COMPARISON OF ANTIEMETIC EFFICACY OF ONDANSETRON, GRANISETRON AND PALONOSETRON IN HIGH-RISK PATIENTS UNDERGOING ABDOMINAL HYSTERECTOMY UNDER GENERAL ANAESTHESIA

Rakesh Kumar Singh[1], Sipra Singh[2]

[1]Professor, Department of Anaesthesiology, Katihar Medical College, Katihar.
[2]Professor, Department of Obstetrics and Gynaecology, Katihar Medical College, Katihar.

ABSTRACT

BACKGROUND

Postoperative nausea and vomiting is (PONV) a very distressing complication and preventive measures are justified when the risk of PONV is very high. Ondansetron is the first 5-HT3 antagonist used alone or in combination for prophylaxis of PONV due to its lower cost. Granisetron and palonosetron are recently introduced 5-HT3 antagonists with greater affinity for 5-HT3 receptor and having longer half-life. Aim of the present study is to compare the antiemetic efficacy of ondansetron, granisetron and palonosetron in high-risk patients undergoing abdominal hysterectomy under general anaesthesia.

METHODS

After obtaining Institutional Ethical Committee approval and written informed consent from all the participants, 150 patients of ASA grade I & II, aged between 20-50 years and weight between 30-60 kg undergoing abdominal hysterectomy under general anaesthesia were assigned randomly in to three groups of 50 patients each using random number table receiving either ondansetron 4 mg (Group O) or granisetron 2 mg (Group G) or palonosetron 0.75 mg (Group P) intravenously just before the induction of anaesthesia. Incidence and severity of nausea and frequency of retching and vomiting were recorded in each group at the end of 2-hour and then at 24-hour and 48-hour intervals.

RESULTS

The incidence of nausea during first two hours postoperatively was found to be 14(28%) in Group O, which was found to be significantly higher than 6(12%) in group G and 4(8%) in group P (p value = 0.016). The incidence of vomiting was found to be 6(12%) in group O, which was found to be significantly higher than 2(4%) in both group G and group P (p value = 0.018). Number of complete responders was significantly higher in Group P and group G as compared to group O. Number of patients requiring rescue antiemetic treatment was significantly high in group O{10(20%)} as compared to 3(6%) in both the group G and group P.

CONCLUSIONS

Newly introduced 5-HT3 antagonists, granisetron and palonosetron are better in efficacy in the prophylaxis of nausea and vomiting. Both granisetron and palonosetron are comparable in efficacy to control postoperative nausea and vomiting.

KEYWORDS

Postoperative Nausea and Vomiting, Ondansetron, Granisetron, Palonosetron.

HOW TO CITE THIS ARTICLE: Singh RK, Singh S. Comparison of antiemetic efficacy of ondansetron, granisetron and palonosetron in high-risk patients undergoing abdominal hysterectomy under general anaesthesia. J. Evid. Based Med. Healthc. 2016; 3(32), 1537-1540. DOI: 10.18410/jebmh/2016/346

INTRODUCTION: Postoperative nausea and vomiting is the 2nd most common postoperative complication.[1,2] Postoperative nausea and vomiting is very distressing and many patients rate it as even worse than postoperative pain. The overall incidence is 30% in normal population.[3] Presence of risk factors significantly increases the incidence of postoperative nausea and vomiting. Risk factors for postoperative nausea and vomiting include female gender, young age, non-smokers, previous history of nausea and vomiting, general anaesthesia, inhalational anaesthetics, perioperative opioid use, long duration of surgery, strabismus surgery, gynaecological surgeries, etc. Patients' risk of developing PONV can be estimated by accounting for independent risk factors simultaneously. Simplified risk score for adult comprising of female gender, non-smoking, history of postoperative nausea and vomiting and postoperative opioid use can be used for assessment of risk of postoperative nausea and vomiting. If none, one, two, three or four of the risk factors are present, incidence of postoperative nausea and vomiting are 10%, 21%, 39%, 61% and 79%[4] respectively. The decision to use prophylactic antiemetic depends on the risk assessment of nausea and vomiting. Use of prophylactic antiemetic is rarely justified when the risk of PONV is low (10-20%).[5,6,7] But when the

