Changes in QTc Interval With Ondansetron vs Palonosetron in Prophylaxis of Postoperative Nausea and Vomiting In Subjects Undergoing General Anaesthesia – A Randomized Controlled Trial

MEDICAL SCIENCE

KEYWORDS : General anaesthesia, Ondansetron, Palonosetron, Postoperative nausea and vomiting, PONV, QTc interval.

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ABSTRACT

Aim: To evaluate two different doses of intravenous ondansetron and palonosetron in causing changes in QTc and also their effectiveness in preventing postoperative nausea and vomiting in patients undergoing general anaesthesia.

Patients & Methods: This prospective, randomized, double blind, placebo control study was done on a total 150 patients undergoing general anaesthesia. Patients were randomized to receive any one of the two doses of intravenous palonosetron (0.025mg, 0.075mg) [Grp.P0.025 & Grp.P0.075] or ondansetron (4mg, 8mg) [Grp. O4 & Grp.O8] or placebo immediately before induction. The primary end-point was to find the changes in QTc values from pre-injection to 5 minutes after injection of study drugs. Time needed for first rescue antiemetic medication was the secondary end point.

Results: Post-injection QTc values in all groups receiving ondansetron and palanosetron were found significantly higher than the placebo group. Grp. O8 recorded maximum QTc prolongation. Between 60 to 120 minutes of injection of study drugs, 93.33% of Group O4 and 23.33% of Group O8 patients required rescue antiemetic. Whereas first rescue antiemetic was not required in any patient of the palonosetron groups before 120mins and none of the patients of the Group P0.075 required any antiemetic before 240 mins.

Conclusion: The efficacy of intravenous palonosetron in controlling postoperative nausea vomiting and its safety profile in respect to QTc prolongation in patients under general anaesthesia is superior to that of intravenous ondansetron.

INTRODUCTION

The activation of nociceptors by pain produce changes in the central nervous system altering the threshold for emesis. HT3 receptor antagonists have higher receptor binding affinity and longer half-life and are thus considered 'gold standard' antiemetics in preventing post operative nausea and vomiting (PONV).[1]

Recent trials have highlighted incidences of antiemetic drug induced QTc interval prolongation and sudden cardiac death. It may be prudent therefore to select agents with least effect on the QTc interval in patients receiving general anaesthesia.[2]

Previous study by J Helmers et-all concluded that a single intravenous dose of 1mg, 8 mg and 16mg ondansetron is effective in preventing postoperative nausea and vomiting in 28%, 44% and 39% patients respectively compared to 29% patients receiving a placebo during the first 24 hour postoperative period.[3] Another trial revealed that there is no statistically significant difference in the QTc prolongation following intravenous administration of either 0.075mg droperidol or 4mg ondansetron[4,5] thus raising a question about the FDA's black box warning regarding droperidol[6]. Study on chemotherapy-induced nausea and vomiting concluded that palonosetron caused a significantly less prolongation of the QTc interval (1msec to 3 msec) than ondansetron or dolasetron (5 msec). Safety profile of palonosetron as a long acting anti-emetic agent has been studied and found favourable in the geriatric patients with multiple coexisting illnesses in the peri-operative period.[7]

The aim of the present study is to evaluate the effects of 4mg and 8mg bolus doses of intravenous ondansetron with that of 0.025mg and 0.075mg palonosetron relative to a placebo on the changes of QTc interval measured from pre-injection to 5 minutes post injection values and efficacy of the drugs in prevention of postoperative nausea and vomiting determined by the time needed for first rescue antiemetic in adult patients undergoing general anaesthesia.

PATIENTS AND METHODS

This prospective randomized, placebo controlled, double- blind study was carried out following approval of the institutional ethics committee. One hundred and fifty adult patients of ASA physical status I and II, on no medication, with normal baseline electrocardiograms were selected for this study.

Patients scheduled to undergo elective inpatient gynaecological surgery (vaginal hysterectomy), skin grafting, and breastsurgery (except aesthetic/cosmetic plastic surgery) were selected. Surgery was expected to be completed within 1hr and patients were scheduled to be hospitalized for at least 72 hr after surgery.

Patients with evidence of uncontrolled clinically significant neurological, renal, hepatic, cardiovascular, metabolic or endocrine dysfunction; patients with at least one of the following risk factors for PONV i.e history of PONV or prone to motion sickness;

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had received cancer chemotherapy within 4 wk or emetogenic radiotherapy within 8 wk before study entry; anticipated difficulty in maintaining bag-mask ventilation or endotracheal intubation, VAS> 4 at extubation; not responding to verbal commands after extubation and nasogastric tube in-situ postoperatively were excluded from the study.

