ORIGINAL ARTICLE

Safety Profile of Various 5HT3 Receptor Antagonists Used for PONV Prophylaxis

Anju Jamwal, Mukta Jatindera, Renu Wakhloo, Rajdeep Kour

Abstract

The current study was done to compare the safety profile of Ondansetron, Ramosetron and Palonosetron. 150 female patients undergoing elective Laparoscopic Cholecystectomy were randomly divided into 3 groups with 50 patients each and received 4mg of Ondansetron, 0.3mg of Ramosetron and 0.075mg of Palonosetron respectively for PONV prophylaxis. Patients were observed for QTc interval changes &other side effects like headache, dizziness, drowsiness and myalagia in addition to incidence of post operative nausea & vomiting. The incidence of QTc interval prolongation at various time intervals and side effects like headache, dizziness, drowsiness, myalagia also did not show any statistically significant difference. We concluded that safety profile and side effects of all the three drugs were comparable when used in this manner. As for as QTc interval change is concerned both ondansetron & Ramosetron caused the prolongation of corrected QTc interval but in no patient it was found to be more than 470 ms.

Key Words

IVRA , Lignocaine, Ropivacaine

Introduction

Post operative nausea and vomiting (PONV) is a common complication after surgery and its incidence remains between 20% and 70%. Not only are nausea and vomiting unpleasant for patients, but the minor complication may increase the risk of pulmonary aspiration, lead to disruption of surgical wound, electrolyte imbalance and dehydration. Because of potential serious nature of PONV extensive research has been undertaken to find successful approaches for its prevention and treatment.There are numerous antiemetic drugs available having different mechanisms of action, and target sites with varying potency and pharmacokinetic profiles. The traditional antiemetic i.e Prokinetics, Dopamnergic antagonists, Phenothiazines, Antihistaminics, Anticholenergics, Butyrophenones, Benzamide and Steroids are associated with adverse effects such as restlessness, dry mouth, sedation, hypotension, extra pyramidal symptoms and dystonic effects.(1)

Clinical experience with Selective 5HT3 receptor antagonists (Ondansetron, Granisetron, Ramosetron, Dolasetron, Tropisetron and Palonosetron) has demonstrated superior efficacy, safety and tolerability over conventional anti emetics. (2) Furthermore, 5HT3 receptor antagonists exhibit no significant drug interaction with common anaesthetic agents and have little or no affinity for receptor sites other than 5HT3 receptors. Though adverse effects associated with a single dose of an antiemetic are small, as compared to the hazards and inconvenience of vomiting yet on going efforts are there to develop safe antiemetic drugs without having any untoward side effects, especially on cardiovascular and respiratory system. Hence, 5HTR3 receptor antagonists were introduced which have a greater margin of safety.

The commonly used drug of 5HT3 receptor antagonist group Ondansetron is a prototype of 5HT3 for the treatment of PONV. (3) Ramosetron is more potent and with longer receptor antagonist effect as compared to Ondansetron. (4) Palonosetron is first of second generation 5HT3 receptor antagonists for the treatment of PONV. This new agent has a higher receptor binding affinity and longer elimination half life of about 40 hrs. (5) Recent receptor binding studies suggest that

From the Deptt. of Anaesthesia, Govt. Medical College Jammu J&K India 180001

Correspondence to : Dr. Anju Jamwal, Asst. Professor, Deptt. of Anaesthesia, Govt. Medical College Jammu J&K India 180001

Palonosetron is further differentiated from other 5HT3RA by binding with 5HT3 receptor in an allosteric positively cooperative manner at sites different from those that bind with Ondansetron and Ramosetron. (6) Though they all are well tolerated, most common adverse events experienced by the patients are headache, dizziness, drowsiness, myalagia (7) and effects on electrocardiogram including QT interval, heart rate corrected. (8) The present study was conducted to study the side effects and thus safety profile of Palonosetron (0.075mg) and its comparison with Ondansetron (4mg) and Ramosetron (0.3mg) for prevention of postoperative nausea and vomiting (PONV) in patients undergoing laparoscopic Cholecystectomy

