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Comparitive Study of Intravenous Ramosetron and Ramosetron with Dexamethasone as Prophylactic Anti-PONV in Patients Coming for Elective ENT Surgeries

Amitha S.[1], Yoganarasimha N.[2]

[1]Assistant Professor, Dept. of Anaesthesiology, Sri Siddharth Medical College, Tumakuru, Karnataka 527107, India. [2]Associate Professor, Dept. of Anesthesiology, Sapthagiri Institute of Medical Sciences, Bengaluru, Karnataka 560090, India.

Abstract

One of the most common and distressing post-operative complication is post-operative nausea and vomiting (PONV). Though PONV can occur after all surgeries but it occurs more frequently among middle ear surgeries, gynecological, obstetric, ocular and breast. Ramosetron a newer 5 HT3 receptor antagonist and dexamethasone, a well known steroid both have its own anti PONV effect, but to determine their combination of therapeutic and side effects we took up this study. This randomized prospective double blinded study was conducted in our Institute. Sixty patients of ASA 1 and 2 were randomized to two groups – Group R (n=30) to receive ramosetron 0.3mg; Group R+D (n=30) to receive Ramosetron 0.3mg + Dexamethasone 8mg. Standard General Anaesthesia protocol was followed. Study drugs were administered at the time of induction. PONV was studied for period of 24hrs. Severity was assessed using PONV Score. The adverse effects were also studied. The incidence of PONV is high in ramosetron alone (R) group, compared to combination (R+D)group, where none of the patients subjected to this group showed either nausea or vomiting (0%) or any other adverse effects. Hence, we concluded that, combination of dexamethasone 8mg with ramosetron 0.3mg can be effectively employed at the time of induction to prevent PONV in patients undergoing ENT surgeries. Both ramosetron and dexamethasone are cost effective and safe for prevention of PONV.

Keywords: PONV; 5HT3 Receptor; Emesis; Nausea; Retching; General Anaesthesia.

Introduction

Postoperative nausea and vomiting, one of the common complications after anaesthesia, occurs after both general and regional anaesthesia. The incidence of postoperative emesis in large studies has been reported to be in the 20-30% range [1].

Nausea is defined as a subjectively unpleasant sensation associated with an urge to vomit. This is felt mainly in the back of the throat and epigastrium, accompanied by loss of gastric tone, duodenal contractions and reflux of the gastric contents into the esophagus. It is associated with prodromal symptoms such as salivation, swallowing, pallor and tachycardia. Retching is defined as laboured spasmodic rhythmic contractions of the respiratory muscles including the diaphragm and chest wall and abdominal wall muscles without expulsion of gastric contents. Vomiting or emesis is the forceful expulsion of gastric contents from the mouth and is brought about by powerful sustained contraction of the abdominal muscles, descent of the diaphragm and opening of the upper oesophageal sphincter [2]. Persistence of nausea and vomiting in the postoperative patient especially in a patient, who is fasting, can result in dehydration, electrolyte imbalance, and delay discharge especially in ambulatory surgery. Persistent retching and vomiting can cause tension in suture lines, venous hypertension, bleeding under skin flaps and increased risk of pulmonary aspiration of vomitus,

Corresponding Author: Yoganarasimha N., Associate Professor, Dept. of Anesthesiology, Sapthagiri Institute of Medical Sciences, Karnataka 560090, India.
E-mail: yogabmc98@yahoo.co.in

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if airway reflexes are depressed from the residual effects of anaesthetic and analgesic drugs.Though PONV can occur after all surgeries but it occurs more frequently among middle ear surgeries, gynecological, obstetric, ocular and breast [1].

To prevent this distressing symptom many monotherapy comparisons and multimodal approach comparisons has been conducted and studied. Studies have shown that use of 5HT3 receptor antagonists and dexamethasone has for prophylaxis in patients at risk of PONV. So we decided to study the efficacy of a combination of two antiemetic drugs in preventing PONV, after a surgery with a high incidence of PONV.

Materials & Methods

Randomized double blinded study was conducted at our institution for a period of six to eight months and data was randomly collected from 60 ASA I and II patients scheduled for ENT surgeries aged between 20-60 years in our Institute.