Financial or Other, Competing Interest: None.
Submission 28-03-2016, Peer Review 11-04-2016,
Acceptance 19-04-2016, Published 21-04-2016.
Corresponding Author:
Dr. Rakesh Kumar Singh,
Professor, Department of Anaesthesiology,
Katihar Medical College, Katihar-854105.
E-mail: drrakeshsingh2008@yahoo.co.in
DOI: 10.18410/jebmh/2016/346

risk is high, 5-HT3 antagonists are the preferred anti-emetics due to the lack of side effects e.g. Sedation, dysphoria and extrapyramidal as seen with use of other commonly used antiemetics like metoclopramide, promethazine and dimenhydrinate.[8,9,10]

Ondansetron is the first 5-HT3 antagonist used alone or in combination for prophylaxis of PONV due to its lower cost. Many studies have proved the superiority of 5-HT3 antagonists over other conventional antiemetic like metoclopramide, promethazine and droperidol. Granisetron and palonosetron are recently introduced 5-HT3 antagonists with greater affinity for 5-HT3 receptor and having longer half-life.

AIM AND OBJECTIVES: Aim of the present study is to compare the antiemetic efficacy of ondansetron, granisetron and palonosetron in high-risk patients undergoing abdominal hysterectomy under general anaesthesia.

MATERIAL AND METHODS: This randomised prospective double blind study was done in Department of Anaesthesiology, Katihar Medical College during the period August 2014 to July 2015. After obtaining institutional ethical committee approval and written informed consent from all the participants, 150 patients of ASA grade I & II, age between 20-50 years and weight between 30-60 kg undergoing abdominal hysterectomy under general anaesthesia were assigned randomly in to three groups of 50 patients each using random number table receiving either ondansetron 4 mg or granisetron 2 mg or palonosetron 0.75 mg intravenously just before the induction of anaesthesia.

Group O: Received Ondansetron 4 mg 5 minutes before induction of anaesthesia.
Group G: Received Granisetron 2 mg 5 minutes before induction of anaesthesia.
Group P: Received Palonosetron 0.75 mg 5 minutes before induction of anaesthesia.

Allocation concealment was done by sealed envelope technique. Patients were excluded if patients had received any antiemetic drug or steroid within 24 hours preceding surgery. Patients having gastrointestinal disease, liver disease, kidney disease, pregnancy, cancer chemotherapy within 4 weeks or radiation therapy within 8 weeks were also excluded.

Study drug was loaded in an unlabelled syringe by a staff and total volume was made to 2 ml with addition of sterile water for injection if required. Study drug was given by the anaesthesiologist unaware of the allocation just before the induction of anaesthesia. Induction was done with propofol in the dose of 2 mg/kg body weight and tracheal intubation was facilitated with vecuronium bromide in the dose of 0.1 mg/kg body wt. Anaesthesia was maintained with N_2O+O_2 (65:35) + Isoflurane (0.6-1.2%). At the end of surgery, residual neuromuscular block was reversed with glycopyrrolate in the dose of 0.001 mg/kg and neostigmine in the dose of 0.006 mg/kg body weight. Postoperative analgesia was maintained with tramadol hydrochloride 100 mg at 8-hour interval and additional dose of 2 mg/kg was given whenever VAS (Visual analogue score) was more than 4. Total opioid consumption in various groups was noted.

Incidence and severity of nausea and frequency of retching and vomiting were recorded in each group at the end of 2-hour and then at 24-hour and 48-hour intervals. Metoclopramide 10 mg was used as rescue analgesic. Nausea was defined as unpleasant subjective urge to vomit. Retching was defined as rhythmic forceful contraction of respiratory muscle without expulsion of any content from mouth whereas vomiting was defined as forceful expulsion of gastric content.

With an α value of 5% and β value of 20% and considering 30% reduction in incidence (from 60% to 42%) of PONV to be significant, sample size was calculated to be 49 patients in each group. A sample size of 50 patients was chosen in each group. ANOVA (analysis of variance) test was used for continuous variables and chi-square test for categorical variable. p value <0.05 was taken as significant. All data were analysed using SPSS 20.

