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"COMPARATIVE EVALUATION OF PALONOSETRON & PALONOSETRON WITH OLANZAPINE FOR PREVENTION OF POST OPERATIVE NAUSEA VOMITING IN PATIENTS UNDERGOING GYNAECOLOGICAL SURGERIES"

Anaesthesiology

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ABSTRACT

Background: The second most frequent post-operative complaint after pain is post-operative nausea and vomiting (PONV). There are numerous factors that can cause PONV, including the length of the procedure, the type of medicines used during anaesthesia, the anaesthetic technique, age, sex, and smoking habits. Depending on the type of operation and related risk factors, the incidence of PONV has been reported to range from 30 to 80%. Without any antiemetic medication, there is a 60% to 80% chance of PONV following general anaesthesia. Prevention of PONV can improve both the physical & phycological recovery of patient post-surgery. Palonosetron is a selective 5-hydroxytryptamine type3(5-HT3) receptor antagonists. It has a greater receptor binding affinity and a much longer half-life, conferring a prolonged duration of action, exceeding 40 hours, compared with other 5-HT3 receptor antagonists.[1] Olanzapine is an atypical antipsychotic agent of the thienobenzodiazepine class, blocks multiple neurotransmitter receptors, including dopaminergic (D1, D2, D3, D4), serotonergic (5-HT2a, 5-HT2c, 5-HT3, 5-HT6), adrenergic (alpha1), histaminic (H1), and muscarinic (m1, m2, m3, m4) receptors.[2] **Aim:** To compare the effect of palonosetron and palonosetron plus olanzapine for prevention of post operative nausea vomiting in patients undergoing gynecological surgeries.

Materials and Methods:

After the approval of institutional ethical clearance committee,

- ASA I and II patients scheduled for elective gynaecological surgeries were selected for study.
- Participants will be divided randomly into 2 groups
- Group A: receiving IV Palonosetron 0.075mg
- Group B: receiving IV Palonosetron 0.075mg + Olanzapine (tab 10mg)
- Olanzapine will be given 2hrs before the induction of anaesthesia.
- IV Palonosetron will be given intra operatively.
- Patients were taught about visual analogue scale (VAS) for nausea vomiting & verbal categorical scale (VCS) for nausea vomiting.
- Based on the opted anaesthesia modality, patient underwent the surgery under general anaesthesia / regional anaesthesia.
- All patients will be observed for the incidence of nausea & vomiting, along with its severity & the need for rescue anti emetics at 1, 2, 6, 12, 24 hours.
- Patients with VAS more than 5 and VCS more than 2 will receive Inj. Metoclopramide 10mg as rescue anti-emetic.

Results:

VAS score and VCS score is better in group B compared to group A during all the assessment. There is statistically significant difference between both the groups with respect to VAS score and VCS score from 6 to 24 hrs. Extra anti-emetic requirement is more in group A compared to group B. There is statistically significant difference between two groups with respect to Extra anti emetic requirement(P=0.001). **Conclusion –** Multimodal therapy of Post operative nausea vomiting with Palonosetron and Olanzapine, improves patient compliance, comfort and faster recovery of the patient during the post operative period.

KEYWORDS

Post operative nausea vomiting, PONV, Palonosetron, Olanzapine.

INTRODUCTION

- Nausea: It is an unpleasant sensation referred to a desire to vomit not associated with expulsive muscular movement.[3]
- Retching: When no stomach contents are expelled even with expulsive muscular efforts.[3]
- Vomiting: It is the forceful expulsion of even a small amount of upper gastrointestinal contents through the mouth.[3]
- Post-operative nausea vomiting (PONV) remains a significant problem in modern anesthetic practice because of the adverse consequences such as delayed recovery, unexpected hospital admission, delayed return to work of ambulatory patients, pulmonary aspiration, wound dehiscence, and dehydration.[4]
- Post-operative nausea vomiting is a complication mostly looked down by most medical professionals due to the availability of many over the counter anti emetic drugs.
- Prevention of PONV can improve both the physical & phycological recovery of patient post-surgery.
- Palonosetron: Selective 5-hydroxytryptamine type3(5-HT3) receptor antagonists. It has a greater receptor binding affinity and a much longer half-life, conferring a prolonged duration of action, exceeding 40 hours, compared with other 5-HT3 receptor antagonists.[1]
- Olanzapine: An atypical antipsychotic agent of the thienobenzodiazepine class, blocks multiple neurotransmitter receptors, including dopaminergic (D1, D2, D3, D4), serotonergic (5-HT2a, 5-HT2c, 5-HT3, 5-HT6), adrenergic (alpha1), histaminic (H1), and muscarinic (m1, m2, m3, m4) receptors.[2]