Sample size estimation was based on a previous pilot study with incidence of 60% postoperative nausea vomiting in untreated patients. A pre-study power analysis was computed which revealed that a minimum of 30 patients per group would be required to verify this difference for 95% confidence limit and 90% power of the test.

Total 150 patients were randomly allocated into five groups with thirty patients in each group through a computer generated random number and was administered injection normal saline (Group C) in placebo group, injection ondansetron 4mg (Group O4), injection ondansetron 8mg (Group O8), injection palonosetron 0.025 mg (Group P 0.025) and injection palonosetron 0.075 mg (Group P0.075).

All the patients were premedicated with oral lorazepam 0.04mg/kg and omeprazole 40 mg on the night prior to the day of operation. Following overnight fasting, before arrival in the operating room a baseline lead II ECG was taken. After receiving the patients into OT an intravenous infusion of lactated Ringer's solution was started. 5-lead ECG, NIBP, $ETCO_2$, BIS and temperature monitors were attached. Study medications were loaded in 10 ml glass syringes and all diluted to 10 ml in normal saline and administered as slow intravenous injection before induction. After pre-oxygenation, patients were induced with injection thiopentone sodium 5mg/kg, injection fentanyl 2µg/kg. Injection vecuronium 0.1 mg /kg was administered after achieving BIS between 45 and 55. Continuous positive pressure ventilation was continued using 50% N_2O in O_2 with isoflurane maintaining BIS value between 45 and 50. HR, NIBP, SpO_2%, $EtCO_2$, temperature changes were monitored and maintained within normal values. Before intubation and five minutes after the injection of study drug ECG in lead II was taken (primary end point of study). Endotracheal intubation was done thereafter. Anaesthesia was maintained with 50% nitrous oxide in oxygen and isoflurane along with top up doses of injection vecuronium and fentanyl. Neuromuscular function was monitored using TOF. Ventilation was adjusted to maintain normocapnoea. Residual neuromuscular blocking agent was reversed with Inj. Neostigmine along with 10µg/kg Inj. Glycopyrrolate after fulfilling the criteria of extubation. VAS for pain was recorded following extubation. Duration to first rescue antiemetic was noted in each group till 360 minutes into the post-operative period (secondary endpoint of study).

Intra-operatively all the data were recorded by an independent observer blinded to the study drugs. Data recorded were NIBP, HR, SpO2%, EtCO2, BIS, before, during and after injection of study drugs at different time intervals throughout the anaesthetic procedure. Duration of anaesthesia, intra-operative blood loss, intravenous fluid and total amount of fentanyl, isoflurane administered, bispectral index (BIS) were recorded.

QT interval changes were monitored in lead II and changes from preoperative base line values (pre-injection) to 5 minutes after injection (post-injection) were noted for each patient. Heart rate was noted at that particular point for each patient. QTc was calculated by the Bazett's formula as $QTc = QT/\sqrt{RR}$[8]. QT interval is accepted as prolonged when QTc values exceeded 440 msec.

Intravenous metoclopramide 10 mg was used as rescue antiemetic. Adverse events, if any, were recorded. Treatment arrangements were kept ready for any precipitated arrhythmias included β blockers & anti-arrhythmics, anti-bradycardia pacing, external cardioverter-defibrillator.

For statistical analysis, all the data were entered into an excel spreadsheet and were analysed using standard statistical software like SPSS version 16 (SPSS Inc, Tulsa Oklahoma) and Statistica 6.0 (2005). Chi- square test was used for categorical variables. All numerical data were presented as mean ± standard deviation. Parametric data were analysed using one way analysis of variance test (ANOVA) followed by Post Hoc Bonferroni test for individual analysis between 2 groups. All tests were two tailed. A *p* value of less than 0.05 was considered statistically significant.

RESULTS

Table I shows no significant differences among the groups with respect to demography, duration of anaesthesia and the type of surgery performed. The groups were also found comparable in terms of hemodynamic (Heart Rate, Mean Blood Pressure) and other anaesthetic parameters like BIS score, Fentanyl Doses and Isoflurane requirements.

