION

Postoperative nausea and vomiting (PONV) is the second most frequent postoperative complaint after pain.[1,2] PONV can cause significant morbidity and remains an unpleasant and persistent clinical problem in the surgical patients after anesthesia.[3] Furthermore, discharge from post-anesthetic care unit may be delayed and hospital stay prolonged, thereby increasing the overall medical cost.[4] The general incidence of vomiting is about 30%, nausea is about 50%, and in a subset of high-risk patients, the PONV rate can be as high as 80% during first 24 hours after emergence.[5]

The 5-hydroxytryptamine type-3 antagonists have proven a particularly valuable addition to the armamentarium against PONV and have been extensively studied and are

currently the primary therapy for PONV prevention because they have fewer side effects such as sedation or extrapyramidal symptoms compared with other anti-emetics. Granisetron has been very popular drug in this class for its efficacy and patient tolerability. Palonosetron is a second-generation 5-HT_3 antagonist that has recently been approved for prophylaxis against PONV. It has unique structural, pharmacological and clinical properties that distinguish it from other agents in its class.[6] An ideal antiemetic used for prevention of postoperative nausea and vomiting should have quicker onset, longer duration of action, provide complete antiemetic control, lack in side effects and be cost effective, and palonosetron in this regard appears to be a good choice.[7]

Thyroidectomy is an operation that causes strong vagal stimulation by surgical manipulation of the neck structures. There is relatively higher incidence of PONV about 60–84% in such surgeries.[8] Moreover, additional factors both related and unrelated to anesthesia may influence PONV, such as age, gender, body weight, history of motion sickness and/or previous PONV, non-smoking status, type and duration of operation, type of induction, maintenance of anesthesia with volatile agents, neuromuscular blocking drug antagonist used, and postoperative pain.[9] PONV is not desirable in such patients as it can lead to hemorrhage and acute airway obstruction adding to overall morbidity and mortality.[10]

Therefore the present study was designed to compare the efficacy and safety of Palonosetron and Granisetron in patients undergoing thyroidectomy.

MATERIAL AND METHODS

This prospective, double-blind, randomized study was conducted after approval from the Institutional review board. 120 female patients of physical status ASA-I & ASA-II, 25-50 years of age, posted for elective thyroidectomy were enrolled in the study. A written consent was taken from all the patients. Criteria for PONV prophylaxis included patients having two or more risk factors including female sex, non-smoker, opioid use & surgery related factors. Pregnant and lactating females, patients with history of motion sickness, gastrointestinal tract, liver and kidney disease were excluded. All the patients were in euthyroid state before surgery. No premedication was given. On arrival to the operation theatre, standard anaesthesia monitoring was instituted with electrocardiogram, non-invasive blood pressure, pulse oximetry, temperature and end tidal carbon dioxide. Intravenous access was secured using 20 gauge intravenous cannula. The patients enrolled were randomly divided into two groups (group-G and group-P). Patients in group-G received 2.5 mg of granisetron and group-P received 0.075 mg of palonosetron intravenously five minutes before induction of anesthesia according to group assignment by an anesthesiologist not involved in the study. Drugs were prepared by an anesthesia technician in a 5ml syringe and all the study medication was diluted in normal saline to make a total of 4ml medication in order to ensure blinding. Baseline parameters were recorded before induction of anaesthesia and thereafter at 5 minutes interval till completion of surgery. General anesthesia was induced using propofol 2mg/kg, fentanyl 2-5mcg/kg & atracurium 0.5mg/kg to facilitate endotracheal intubation. Anesthesia was maintained with 0.5-1% isoflurane & 60% nitrous oxide in oxygen. At the end of surgery, neuromuscular paralysis was reversed with neostigmine 60mcg/kg & glycopyrrolate 5-8 mcg/kg. Patients received injection paracetamol one gram intravenous infusion every 8 hours for postoperative analgesia. Incidence of nausea and vomiting, severity of nausea and vomiting (Rhode's index), need for rescue anti emetics and side effects if any were evaluated at 0-2 hours, 2-24 hours and 24-48 hours after surgery by another anesthesiologist/ trained nurse not involved in the study.