Inclusion criteria:

1. Patients belonging to ASA class 1 & 2.
2. Age group: 18 – 60 years
3. Sex: females
4. Patients undergoing gynaecological procedures under general anaesthesia and regional anaesthesia
5. Weight: BMI <29.9 kg/m2
6. Patient who has given valid informed consent.

Exclusion Criteria:

1. Patients with hepatic diseases, renal diseases, neurological & endocrine abnormalities.
2. Patients with history of motion sickness.
3. All emergency surgical procedures.
4. Pregnant or lactating females.
5. Patients with history of GERD.
6. Patients with history of hypersensitivity reaction to Olanzapine / Palonosetron.
7. Patients with multiple drug allergy.

Methodology:

After the approval of institutional ethical clearance committee,

- ASA I and II patients scheduled for elective gynaecological surgeries will be selected for study.
- After participant selection and consent, the standard anaesthesia protocol will be applied.
- Pre-anaesthetic check-up will be done, informed consent for

anaesthesia will be taken.
- Participants will be divided randomly into 2 groups
- Group A: receiving IV Palonosetron 0.075mg
- Group B: receiving IV Palonosetron 0.075mg + Olanzapine (tab 10mg)
- Olanzapine will be given 2hrs before the induction of anaesthesia.
- IV Palonosetron will be given intra operatively.
- Patients will be advised overnight fasting – 6hrs for solids, 4hrs for semisolids and 2hrs for liquids.
- Patients will be taught about visual analogue scale (VAS) for nausea vomiting & verbal categorical scale (VCS) for nausea vomiting.
- All patients will be given Tab. Alprazolam 0.5 mg and Tab. Ranitidine 150 mg on the previous night of surgery.
- On arrival to operating room, iv line will be secured and lactated ringer solution will be infused 4–6 ml/kg/h.
- On the operation table, routine monitoring of non-invasive blood pressure (NIBP), heart rate, electrocardiography (ECG), oxygen saturation (Spo2), end-tidal co2 (etCo2) will be started & vital parameters will be recorded.
- Based on the opted anaesthesia modality, patient will undergo the surgery under general anaesthesia / regional anaesthesia.
- All patients will be observed for the incidence of nausea & vomiting, along with its severity & the need for rescue anti emetics at 1, 2, 6, 12, 24 hours.
- Patients with VAS more than 5 and VCS more than 2 will receive Inj. Metoclopramide 10mg as rescue anti-emetic.

OBSERVATION AND RESULTS

Table 1: Age Distribution of Study Groups

Group	Number	Mean	S.D	T	P value
Group-A	104	48.47	6.3	0.08	0.93
Group-B	104	47.87	8.4		

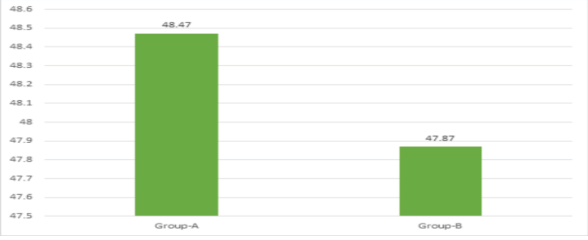

Figure 1: Age Distribution of Study Groups

The two groups are comparable with respect to age.

Table 2: ASA grading among study groups

Group	Grade 1	Grade 2	Total	Chi square	Pvalue
Group A	94	10	104	0.13	0.78
Group B	96	8	104		
Total	90	18	208		

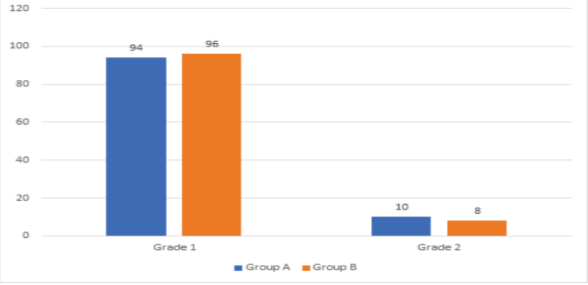

Figure 2: ASA grading among study groups

The two groups are comparable with respect to ASA grading.