Inclusion Criteria

1. ASA 1and ASA 2 patients.
2. 20-60 age group.

Exclusion Criteria

1. Documented hypersensitivity to any of the study drugs,
2. Patients with history of migraine, motion sickness or previous PONV.
3. Patients who are pregnant or menstruating.
4. Patients who have taken antiemetic drugs within 24 hours before surgery.
5. Patients with history of neurological or renal diseases.

Written informed consent was taken from all patients. Pre-anaesthetic medication was given with Ranitidine 150mg and Tab Alprazolam 0.5mg, the night before and morning of surgery. SpO_2, NIBP, ECG monitors were attached. The baseline values were recorded. IV access was established. Patients were randomly allocated into two groups.

1. Those who receive Ramosetron alone (0.3 mg) IV. (Group R)
2. Those who receive Ramosetron (0.3 mg) and Dexamethasone 8mg IV. (Group-R+D)

The drugs were given 5 minutes before induction of anaesthesia by anesthetists who were not involved in the study, for making the study double blinded.

Anaesthesia was induced after premedication with inj. Glycopyrolate 0.2 mg, Midazolam 1 mg, Fentanyl 1 microgram/kg with inj. Thiopentone sodium 5 mg/kg and intubation achieved with succinylcholine 1.5 mg/kg. Proper size cuffed oral endotracheal tube was inserted. Anaesthesia was maintained with N_2O 66%, O_2 33%, Halothane 0.5-1% and intermittent doses of Vecuronium Bromide. Ventilation was controlled mechanically and was adjusted to keep $ETCO_2$ between 30 and 35 mm of Hg. Reversal of muscle relaxation was done with Glycopyrolate 0.01mg/kg body weight and neostigmine 0.05 mg/kg and patient was extubated.

Postoperatively all episodes of PONV experienced by the patient during the first 24 hours after anaesthesia, was recorded by direct questioning. These were assessed by a nausea and vomiting score. Rescue anti-emetic (dexamethasone) was used if patient had nausea or vomiting.

At the end of the study, the data was compiled systematically and was subjected to statistical analysis using 'Chi-square' test and Microsoft excel and Epi info version 3.4.3.

Results

Study Design

The study was conducted on 60 individuals of ASA class I and II, scheduled to undergo various ENT operations under General Anaesthesia. Patients were randomly allocated to two groups

Group R [n=30]- Ramosetron 0.3mg

Group R+D [n=30]- Ramosetron 0.3 mg +Dexamethasone 8mg IV

All patients were followed up for 24 hrs post operatively. Any episode of Nausea, Retching and Vomiting was recorded and assessed using PONV score. Score 0=no nausea; 1=nausea only; 2= nausea with retching; 3=vomiting. The results obtained were analyzed after completion of the study. The results obtained were analyzed using Epi info version 3.4.3.

We studied 60 patients belonging to age group of 20-60 years, posted for ENT surgeries, the mean age of the patients in group R, group R+D were 29.7(4.76) and 30.1(4.48) years respectively. In our study, there was no clinically or statistically significant difference with respect to age distribution, weight and body mass index [Table 1].

There was no difference in the duration of anaesthesia in both study groups. (p=0.541) [Table 2].

Blood pressures were recorded throughout the surgery and mean of these recordings were taken from both group. Hemodynamic parameters were comparable in both the groups and difference observed was not statistically significant [Table 3,4].

Comparison of PONV Scores

Nausea and Vomiting occurring within first 1hr was defined as early PONV and 1-24 hours as delayed PONV. Scores were tabulated and compared (Table 5).

Compete response was noted in 63.33% and 100% in group R and group R+D respectively. Incidence of Nausea (Score-1) was 16.6% and nil in Group R and Group R+D respectively. Nausea with Retching (Score-2) was 13.33% in Group R and was absent in Group R+D. Vomiting (Score 3) was 6.67% and nil in Group R and Group R+D respectively. There were no adverse effects noted in any of the groups in first 1 hrs. Test of significance and 'p' value cannot be calculated as there was no history of vomiting in one of the group (Figure 1).

Complete response (score 0) was observed after 1 hour in both the groups. However, the patients were followed up for remaining study period for any adverse effect. And there were no adverse effects noted any of the groups in first 1-24 hrs.

