

# Comparative electrocardiographic effects of intravenous ondansetron and granisetron in patients undergoing surgery for carcinoma breast: A prospective single-blind randomised trial

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## ABSTRACT

**Background:** Postoperative nausea and vomiting (PONV) are common and distressing symptoms after surgery performed under general anaesthesia. 5-hydroxytryptamine<sub>3</sub> antagonists are routinely used for prevention and treatment of PONV. The aim of our study was to compare the incidence of QTc prolongation and quantify the amount of QTc prolongation with ondansetron and granisetron. **Methods:** This prospective, randomised, single-blind study was carried out in the OT and Recovery Room (RR) of a tertiary referral cancer centre. After obtaining Institutional Review Board approval and written informed consent from the patients, 70 patients undergoing elective surgery for carcinoma breast were included. In the RR, patients randomly received 8 mg of ondansetron or 1 mg of granisetron intravenously. Serial ECGs were recorded at various intervals, Non-invasive blood pressure and SpO<sub>2</sub> were also recorded. Chi-square test and Mann-Whitney test were used for statistical analysis. **Results:** The demographics were similar in both groups. The incidence of significant QTc prolongation was significantly higher in the ondansetron group (22 of 37 (59.4%) vs. 11 of 33 patients (33.33%) ( $P < 0.05$ )). There was an increase in the QTc interval in both the groups as compared to the baseline. The median prolongation in QTc interval from baseline was much more in the ondansetron group; this was statistically significant only at 5 and 15 min. **Conclusion:** Granisetron may be a safer option than ondansetron for prevention and treatment of PONV due to lesser prolongation QTc interval. (ClinicalTrials.gov ID: NCT01352130)

**Key words:** 5-hydroxytryptamine<sub>3</sub> antagonists, granisetron, ondansetron, postoperative nausea and vomiting, QTc interval

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Website: [www.ijaweb.org](http://www.ijaweb.org)

DOI: 10.4103/0019-5049.108560

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## INTRODUCTION

Postoperative nausea and vomiting (PONV) are common and distressing symptoms after surgery performed under general anaesthesia, with an incidence as high as 60%.<sup>[1]</sup> Female patients experience PONV more often and it is more severe than that experienced by male patients.<sup>[2]</sup> Moreover, the phase of the menstrual cycle influences the incidence of PONV.<sup>[3]</sup> A variety of antiemetic strategies have been tried to prevent and treat PONV. Currently 5-hydroxytryptamine<sub>3</sub> (5HT<sub>3</sub>) antagonists like ondansetron, granisetron and dolansetron are the

“gold standard” antiemetics because of their safety and efficacy compared to other alternatives.<sup>[4]</sup> But these drugs are known to produce multiple effects on the electrocardiogram and in particular prolong the Q-T interval, heart rate corrected (QTc).<sup>[5,6]</sup> The overall ECG changes and specifically QTc prolongation are serious side effects which are rare but with possibility of fatal arrhythmias polymorphic ventricular tachycardia (*torsade de pointes*). The comparative effects of the 5HT<sub>3</sub> antagonists on QTc interval are not well studied. Ondansetron is cheaper but shorter acting, while granisetron is longer acting but more expensive. Our aim was to compare the incidence

**How to cite this article:** Ganjare A, Kulkarni AP. Comparative electrocardiographic effects of intravenous ondansetron and granisetron in patients undergoing surgery for carcinoma breast: A prospective single-blind randomised trial. Indian J Anaesth 2013;57:41-5.

of QTc prolongation and quantify the amount of QTc prolongation with ondansetron and granisetron.

## METHODS

This prospective, randomised, single-blind study was conducted after Institutional Review Board approved the study protocol, consent form and the randomisation form, in the operating rooms and Recovery Room (RR) of a tertiary referral cancer institute. Seventy consecutive ASA I-III patients (age 18-60 years) undergoing breast surgery for carcinoma breast were included in the study after obtaining written informed consent. Patients refusing consent, those having baseline prolonged QTc interval, with arrhythmias or conduction defects, and those with abnormal serum levels of potassium, calcium, and magnesium were excluded. Anaesthesia technique was not standardised. The technique of induction of anaesthesia, maintenance and reversal of anaesthesia was left to the discretion of the staff anaesthetist in the operating theatre. The data on comorbidities, preoperative medications for the comorbidities, premedication, induction agents, analgesics, muscle relaxants and inhalation agents were collected.

