Evaluation of Ondansetron-induced QT interval prolongation in the prophylaxis of postoperative emesis

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Abstract

Background: To avert nausea and vomiting the 5-Hydroxytryptamine3 (5-HT3) antagonists have become the first line of treatment ifassociated with cardiovascular effects andappear to cause QT prolongation. **Objective:** Evaluate the effect of 1 mg, 4 mg, and 8 mg bolus doses of intravenous Ondansetron, relative to placebo, in prevention of postoperative nausea and vomiting (PONV) and to find out the changes of QT interval corrected for heart rate (QTc). **Materials and Methods:** This prospective randomized, placebo-controlled, double-blind study was carried out among 136 adult participants of both sexes in a tertiary care postgraduate teaching institute at Kolkata. mg, 4 mg or 8 mg inj. Ondansetron was diluted to 10 ml with normal saline, was infused 30 min before extubation in relation with a control group. Time to first rescue antiemetic medication and in QTc interval at different time intervals, in each group was noted in different in the various surgical operation theaters (OTs). **Results:** Requirement of the first rescue antiemetic in the postoperative period between 60 to 120 min in the mg, 4 mg or 8 mg Ondansetron groups was in 28%, 24% and 7% participants respectively; between 120 to 240 min in 63%, 72% and 57% respectively; and within 360 min in 9%, 4% and 36% respectively. Significant and maximal QTc prolongation was observed in the participants with mg or 8 mg Ondansetron 3 and 5 min of drug administration. **Conclusions:** One mg Ondansetron in healthy adult participants can effectively prevent PONV causing no or insignificant prolongation of QTc interval.

Key words: Ondansetron, postoperative nausea vomiting, QT interval corrected for heart rate

INTRODUCTION

Postoperative nausea and vomiting (PONV) can cause considerable distress and discomfort to participants undergoing surgery. Several classes of antiemetic agents exist to combat these side-effects, though the 5-HT₃ receptor antagonists have become the first line of treatment

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and are considered the "gold standard" in antiemetic therapy.^[1] Compared with the older generation antiemetic drugs, 5-HT₃ receptor antagonists are effective, well tolerated, and associated with few side-effects.

Most research on the 5-HT3 receptor antagonists has been performed with Ondansetron, which has greater antivomiting than antinausea effects.^[2]

Not all surgical patients will benefit from antiemetic prophylaxis; thus, identification of patients who are at increased risk is imperative.^[3]

Indeed, Ondansetron is associated with cardiovascular effects, appears to cause QT interval corrected for heart

rate (QTc) prolongation similar to that with Droperidol; Droperidol and Ondansetron induced similar clinically relevant QTc interval prolongations. When used in the treatment of PONV, a situation where prolongation of the QTc interval seems to occur, the safety of 5-hydroxytryptamine Type 3 antagonists may not be superior to that of low-dose Droperidol. Thus Ondansetron should be used with extreme caution in participants who suffer from or may develop prolongation of cardiac conduction intervals, thereby requiring dose adjustment. The QTc interval is a reflection of the action potential in the cardiac cells. Homogenous or heterogeneous changes in the duration of action potential lead to alteration of QTc interval. Repolarization disorders are responsible for life-threatening arrhythmias like torsades de pointes. Repolarization like torsades de pointes.

The effect of a single intravenous dose of 1 mg, 8 mg, 16 mg Ondansetron in preventing PONV was investigated in a randomized, double-blind, placebo-controlled, multicenter, international study and it showed that the maximum number of participants experienced no postoperative emesis in the 8 mg Ondansetron recipient group than in the placebo group for the first 24-h postoperative period. [7]

The study showed that 2.7-3.5% QTc prolongation at 5 min after pre-induction injection of treatment medications, equal to 11.3 \pm 24.3 millisecond (ms) with 1.25 mg droperidol alone, and 9.9 \pm 34.7 ms with 4 mg Ondansetron alone.^[8]

A comparative study between droperidol (0.75 mg IV) and Ondansetron (4 mg IV) in adults with PONV showed that the maximal QTc prolongation with droperidol was 17±9 msec, occurring at 2 min after administration and with Ondansetron it was 20±13 msec, occurring after 3 min.^[9]

Ondansetron is effective in the prevention and treatment of PONV associated with surgery. Yet, QTc prolongation by 1 mg Ondansetron has not yet been properly analyzed, though its prophylactic antiemetic effect was studied. We therefore aimed to evaluate the effect of 1 mg, 4 mg, and 8 mg bolus doses of intravenous Ondansetron, relative to placebo, in prevention of PONV and the changes of QTc interval in healthy adult volunteers.