Table 3: Extra antiemetic requirement among study participants

Group	Number	Mean	S.D	t	Df	P value
Group-A	104	2.98	0.78	3.31	58	0.001
Group-B	104	2.12	1.01			

Extra anti-emetic requirement is more in group A compared to group B. There is statistically significant difference between two groups with respect to Extra anti emetic requirement. (P=0.001)

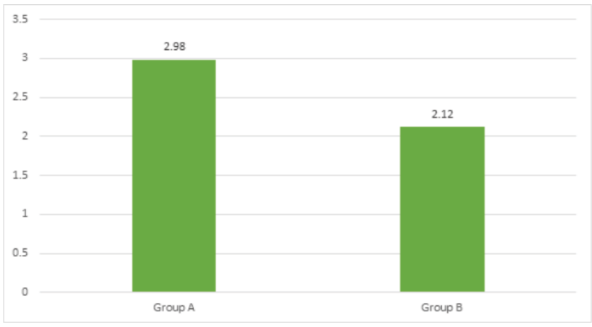

Figure 3: Extra anti-emetic requirement among study participants

Table 4: Systolic blood pressure among study participants

Time of assessment	Group A		Group B		P
	Mean	SD	Mean	SD	
1 hr	121.53	2.52	121.83	2.41	0.77
2hr	118.13	2.61	118.10	2.51	0.88
6hr	115.33	1.98	115.37	1.88	0.87
12 hr	111.27	1.72	112.07	1.62	0.54
24 hr	107.80	5.21	108.43	5.12	0.63

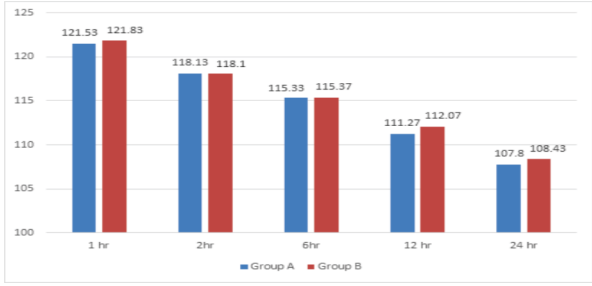

Figure 4: Systolic blood pressure among study participants

Two groups are comparable with respect to systolic blood pressure.

Table 5: Diastolic blood pressure among study participants

Time of assessment	Group A		Group B		P
	Mean	SD	Mean	SD	
1 hr	77.93	1.78	78.67	1.68	0.73
2hr	77.60	1.88	77.30	1.78	0.40
6hr	74.57	1.92	75.73	1.83	0.22
12 hr	73.23	2.12	73.40	2.10	0.89
24 hr	71.07	2.34	72.07	2.24	0.47

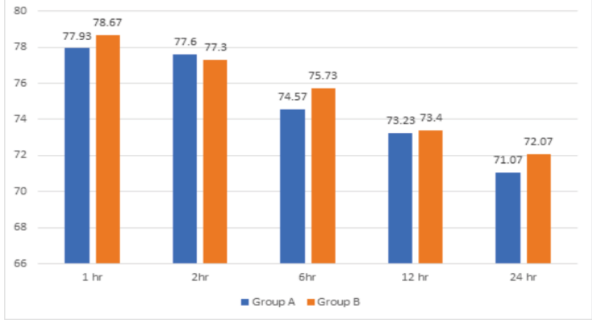

Figure 5: Diastolic blood pressure among study participants

Two groups are comparable with respect to diastolic blood pressure.

Table 6: Heart rate among study participants

Time of assessment	Group A		Group B		P
	Mean	SD	Mean	SD	
1 hr	86.53	2.12	88.61	2.02	0.78
2hr	89.13	3.18	89.20	3.08	0.84
6hr	91.37	4.12	90.60	3.98	0.44
12 hr	91.43	4.78	91.17	3.21	0.87
24 hr	90.70	2.78	89.07	2.12	0.24

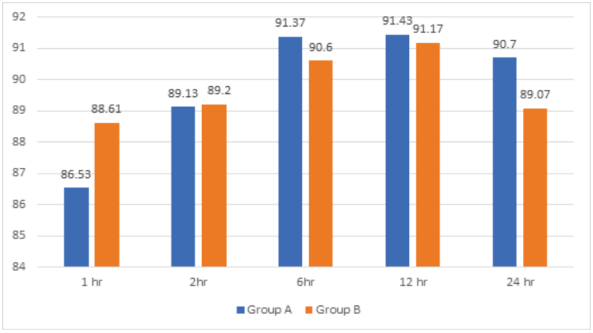

Figure 6: Heart rate among study participants

Two groups are comparable with respect to Heart rate.

