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A RANDOMIZED, DOUBLE-BLIND STUDY OF PALONOSETRON COMPARED WITH ONDANSETRON IN PREVENTING POSTOPERATIVE NAUSEA AND VOMITING AFTER MODIFIED RADICAL MASTECTOMY SURGERY.

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ABSTRACT **BACKGROUND :** Palonosetron is a new potent 5-hydroxytryptamine 3 antagonist. Although used for chemo induced emesis, data is lacking for PONV. The high incidence of nausea and vomiting after breast surgery is well documented. This study compared the effects of i.v.ondansetron and palonosetron administered at the time of induction for preventing postoperative nausea and vomiting (PONV) in these high-risk patients .**METHODS :**The aim was to compare Ondansetron 8 mg and Palonosetron 0.075mg administered intravenously for prevention of post operative nausea and vomiting in patients undergoing modified radical mastectomy 24 hours postoperatively, by a randomised , controlled, double blind study. 70 female non smoking patients scheduled for elective modified radical mastectomy were, allocated randomly into 2 groups . Patients received either Palonosetron 0.075mg (GROUP P) or ondansetron 8mg (GROUP O) intravenously, immediately before induction of general anaesthesia. The occurence of nausea, vomiting, retching, need for rescue antiemetics and side effects were monitored for a period of 24 hours after surgery. The compete response rate and overall PONV for 0 - 24 hours were calculated. **RESULTS :** The demographic profile of the patients were comparable. The incidence of a complete response (no PONV, no rescue antiemetics) during 0 - 24 hours in post operative period was significantly high in GROUP P (85.7% vs 62.9%, p=0.02) than GROUP O. The incidence of nausea was significantly low in GROUP P (14.3% vs 37.1%). There was no statistically significant difference between the 2 groups in vomiting, retching, side effects and need for rescue antiemetics. Thus overall PONV was low in GROUP P (14.3% vs 37.1% p = 0.02 statistically significant.) We conclude that Palonosetron 0.075mg was more effective for preventing PONV in patients undergoing modified radical mastectomy surgery.

KEYWORDS : ondansetron;palonosetron; postoperative nausea and vomiting : modified radical mastectomy

INTRODUCTION

Incidence of post operative nausea and vomiting is very high in the range of 20-30% and anaesthesia plays a major role for this "big little problem" [1,2] The decrease in the intensity of the problem is because of the use of less emetic anaesthetic agents and identification of risk factors. PONV leads to dehydration, electrolyte imbalance and may also rarely leads to oesophageal tears (Mallory – Weiss syndrome), [3] and aspiration pneumonia. [4]

These factors can cause delayed discharge, increased morbidity, and a life-long aversion to surgery. Despite improvements in anaesthesia and surgical techniques, 25% and 52% of all patients still experience nausea and vomiting respectively . [5]Breast surgery, general anaesthesia and female population has been found to have very high incidence of PONV . Between 60% and 80% of patients undergoing mastectomy with axillary dissection experience PONV . [6] Ondansetron,[7,8,9] a selective 5HT3 receptor antagonist possess property of superior antiemetic prophylaxis has been used widely for the treatment of postoperative nausea and vomiting. Palonosetron,[10,11,12] a newly developed 5-HT_3 antagonist, has a unique mechanism of allosteric binding, with more potent and persistent effects. Not much study has been done for its effects on PONV. So this study has been done to compare the effectiveness of ondansetron and palonosetron for controlling post operative nausea and vomiting and also to compare their side effects in patients undergoing elective modified radical mastectomy surgery.

METHODS:

After Institutional Ethics and scientific Committee approval, 70 patients of American Society of Anaesthesiologists physical status 1 or 2 patients between the ages of 21 and 75 years, undergoing general anaesthesia for modified radical mastectomy were randomly selected and double blinded for the study after informed consent. Randomisation was done by computer generated randomised numbers. The study was conducted for a duration of six months, in which the total of 70 cases were randomly divided into two groups- group P (Palanosetron) and Group O (Ondansetron). All subjects had the following PONV risk factors: female, non-smoker, and use of opioid analgesics after surgery. The exclusion criteria included emergency surgery patients with H/O GERD, full stomach or took antiemetics, steroids within 1 day of surgery, h/o vomiting from organic cause and patients with H/O drug allergy to HT3 antagonists.