In overall 24 hours, the incidence of PONV was 36.6% in group R and 0% in Group R+D [Table 6]. There was no requirement of rescue antiemetics in Group R+D [table 7].

The adverse effects were not observed in both groups at any time interval during the study period.

Discussion

Post operative nausea and vomiting (PONV) is a common problem and distressing symptom in surgical patient population. Post operative vomiting will harm skin flaps, abdominal wall sutures, vascular anastomoses, and other areas recently

Table 1: Demographic characteristics of study subjects

Characteristics	Group R	Group R+D	p value
Age (± SD)	29.7 (4.76)	30.1 (4.48)	0.730
Weight (± SD)	57.93 (7.95)	58.7(8.25)	0.714
BMI (± SD)	22.04 (2.77)	22.15 (3.41)	0.890

Table 2: Distribution of duration of anesthesia in both the groups

	Group R	Group R+D	P value
Duration of Anesthesia (+SD) in minutes	100.83 (18.62)	97.83 (19.19)	0.541

Table 3: Distribution of systolic blood pressure in both groups

Systolic blood pressure (mmHg)	Group R N=30	Group R+D N=30	p value
Mean(+SD)	124.21(11.06)	121.35(10.41)	0.306

Table 4: Distribution of diastolic blood pressure in both groups

Diastolic blood pressure(mmHg)	Group R N=30	Group R+D n=30	p value
Mean (+SD)	73.28(8.23)	75.48(8.92)	0.324

Table 5: Comparison of vomiting in both groups

History of vomiting	R	R+D	Total
Immediate	2	0	2
15 min	3	0	3
30 min	3	0	3
1st hour	3	0	3
2nd hour	0	0	0
12th hour	0	0	0
24th hour	0	0	0
Total	11	0	11

(Test of significance and 'p' value cannot be calculated as there was no history of vomiting in one of the group.)

