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PROPHYLAXIS OF POSTOPERATIVE NAUSEA AND VOMITING LAPAROSCOPIC PROCEDURES WITH 5-HT3 RECEPTOR ANTAGONISTS, A RANDOMIZED CONTROLLED TRIAL.

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ABSTRACT… In this study we aim to study the efficacy of Ramosetron and Palonosetron in preventing post-operative nausea and vomiting in high risk patients. **Study Design:** A randomized controlled trial. **Setting:** A Large Tertiary Care Centre in Karachi. **Period:** 9 months from January 2017 to September 2017. **Materials and Methods:** N=81 participants took part in the study. The patient population was divided into three groups.. Patients belonging to group A received Palonosetron 0.075mg mixed with normal saline in a mixture of 3ml, prior to induction, and received 3ml of normal saline half an hour prior to the end of the procedure. Patients in group B received 3ml of normal saline prior to induction and a mixture of 0.3mg of Ramosetron mixed with normal saline as 3ml half an hour before end of procedure. In group C patients received normal saline 3ml both before induction and half an hour prior to end of surgery. **Results:** The patient demographics were similar in all the groups and no significant difference was found. The incidence of post-operative nausea and vomiting during 2 hours post operatively was 41.97%, the incidence of nausea at 2 hours was in group A= 33.33%, in group B= 29.62%, in group C= 62.96% respectively, having a p value of 0.014 refer to table 2. After 48 hours of surgery the overall incidence of vomiting in the groups was not significant having a p value of 0.428 and an incidence of 6.172%. **Conclusion:** Palonosetron and Ramosetron are equally effective in prevention of post-operative nausea and vomiting in high risk patients undergoing laparoscopic gynecological procedures.

Key words: Anti-Emesis, Laparoscopy, Palonosetron, Post-Operative Nausea and Vomiting, Ramosetron.

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INTRODUCTION

The most common post operative complication is nausea and vomiting with an incidence of 20 to 30% in the normal population and as high as 70% in the high risk population.[1,2] The most common risk factors for post operative nausea and vomiting are female gender, history of post operative nausea and vomiting, non smoker, motion sickness and peri-operative use of opioids, laparoscopic surgeries are known to have an increased incidence of post operative nausea and vomiting as compared to open abdominal surgeries.[3,4] The high risk group for post operative nausea and vomiting are patients who are non smokers, undergo gynecologic laparoscopic surgery and have a history postoperative opioid use. In these high risk patients intravenous anesthesia is recommended. Selective serotonin receptor antagonists such as Palonosetron and Ramosetron are used to prevent post operative nausea and vomiting. Evidence is lacking in the use of these drugs in high risk patients undergoing laparoscopic gynecological procedures utilizing total intravenous anesthesia. In this study we aim to study the efficacy of Ramosetron and Palonosetron in preventing post operative nausea and vomiting in high risk patients.

MATERIALS AND METHODS

The type of study is a prospective double blind randomized controlled trial, conducted for a period of 9 months duration from January 2017 to September 2017 at a large tertiary care centre in Karachi, Pakistan. After getting approval from

the hospital ethics committee, n=81 participants who signed a fully informed consent took part in the study. All the participants in the study belonged to American Society of Anesthesiology classification I and II. The age range of patients was 19 years with a minimum of 20 years and a maximum age of 49 years respectively. All the patients were female, non smokers and were given patient controlled analgesia intravenously for pain control after the procedure. The exclusion criteria were patients who were active smokers, had an anaphylactic reaction to the drugs used in the study, did not want to use patient controlled analgesia or belonged to American Society of Anesthesiology Class 3 or greater. The patient population was divided into three groups. In all the groups the vitals of the patients were recorded including blood pressure monitoring, peripheral oxygen saturation, bispectral index and electrocardiogram.

Total intravenous anesthesia was induced utilizing propofol and remifentanil, target controlled infusion of propofol and remifentanil were set at 3.0 ug/ml and 3.0 ng/ml respectively. For tracheal intubation Rocuronium 0.6mg/kg was given intravenously. A bispectral index of 40-60 was achieved by adjusting the TCI effect site concentrations of propofol. The TCI effect site concentrations for remifentanil were set to maintain a mean arterial pressure within the range of 20% of pre-induction values respectively. Patients belonging to group A received a mixture of Palonosetron 0.075mg mixed with normal saline in a mixture of 3ml, prior to induction, and received 3ml of normal saline half an hour prior to the end of the procedure. Patients in group B received 3ml of normal saline prior to induction and a mixture of 0.3mg of Ramosetron mixed with normal saline as 3ml half an hour before end of procedure. In group C patients received normal saline 3ml both before induction and half an hour prior to end of surgery. All the medications and mixtures were prepared by a nurse who was not involved in the research, and the mixtures were made to look identical for blinding purposes.