Standard anaesthetic regimen were used for all patients. All patients were fasted after midnight. All surgeries were done by the same surgeon. On the operation table , routine monitoring ECG, pulseoximetry, NIBP were started and baseline parameters like heart rate(HR), blood pressure (systolic, diastolic and mean) and arterial oxygen saturation (SpO_2) were recorded. An intravenous line was secured and before induction of general anaesthesia, either ondansetron or palonosetron was injected according to the group assigned. In group O, 8 mg of ondansetron and for group P 0.075 mg of palonosetron was injected as a bolus. After pre-oxygenation, general anesthesia was induced with fentanyl 2mcg/kg, Propofol 2mg/kg , vecuronium 0.1mg/kg , O_2 and 1% isoflurane. Patients were intubated with appropriate size ET tube and placement confirmed with ETCO2. Paracetamol 1g and lornoxicam 8mg were given after induction. Anesthesia was maintained with air : O_2 50% : 50% , Isoflurane 1% At the end of surgery after adequate spontaneous respiratory effect , patients were reversed with neostigmine 0.05mg/kg and glycopyrrolate 0.01mg/kg and extubated fully awake. For postoperative analgesia all patients received paracetamol 1g was continued 8th hourly , lornoxicam 12th hrly post operatively and Inj Morphine 5 - 7.5 mg was given subcutaneously 8th hourly . All patients were sent to post anaesthesia care unit (PACU) for monitoring. Another anaesthetist blinded to the groups assigned evaluated all episodes of nausea, vomiting, retching and need for rescue medication for 24 hours . Nausea was defined as an unpleasant feeling associated with an urge to vomit. Retching was defined as spasmodic laboured contraction of respiratory muscles without expulsion of gastric contents. Vomiting is forceful expulsion of gastric contents. Metoclopromide 10mg iv was given as rescue antiemetic when an episode of PONV occurred or when patient requested rescue anti-emetic medication, after the severity of nausea or retching was recorded. The evaluation of nausea, severity was based on a four point scale (0 - no nausea, 1 - mild, 2 - moderate, 3 - severe nausea). Primary outcome measure was proportion of patients with complete response CR (no emetic episodes and required no rescue antiemetics). 0-24 hours post-operatively. Secondary outcome measures were proportion of patients with no emetic episodes, severity of nausea, vomiting , retching and need for rescue antiemetics in different time periods 0-2hrs, 2 -12 hrs and 12- 24hours. Side-effects like headache , dizziness were also evaluated. All statistical analyses were performed using IBM SPSS statistics. The Student's t-test was used to compare intergroup differences. P-value < 0.05 was regarded as statistically significant .

RESULTS

70 female patients belonging to ASA 1 & 2 , undergoing modified radical mastectomy surgery were selected and randomly assigned to study the effect of ondansetron and palanosetron on PONV. Overall PONV was low in GROUP P 14.3% vs 37.1%(p = 0.02). The

incidence of a complete response during 0 - 24 hours in post operative period was significantly high in GROUP P (85.7% vs 62.9%, p=0.02) than GROUP O. The incidence of nausea was significantly low in GROUP P (14.3% vs 37.1%). There was no statistically significant difference between the 2 groups in vomiting, retching, side effects and need for rescue antiemetics.statistically significant. The incidence of side-effects, such as headache, dizziness was similar in both the groups.

Table 1 Subject and anaesthetic characteristics. Values are mean , or (%).

	ONDANSETRON (n=35)	PALONOSETRON (n=35)
Mean age (yr)	50.94	52.54
Weight (kg)	62.37	64.06
Height (cm)	153	154.71
Anaesthesia time (Min)	47.4	43.5
ASA I/II %	42.9/57.1	45.7/54.3
H/O of PONV/ motion sickness %	12.9	11.4
Difficult mask ventilation %	17.1	25.7
Chemo received %	43.3	32

Table 2 RESULTS

	Group P	Group O	P VALUE
NAUSEA 0-2 HRS	1	3	0.357
2-12 HRS	4	7	0.221
12 - 24 HRS	0	3	0.208
0-24 HRS	5	13	0.02
RETCHING 0-2 HRS	0	1	0.314
2-12 HRS	1	0	0.314
12-24 HRS	0	1	0.314
0-24 HRS	1	2	0.55
VOMITING 0-2	1	1	1
2-12 HRS	1	2	0.55
12 - 24 HRS	0	2	0.151
0-24HRS	2	5	0.232
RESCUE MEDICATION 0-2	1	0	0.314
2-12	1	3	0.303
12 - 24 HRS	0	2	0.151
0-24 HRS	2	5	0.232
PONV 0-24 HRS	5	13	0.02
COMPLETE RESPONSE	30	22	0.02

ADVERSE EFFECTS :

The adverse effects were minimal and not alarming and were comparable between both the groups. Only one patient in each group complained headache. They were not statistically significant.

DISCUSSION

The incidence of PONV reaches 10–78% depending on factors related to the operation, anaesthesia and the patient. Between 60% - 80% of patients undergoing mastectomy with axillary dissection experience PONV. [6]The incidence of PONV may be associated with many factors including: age , gender, prior history of motion sickness or PONV, smoking status, postoperative opioid use, type and duration of surgery, anaesthesia and ambulation. The anaesthetic technique, surgery duration, the demographic variables between both the groups were comparable. Considering these it can be made that the differences between the two groups as regard to the incidence of PONV must be due to the antiemetic administered.