Nausea was defined as subjectively unpleasant feeling associated with the awareness of urge to vomit[11].Retching was defined as labored, spasmodic, contraction of the respiratory muscle without expulsion of gastric contents and Vomiting was defined as actual physical phenomenon of forceful expulsion of gastric contents from mouth.[11] If the patient felt severe nausea or requested rescue antiemetic medication, metoclorpramide 10mg was injected intravenously immediately after recording PONV severity. Side effects like headache, dizziness and drowsiness were recorded. The primary outcome evaluated was the incidence of nausea/vomiting during the period.

Parameters were statistically evaluated at the end of the study using unpaired Students t-test, chi-square test and Fisher`s exact Test. All the continuous variables of the study were shown in terms of descriptive statistics (Mean and Standard Deviation) and the categorical variables in terms of frequency and percentages. For the comparison of two groups, we applied statistical tests like unpaired students t-test, chi-square test and Fisher's exact test. All the results obtained have been discussed on 5% level of significance i.e. p-value < 0.05 considered as significant. The Statistical Software SPSS V-20 was used to analyze the data.

RESULTS

The subject characteristics such as age, weight, ASA status, duration of surgery were similar in both groups (Table 1). The incidence of PONV during 24-48 hours postoperative period was lower in palonosetron group than in granisetron group (8.33% vs 31.66%, p-value=0.001) and was statistically significant however statistically insignificant differences were observed between the two groups at 0-2 hours (6.7% vs 11.7%) and 2-24 hours(10% vs 16.7%). (Table 2 and Fig. 1)

Incidence of complete responders (patients with no incidence of PONV during the 48 hours postoperatively)

was 75% (45 patients) in group-P (Palonosetron) compared to 55% (33 patients) in group-G (Granisetron) and the comparison was statistically significant with p-value of 0.035 (Table 3). Severity of PONV was assessed by RINVR (Rhodes Index of Nausea, Vomiting and Retching) -Appendix I.[12] Scores of 1-8, 9-16, 17-24, and 25-32 were categorized as mild, moderate, great, and severe, respectively. The severity of nausea and vomiting was significantly lower in the palonosetron group as compared to granisetron group at all study intervals.

There were 4 patients (6.7%) at 0-2 hours, 6 patients (10%) at 2-24 hours and 5 patients (8.33%) at 24-48 hours with mild PONV in group-P (Palonosetron), whereas in group-G (Granisetron), 6 patients(10%) at 0-2 hours, 9 patients(15%) at 2-24 hours and 13 patients (21.7%) at 24-48 hours had mild severity of PONV. In group-G (Granisetron), 1 patient at 0-2 hours, 1 patient at 2-24 hours and 6 patients at 24-48 hours had moderate PONV postoperatively. However, no patient in the group-P (Palonosetron) had moderate PONV at any time during the observation period. The difference between the two groups was statistically significant with respect to moderate severity at 24-48 hours (p-value = 0.027). None of the patients in the two groups had any episode of severe PONV (Table 4). The number of patients requiring anti-emetics was statistically insignificant between the two groups at 0-2 hours and 2-24 hours postoperatively. However, the difference was statistically significant (p-value=0.025) at 24-48 hours postoperatively with 11 patients (18.33%) requiring rescue anti-emetics in group-G (Granisetron) and 2 patients (3.33%) in group-P (Palonosetron). Total number of rescue anti-emetics used in both the groups during 0-48 hours was 28, out of which 22(78.57%) were used in group-G (Granisetron) and 6 (21.43%) used in group-P (Palonosetron). (Table 5)

Headache and Dizziness were the only side effects observed in both the groups in our study. Incidence of side effects between the two groups was statistically insignificant with p-value > 0.05. (Table 6)

Table-1: Mean Age, Weight, Physical status and Duration of Surgery in the two groups

	Group P (n=60)	Group G (n=60)	p-value	Remarks
Mean Age(yrs)±SD	36.73 ± 9.30	36.43 ±8.09	0.85	NS
Mean Weight(kgs) ±SD	61.10 ± 3.78	61.35 ±3.66	0.71	NS
ASA I / ASA II	36 / 24	40 / 20	0.449	NS
Duration of surgery(min) ±SD	103.22 ± 9.44	103.25 ± 9.18	0.98	NS