All the patients received Fentanyl 1mcg/kg half an hour prior to the end of the procedure. Patient Controlled Analgesia was started after the procedure having a total volume of 100ml which contained 20mcg/kg of fentanyl mixed with normal saline. The patient controlled analgesia devices were set in a manner to administer a basal infusion at a rate of 0.5ml/hr and bolus of 2ml as patient demands with a lock out time of 15mins. All the data was recorded in a predesigned proforma and included variables such as pain, nausea, vomiting, retching, additional analgesics utilized and the use of anti emetics if utilized. Visual analog scale score was used to record the pain, with a value of 0 for no pain and a value of 10 for worst pain imaginable. If a patient had a VAS score of greater than 4, Ketorolac, 30mg was administered as an additional analgesic for a maximum dose of 90mg per day. Postoperative nausea was measured on a scale from 0 to 10, with 0 zero being no nausea and 10 being the worst nausea imaginable. If the patient scored greater than 4 on the nausea scale 4mg of Ondansetron was administered intravenously for antiemesis. The assessments were done by anesthesiologists who were blinded to the study and measurements were recorded at 30, 60, 90, 120 mins then at 6 hours and 48 hours post surgery. The statistical analysis was done using IBM SPSS version 21.0. Chi square test was done to compare the categorical variables, analysis of variance or ANOVA was used to compare the continuous variables. A p value of less than 0.05 was considered to be statistically significant.

RESULTS

The study population consisted of n=81 patients. The patient demographics were similar in all the groups and no significant difference was found refer to Table-I. The incidence of post operative nausea and vomiting during 2 hours post operatively was 41.97%, the incidence of nausea at 2 hours was in group A= 33.33%, in group B= 29.62%, in group C= 62.96% respectively, having a p value of 0.014 refer to Table-II. After 48 hours of surgery the overall incidence of vomiting in the groups was not significant having a p value of 0.428 and an incidence of 6.172%. Table-II shows the nausea scores at various time intervals. The nausea score in the study groups (the Palonosetron and Ramosetron groups) was

lower than the control group, but the results are not statistically significant. The nausea scores varied at the assessment time points having a p value of <0.001 but the change was unaffected by the study groups p value of 0.227 respectively. One patient suffered from headache and vertigo in the Ramosetron group, however the finding was not statistically significant.

Variable	Group A	Group B	Group C	P-Value
Age in years	40.02 +/- 9.80	37.50 +/- 8.60	38.00 +/- 9.05	0.444
Height in cm	159.02 +/- 5.01	160.08 +/- 5.54	160.52 +/- 6.16	0.255
Weight in kg	59.20 +/- 9.55	58.63 +/- 11.16	59.52 +/- 8.62	0.874
Body Mass Index (kb/m^2)	23.40 +/- 3.50	22.72 +/- 4.50	22.89 +/- 3.74	0.809
ASA Classification				
Class I	18 (66.66%)	18 (66.66%)	19 (70.37%)	0.950
Class II	9 (33.33%)	9 (33.33%)	8 (29.62%)	
Duration of Surgery in min	68.32 +/- 21.16	73.87 +/- 25.65	65.50 +/- 16.38	0.278
Time of Anesthesia in min	111.50 +/- 20.36	116.20 +/- 25.87	107.21 +/- 17.67	0.218
Type of Surgery				
Cystectomy	15 (55.55%)	12 (44.44%)	11 (40.74%)	0.549
LAVH	12 (44.44%)	15 (55.55%)	16 (59.25%)	
Post operative Pain VAS Score				
1 hour	5.12 +/- 2.16	4.84 +/- 1.80	5.40 +/- 1.87	0.562
24 hour	3.00 +/- 0.91 ab	2.82 +/- 0.66 a	3.46 +/- 1.06 b	0.028

Table-I. Patient demographics.

Variable	Group A	Group B	Group C	P-Value
Incidence of PONV				
120 min	9 (33.33%)	8 (29.62%)	17 (62.96%)	0.014
48 hours	15 (55.55%)	8 (29.62%)	15 (55.55%)	0.104
Overlap	7 (25.92%)	5 (18.51%)	14 (51.85%)	0.065
Vomiting	1 (3.703%)	3 (11.11%)	1 (3.703%)	0.428
Moderate				
120min	4 (14.81%)	3 (11.11%)	6 (22.22%)	0.585
48 hours	4 (14.81%)	3 11.11%)	7 (25.92%)	0.585
Overlap	1 (3.703%)	1 (3.703%)	2 (7.40%)	0.856
Nausea				
30 min	1.46 +/- 0.50 a	1.10 +/- 0.42 a	2.25 +/- 0.50 a	0.227
60 min	0.79 +/- 0.28 a	0.98 +/- 0.49 a	1.84 +/- 0.43 a	
90 min	0.55 +/- 0.20 a	0.83 +/- 0.44 a	1.00 +/- 0.30 b	
120 min	0.67 +/- 0.54 a	0.77 +/- 0.41 a	0.93 +/- 0.33 b	
6 hours	0.84 +/- 0.32 a	0.76 +/- 0.31 a	1.79 +/- 0.54 ab	
48 hours	0.61 +/- 0.23 a	0.28 +/- 0.16 a	0.53 +/- 0.22 bc	

Table-II. Prevalence of nausea and vomiting in the three study groups.