Table 1. Demographic profile of the study groups

	Gr. C control ,n=30	Gr.O4 n=30	Gr.O8 n=30	Gr p 0.2 n=30	GR P 0.075 n=30
Age(yr)	36 ± 5.5	40 ± 6.2	42 ± 1.4	34 ±4.6	41 ± 5.1
Sex(M:F.)(%)	45 : 55	42: 58	54:46	51:49	48:52
BMI (Kg / m2)	21 ± 2..1	22 ± 0,22	21.4 ± 0.86	20.8± 1.12	20.8±0.9
Duration of anaesthesia (min) ± SD	35± 8.3	40 ± 15.4	50 ± 8.2	45 ± 12.3	40 ± 10.3
Types of surgery performed (%)					
1.Breast surgery(%)	21	29	31	29	30
2.Vaginal hysterectomy (%)	33	28	24	25	26
3.Skin grafting surgery (%)	18	24	22	21	28
4.Reconstructive surgery (%)	28	19	23	25	16

Table 2 shows the distribution of patients according to the time interval of incidence of post-operative nausea and vomiting requiring rescue anti-emetic drug. It is seen that 28 (93.3%) patients of Grp O-4 required anti-emetic within 120 minutes and

25 (83.3%) of patients of Grp O-8 received the same within 240 minutes. Whereas 9 (30.3%) patients of Grp P-0.025 and none from Grp P 0.075 required antiemetic within 240 minutes.

Table 2. Distributions of patients of different study groups according to the time required for the rescue anti-emetic

	1min	3min	5min	10min	15min	20min	40min	60min	120min	240min	360min
Gr. C	0	0	0	0	0	0	0	29	1	0	0
Gr O4	0	0	0	0	0	0	0	0	28	2	0
Gr O8.	0	0	0	0	0	0	0	0	7	18	5
Gr.P 0.025	0	0	0	0	0	0	0	0	2	7	21
Gr P 0.075.	0	0	0	0	0	0	0	0	0	0	23

Table 3 shows the frequency analysis by mean, median standard deviation, variance and range of the QTc in the pre-injection and post-

injection period within the groups.

Table 3 : Frequency analysis of Pre-injection (PrI) and Post-injection(PoI) QTc values(mm) in study groups

Sr. no	Group		Mean	Median	Std. Deviation	Variance	Range	Minimum	Maximum
1	Gr.C n=30	Pr I	0.335	0.34	0.032	0.001	0.1	0.3	0.4
		Po I	0.38	0.35	0.03	0.001	0.09	0.29	0.38
2	Gr.O4 n=30	Pr I	0.35	0.35	0.035	0.001	0.12	0.29	0.41
		Po I	0.39	0.39	0.037	0.001	0.13	0.33	0.46
3	Gr.O8 n=30	Pr I	0.37	0.37	0.049	0.002	0.16	0.29	0.45
		Po I	0.46	0.46	0.03	0.001	0.11	0.4	0.51
4	Gr.P0.025 n=30	Pr I	0.35	0.36	0.039	0.002	0.16	0.29	0.45
		Po I	0.4	0.39	0.036	0.001	0.13	0.33	0.46
5	Gr.P 0.075 n=30	Pr I	0.36	0.36	0.034	0.002	0.16	0.29	0.45
		Po I	0.41	0.40	0.04	0.001	0.1	0.4	0.5

Table 4 shows intra-group analysis of the pre-injection and post-injection QTc values. In control group (Grp C) there is no significant difference between the preinjection QTc and the postinjection QTc as seen by a P value-0.567(>0.05). However among all the other study groups the difference is significant (P<0.05)

Table 4 Paired Sample t-Test for the difference between pre-injection(PrI) and post-injection(PoI)QTc values within study groups

	Grp C N=30	Grp O 4 N=30	Grp O 8 N=30	Grp P 0.025 N=30	Grp P 0.075 N=30
Sig. (2-tailed) P value for difference between PrI&PoIQTc	0.567 (>0.05)	<0.05	<0.05	<0.05	<0.05

Inter group analysis of the pre-injection and post-injection QTc values were done by ANOVA to test for any significant differences between study groups. The post-injection QTc values showed significant differences and hence were further subjected to Post-hoc Bonferroni test to compare each pair of groups as shown in *Table 5*. Significance was found in comparison between control group and all other study groups and also the values of Grp O 8mg revealed significant differences with rest of the groups.