Table 6: Incidence of vomiting in both the groups in 24 hrs

Group	Percentage
R	36.6%
R+D	0%

Table 7: Requirement of rescue antiemetic

Group	Percentage
R	33.3%
R+D	0%

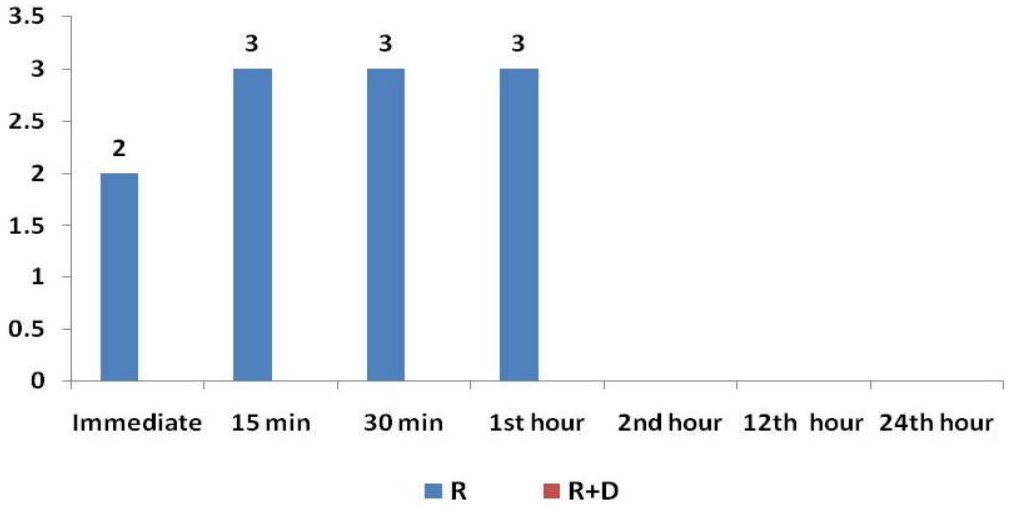

Fig. 1: Comparison of vomiting in both groups

operated on [4]. It increases intra-ocular, intra-cranial pressure and may also cause tachycardia, electrolyte imbalance, wound dehiscence, esophageal tears and aspiration pneumonitis [4]. Anti emetic drugs including anti histamines, butyrophenonoes, dopamine receptor antagonists were used a few years ago. These anti emetic had undesirable side effects like excessive sedation, hypotension, dry mouth, dysphasia, hallucinations and extra-pyramidal symptoms and they are now rarely used. In 1981, Dexamethasone was found to be an effective anti emetic in patients undergoing chemotherapy with limited side effects and its use in prophylaxis for PONV was started 2 years later [5,6]. In 1990, 5HT3 antagonists were introduced [7,8]. Gregory et al reported the effectiveness of 5HT3 antagonists in prevention of chemotherapy induced nausea and vomiting [8,9]. Combinations of anti-emetic drugs with different mechanisms of action are known to be effective and have been studied for the prophylaxis of PONV with variable results. The common drug that is used in combination therapy in many of the studies was dexamethasone [9,13]. Majority of combination therapies studied for prevention of PONV are combination of dexamethasone with either ondansetron or granisetron. Very few studies have compared the efficacy of newer drug Ramosetron and its combination with dexamethasone. In our study we compared Ramosetron and Ramosetron with dexamethasone for prevention of PONV in ENT surgeries under general anaesthesia.

Selection of Study Population

Apfel et al described female gender, previous history of PONV or motion sickness, non-smoking status and postoperative use of opioids as important risk factors for PONV [14]. Sinclair et al described female gender, previous history of PONV or motion sickness, non-smoking status and postoperative duration, type of anesthesia and surgery as the important risk factors for PONV [14]. Among high-risk patients, the incidence of PONV can be as high as 70% to 80% [15,16].

Patients with history of motion sickness, migraine, nausea and vomiting in preoperative period and patients with renal, gastro-intestinal disorders and liver disorders were excluded.

Type of Anaesthesia

Regional anaesthesia- spinal and epidural anaesthesia is the most popular and most frequently used technique for abdominal and pelvic surgeries in adults. Sinclair et al [2,17] found the risk for PONV is nine times less among patients receiving regional anesthesia than those receiving general anesthesia.

The incidence of PONV is high in general anaesthesia [2]. Use of volatile anesthetics, nitrous oxide, large-dose neostigmine (>2.5 mg) and use of intraoperative or postoperative opioids in general anaesthesia are associated with high incidence of PONV [2,15]. Propofol is known to reduce the incidence of PONV [2] and is also used in the treatment of refractory vomiting and hence was avoided in the present study. Thiopentone was used in our study as it has no antiemetic effect and is the most commonly used intravenous induction anaesthetic agent in our institution

Inhalational Anaesthetic Agent

Nitrous oxide is known to increase PONV by direct CNS stimulation of vomiting centre,[2] interaction with opioid receptors, stimulation of the sympathetic nervous system with catecholamine release, changes in middle ear pressure and distension of air containing spaces. The newer inhalational agents namely desflurane and sevoflurane have a lower incidence of PONV.

Apfelet al [17] suggested that avoiding nitrous oxide reduced PONV risk by 12%. Kortilla et al, Muir et al and Felts et al suggested that nitrous oxide does not significantly affect the incidence of PONV in adults when halogenated inhalational agents are used.[2]In our institution nitrous oxide and 0.5% of halothane are part of the general anaesthesia protocol. Hence, in our study nitrous oxide and halothane 0.5% was used in all cases as we wanted to test the efficacy of the combination of antiemetics chosen in the present study in prevention of PONV with standard anaesthesia protocol employed in the institute.

Perioperative analgesics: Intra and perioperative use of opioid increases the risk of PONV [15]. Elia et al [18] in a randomized study suggested that use of NSAIDS reduced the risk of PONV. In our study pain was managed in a multi modal way in the perioperative period, using inj Fentanyl 2microgram/kg IV as premedicant.

Use of neostigmine: Meta analyses by Trameret al [16] demonstrated that high-dose neostigmine (>2.5 mg) is associated with increased PONV and that reducing the dose can decrease PONV risk. However, Cheng et al [17] in their study, questioned the clinical importance of neostigmine PONV. Residual neuro-muscular blockade is associated with dangerous complications than a questionable raise in incidence of PONV. Therefore in our study neostigmine was not avoided but used in total dose of 2.5 mg for reversal of residual neuromuscular blockade in all patients.