RESULTS: All the groups were comparable with regard to age, weight, height, ASA grade, duration of surgery and opioid consumption over the study period and no significant differences were observed (Table 1).

Parameter	Group O	Group G	Group P	P value
Age (Years, Mean±SD)	44.50±4.70	46.50±4.72	45.30±4.45	0.97
Weight (Kg, Mean±SD)	48.78±6.19	50.80±6.09	50.02±6.04	0.234
Height (Cm, Mean±SD)	149.10±6.74	151.20±7.43	151.24±6.88	0.223
ASA Grade Number I/II	18/32	16/34	21/29	0.580
Opioid consumption (mg, Mean±SD)	748.00±121.62	774.00±112.14	760.00±112.48	0.532

Table 1: Patient Characteristics

Maximum incidences of nausea and vomiting were observed in first two hours of surgery. The incidence of nausea during first two hours postoperatively was found to be 14(28%) in Group O, which was found to be significantly higher than 6(12%) in group G and 4(8%) in group P (p value = 0.016). The incidence of vomiting was found to be 6(12%) in group O, which was found to be significantly higher than 2(4%) in both group G and group P (p value = 0.018). The incidence of nausea and vomiting over other study intervals i.e. over 24 hours and 48 hours were comparable and no significant differences were observed. Number of complete responders (no nausea and vomiting over the entire duration of surgery) were 39 (76%) in group P, 37 (74%) in group G and 18(36%) in group O. Number

of complete responders was significantly higher in Group P and group G as compared to group O. Number of patients requiring rescue antiemetic treatment was significantly high in group O {10(20%)} as compared to 3(6%) in both the group G and group P (Table 2).

Nausea/ vomiting Over time duration	Group O	Group G	Group P	P value
Up to 2 hours Nausea vomiting	14(28%) 6(12%)	6(12%) 2(4%)	4(8%) 2(4%)	0.016 0.018
Between 2 hrs to 24 hrs Nausea Vomiting	6(12%) 3(6%)	3(6%) 1(2%)	3(6%) 1(2%)	0.437 0.437
Between 24 hrs.- 48 hrs. Nausea Vomiting	3(6%) 1(2%)	1(2%) 0	1(2%) 0	0.443 0.365
Complete response (No nausea/ vomiting)	18(36%)	37(74%)	39(76%)	0.000
Antiemetic requirement (No.)	10(20%)	3(6%)	3(6%)	0.032

Table 2: Incidence of Nausea and Retching/Vomiting

The incidences of adverse effects were comparable in all the study groups and no significant differences were observed. No patient in any study group developed any serious adverse effect (Table 3).

Adverse effect	Group O	Group G	Group P	P value
Pruritus	3(6%)	2(4%)	2(4%)	0.861
Dizziness	3(6%)	4(8%)	5(10%)	0.762
Fever	2(4%)	1(2%)	1(2%)	0.773
Headache	3(6%)	2(4%)	2(4%)	0.861
Chest tightness	1(2%)	1(2%)	1(2%)	1.000

Table 3: Comparison of Adverse Effects

DISCUSSION: In this prospective double blinded randomised control trial, we compared the antiemetic efficacy of ondansetron with recently introduced 5-HT3 antagonists, granisetron and palonosetron. All the patients in the study had at least three risk factors including female gender, non-smoker and post-operative use of opioid. The incidences of PONV were significantly higher in patients receiving ondansetron for prophylaxis of PONV (Group O). Incidence of PONV was found to be 67%. Our findings are consistent with findings of Chai Y S et al, who found high incidence of PONV despite prophylactic use of ondansetron. High incidence of PONV in group O may be due to the fact that ondansetron is metabolised via CYP2D6 such that select genetic polymorphism of P450 enzyme can lead to ultrarapid metabolism.[11,12] Due to this ultra-rapid metabolism ondansetron is found to be most effective when given at the end of surgery rather than just before induction as in this study. The half-lives of recently introduced 5-HT3 antagonist are very high; $t^{1/2}$ of granisetron is 10 hours and that of palonosetron is 40 hours.