Material and Methods

After obtaining approval from institutional ethics committee IEC/T11/2013/06b and informed written consent, 150 female patients in age group of 25-55 yrs & ASA grade-I and II undergoing laparoscopic Cholecystectomy were selected for the study. Patients who received antiemetic 24 hours before surgery, concomitant administration of steroids and psychotropic drugs, pregnant or lactating women, patient with known prolonged QTc interval or bundle branch block, patients on chemotherapy and allergy to the drugs used in the study were excluded from the study. Pre anaesthetic check-up was done a day prior to surgery. Patients were kept fasting for 8hrs before surgery I/v line with ringer lactate was started in the OT monitors were attached for basic monitoring. Baseline ECG was also recorded. Study medication was given 3 min before induction of anaesthesia. GROUP O patients received Ondansetron 4mg, GROUP R patients received Ramosetron 0.3mg and GROUP P patients received Palonosetron 0.075mg simultaneously patients were pre oxygenated. For Induction injection Propofol 2mg/kg i/v& Injection Tramadol1mg/kg i/v was given, Injection Atracurium Besylate 0.5 mg/kg i/v was given to facilitate tracheal intubation. Maintenance was done with O2 +N20 (40:60) and Top-up doses of injection Atracurium Besylate 0.1mg/kg. Monitoring of HR, SBP, DBP, MAP, ETCO2 and SPO2 was done intraoperatively.

After obtaining baseline ECG, continuous ECG was observed for any changes and recording of lead-II was done with Life-Pak 20- defibrillator and monitor at 0min, 3min, 15 min, 1hr and 2hr interval. QTc was calculated by using Bazett formula:

"QTc=QT/RR sq root"

QTc is defined to be prolonged when value exceed 470 ms in female but we analyzed the prolongation from the baseline value (0min). Residual effect of muscle relaxant was reversed with injection Glycopyrrolate 10mcg/kg i/v and injection Neostigmine 50mcg/kg i/v. In the post operative period patient was monitored for all vital signs, nausea, vomiting and pain. Another ECG was obtained at 2 hours (of giving study drugs) in the recovery

Fig 1. Graphical Representation of QTc Interval Prolongation in Group O, Group R & Group P