Type of Surgery

The incidence of emesis after general anaesthesia is influenced also by the type of surgical procedure; irrespective of the anesthetic technique used [2]. The highest incidence is noted in women undergoing laparoscopic ovum retrieval procedures (54%) [2]. Types of procedures with high incidence of PONV include major gynecological surgeries, Laparoscopic, orthopedic, ear nose throat, thyroid and breast etc.

In our study patient undergoing ENT surgeries were selected in both the groups as incidence of PONV found to be high.

Selection of Antiemetic Drugs

• *5HT3 Receptor Antagonists*

5HT3 antagonists were introduced in 1990. The 5-HT_3 receptor antagonists suppress nausea and vomiting by inhibiting serotonin binding to the 5-HT_3receptors. The highest concentration of5-HT_3receptors in the central nervous system (CNS) are found in the STN (solitary tractus nucleus) and chemoreceptor trigger zone (CTZ), and 5-HT_3antagonists suppress nausea and vomiting by acting at these sites [19].

Selective serotonin type 3 receptor antagonists are considered first line of therapy when therapeutic intervention to prevent PONV is considered [20]. The 5-HT3 antagonists have a favorable side effect profile and are considered equally safe [20]. Ondansetron, Dolasetron, Granisetron, Tropisetron and a newer drug Ramosetron are recommended in the prophylaxis of PONV. We selected newer drug Ramosetron to know its efficacy in prevention of PONV.

Dexamethasone

In 1981, Dexamethasone was found to be an effective anti emetic in patients undergoing chemotherapy with limited side effects. The mechanism of action of corticosteroids is unknown but may be related to inhibition of prostaglandin synthesis, decrease in 5HT3 levels in central nervous

system or by an anti inflammatory action at operative sites [12,21]. Animal experiments suggest that it exerts its antiemetic effects through central inhibition of the nucleus tractus solitarii but not the area postrema [1].

Combination of Antiemetics

The concept of combination therapy was introduced by Parikhin chemotherapy induced nausea and vomiting [12,13]. For patients at high risk of PONV use of a 5HT3 receptor antagonist, in combination with another antiemetic drug with a different mechanism and site of action is advised. Dexamethasone acts on nucleus tractus solitarius but not in CTZ where as 5-HT3 receptor antagonist also acts on CTZ [1]. SAMBA [23] guidelines suggest that adults at moderate risk for PONV should receive combination therapy with one or more prophylactic drugs from different classes. It is also found that combinations act synergistically. Single drug therapy has frequent failure rates in situations with severe and frequent PONV. Combination therapy has superior efficacy compared to monotherapy for PONV prophylaxis [20]. McKenzie demonstrated that dexamethasone in combination with Ondensetron was effective than single drug therapy [22]. In view of these observations, in the present study combination of antiemetics was employed.

Dosage

Combination of ramosetron 0.3mg with dexamethasone 8 mg is cost effective and reduces the adverse effects like headache which is commonly seen at a dose of 0.6 mg. The study suggests that regardless of bodyweight, 0.3 mg of ramosetron is minimum effective dose as a prophylaxis against PONV in patient undergoing ENT surgeries [21].

Conclusion

From the present study

1. PONV in the post operative period can last up to 24 hours, though the incidence and severity is maximum in the first hour.
2. Incidence of PONV in patients who received ramosetron 0.3 mg found to be 36.66%.
3. Combination of ramosetron 0.3mg with dexamethasone 8 mg administered at the time of induction effectively reduces the incidence of PONV in all patients.
4. Combination of ramosetron 0.3mg with dexamethasone 8 mg is cost effective and reduces the adverse effects like headache which is commonly seen at a dose of 0.6 mg of ramosetron.
5. The study suggests regardless of bodyweight 0.3 mg of ramosetron is minimum effective dose as a prophylaxis against PONV in patient undergoing ENT surgeries.

