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Research Article

A STUDY OF ANALOGY AND COLLATION OF INTRAVENOUS ONDANSETRON AND INTRAVENOUS RAMOSETRON FOR THE PREVENTION OF POST OPERATIVE NAUSEA AND VOMITING FOLLOWING MIDDLE EAR SURGERIES IN A SOUTH INDIAN TERTIARY CARE HOSPITAL : A PROSPECTIVE, RANDOMIZED, DOUBLE BLIND STUDY

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ABSTRACT

Postoperative nausea and vomiting (PONV) are problems encountered after general anaesthesia. 5-HT_3 receptor antagonists are commonly used to treat or prevent PONV. In our study, we have evaluated the efficacy and safety considering the analogy and collation between i.v Ondansetron (4mg) and i.v Ramosetron (0.3 mg) in patients undergoing middle ear surgery in a south Indian tertiary care hospital. We found that, the average PONV Impact Scale Score (ISS) and the average Visual Analogue Scale (VAS) for post-operative nausea and vomiting was 0.005 ($p<0.05$) for i.v Ondansetron (4mg) and 0.028 ($p<0.05$) for i.v Ramosetron (0.3 mg). The incidence of a complete response during 2-6 and 24-36 hour period was 64% and 78.7% for i.v Ondansetron (4mg) respectively with the primary outcome measure of 0.047 ($p < 0.05$). But the incidence of a complete response during 2-6 and 24-36 hour period was 66.7% and 81.3% for i.v Ramosetron (0.3 mg) with the primary outcome measure of 0.041 ($p < 0.05$). Analogy and collation profile of adverse effects between i.v Ondansetron (4mg) and for i.v Ramosetron (0.3 mg) shows that i.v Ramosetron (0.3 mg) has less incidence of adverse effects than i.v Ondansetron (4mg). In our study, it is evident that i.v Ramosetron (0.3 mg) was not only potent but it was also more efficacious and safer alternative to i.v Ondansetron (4mg) to prevent PONV.

Keywords: Analogy, Collation, Ondansetron, Postoperative nausea and vomiting, Ramosetron

INTRODUCTION

Postoperative nausea and vomiting (PONV) are common problems after general anaesthesia. Besides the unpleasant experience to the patient, PONV causes multiple medical complications. This has an incidence of approximately 20%-30% [1, 2]. Persistent nausea and vomiting may result in conditions like dehydration, electrolyte imbalance and delayed discharge, particularly after ambulatory surgeries[3]. PONV increase the risk of pulmonary aspiration in case of residual effects of anaesthesia. The influence of various agents on PONV is well documented. PONV results in increased patient discomfort and dissatisfaction and increased costs related to length of hospital stay[4-6]. Certain procedures such as gynaecological surgeries, laparoscopic surgeries, middle ear surgeries, strabismus surgeries are associated with higher incidence of PONV [7, 8].

Among the anti-emetics, 5-HT_3 receptor antagonists are most commonly administered drug to treat or prevent PONV, but there are obvious differences in the pharmacokinetic and pharmacodynamic profile among the drugs belonging this class[9]. The 5-HT_3 receptor antagonists suppress nausea and vomiting by inhibiting serotonin from binding to the 5-HT_3 receptors. 5-HT_3 receptors are found in the highest concentration in solitary tract nucleus (STN) and the chemoreceptor trigger zone (CTZ) of the central nervous system. It is known that these agents suppress nausea and vomiting at the STN and CTZ sites by preventing serotonin from activating and sensitizing the vagal afferent nerves which causes nausea and vomiting[10].

Ondansetron (Prototype), Granisetron, Palenosetron and Tropisetron are 5HT_3 antagonists. Current studies report that Ondansetron, a 5-HT_3 receptor antagonist, is very effective in prophylaxis for PONV when taken orally or intravenously. Studies have shown that intravenous Ondansetron 4 mg was a better treatment than intravenous Metoclopramide 10 mg, but higher doses of Ondansetron (16 mg) were no more effective than lower doses[11.12].

Newer generations of 5-HT_3 receptor antagonists were developed with higher receptor affinity and longer duration of action, such as Ramosetron, which has been shown to exert more potent and sustained antiemetic efficacy than the first generation[13, 14].