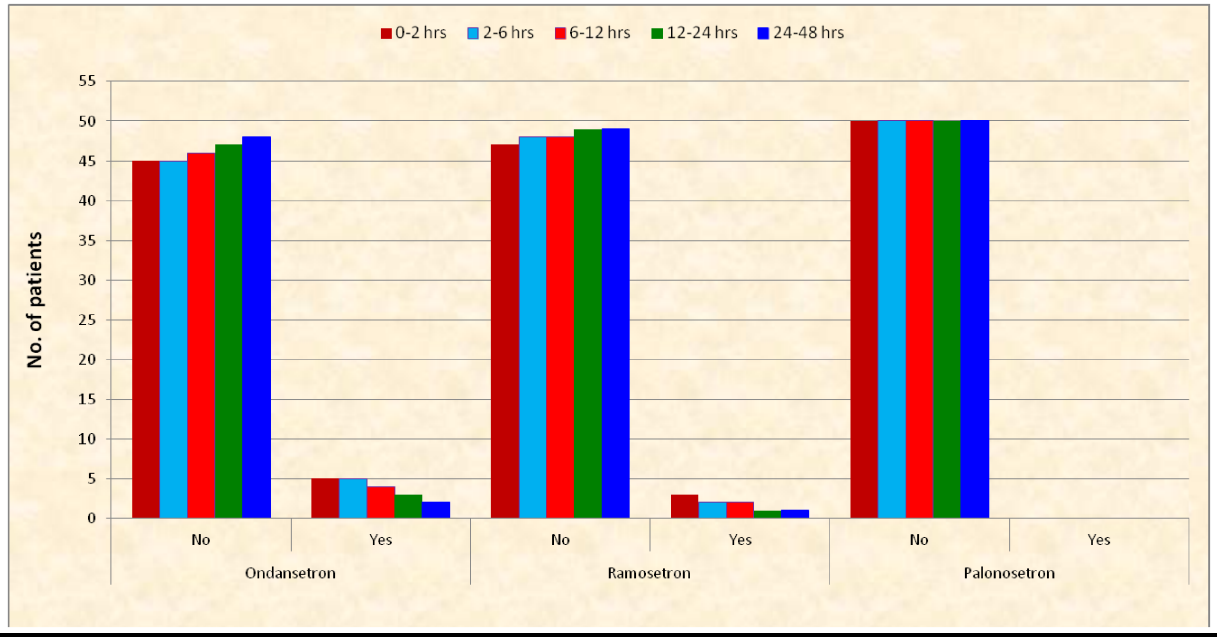

Table 1. Demographic Profile and Duration of Surgery

Parameters	Gr O (n=50) Mean ± S.D	Gr R (n=50) Mean ± S.D	Gr P (n=50) Mean ± S.D	P- Value
Age (years)	38.32 ±10.59	38.46 ± 9.15	38.94 ± 9.99	0.95 NS
Weight (kgs)	58.94 ± 5.09	59.04 ± 4.81	58.08 ± 5.84	0.61 NS
Duration of surgery	65.20 ± 12.90	71.22 ± 12.39	69.50 ± 11.92	0.06 NS

Table 2. Group comparison of VRS Score for Nausea

Time interval	VRS score for nausea (No. of patients)											
	Group O(n=50)				Group R (n=50)				Group P(n=50)			
	No	Mild	Moderate	Severe	No	Mild	Moderate	Severe	No	Mild	Moderate	Severe
0-2 hrs	45	5	0	0	46	4	0	0	48	2	0	0
2-6 hrs	46	4	0	0	48	2	0	0	48	2	0	0
6-12 hrs	42	8	0	0	44	6	0	0	50	0	0	0
12-24 hrs	37	9	4	0	44	4	2	3	50	0	0	0
24-48 hrs	39	9	2	0	41	3	5	1	50	0	0	0
Total (%)	83.6	14.0	2.4	0	89.2	7.6	2.8	1.2	98.4	1.6	0	0

Table 3. Group comparison of Vomiting

Time interval	(No. of patients)											
	Group O(n=50)				Group R(n=50)				Group P(n=50)			
	No	Mild	Moderate	Severe	No	Mild	Moderate	Severe	No	Mild	Moderate	Severe
0-2 hrs	46	3	1	0	40	10	0	0	48	2	0	0
2-6 hrs	48	2	0	0	46	4	0	0	49	1	0	0
6-12 hrs	47	3	0	0	43	7	0	0	48	2	0	0
12-24 hrs	33	17	0	0	44	5	1	0	50	0	0	0
24-48 hrs	31	12	6	1	37	2	8	3	50	0	0	0
Total (%)	82.0	14.8	2.8	0.4	84	11.2	3.6	1.2	98.0	2.0	0	0

Table 4. Group Comparison for QT Interval Prolongation

Time interval	QT INTERVAL CHANGES(No. of patients)						p-value	
	Group O(n=50)		Group R(n=50)		Group P(n=50)			
	No	Yes	No	Yes	No	Yes		
0min	50	0	50	0	50	0	0.082	NS
3 min	46	4	50	0	50	0	0.060	NS
15min	45	5	50	0	50	0	0.126	NS
1hr	47	3	49	1	50	0	0.168	NS
2hr	48	2	49	1	50	0	0.599	NS

room. Close monitoring was done for 48 hrs for complain of nausea, vomiting and side effects like headache, dizziness, drowsiness , myalagia at intervals of 0-2, 2-6, 6-12, 12-24 and 24-48 hours post surgery by direct questioning to the patient or to her attendant by the same anesthetist. Injection metoclopramide 10 mg i.v was used as rescue antiemetic.

Statistical Analysis

Statistical analysis of the data was done using student t-test and chi-square test using SPSS-16 software.

Table 5: Incidence of Adverse Effects

Parameters	Gr O (%)	Gr R (%)	Gr P (%)	P- Value
QTc interval	7,6	2.6	0	0.016
Drowsiness	9.6	6.0	1.2	0.035
Dizziness	7.2	5.2	0	0.031
Myalgia	7.6	3.6	0	0.018
Headache	8.8	7.2	2.0	0.106

Results

There was no statistically significant difference in all three groups with respect to age, weight and duration of surgery. we found that 83.6%, 89.2% & 98.4% of patients in group O, group R & group P didn't show any incidence of nausea and 82% in group O,84% in group R &98% in group P didn't have any incidence of vomiting. QTc unterval prolongation from baseline was also comparable in all groups, at all time intervals. Incidence of drowsiness, dizziness, myalagia & headache were 9.6%,7.2%,7.6% & 8.8% in group O,6.0%,5.2%,3.6% &7.2% in group R and 1.2%,0%,0% &2% in group P respectively, which was statistically insignificant.