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References

1. Apfel CC, post operative nausea and vomiting, 7th edition, Churchill-Livingstone Elsevier publications. Miller's anaesthesia, pp 2729-51.
2. Watcha MF, White PF. Postoperative nausea and vomiting: Its etiology, treatment and prevention. Anesthesiology 1992;77:162-82.
3. Gan T J, Meyer T A, Apfel C C, Chung F. Consensus Guidelines for Managing Postoperative Nausea and Vomiting, AnesthAnalg 2003;97:62–71.
4. Andrew PLR.Physiology of nausea and vomiting. Br J Anaesth 1992;69:2-19.
5. Anne M Heffernan, David J Rowbotham.Post operative nausea and vomiting-Time for balanced Anti-Emesis? British Journal of Anaesthesia, Editorial 2000;85(5):675-7.
6. Gan, Tong J, "Receptor Antagonists for Postoperative Nausea and Vomiting-Are They All the Same?", CNS Drugs 2005;19(3):225-238.
7. FujiY, Tanaka H, Toyooka H. Reduction of postoperative nausea and vomiting with Granisetron. Can J Anaesthesia 1994;41(4):291-294.
8. Fujii Y, Tanaka H, ToyookaH. Optimal Anti-Emetic dose of granisetron for prevention of post operative nausea and vomiting. Can J Anaesth 1994;41(9): 794-7.
9. Olando L, Carrascosa F, Pueyo F J et al. Combination ofOndansetron and dexamethasone in the prophylaxis of post operative nausea and vomiting British Journal of Anaesthesia 1996;76:835-40.

10. Fujii Y, Tanaka H, Toyooka H, Granisetron-dexamethasone combination reduces post operative nausea and vomiting.Can J Anaesth 1995;42(5): 387-90.
11. Wilson J, Dimunsh BJ, Lindeque, scheinin H, Helibo HS Hansen et al Single dose iv granisetronin prevention of post operative nausea andvomoting;Br J Anaesth 1996;76:515-8.
12. Fujii Y, Saitoh Y, Tanaka H et al, Granisetron-dexamethasone combination for reducing nausea and vomiting during and after spinal anesthesia for cesarean section. AnesthAnalg 1999;88:1346-50.
13. Rajeeva,bharadwajN,Batra et alComparison of Ondansetron with Ondansetron and dexamethasone in prevention of PONV in diagnosticlaproscopy;Can J Anaesth 1999;46(1):40-44.
14. Pierre S, Benais H, PouymayouJ, Apfel's simplified score may favourably predict the risk of postoperative nausea andVomitingCan J Anaesth 2002;49(3): 237–242.
15. Gan T J, Review article-RiskFactors for Postoperative Nausea and Vomiting, AnesthAnalg 2006;102: 1884–98.
16. Trame'r MR, Fuchs-Buder T. Omitting antagonism of neuromuscular blockade: effect on postoperative nausea and vomiting and risk of residual paralysis. A systematic review.Br J Anaesth 1999;82:379–86.
17. Cheng CR, Sessler DI, Apfel CC. Does neostigmine administration produce a clinically important increase in postoperative nausea and vomiting? AnesthAnalg 2005;101:1349–55.
18. Elia N, Lysakowski C, Tramer MR. Does multimogal analgesia with acetaminophen, nonsteroidalanti inflammatory drugs, or selective cyclooxygenase-2 inhibitors andpatient-controlledanalgesia morphine offer advantages over morphine alone? Meta-analyses of randomized trials. Anesthesiology 2005;103: 1296–304.
19. Brunton, Laurence L, Lazo, John S et al, Goddman and Gilman's The Pharmacological Basis of Therapeutics, New York: McGraw-Hill, 2006; pp.1000-1003, ISBN 0-07-1442280-3.
20. Gan TJ, Meyer AT, Apfel CC, Chung F et al. Consensus Guidelines for Managing Postoperative Nausea and Vomiting. AnesthAnalg 2003;97:62–71.
21. Henzi I, Walder B, Tramer M R Dexamethasone for the prevention of post operative nausea and vomiting: A Quantitative systematic review. Anaesthanalg 2000; 90:186-94.
22. Mc Kenzi, Tantisira B, Karambelkar D J, Riley t j et al Comparison of Ondansetron with Ondansetron PlusDexamethasone in the Prevention of Postoperative Nausea and Vomiting;AnesthAnalg 1994;79:961-4.
23. Gan TJ, Meyer AT, Apfel CC, Chung F et al. Society for Ambulatory Anesthesia Guidelines for the Management of Postoperative Nausea and Vomiting. AnesthAnalg 2007;105:1615-28.