MATERIALS AND METHODS

This prospective randomized, placebo-controlled, double-blind study was carried out in various surgical operation theaters (OTs) of a tertiary care postgraduate teaching hospital at Kolkata between October 2008 and April 2009 after obtaining approval of the institutional ethics committee and informed consent of the participants.

One hundred and thirty-six adult participants of both sexes, ASA physical Status I and II, on no prescription of over-the-counter medication, with normal baseline electrocardiograms posted for breast surgery, vaginal hysterectomy, skin grafting surgery and reconstructive limb surgery were included in this study.

Participants were excluded from the study if they were known to have history of gastrointestinal disease, hormonal therapy, evidence of uncontrolled clinically important neurological, renal, hepatic, cardiovascular, metabolic or endocrine dysfunction or clinically important abnormalities in laboratory screening tests, vomiting during the 24-h period before surgery, VAS> 4 at extubation, if the participants were not extubated after 30 min following study medication, were not responding to verbal commands after extubation, reaction to the study drug, had a nasogastric tube *in situ* postoperatively, weighed <45 kg Or >90 kg, or were pregnant or lactating women.

Sample size estimation was done by a previously conducted pilot study that revealed an incidence of 60% PONV in untreated participants. Thereafter a pre-study power analysis was computed which revealed that a minimum of 34 participants per group would be required to verify this difference at 95% confidence limit and 90% power of the test.

Following overnight fasting, all the participants were premedicated with oral lorazepam 0.04 mg/kg and tab omeprazole 40 mg 2 h prior to induction of anesthesia. On arrival in the operating room, an intravenous infusion was started with lactated Ringer's infusion.

Five-lead Electrocardiogram (ECG), Saturation of peripheral oxygen (SpO₂), non-invasive Blood pressure (NIBP), edn tidal carbon-di-oxide (ETCo₂), airway pressures and temperature were monitored intra-operatively. After proper pre-oxygenation, participants were induced with inj. thiopentone 5 mg/kg and inj. fentanyl 2 µg/kg. Tracheal intubation was facilitated after achieving adequate muscle relaxation using inj. vecuronium 0.1 mg/kg. Anesthesia was maintained with 50% nitrous oxide and 0.5% sevoflurane in oxygen with top-up doses of inj. vecuronium and fentanyl to maintain bispectoral index (BIS) between 45 and 60. Neuromuscular function was monitored in the right adductor pollicis muscle using tactile Train of Four (TOF). Ventilation was adjusted to maintain normocapnoea (EtCO₂:35 - 40 mm Hg).

Approximately one hour before skin closure, the participants were randomly allocated into four groups with 34 participants in each group through a computer-generated random number, and were administered inj.

Ondansetron 1 mg (0.02 mg/kg) in Group O1, 4 mg (0.08 mg/kg) in Group O4 and 8 mg (0.16 mg/kg) in Group O8 and normal saline in placebo group (Group P).

Study medication was 10 ml of either placebo (normal saline) or inj. Ondansetron 1 mg, 4 mg or 8 mg all diluted to 10 ml in normal saline and this was administered as an infusion over five minutes duration, 30 min before extubation on anticipation of PONV. The anesthesiologist who administered the study drugs was blinded about the nature of treatment. Inhalational agent was discontinued 30 min before skin closure while N_2O was stopped 10 min before extubation. Residual neuromuscular blocking effect was reversed with 50 $\mu g/kg$ neostigmine along with 10 $\mu g/kg$ glycopyrrolate after fulfilling the criteria of extubation. Postoperative analgesia was maintained by inj. diclofenac sodium and paracetamol suppository.

Intra-operatively all the data were recorded by an independent observer blinded to the study drugs. Data recorded were noninvasive arterial blood pressure, heart rate (before, during and after inj. of study drug) which was continuously monitored and noted at 5-min intervals, duration of anesthesia, intraoperative blood loss, intravenous fluid, total amount of fentanyl administered and visual analogue score (VAS) at extubation.

QTc interval changes were monitored in chest lead II for each participant and changes from preoperative baseline value to 1, 3, 5, 10, 15, 20, 40, 60, 120, 240, and 360 min post dose period were noted for each participant. Heart rate was noted at that particular point for each patient. QTc was calculated by the Bazett's formula QTc = QT / √RR. [10] QT interval was accepted as "prolonged," when QTc values exceeded 440 ms.

Intravenous metoclopramide 10 mg was used as rescue antiemetic. Adverse events, if any, were also recorded.