Table 7: VAS score among study participants

Time of assessment	Group A		Group B		P
	Mean	SD	Mean	SD	
1 hr	1.4	0.28	1.0	0.14	0.84
2hr	1.3	0.12	0.9	0.11	0.73
6hr	4.2	1.12	3.8	1.08	0.04
12 hr	4.0	1.08	3.5	1.2	0.03
24 hr	3.8	0.98	3.4	1.3	0.01

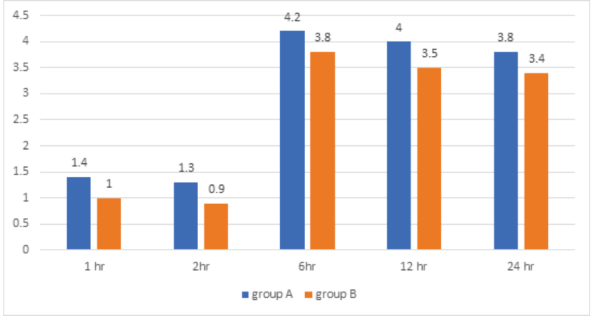

Figure 7: VAS score among study participants

VAS score is better in group B compared to group A during all the assessment. There is statistically significant difference between both the groups with respect to VAS score from 6 to 24 hrs.

Table 8: VCS score among study participants

Time of assessment	Group A		Group B		P
	Mean	SD	Mean	SD	
1 hr	0.82	0.12	0.76	0.56	0.93
2hr	0.78	0.22	0.69	0.12	0.86
6hr	1.2	0.24	0.98	0.42	0.02
12 hr	1.4	0.32	1.02	0.1	0.01
24 hr	1.5	0.31	1.12	0.12	0.01

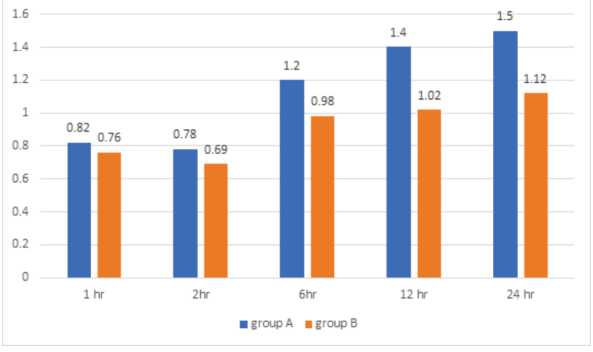

Figure 8: VCS score among study participants

VCS score is better in group B compared to group A during all the assessment. There is statistically significant difference between both the groups with respect to VCS score from 6 to 24 hrs.

DISCUSSION

PONV is a complication that causes discomfort and dissatisfaction in patients who undergo surgery. There are many methods for its prevention and treatment. Never the less the incidence rate of PONV is 20-30%. It is affected by factors related to surgery, anesthesia, and the patient [6].

There are many mediators and diverse pathways in PONV, and their mechanisms are complex and unclear [7]. Known risk factors for PONV include female sex, younger age, opioid use, non-smoking status, history of motion sickness or PONV, long anesthesia duration, and use of inhalation anaesthetics [8]. In this study, the risk factors did not differ between the two groups, as both groups had two or more risk factors for PONV. The two groups are comparable with respect to age and ASA grading.

Palonosetron is a second-generation 5-HT_3 receptor antagonist with different properties compared to older 5-HT_3 receptor antagonists.