Various 5-HT3 antagonists have been used to prevent PONV, and most studies have been done with ondansetron. Ondansetron [7,8,9] inhibits emetic symptoms by binding with the 5-HT3 receptor located in the central chemoreceptor trigger zone and the gastrointestinal tract. The complete response for patients who received ondansetron in studies done by Sunget al. [13] 62% , Mckenzie R et al [14] study 60% was only around 60 % similar to our study 62.9% . The 24 hour incidence of PONV in patient who received ondansetron was more than 30% and the rescue antiemetic requirement was around 15% other studies (Sadasivam.S et al [15] 33.3%) similar to our study 37.1% PONV and the rescue antiemetic requirement 14.3%.

Palonosetron [10,11,12] is a unique second generation 5-HT3 antagonist which has unique structural, pharmacological and clinical properties that distinguish it from other 5- HT3 antagonists. It is a allosteric 5 HT3 receptor antagonist, whereas the previously developed 5 HT3 antagonist compete directly with seratonin. This allosteric binding creates a conformational change in the serotonin receptor ,so that serotonin is indirectly inhibited. consequently , it has greater binding affinity , leading to greater potency and longer biological half life. Palonosetron also inhibits responses induced by substance P, thedominant mediator of delayed emesis after chemotherapy, through differential inhibition of 5-HT3 / neurokinin-1 receptor. This could decrease the need for combination therapy generally required for PONV prevention in high-risk patients. palonosetron does not prolong the QTc interval, in contrast to older 5-HT3 antagonists .

Kovac AL et al [16]. found that 0.075 mg palonosetron significantly reduced PONV in the first 24 h after anaesthesia, compared with placebo. A single injection of 0.075 mg is now approved dose for preventing PONV for upto 24hrs after surgery. Tramer [17] in his metanalysis suggested that, 8 mg ondansetron was optimal to prevent PONV. Thus, 0.075 mg palonosetron and 8 mg ondansetron were chosen for PONV prophylaxis.

In the present study, palonosteron 0.075 mg was more effective at reducing PONV than ondansetron 8 mg. The incidence of PONV and nausea was significantly lower in the palonosetron group than in the ondansetron group during the overall 0 – 24 h time interval ($P < 0.05$). More patients in the palonosetron group had a complete response 85.7% and the difference was statis. tically significant for the 0 – 24 h time interval ($P = 0.02$), which was almost similar to study done by Dhurjoti et al [18], S.K.S and Shaikh [19]and Gralla et al [20]. This could reflect the high receptor affinity of palonosetron for 5-HT3 and the longer duration of action. PONV in patients who received Palonosetron in our study was 14.3% , which was in concurrance with study conducted by Bicer et al [21](15.4%) , S.K.Park [22]. In study done by Y.E.Moon [23], Bajwa et al [24] the incidence of nausea and vomiting and nausea severity was significantly lower in Palonosetron group similar to our study.The need for rescue antiemetics, vomiting and the incidence of adverse effects were not significantly different between the two groups. The next main comparison was the incidence of complications between the two groups. The results show that the incidence of complications were minor and were not significant between the two groups. The side effects noted were minor episodes of headache in each group but were not stastically significant.

There were several limitations to our present study. The efficacies of palonosetron and ondansetron were compared based on the known optimal doses, without knowledge of equipotent doses.The baseline incidence of PONV was not evaluated by the inclusion of a placebo group because it would be unethical to withhold prophylactic antiemetic drugs in patients at high risk for PONV. However, further studies are required to study palonosetron in more patients at more diverse surgical settings.

CONCLUSION :

In our study, we have compared the efficacy of ondansetron 8 mg I.V. and palonosetron 0.075mg I.V. given prophylactically just before induction of anaesthesia in adult patients undergoing elective modified radical mastectomy surgeries under general anaesthesia.

In conclusion, we have found that palonosetron at a dose of 0.075mg is safe and well-tolerated and proved more effective than ondansetron 8 mg in the prevention of PONV in patients undergoing modified radical mastectomy surgery.

Fig 1 NAUSEA

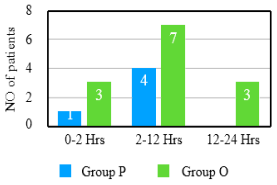


Fig 2 RETCHING

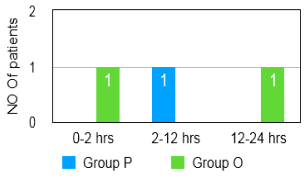


Fig 3 Vomiting

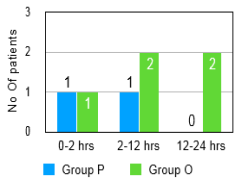


Fig 4 RESCUE MEDICATIONS

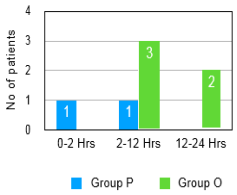


Fig 5 COMPLETE RESPONSE

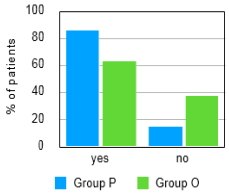
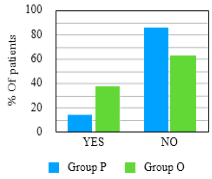


Fig 6 PONV



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