The number of complete responders was significantly higher in patients receiving granisetron (Group G) and palonosetron (Group P) as compared to ondansetron (Group O). No significant difference was found between group G and group O. Our findings are consistent with the findings of Won Suk Lee et al,[13] who found all the newly introduced 5-HT3 antagonists like palonosetron, granisetron and ramosetron to be equally effective in prevention of post-operative nausea and vomiting. Complete responders in palonosetron, granisetron and ramosetron were found to be 60%, 68.6% and 74.3% respectively and no significant differences were observed.

Most common side effects in our study were found to be dizziness and headache and were in accordance with the study of Habbi A Set al.[14]

LIMITATIONS: We did not include any control group in our study because placebo does not control PONV. Aspinall and Goodman[15] suggested that if active drugs are available placebo controlled trial should not be practiced because PONV is very distressful and associated with poor outcome. We used the optimal dosages of the drug (commercially available strength) and not the equipotent doses for the control of PONV, Equipotent doses of recently introduced 5-HT3 antagonists is yet to be discovered.

CONCLUSION: Present study clearly shows that the newly introduced 5-HT3 antagonists, Granisetron and Palonosetron are better in efficacy in the prophylaxis of nausea and vomiting. Both Granisetron and Palonosetron are comparable in efficacy to control post-operative nausea and vomiting.

REFERENCES:

1. Palazzo M, Evan R. Logistic regression analysis of fixed factors for postoperative sickness. A model for risk assessment. Br J Anesth 1993;70:135-140.
2. Cohen MM, Duncan PG, DEBoer DP, et al. The postoperative interview: assessing risk factors for nausea and vomiting. Anesth Analg 1994;78(1):7-16.
3. Dolin SJ, Cashman JN, Bland JM. Effectiveness of acute postoperative pain management: I. evidence from published data. Br J Anesth 2002;89(3):409-423.
4. Apfel CC, Larra E, Koivuranta Met, et al. A simplified risk score for predictive postoperative nausea and vomiting: conclusion from cross validation between two centers. Anesthesiology 1999;91(3):693-700.

5. Apfel CC, Kortilla K, Abdalia M, et al. A factorial trial of six interventions for the prevention of postoperative nausea and vomiting. N Engl J Med 2004;350:2445-2451.
6. Kovac AL. Prevention and treatment of postoperative nausea and vomiting. Drugs 2000;59(2):213-243.
7. Chatterjee S, Rudra A, Sengupta S. Current concepts in the management of postoperative nausea and vomiting. Anesthesiol Res Pract 2011;748031.
8. Alon E, Himmelseher S. Ondansetron in the treatment of postoperative vomiting: a randomized, double-blind comparison with droperidol and metoclopramide. Anesth Analg 1992;75(4):561-565.
9. Basu A, Saha D, Hembrom BP, et al. Comparison of palonosetron, granisetron and ondansetron as anti-emetics for prevention of postoperative nausea and vomiting in patients undergoing middle ear surgery. J Indian Med Assoc 2011;109(5):327–329.
10. White PF, Scuderi PE. Prevention of postoperative nausea and vomiting (PONV): a dose-ranging study involving palonosetron, a potent 5-HT3 receptor antagonist. Anesthesiology 2005;103:A703.
11. Swaika S, Pal A, Chatterjee S, et al. Ondansetron, ramosetron or palonosetron: which is a better choice of antiemetic to prevent postoperative nausea and vomiting in patients undergoing laparoscopic cholecystectomy? Anesthesia Essays Res 2011;5(2):182–186.
12. Eberhart LHJ, Hogel J, Seeling W, et al. Evaluation of three risk score to predict postoperative nausea and vomiting. Acta Anesthesiol Scand 2000;44(4):480-488.
13. Won Suk Lee, Kwang Beam Lee, Soy Lim, et al. Comparison of palonosetron, granisetron and ramosetron for the prevention of postoperative nausea and vomiting after laparoscopic gynecological surgery: a prospective randomized trial. Bio medical Central Anesthesiology 2015;15:121.
14. Habib AS, Gan TJ. Evidence-based management of postoperative nausea and vomiting: a review. Can J Anaesth 2004;51(4):326-341.
15. 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(7009):844-846.