The patients ( $N=70$ ) were divided into two groups by computer-generated random numbers by the statisticians in the Clinical Research Secretariat (CRS) in our institute. Block randomisation was done with blocks of 10 to allow stratification of the patients depending on whether they had received anthracycline-based neoadjuvant chemotherapy. The list of randomisation numbers and clinical details was maintained in the CRS.

Postoperatively, once the patient arrived in the recovery room, one of the investigators called the CRS on phone, after completing the randomisation form and gave the patient details. The statistician allocated the drug the patient should receive, which was then prepared by the investigator, either ondansetron 8 mg (group O) or granisetron 1 mg (group G). A baseline 12-lead electrocardiogram was obtained before the drug was administered. After baseline ECG, patients in group O were given intravenous (i.v.) 8 mg ondansetron and patients in group G were given 1 mg granisetron over 30 s. Subsequently, serial 12-lead ECGs were done at 2 min, 5 min, 15 min, 1 h and 2 h. Pulse, blood pressure and SpO<sub>2</sub> were also monitored at those intervals. Unfiltered electrocardiograms were recorded at paper speed of 25 mm/s and at normal

amplitude with an HP Vigilent Pagewriter 100™ device which automatically calculates and prints the heart rate and the duration of various ECG intervals. The investigators independently read and analysed the ECG to confirm that the intervals obtained with the ECG machine were indeed accurate. QT and R-R intervals were measured for calculation of corrected QT (QTc) interval. The corrected QT (QTc) interval was calculated by using the formula described by Bazette ( $QTc=QT \text{ interval}/\sqrt{RR \text{ interval}}$ ).

## Statistical analysis

A sample size calculation was performed (according to mean changes (difference of means) in QTc interval) to find out the number of patients needed to find a significant difference between the two drugs. To detect a QTc change from baseline of greater than 5 ms with  $\alpha$  and  $\beta$  error of 0.05 and 0.20, respectively, and assuming a Standard Deviation (SD) of QTc change of 10 ms, using a one-sided test, a minimum of 35 subjects were needed in each group.

Chi-square test and Mann-Whitney test were used for comparing variables (SPSS version 16). A  $P<0.05$  was considered statistically significant.

## RESULTS

Seventy patients with carcinoma breast scheduled to undergo elective surgery were included in the study after obtaining written informed consent. Preoperatively no patient was on drugs that prolongs QT interval. Of these 70 patients, 37 patients were randomised to receive i.v. ondansetron while 33 were randomised to receive granisetron. In the ondansetron group, one patient was not administered the medication as his baseline QTc was  $>500$  ms. There were no differences in the groups when compared for age, male to female ratio, average duration of anaesthesia, preoperative comorbid conditions and number of patients who had received anthracycline-based chemotherapy (17 of 37 in group O vs. 16 of 33 in group G) [Table 1]. Preoperative serum electrolytes were normal in all patients. The number of patients receiving propofol and thiopentone was similar in both the groups. All patients received isoflurane during the procedure. None of these patients were on treatment with antiarrhythmic drugs. The heart rate, blood pressure and oxygen saturation were similar in the two groups for 2 h after administration of study drugs. The mean QTc duration was similar throughout in both the groups at each time interval [Table 2]. We

then compared the prolongation of QTc intervals after administration of the study medication in two ways. We assumed prolongation of QTc beyond 440 ms to be significant.<sup>[7]</sup> Higher number of patients in ondansetron group, i.e., 22 of 37 (59.45%) (granisetron 11 of 33 patients (33.33%)), had clinically significant prolongation (i.e., beyond 440 ms) in the QTc interval ( $P<0.05$ ) [Table 3]. The maximum QTc interval measured was 513 ms in ondansetron group and 491 ms in the granisetron group. The QTc prolongation persisted even at the end of 2 h in one patient each in both groups, while QTc interval returned to baseline at the end of 2 h in all other patients. No ventricular arrhythmias were noted in either group.

We also compared the qualitative difference of drugs on the QTc interval, i.e., the difference in QTc interval from baseline. Since the difference in QTc prolongation (i.e., from any time point to baseline) was not satisfying test of normality (i.e., Kolmogorov-Smirnov test), we used Mann-Whitney test (a non-parametric test) to compare median QTc changes between the ondansetron and granisetron groups. The median difference, which may have been either prolongation or shortening, in QTc intervals was compared to baseline, i.e., before administration of study medication. There was an increase in the QTc interval in both the groups when compared to the baseline [Table 4]. The prolongation appeared at 2 min after administration of the study medications and the QTc remained prolonged up to an hour. Qualitatively the prolongation in QTc intervals was much more in the ondansetron group, when compared with granisetron group. However, this prolongation was statistically significant only at 5 min and 15 min. The median QTc interval actually shortened in the patients from the granisetron group.