NS = Not Significant; P = Palonosetron; G = Granisetron

Table 2: Incidence of PONV in the two groups at 0-2 hours, 2-24hours and 24-48 hours postoperatively

Time interval	Group-P(n=60)	Group-G(n=60)	p-value	Remarks
0-2 hours	4(6.7%)	7(11.7%)	0.34	NS
2-24 hours	6(10%)	10(16.67)	0.28	NS
24-48 hours	5(8.33)	19(31.66)	0.001	HS

NS=Not Significant; HS=Highly Significant; P = Palonosetron; G = Granisetron

Table 3: Complete Responders (Patients with No PONV over 0-48 Hours) in the two groups

Group	Total No. of Patients	Complete responders	Percentage	p-value	Remarks
P	60	45	75	0.035	S
G	60	33	55		

NS = Not Significant; S = Significant;P = Palonosetron; G = Granisetron

Table 4: Severity of PONV at different time intervals in patients of the two groups as per RINVR (Rhodes Index of Nausea, Vomiting and Retching)

Time interval	Severity	Group-P(n=60)	Group-G(n=60)	p-value	Remarks
0-2 Hours	**Mild**	4(6.7%)	6(10%)	0.509	NS
	Moderate	0	1(1.7%)	1	NS
2-24 Hours	**Mild**	6(10%)	9(15%)	0.40	NS
	Moderate	0	1(1.7%)	1	NS
24-48 Hours	**Mild**	5(8.33%)	13(21.7%)	0.041	S
	Moderate	0	6(10%)	0.027	S

S = Significant; NS = Not Significant; P = Palonosetron; G = Granisetron

Table 5: Patients requiring rescue antiemetics in the two groups at 0-2 hours, 2-24 hours and 24-48 hours

Time Interval	Group - P(n=60)		Group - G(n= 60)		p-value	Remarks
	1 Dose	2 Doses	1 Dose	2 Doses		
0-2 hours	2(3.33%)	0	3(5%)	0	1.00	NS

2-24 hours	2(3.33%)	0	5(8.33%)	0	0.439	NS
24-48 hours	2(3.33%)	0	8(13.33%)	3(5%)	0.025	S

S = Significant; NS = Not Significant;P = Palonosetron; G = Granisetron

Table 6: Comparative evaluation of side effects between the two groups:

Parameters	Group-P(n=60)	Group-G(n=60)	p-value	Remarks
Headache	1(1.7%)	3(5%)	0.619	NS
Dizziness	2(3.33%)	2(3.33%)	1.00	NS

NS = Not Significant; S = Significant; P = Palonosetron; G = Granisetron

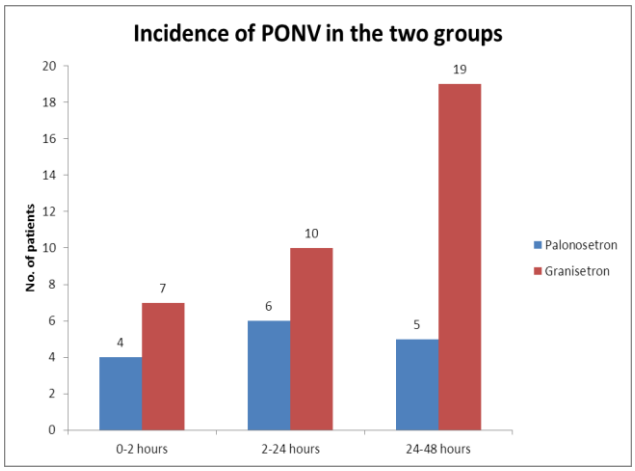

Fig 1: Incidence of PONV in two groups at different intervals of time.