- The chemical structure differs, as palonosetron has a fused tricyclic ring system unlike the first-generation drugs that have a 3-substituted indole structure resembling serotonin.
- The affinity for the 5-HT_3 receptor is much higher than that of first-generation drugs (pKi = 10.45) and plasma half-life is > 40 h.
- Palonosetron displays allosteric binding with positive cooperativity and triggers receptor internalization resulting in long-term inhibition of receptor function, whereas the older 5-HT_3 receptor antagonists selectively antagonize serotonin through competitive bimolecular binding and occupancy at the 5-HT_3 receptor. This unique binding activity makes palonosetron work effectively.
- In addition, its long duration of action comes not only from its long half-life but also from the long-term inhibition of receptor function by inducing receptor internalization [9].

Superior results have been reported for palonosetron in studies that compared the preventive effects of acute and delayed CINV with those of ondansetron or dolasetron [10]. Palonosetron is the only 5-HT_3 receptor antagonist used for the prevention of both acute and delayed CINV [10].

Two pivotal placebo-controlled trials were conducted to evaluate the dose-response efficacy and safety of three different doses of palonosetron for preventing PONV within 72 h after surgery. Those studies demonstrated that 0.075 mg of palonosetron i.v. was the most effective and well tolerated, and had the best prophylactic effect mainly in the first 24 h after surgery, and it was subsequently approved by the US Food and Drug Administration for preventing PONV for up to 24 h after surgery.

Kim et al. compared the prophylactic effects of preoperative palonosetron (0.075 mg, IV) with a regimen of preoperative ondansetron (8 mg, IV) and 16 mg added to PCA in women undergoing laparoscopic gynaecological surgery using fentanyl IV-PCA for 72 h postoperatively, but they found no significant differences between the two groups in the incidence rates of PONV at any of the evaluation time points (2, 24, 48, and 72 h), despite giving the bolus before inducing anesthesia.

Although we found that the prophylactic efficacy of palonosetron for the first 24 h was comparable to that of ondansetron, palonosetron has many advantages that make it more promising and useful than ondansetron. Palonosetron has no QT prolongation issue in terms of safety. It also has a longer duration of action that produces a prophylactic effect in delayed PONV, particularly post-discharge nausea and vomiting, which is a growing problem in outpatient anesthesia. Palonosetron 0.075 mg is reported to be more effective in PONV prevention than 0.025 mg and 0.050mg.

Olanzapine as an antiemetic represents a new use of an antipsychotic drug. Olanzapine probably reduces delayed nausea (RR 1.71, 95% CI 1.40 to 2.09; 585 participants; 3 studies) and vomiting (RR 1.28, 95% CI 1.14 to 1.42; 702 participants; 5 studies). Sub-group analysis: 5 mg versus 10 mg. Planned subgroup analyses found that it is unclear if 5 mg is as effective an antiemetic as 10 mg. There is moderate-quality evidence that oral olanzapine probably increases the likelihood of not being nauseous or vomiting during chemotherapy from 25% to 50% in adults with solid tumours, in addition to standard therapy, compared to placebo or no treatment. There is uncertainty whether it increases serious adverse events. It may increase the likelihood of other adverse

events, probably increasing somnolence and fatigue. Patients in the group B had better satisfaction compared to group A. There is statistically significant difference between two groups. (P<0.05) Extra antiemetic requirement is more in group A compared to group B. There is statistically significant difference between two groups with respect to Extra anti-emetic requirement (P=0.001)

VAS score is better in group B compared to group A during all the assessment. There is statistically significant difference between both the groups with respect to VAS score from 6 to 24 hrs.(P<0.05) VCS score is better in group B compared to group A during all the assessment. There is statistically significant difference between both the groups with respect to VCS score from 6 to 24 hrs.(P<0.05)

When compared to ondansetron infusion and a single dose of palonosetron, daily olanzapine is superior treatment of breakthrough CINV in patients undergoing HSCT. A single dose of palonosetron does not significantly reduce emesis but is effective for the treatment of nausea up to 24 hours.

Two groups are comparable with respect to systolic and diastolic blood pressure and heart rate.

This is similar to the study by Choudhary J et. al in which he told that intravenous administration of granisetron and palonosetron does not attenuate the hemodynamic changes in patients undergoing abdominal hysterectomy while Olanzapine use was associated with a mean increase in heart rate compared to placebo (adults: +2.4 beats per minute vs no change with placebo; adolescents: +6.3 beats per minute vs -5.1 beats per minute with placebo). This increase in heart rate may be related to olanzapine's potential for inducing orthostatic changes.

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Conflict Of Interest:
No conflict of interest

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