## DISCUSSION

In this study, we compared the effect of i.v. ondansetron and granisetron on the electrocardiogram, with particular reference to the QTc interval. All patients were scheduled to undergo elective surgery for carcinoma of breast under general anaesthesia. We found a statistically significant difference in the incidence of QTc prolongation (to >440 ms) in patients who were given ondansetron. The QT interval is an ECG measurement of the time between the earliest ventricular activation and termination of ventricular recovery. It is influenced by adrenergic stimuli, heart rate and drugs. Because the QT interval includes

**Table 1: Demographics, comorbidities, anthracycline-based chemotherapy and anaesthetic technique**

Variable	Group O (n=37)	Group G (n=33)	P value
Age (years)	47.14±9.2	52.27±13.8	0.076
Weight (kg)	56.24±8.9	56.24±9.5	1.000
Hypertension (yes)	6	8	0.551
Diabetes mellitus (yes)	3	2	1.000
Propofol (no. of pts)	20	17	0.76
Thiopentone (no. of pts)	17	16	0.55
Duration of surgery (min)	92±20	96±30	0.739
Anthracycline-based chemotherapy (yes)	17	16	1.000

**Table 2: Comparison of corrected QT interval (ms) at each time point**

Time	Group O (Mean±SD)	Group G (Mean±SD)	P value*
0 min	401.62±36.417	405.85±32.900	0.614
2 min	416.64±45.120	411.70±36.155	0.619
5 min	416.39±41.164	414.61±30.897	0.841
15 min	410.97±46.894	405.39±32.180	0.570
1 h	409.72±42.273	410.09±28.685	0.967
2 h	400.42±36.808	405.55±26.960	0.515

\*Mann=Whitney test

**Table 3: Incidence of corrected QT prolongation**

Group	Pts with prolonged QTc (%)*	Pts without prolonged QTc (%)	Total
Ondansetron	22 (59.45)	15 (40.55)	37
Granisetron	11 (33.33)	22 (66.67)	33
Total	33	37	70

$P<0.05$  (Chi-square test), \*Denotes patients with QTc prolongation beyond 440 ms

**Table 4: Change in corrected QT interval from baseline**

QTc difference	Group O Median (IQR)	Group G Median (IQR)	P value*
2 min	8.0000 (0, 18.5)	2.0000 (-7, 10)	0.069
5 min	9.5000 (0.25, 18.75)	2.0000 (-11, 8.5)	0.007 <sup>§</sup>
15 min	4.0000 (-3.5, 21.5)	-2.0000 (-7.5, 3.5)	0.027 <sup>§</sup>
1 h	0.5000 (-12.75, 10.75)	-5.0000 (-16, 7)	0.307
2 h	-6.5000 (-17, 3.00)	-6.0000 (-19, 5)	0.909

<sup>§</sup> $P<0.05$ , \*Mann=Whitney test

ventricular depolarisation, it's role as a measurement for ventricular repolarisation may be limited. It may be difficult to distinguish the terminal portion of the T waves from U waves. Another limitation is that a single ECG lead may not be sensitive to non-uniform recovery of excitation in local cardiac regions. Prolongation of the QT interval is associated with an increased risk of ventricular tachyarrhythmias in patients with the congenital long QT syndrome and other cardiac diseases.

Patients undergoing surgery for carcinoma of breast are known to have extremely high incidence<sup>[1]</sup> (60%)

of PONV and are routinely given 5HT<sub>3</sub> antagonists. The duration of surgery is quite short (up to 2 h) and patients are unlikely to become hypothermic. Hypothermia, which is a known factor<sup>[8]</sup> for prolongation of QTc interval, could not thus confound our findings. Normally antiemetic drugs are administered intraoperatively; however, we elected not to do so for two reasons. Firstly, it would have been difficult to obtain a baseline electrocardiogram intraoperatively. Secondly, many i.v. and volatile anaesthetic agents such as propofol, thiopentone, isoflurane and sevoflurane are known<sup>[9,10]</sup> to cause QTc prolongation; and the effects of the anaesthetic agents would have thus confounded our findings.