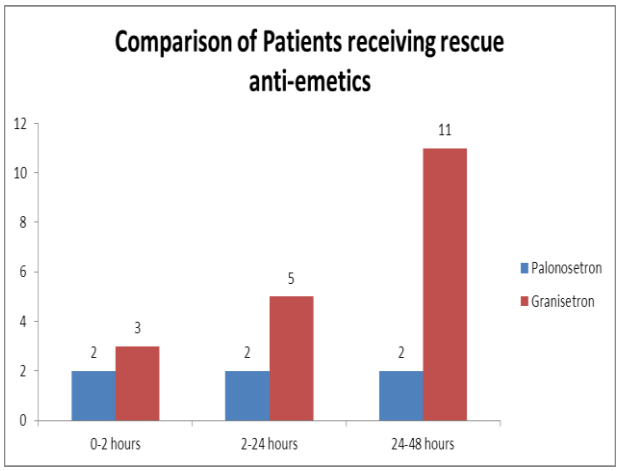

Fig 2: comparison of patients receiving rescue anti-emetics in two groups.

Appendix I

Rhodes Index of Nausea, Vomiting and Retching (RINVR).

		0	**1**	**2**	**3**	**4**
1)	In the last 2, 2-24, 24-48 hours, I threw up ( ) times.	I did not throw up	1-2	3-4	5-6	7 or more
2)	In the last 2, 2-24, 24-48 hours, from retching and dry heaves, I have felt ( ) distress.	No	Mild	Moderate	Great	Severe
3)	In the last 2, 2-24, 24-48 hours, from vomiting or throwing up, I have felt ( ) distress	No	Mild	Moderate	Great	Severe
4)	In the last 2, 2-24, 24-48 hours, I have felt nauseated or sick to my stomach.	Not at all	1 hour or less	2-3 hours	4-6 hours	More than 6 hours
5)	In the last 2, 2-24, 24-48 hours, from nausea/sickness to my stomach, I have felt ( ) distress.	No	Mild	Moderate	Great	Severe
6)	In the last 2, 2-24, 24-48 hours, each time I threw up, I produced a ( ) amount.	Very large (3 cups or more)	Large (2-3 cups)	Moderate (1/2-2 cups)	Small (up to 1/2 cups)	I did not throw up
7)	In the last2, 2-24, 24-48 hours, I have felt nauseated or sick to my stomach ( ) times.	No	1-2	3-4	5-6	7 or more
8)	In the last 2, 2-24, 24-48 hours, I have had periods of retching or dry heaves without bringing anything up ( ) times.	No	1-2	3-4	5-6	7 or more

Total experience score: sum of all scores, 1-8: mild, 9-16: moderate, 17-24: great, 25-32: severe.

DISCUSSION

Postoperative Nausea and Vomiting (PONV) are frequently listed by patients as their most important peri-operative concerns[13] and together they have an incidence of about 20-30% in patients undergoing surgeries.[14] Guidelines provide a comprehensive evidence based reference tool for prevention and treatment of PONV in patients undergoing surgical procedures. Not all patients undergoing surgeries will benefit from antiemetic prophylaxis, and thus, identification of patients who are at increased risk using available risk scores leads to the most effective use of therapy and cost benefit.[15] There are numerous antiemetic drugs with different mechanisms of action,

target sites, varying potencies and pharmacokinetic profiles that have been used for prophylaxis and treatment of PONV. Routinely employed drug classes are dopaminergic antagonists, $5HT_3$ antagonists, butyrophenones, anticholinergics, phenothiazines, anti-histaminics, benzamides and steroids.[16] When nausea and vomiting occur postoperatively, treatment should be an antiemetic from a pharmacological class that is different from the prophylactic drug initially given.[17] The 5-HT3 antagonists are the only drugs that have been adequately studied for treatment of existing PONV, and in this respect have proven to be highly effective.[18] Various 5-HT3 antagonists have been used to prevent PONV. Palonosetron is a second-generation 5-HT3 antagonist with unique pharmacodynamic characteristics. Palonosetron is an allosteric 5-HT3 receptor antagonist, whereas the previously developed 5-HT3 antagonists compete directly with serotonin.[19] Allosteric binding creates a conformational change in the serotonin receptor so that serotonin binding is indirectly inhibited.[19] Consequently, palonosetron has higher affinity with 5-HT3 receptors, which ultimately leads to greater potency and longer duration of action in comparison with standard 5-HT3 antagonists.[20] Palonosetron also inhibits responses induced by substance P, the dominant mediator of delayed emesis after chemotherapy, through differential inhibition of 5-HT3/neurokinin-1 receptor crosstalk.[21] The dose of granisetron 2.5 mg (approximately 45µg kg^{-1}) selected for this study was within its effective dose range (40-80µg kg^{-1}). However, the dose of palonosetron to be used for the prevention of PONV is not established but was extrapolated from the dose used in the clinical trials.