In view of this, the present study was undertaken to assess the analogy and collation between i.v Ondansetron and i.v Ramosetron in patient undergoing middle ear surgery in a south Indian tertiary care hospital.

MATERIAL AND METHODS

Institutional Ethics Committee approval was obtained from K.S. Hegde Hospital, NITTE University, Mangalore, Karnataka, India vide Ref. No. INST.EC/E.C/40/2012-13 dated 03/10/2012. Informed written consent was taken from each patient enrolled in the study. The study was prospectively conducted from November 2012 to August 2014.

Patients aged from 15 years to 60 years, patients scheduled to undergo elective middle ear surgeries under general anaesthesia(Mastoid surgeries, Tympanoplasties, Myringoplasty, Ear ossicles surgeries, eg. Stapedectomy); patients with American Society of Anaesthesiologists (ASA) physical status I-II; patients scheduled to be hospitalised for 36 hours after surgery were included in the study.

Patients with history of gastro-oesophageal reflux, patients with vomiting from any organic cause; any drug with a potential anti-emetic effect within 24 hours prior to the administration of anaesthesia; any vomiting, retching, or nausea in the 24 hours preceding the administration of anaesthesia, patients chronically on opioid analgesics, patients undergoing day care surgeries were considered to be exclusion criteria for the study.

Sample size: 95% Confidence interval, with a power of study 80 % and expecting a reduction of 2.7 odds with a regular incidence of nausea and vomiting being around 62% and 75 patients in each group with an allocation ration of 1:1 were selected.

Patients were randomly allocated to either of the group viz Group I- Ondansetron (i.v 4mg) or Group II- Ramosetron (i.v 0.3 mg) by computerized randomization table consisting 75 patients in each.

Each patients received the drug as scheduled after the operation and outcome measures were incidence of complete response (no incidence of nausea , vomiting or retching), nausea, retching, vomiting and need for rescue antiemetic in the 2 groups in 0-2, 2-6, 6-24, 24-36 hours and Severity of nausea and vomiting in the 2 groups in 0-2, 2-6, 6-24, 24- 36 hours

The results were also based on the following PONV Impact Scale:

Have you vomited or had dry retching? Scores- 0=No 1=Once, 2=Twice, 3=Three or more times

Have you experienced a feeling of nausea? Scores- 0=Not at all, 1=Sometimes, 2=Often or most of the time, 3=All of the time

To calculate the PONV impact scale score, the numerical responses to questions 1 and 2 were added A PONV Impact Scale score of 5 or more defined clinically important PONV.

The intensity of nausea was determined using a 10 cm Visual Analogue Scale (VAS), the limits being from 'no nausea' to 'nausea as bad as it could be.

1. Complete response: No emetic episode
2. Major response: One emetic episode
3. Treatment failure: 2 or more episode or the receipt of a rescue anti emetic

Statistical Analysis

Mann-Whitney U test where severity of nausea is scored for different interventions and Fredman test for repeated measure analysis. Data was analysed using IBM SPSS statistics for windows, Version 20.0. Armonk, NY: IBM Corp. The primary outcome measures were compared using the chi squared test. Chi square test was used for the categorical variables. P value of <0.05 was considered significant.

RESULTS

In our study there were 62 (41.33%) male patients and 88 (58.67%) female patients in total. There were 34 (45.33%) male patients and 41 (54.77%) female patients in Group I (i.v Ondansetron, 4 mg) and 28 (37.33%) male patients and 47 (62.77%) female patients in Group II (i.v Ramosetron 0.3mg).