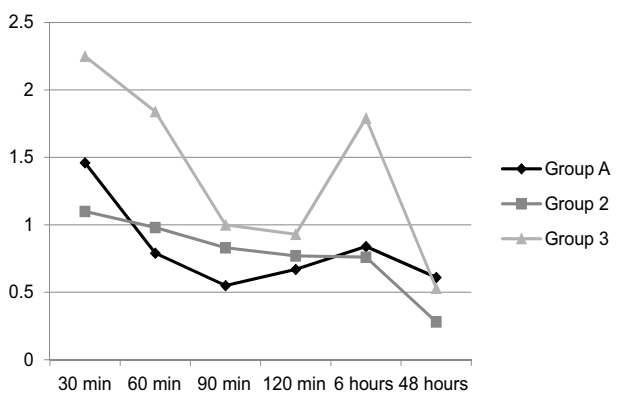

Figure-1. The changes in nausea scores with time.

DISCUSSION

We did not find any difference in the severity of post operative nausea and vomiting between the Ramosetron and Palonosetron group in the high risk patients (female gender, non smoking, and history of Perioperative opioid). However the incidence of post operative nausea and vomiting was lower in the study groups as compared to the normal saline group. The mechanism of post operative nausea and vomiting is unclear, the emetic center in the medulla is activated by a variety of stimuli and signals from the chemoreceptor trigger zone, cerebellum, glossopharyngeal and

vagal afferent nerves, higher cortical centers and the vestibular apparatus. Other receptors such as 5-HT3, dopamine type 2, muscarinic and opioid receptors also play a role.[5] Combination with various emetics thus is justified mode of treatment to cover the variety of stimuli and receptors triggering emesis. Post operative nausea and vomiting is related to many adverse events such as electrolyte imbalance, wound dehiscence, prolonged hospital stay and aspiration of gastric contents.[1] The risk factors in our study were patients of female gender, less than 50 years of age, non smoking status and previous history of post operative nausea and vomiting. Non smoking status is considered a risk factor as prior exposure to tobacco smoke can desensitize the chemoreceptor trigger zone for anesthetic gases. The chemicals in cigarette smoke may also have anti emetic effects.[6] Other risk factors for post operative nausea and vomiting were surgery duration of more than one hour, laparoscopic surgery and higher doses of opioid use.[7]

The 5-HT3 receptor antagonists are specific and selective for post operative nausea and vomiting. These drugs affect the 5-HT3 receptors on the chemoreceptor trigger zone and the vagal afferents in the gastrointestinal tract.[8] Palonosetron is a recently developed 5-HT3 receptor antagonist having a half life of 40 hours and a moderate level of plasma binding (62%).[9,10] Ramosetron is found to have a higher affinity as compared to Granisetron and Ondansetron. The efficacy of Ramosetron was well maintained in the 48 hour period post operatively.[11] In a study by Chun et al Palonosetron 0.075 mg injection reduced the incidence of post operative nausea and vomiting as compared to the placebo group in the 24 to 72 hours postoperative period.[12] In another study authors Lee et al found that the efficacy of Palonosetron, Granisetron and Ramosetron were similar for the prevention of post operative nausea and vomiting.[13] In our study the incidence of post operative nausea and vomiting was lower in the control group as well as compared to other studies (63% versus 80%).[3] This difference could be due to the use of total intravenous anesthesia in our study which is known to decrease the incidence of post operative nausea and vomiting. The administration of anti emetic medications is riddled with side effects as well. These side effects include dizziness, headache and QT prolongation.[14,15] Therefore it is recommended that patients baseline risk be calculated according a validated risk score.[4,16,17] The Apfel simplified risk score is one such validated risk score. It is based off of four risk factors namely history of post operative nausea and vomiting, female gender, smoking status, motion sickness and post operative opioid use. Presence of any three of the afore mentioned risk factors would label the patient as high risk with an incidence rate of post operative nausea and vomiting reaching 60 to 80%.[3] Adult patients with moderate to high risk for post operative nausea and vomiting should be administered 1 or 2 interventions for anti emesis according to the guidelines published by SAMBA.[18] Our study also had some limitations, first of all we compared Ramosetron and Palonosetron at optimal doses as compared to equipotent doses. We found incidence of post operative nausea and vomiting to be more than 30% despite use of these medications, therefore further research is required to determine the combination therapy with 5-HT3 antagonists and other antiemetic drugs of a different mechanism of action, as that would result in efficient prophylaxis.

CONCLUSION

According to the results of our study we found that Palonosetron and Ramosetron are equally effective in prevention of post operative nausea and vomiting in high risk patients undergoing laparoscopic gynecological procedures.

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AUTHORSHIP AND CONTRIBUTION DECLARATION

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