We included only female patients in our study to remove any gender bias between the two groups because incidence of PONV in females has been reported to be very high and is approximately two to three times more prevalent in adult women than men.[22] We did not include a control group receiving placebo in our study as Aspinall and Goodman have suggested that if active drugs are available, placebo controlled trials may be unethical because PONV are very much distressing after surgery.[23] During the present study, anesthetic and surgical factors were well controlled, so that any difference in emesis free episodes can be attributed to the study drugs and goes in accordance with the studies conducted by Tramèr et al.[24]

In our study we found more incidence of PONV in patients receiving Granisetron compared to those receiving palonosetron over 48 hours postoperatively. This difference in incidence of PONV was more over 24-48 hour time period. The results were significant when statistically evaluated. Our results are in accordance with the results obtained by Dhurjoti Prosad Bhattacharjee, Satrajit Dawn, Sushil Nayak, et al.(2011) who in their double blinded study compared palonosetron and granisetron to prevent postoperative nausea and vomiting after laparoscopic cholecystectomy and found that prophylactic therapy with palonosetron is more effective than granisetron and more so during 24-48 hours postoperatively.[25] Kumkum Gupta, Ivesh Singh, Prashant K. Gupta, et al. (2014) in their study compared palonosetron, ondansetron, and granisetron for antiemetic prophylaxis of postoperative nausea and vomitingand concluded that palonosetron is better drug for antiemetic prophylaxis of PONV in patients undergoing laparoscopic cholecystectomy under general anesthesia as compared to ondansetron and granisetron due to its prolonged duration and minimal side effects.[26] Basu A, Saha D, Hembrom BP, et al. (2011) compared palonosetron, granisetron and ondansetron as antiemetics for prevention of postoperative nausea and vomiting in patients undergoing middle ear surgery. 75 patients were randomly divided into 3 groups to receive palonosetron (0.25 mg), granisetron (3mg) or ondansetron (8 mg). They concluded that a single dose of palonosetron is superior to granisetron or ondansetron in complete prevention of nausea and vomiting after middle ear surgery during the first 24 hours period.[27] Saito M, Aogi K, Sekine I, et al. (2009) compared palonosetron plus dexamethasone with granisetron plus dexamethasone for prevention of nausea and vomiting during chemotherapy and concluded that palonosetron exerts efficacy which is non-inferior to granisetron against chemotherapy induced nausea and vomiting in the acute phase (<24 hours) and significantly better than that of granisetron in the delayed phase (24-120 hours) with a comparable safety profile for the two treatments.[28] The above results suggest that palonosetron has an antiemetic effect which lasts longer than granisetron. The exact reason for the difference in effectiveness between granisetron and palonosetron is not known but may be related to the half lives (granisetron 8-9 hrs versus palonosetron 40 hrs) and/or the binding affinities of $5\text{-}HT_3$ receptor antagonists (palonosetron interacts with $5\text{-}HT_3$ receptors in an allosteric, positive cooperative manner at sites different from that bind with granisetron).[19]

In our study, the severity of PONV in the patients receiving palonosetron was comparable with the patients receiving granisetron at 0-2 hours and 2-24 hours whereas it was statistically significant (p-value=0.027) at 24-48 hours with more severity in the patients receiving granisetron compared to palonosetron. Also, Palonosetron was very effective in preventing nausea and vomiting for a longer period of time with a single dose, and therefore decreasing need for repeat anti-emetics & making it more cost-effective. Y.E.Moon, Joo J, J.E.Kim, et al. (2012) compared the antiemetic effect of ondansetron and palonosetron in thyroidectomy patients. In their study they found that the incidence of PONV during the 24 h postoperative period was lower in the palonosetron group than in the ondansetron group. No differences were observed between the groups during the first 2 h. However, the incidence of nausea and vomiting and nausea severity were significantly lower in the palonosetron group than in the ondansetron group during