Table 1: Average PONV impact scale score (ISS) and the average VAS score for post operative nausea and vomiting

Group	N	PONV (mean ± SD)	VAS (mean ± SD)	T table	df	P value
Group I (Ondasetron 4mg, i.v)	75	1.61±1.432	4.39±1.345	2.841	148	0.005***
Group II (Ramosetron 0.3mg, i.v)	75	0.97±1.325	3.5±1.469	2.266	51	0.028***

Observations are mean ± SD. Mann-Whitney U test. *p>0.05- Not significant, ***p<0.05- Significant
N- Number of patients, i.v-intravenous, VAS- Visual Analogue Scale, PONV- Postoperative Nausea Vomiting, T- 'T' Table, df- Degree of freedom, p-Probability value

Table 2: The incidence of a complete response during 2-6 and 24-36 hour period comparing Ondasetron with Ramosetron along with primary outcome measures

Groups	Period	Comparison of complete response (%)	Primary outcome measures (p value)
Group I (Ondasetron 4mg, i.v)	2-6 hrs	64	0.047***
Group II (Ramosetron 0.3mg, i.v)	2-6 hrs	78.7	
Group I (Ondasetron 4mg, i.v)	24-36 hrs	66.7	0.041***
Group II (Ramosetron 0.3mg, i.v)	24-36 hrs	81.3	

Observations are mean ± SD. Chi squared test. *p>0.05- Not significant, ***p<0.05- Significant, ***p<0.05- Significant i.v-intravenous

Table 3: Analogy and collation profile of adverse effects between Ondasetron and Ramosetron

	Group I (Ondasetron 4mg, i.v)		Group II (Ramosetron 0.3mg, i.v)		
Adverse Effects	**Counts**	**Percentage (%)**	**Counts**	**Percentage (%)**	**P Value**
Headache	4	5.3	3	4	0.699*
Drowsiness	1	1.33	1	1.33	1*
Dizziness	3	4	2	2.67	0.649*
Itching	0	0	0	0	1*
Total	8	10.67	6	8	0.772*

Observations are mean ± SD. Mann-Whitney U test. I.v-intravenous, *p>0.05- Not significant, ***p<0.05- Significant

DISCUSSION

Anti-emetics are used to prevent episodes of vomiting, minimize or lessen the frequency and severity of nausea, and also to minimize or remove the need for PONV rescue medications. 5-HT_3 receptor antagonist have proven efficacy in the prevention and treatment of PONV, with reduced adverse effects[15].

5-HT_3 receptor antagonists are found to be generally safer drugs at the usual doses used to prevent or treat PONV, with no effect on sedation or associated extra pyramidal symptoms compared to other antiemetics[16].

In our study, we have evaluated the efficacy and safety considering the analogy and collation between i.v Ondansetron (4mg) and i.v Ramosetron (0.3 mg) in patients undergoing middle ear surgeries in a south Indian tertiary care hospital.

We found that, the average PONV Impact Scale Score (ISS) and the average VAS score for post-operative nausea and vomiting was 0.005 ($p<0.05$) for i.v Ondansetron (4mg) and 0.028 ($p<0.05$) for i.v Ramosetron (0.3 mg) which signifies that i.v Ramosetron (4mg) with not much difference for PONV (Table 1).

The incidence of a complete response during 2-6 hrs and 24-36 hrs period was 64% and 78.7% for i.v Ondansetron (4mg) respectively with the primary outcome measure of 0.047 ($p < 0.05$). But the incidence of a complete response during 2-6 and 24-36 hour period was 66.7% and 81.3% for i.v Ramosetron (0.3 mg) with the primary outcome measure of 0.041 ($p < 0.05$). This shows that i.v Ramosetron (0.3 mg) has shown better efficacy both with complete response and primary outcome measure (Table 2).

Analogy and collation profile of adverse effects between i.v Ondansetron (4mg) and for i.v Ramosetron (0.3 mg) shows that i.v Ramosetron (0.3 mg) has less incidence of adverse effects than i.v Ondansetron (4mg) in terms of counts and percentage (Table 3).

One of the previous studies involving HPLC analysis of ondansetron was proven to be of great importance in pharmaceutical analysis[17]. However, studies involving the comparative analysis involving Ramosetron and Odansetron by correlating with HPLC will give a good idea regarding its role in clinical setting for PONV.

In conclusion, it is evident from our study that, i.v Ramosetron (0.3 mg) was not only potent when compared with i.v Ondansetron (4mg), but it was also more efficacious and safer to prevent episodes of vomiting, eliminate or lessen the severity of nausea, and remove the need for PONV rescue medications with lesser adverse effects.

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