The current standard of care for carcinoma breast entails preoperative anthracycline-based neoadjuvant chemotherapy. A large number of our patients scheduled for surgery for carcinoma of breast will thus have received anthracycline. In the current study, 33 out of 70 patients had received anthracycline as part of their chemotherapy regimen preoperatively. Anthracycline itself is known to predispose the patient to prolongation of QTc interval.<sup>[11]</sup> If the anaesthesia technique or other drugs such as antiemetic drugs further prolong QTc intervals, these patients will be at a higher risk for development of potentially fatal ventricular arrhythmias. Normally the antiemetic drugs are given without the ECG monitoring. Other factors, such as pain or stress-induced sympathetic stimulation or perioperative electrolyte changes in potassium and magnesium, may be responsible for prolongation of ventricular repolarisation.

In the present study, we excluded patients with preexisting evidence of myocardial disease, and endocrine or metabolic disturbances. We did baseline ECGs to exclude those with preexisting prolongation of QTc interval, and one such patient was excluded from the study (ondansetron group-baseline QTc interval 510 ms). We found higher incidence of prolongation of QTc interval with ondansetron than granisetron which was transient and reversible. In fact, there was a shortening of QTc interval when compared to baseline in patients in granisetron group. In a recent study<sup>[12]</sup> of patients hospitalised with heart failure and acute coronary syndrome, ondansetron prolonged QTc duration in 31-46% of patients. This prolongation lasted an average of 120 min.

Kuryshv *et al.*<sup>[13]</sup> studied the effect of 5HT<sub>3</sub> antagonists on human cardiac channels. They found ondansetron

causes more profound blockade of Human Ether-à-go-go Related Gene (HERG) K<sup>+</sup> channel than granisetron in a concentration-dependant manner. Blockade of HERG K<sup>+</sup> channel is responsible for prolongation of ventricular repolarisation and thus prolongation of QT interval, while Na<sup>+</sup> channel is more potently blocked by granisetron than ondansetron. This Na<sup>+</sup> channel blockade is responsible for prolongation of ventricular depolarization and is likely to cause QRS widening. Thus, 5HT<sub>3</sub> antagonists were responsible for lengthening of both ventricular depolarisation and repolarisation.<sup>[13]</sup>

Our findings of significant prolongation of QTc interval caused by ondansetron are similar to those reported by Benedicts and colleagues.<sup>[14]</sup> They reported a significant increase in QTc interval following administration of 32 mg of i.v. ondansetron and a decrease in heart rate. The heart rates in our patients did not decrease probably because the doses used by us were not very large. Though we do not routinely use such high doses in the perioperative period, high doses are very often used for treatment of intractable vomiting in patients receiving chemotherapy in our hospital. Charbit *et al.* also demonstrated that ondansetron alone and in combination with droperidol prolonged QTc interval when used in prevention of PONV<sup>[15]</sup> and in volunteers.<sup>[16]</sup> Other studies have also reported that the mean post-dose QTc interval for ondansetron was significantly greater than that for granisetron.<sup>[17]</sup> We did not find a significant change in mean heart rate and mean PR interval in either group. The QTc effects caused by the study medications were short lived, and in most patients, the QTc had returned to baseline by 2 h. This is contrary to the finding of other studies which have reported more prolonged effect (4-8 h) of ondansetron and dolaseron.<sup>[11]</sup> Other researchers<sup>[18,19]</sup> have also reported minimal effects of granisetron on cardiac rhythm, QRS duration, or QTc intervals. They observed minor changes in the PR time following i.v. injection of granisetron, which does not seem to be of clinical relevance. We did not find ventricular arrhythmias in either group. However, with both ondansetron and granisetron, cardiac arrhythmias have been reported.<sup>[6,20,21]</sup>

## CONCLUSION

We found that there was an increased incidence of QTc prolongation in patients who received ondansetron than those who received granisetron, and qualitatively, the prolongation was less in patients

receiving granisetron. Though none of our patients had arrhythmias and we did not compare other side effects of either drugs, it is may be safer to use granisetron particularly if the patient has preexisting QTc prolongation.

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**Source of Support:** Nil, **Conflict of Interest:** None declared

## Announcement

### Dr. TN Jha and Dr. KP Chansoriya travel grant

From the year 2011, the Dr. TN Jha and Dr. KP Chansoriya travel grant will be awarded to the participants from 15 states. All the states can select their candidate during their annual conference and send them with the recommendation of the Secretary. Only one candidate is allowed from each state. In case, if two states have a combined annual meet but separate as per the records, have to select one candidate from each state. If more than 15 states recommend the candidates for the award, selection will be made on first come first served basis.

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