2–24 h.The evaluation of nausea severity was based on a four point scale (0, no nausea; 1, mild nausea; 2, moderate nausea; 3, severe nausea).[29] Jung Woo Park, Jin Woo Jun, Yun Hee Lim, et al (2012) made a comparative study to evaluate the effect of palonosetron monotherapy versus palonosetron with dexamethasone combination therapy for prevention of postoperative nausea and vomiting. They evaluated PONV by using the Rhodes index (Rhodes index of nausea, vomiting and retching, RINVR) and concluded in their study that the combination therapy of palonosetron with dexamethasone and the monotherapy of palonosetron did not have any differences in patients with high risk factors for preventing postoperative nausea and vomiting.[30]

Mild Headache and dizziness were the side effects observed in a few patients in both the groups in our study. There were no serious side effects seen in any of the patients.

PONV is a key concern for patients undergoing surgery under general anesthesia and many patients rate it worse than postoperative pain.[13,31] In high risk surgeries for PONV like thyroidectomy, PONV can lead to life threatening complications.[10] Keeping in view these facts, use of an antiemetic becomes justified and palonosetron seems to be a good choice better than popular drugs like granisetron as seen in our study. Palonosetron is cost effective and its single dose is highly effective for more than 48 hours which makes it very convenient for the patients.

The limitation of our study was that we compared the efficacy of palonosetron and granisetron based on the currently known optimal doses from the previously conducted studies.

CONCLUSION

From our study, it is concluded that palonosetron is a better drug for antiemetic prophylaxis of PONV in patients undergoing thyroidectomy under general anesthesia when compared to granisetron. Anti-emetic prophylaxis with these two 5-HT_3 antagonists provided clinically effective prevention of postoperative nausea and vomiting in our study with statistically significant difference in their efficacy and duration.

REFRENCES

1. Palazzo M, Evans R. Logistic regression analysis of fixed patient factors for postoperative sickness: A model for risk assessment. *Br J Anaesth, 1993;* 70(2): 135.
2. Eberhart LHJ, Hogel J, Seeling W, et al. Evaluation of three risk scores to predict postoperative nausea and vomiting.*Acta Anaesthesiol Scand, 2000;* 44(4): 480.
3. Christian C Apfel. Postoperative nausea and vomiting. *Miller's Anesthesia 8th edition 2014*; chapter 97: 2948.
4. Hill RP, Lubarsky DA, Phillips-Bute B, et al. Cost-effectiveness of prophylactic antiemetic therapy with ondansetron, droperidol, or placebo. *Anesthesiology, 2000*; 92: 958–67.
5. Sinclair DR, Chung F, Mezei G. Can postoperative nausea and vomiting be predicted? *Anesthesiology, 1999*; 91: 109–18.
6. Neil A Muchatuta, Michael J Paech. Management of postoperative nausea and vomiting: focus on palonosetron. *Ther. Clinical Risk Management 2009*; 5: 21-34.
7. Julian Raynov. Antiemetics: side effects and reactions. *Archive of Oncology, 2001*; 9(3): 151-3.
8. Ewalenko P, Janny S, Dejonckheere M, et al. Antiemetic effect of subhypnotic doses of propofol after thyroidectomy. *Br J Anaesth, 1996*; 77: 463–7
9. Watcha MF, White PF. Postoperative nausea and vomiting. Its etiology, treatment, and prevention. *Anesthesiology, 1992 Jul*; 77(1):162-84.
10. Gauger PG, Shanks A, Morris M, et al. Propofol decreases early postoperative nausea and vomiting in patients undergoing thyroid and parathyroid operations. *World J Surg, 2008*; 32: 1525–34
11. Scuderi PE. Pharmacology of antiemetics. *Int Anesthesiol Clin, 2003*; 41: 41–66.
12. Tae Hee Kim, Byung Moon Choi, Ji Hyun Chin, et al. The reliability and validity of the Rhodes Index of nausea, vomiting and retching in postoperative nausea and vomiting. *Korean J Anesth, 2007*; 52(6): 59-65.
13. Eberhart L.H.J, A.M. Morin, H. Wulf, et al. Patient preferences for immediate postoperative recovery. *British Journal Anaesthesia, 2002*; 89(5): 760-1.
14. Dolin SJ, Cashman J, Bland JM. Effectiveness of acute postoperative pain management: I. Evidence from published data. *Br J Anaesth, 2002;* 89(3): 409.
15. Tong J. Gan, Pierre Diemunsch, Ashraf S. Habib, et al. Consensus guidelines for the management of postoperative nausea and vomiting. *Anesthesia and analgesia, 2014 Jan*; 118(1): 85-113.
16. Neil A Muchatuta, Michael J Paech. Management of postoperative nausea and vomiting: focus on palonosetron. *Ther. Clinical Risk Management, 2009*; 5: 21-34.
17. Habib AS, Gan TJ. The effectiveness of rescue antiemetics after failure of prophylaxis with ondansetron or droperidol: a preliminary report. *J Clin Anesth, 2005*; 17: 62–5.
18. Meyer TA, Roberson CR, Rajab MH, et al. Dolasetron versus ondansetron for the treatment of postoperative nausea and vomiting. *Anesth Analg, 2005*; 100: 373–7.
19. Rojas C,Stathis M, Thomas AG, et al. Palonosetron exhibits unique molecular interactions with the 5-HT3 receptor. *Anesth Analg, 2008*; 107: s469–78.
20. Yang LP, Scott LJ. Palonosetron: in the prevention of nausea and vomiting. *Drugs, 2009*; 69: 2257–78.
21. Rojas C, Li Y, Zhang J, et al. The antiemetic 5-HT3 receptor antag- onist palonosetron inhibits substance P-mediated responses in vitro and in vivo. *J Pharmacol Exp Ther, 2010*; 335: 362–8.