Table 5 Post-hoc Bonferroni Test for post-injection QTc values of study groups

Dependent variable.	(I) Group	(J) Group	Mean Difference (I-J)	Std Error	Sig	95% Confidence interval	
						Lower bound	Upper bound
Po I Bonferroni	GrC	Gr O4	-0.056	0.00879	0.000	-0.0811	-0.0309
		Gr O8	-0.120	0.00879	0.000	-0.1457	-0.0956
		Gr P 0.025	-0.058	0.00879	0.000	-0.0837	-0.0336
		Gr P 0.075	-0.073	0.00879	0.000	-0.0987	-0.0486
	Gr.O4	GrC	0.056	0.00879	0.000	0.0309	0.0811
		Gr O8	-0.064	0.00879	0.000	-0.0897	-0.0396
		Gr P 0.025	-0.002	0.00879	1.00	-0.0277	0.0224
		Gr P 0.075	-0.017	0.00879	0.463	-0.0427	0.0074
	Gr.O8	Gr C	0.120	0.00879	0.000	0.0956	0.1457
		Gr O4	0.064	0.00879	0.000	0.0396	0.0897
		Gr P 0.025	0.062	0.00879	0.000	0.0369	0.0871
		Gr P 0.075	0.047	0.00879	0.000	0.0219	0.0721
	Gr.P0.025	Gr C	0.058	0.00879	0.000	0.0336	0.0837
		Gr O4	0.002	0.00879	1.00	-0.0224	0.0277
		Gr O8	0.062	0.00879	0.000	-0.0871	-0.0369
		Gr P 0.075	0.015	0.00879	0.901	-0.0401	0.0101
	Gr.P0.075	Gr C	0.073	0.00879	0.000	0.486	0.0987
		Gr O4	0.017	0.00879	0.463	-0.0074	0.0427
		Gr O8	0.047	0.00879	0.000	-0.0721	-0.0219
		Gr P 0.025	0.015	0.00879	0.901	-0.0101	0.0401

DISCUSSION

Postoperative nausea and vomiting continues to pose problems for surgical patients. However, emerging differences among the various anaesthetic and non-anaesthetic agents suggest that the incidence and/or intensity of adverse events should not be regarded as a class effect. Rather the side-effect profiles of individual drugs need to be considered separately along with comorbid conditions of the patient.

A prolonged electrocardiographic QT interval may be harmful during general anaesthesia. It is prudent therefore, to select anaesthetic agents with least effect on the QT interval.

Simon D Whyte et-all in their study examined the effects of propofol and sevoflurane on QTc and TDR(Transmural dispersion of Repolarization) as a predictor of Torsedes in children.[9] Sevoflurane, isoflurane and thiopentone have been reported to prolong QTc but the clinical significance remains unclear and usually concluded that anaesthesiologists should be aware of a potential increased risk of Torsedes de Pointes with these drugs. In this context the purpose of the present study is to evaluate the effect of different doses of ondansetron and palanosetron on QTc interval during the induction of general anaesthesia excluding the confounding adrenergic stimulation of airway manipulation or surgery.

Palonosetron is a 5-HT_3 receptor antagonist with a greater binding affinity and longer half-life than older 5-HT_3 antagonists. Studies suggest that palonosetron interacts with 5-HT_3 receptors in an allosteric, positively cooperative manner at sites different from those that bind with ondansetron and granisetron and this may be associated with long-lasting effects on receptor-ligand binding and functional responses to serotonin.

In our present study except the placebo group, all the other groups i.e. Gr.O4, Gr.O8, Gr.P0.025 and Gr. P0.075 revealed a significant difference among the pre-injection QTc and the post-injection QTc readings as seen by the *P* value. This might indicate a need for routine QT analysis in preoperative check-up for the patients undergoing general anaesthesia to prevent additive QT dispersion to that can lead to dreaded arrythmias.

Inter-group analysis showed significant differences in post- injection QTc values in all study groups compared to control. Although no significant difference was found amongst the post-injection QTc values of Grp O4, Grp P0.025 and Grp P0.075, the ondansetron 8mg group (Grp O8) produced significantly higher QTc values compared to all other study drug groups and even recorded values higher than the accepted normal upper limit of QTc interval (440msec).

In respect to the efficacy of the study drugs in preventing PONV it was found that majority of patients in control group required rescue anti-emetic within 60 minutes. 93.3% patients of Grp O4 required anti-emetic within 120 minutes and 83.3% of patients of Grp O8 received the same within 240 minutes. Consistent with the long duration of action of palanosetron as found in earlier studies our study also showed only 30% patients of Grp P0.025 and none from Grp P0.075 required any antiemetic within 240 minutes.

CONCLUSION

A lower dose of ondansetron (4mg) was found ineffective in controlling PONV in most of the patients. Although higher dose of ondansetron (8mg) produced better control of PONV but it was found to be related to significantly higher QTc prolongation compared to other study groups. A single intravenous dose of 0.075-mg of palonosetron significantly reduced the severity of nausea and emesis in comparison to ondansetron 8 mg and produced lesser QTc prolongation as well. The efficacy intravenous

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palonosetron (0.075mg) in controlling postoperative nausea vomiting and its safety profile with respect to QTc prolongation in patients under general anaesthesia is superior to that of intravenous ondansetron.

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