Discussion

we observed that the three groups Ondansetron (Group O), Ramosetron (Group R) and Palonosetron (Group P) were clinically matched with respect to patients demographic data (Age , weight) and duration of surgery (P>0.05). (*Table 1*) Incidence of nausea was 1.6% in Palonosetron group,10.4% in Ramosetron group &16.4% in ondansetron group. (*Table 2*) Chattopadhyay *et al* (9) also showed that the severity of nausea was a lesser in Palonosetron group than Ramosetron group during the 2-24 and 24-48 h. On comparing the three groups with respect to vomiting, 98%, 84% and 82% in Group P, Group R and Group O respectively did not have any episode of vomiting. Kim S H *et al* (10) as well observed that the incidence of vomiting was lower in Palonosetron than in Ondansetron and Ramosetron and Kim S I *et al* (4) also reported no significant difference in the incidence of vomiting between the Ramosetron 0.3mg and ondansetron 8mg In our study QTc interval was prolonged from base line value at all time intervals in ondansetron group. [*Table 4]* A prolongation of QTc in patients receiving Inj Ondansetron was also observed by Charbit *et al* (7). Gupta K *et al* (11) observed that 1 mg i/v ondansetron effectively prevented PONV without causing prolongation of QTc interval whereas significant QTc prolongation was noted with 4mg and 8mg ondansetron given in healthy adult participants. Hafermann M J *et al* (12) concluded that i/v ondansetron in doses approved by FDA can significantly prolong QTc interval leading to Torsades de pointes in high risk cardiac patients. In Ramosetron we observed prolongation at 1hr & 2hr where as in Palonosetron group no patient showed prolongation. Lee J *et al* (13) in 2014 reported that prolongation of QTc interval with Inj Palonosetron might occur. The reason for this could be that they included patients who were concomitantly taking other drugs too, which we did not include in our study (as is cited in their article).Kim H J *et al* (14) showed that preanaesthetic administration of Palonosetron (0.075mg) did not affect the QTc interval during intraoperative period.

Though QTc interval was prolonged from the baseline levels in ondansetron group & Ramosetron group but statistically all the three groups were comparable and in no patient QTc interval was more than 470 ms [*Fig 1*] . ECG interval changes are a class effect of 5-Hydroxytryptamine 3 receptor antagonists. Theoretical concern regarding cardiovascular adverse events with these agents is not supported by clinical experience. The significant benefits of these agents outweigh the theoretical small risk of meaningful cardiovascular event (3). 5HT3 receptor antagonists, also have other side effects such as headache, dizziness, drowsiness and myalagia. In our study the three groups (O, R & P) showed no difference in the incidence of these side effects [*Table 5*] .These results are in accordance with the studies conducted by different authors (4, 15,16). Ansari M M *et al* (1) as well, reported that adverse effects were mild and transitory in nature and difference between Ramosetron and Ondansetron groups was statistically not significant. From result of our study side effects profile of Palonosetron seems to be superior as only 2% of patients experienced headache, 1.2% showed Drowsiness & no patient complained of dizziness and myalagia as compared to Ramosetron and Palonosetron [*Table 5*] .Bajwa S S *et al* (2) Also reported that Side

effect profile of Palonosetron is more favorable when compared to ondansetron.

Conclusion

We concluded that both i.v ondansetron & Ramosetron might induce the prolongation of corrected QT interval. However no patient in Palonosetron group showed an increase in QTc interval. Thus in high risk patients with cardiac disease Palonosetron might be a safer agent. Further research work needs to be done in evaluating the efficacy in patients with already prolonged QTc interval, albeit caution has to be taken while using these drugs in patients at high cardiac risk group and in all those medical situations which predispose to arrythmias. Other adverse effects e.g. headache, dizziness, drowsiness and myalagia with single i.v dose of study drugs are not of serious nature though side effect profile of Palonosetron seem to be superior

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