22. Apfel CC, Heidrich FM, Jukar-Rao S, et al. Evidence based analysis of risk factors for postoperative nausea and vomiting. *Br J Anaesth, 2012 Nov*; 109(5): 742-53.
23. Aspinall RL, Goodman NW. Denial of effective treatment and poor quality of clinical information in placebo controlled trials of ondansetron for postoperative nausea and vomiting: a review of published trials. *BMJ, 1995*; 311: 844–6.
24. Tramer MR. A rational approach to control postoperative nausea and vomiting: Evidence from systemic reviews. Part II Recommendations for prevention and treatment. *Acta Anaesthesiol Scand, 2001*; 45: 14‑9.
25. Dhurjoti Prosad Bhattacharjee, Satrajit Dawn, Sushil Nayak, et al. A comparative study between palonosetron and granisetron to prevent post-operative nausea and vomiting after laparoscopic cholecystectomy. *J anaesthesiology Clinical Pharmacology, 2010 Oct-Dec*; 26(4): 480-483.
26. Kumkum Gupta, Ivesh Singh, Prashant K. Gupta, et al. palonosetron, ondansetron and granisetron for antiemetic prophylaxis of postoperative nausea and vomiting - A comparative evaluation. *Anesthesia: Essays Researches, 2014*; 8(2): 197-201.
27. Basu A, Saha D, Hembrom BP, et al. Comparison of palonosetron, granisetron and ondansetron as antiemetics for prevention of postoperative nausea and vomiting in patients undergoing middle ear surgery. *J Indian Med Assoc, 2011 May*; 109(5): 327-9.
28. Saito M, Aogi K, Sekine I,et al. Palonosetron plus dexamethasone versus granisetron plus dexamethasone for prevention of nausea and vomiting during chemotherapy: a double-blind, double-dummy, randomised, comparative phase III trial. *Lancet Oncol, 2009 Feb*; 10(2): 115-24.
29. Moon YE, Joo J, Kim JE, et al. Antiemetic effect of ondansetron and palonosetron in thyroidectomy: a prospective, randomised, double blind study. *BJA, 2012*; 108(3): 417-22.
30. Jung Woo Park, Jin Woo Jun, Yun Hee Lim, et al. Comparative study to evaluate the effect of palonosetron monotherapy versus palonosetron with dexamethasone combination therapy for prevention of post-operative nausea and vomiting. *Korean J anesthesiology, 2012 October*; 63(4): 334-339.
31. Macario A, Weinger M, Carney S, et al. Which clinical anesthesia outcomes are important to avoid? The perspective of patients. *Anesth Analg, 1999 Sep*; 89(3): 652-8.