*Primary Endpoint: Time to first rescue antiemetic medication in each group.

*Secondary variables: Changes in QTc interval at different time intervals in each group.

Treatment arrangements kept ready for any precipitated arrhythmias included β blockade anti-bradycardia pacing, implantable automatic cardioverter-defibrillator (ICD). [11-13]

Statistical analysis

All data were entered into an Excel spreadsheet and were analyzed using standard statistical software like SPSS and Statistica. Chi-square test was used for categorical variables. All numerical data were presented as mean \pm standard

deviation. Parametric data were analyzed using one-way analysis of variance test (ANOVA). Nonparametric data were analyzed using Kruskal Wallis test. All tests were two-tailed. A *P* value of less than 0.05 was considered statistically significant.

RESULTS

One hundred and thirty-six adult participants of both sexes were comparable in terms of mean age, sex, Body Mass Index (BMI), and duration of anesthesia. There were no significant differences among the groups with respect to type of surgery performed (Chi square 0.5371, df 9, P=1.00) [Table 1].

Comparable operative data with respect to mean intraoperative intravenous fluid administration, mean estimated blood loss and mean intra-operative fentanyl use, in the different study groups showed that there were no marked differences among the groups in respect to the abovementioned operative parameters [Table 2].

There were no significant differences among the groups with respect to VAS score on extubation (P=0.857). But VAS score was significantly different among the groups at 40 min (P<0.0001) and at 60 min (P=0.0077) [Table 3].

The study revealed that first rescue antiemetic requirement was not administered before 60 min in any group receiving Ondansetron. In the placebo group first rescue antiemetic was required at 10 min after extubation. The percentage (%) of participants in the 1 mg (Gr.O1), 4 mg (Gr.O4), and 8 mg (Gr.08) Ondansetron groups who experienced

Table 1: Clinico-social cofactors of the study participants

Cofactors Group **Group 1** Group 4 **Group 8 Placebo** mg mg mg Mean age (yr) 40 ± 4.3 42 ± 0.2 42 ± 1.4 40 ±5.3 ± SD 40:60 44:56 Sex (M: F.)(%) 40:56 52:48 Mean BMI (kg / 22.6 ± 22.6 ± 22.4 ± 1..2 23.4 ± 0.12 m²) ± SD 2.12 2.12 90 ± 41.3 $100 \pm 22.6 \quad 90 \pm 34.3$ 90 ± Mean duration of anesthesia (min) 44.3 ± SD Types of surgery Group Group 1 Group 4 Group 8 performed Placebo mg (%) mg (%) mg (%) (%) (n=34) (n=34)(n=34)(n=34)10 (30 Breast surgery 10 (29.41) 9 (26.47) 9 (26.47) Vaginal 7 (20.59) 8 (23.53) 8 (23.53) 9 (26.47) hysterectomy Skin grafting 9 (26.47) 8 (23.53) 8 (23.53) 8 (23.53) surgery Reconstructive 8 (23.53) 8 (23.53) 9 (26.47) 8 (23.53) surgery

first PONV and needed rescue antiemetic between 60 to 120 min were 28%, 24%, and 7% respectively. The percentage (%) of participants in the 1 mg (Gr.O1), 4 mg (Gr.O4) and 8 mg (Gr.08) Ondansetron groups who experienced first PONV and needed first rescue antiemetic between 120 to 240 min interval from initial dose, were 63%, 72%, and 57% respectively. In Gr. O8, 36% of participants required their first antiemetic between 240 to 360 min [Table 4].

Participants of Gr. P and Gr.O1 maintained an insignificant change in QTc (mm) throughout the study period with exception at 40 min, a slight increase due to extubation-related sympathetic effect. Significant and maximal QT prolongation in the 8 mg (Gr.O8) recipient participants was revealed within 3 min of administration and in the 4 mg (Gr. 04) recipient participants within 5 min of administration, which was within the normal range, prior to administration of inj. Ondansetron [Table 5].

Table 2: Distribution of patients' groups as per operative data

	Group Placebo	Group 1 mg	Group 4 mg	Group 8 mg				
Mean intra-operative intravenous fluid (ml) ± SD	1500 ± 200	1400 ± 400	1500 ± 300	1500 ± 400				
Mean Estimated blood loss (ml) ± SD	150 ± 20	180 ± 20	160 ± 25	180 ± 20				
Mean Intraoperative fentanyl use (µg) ± SD	180 ± 54.2	225 ±12.3	235 ±10.8	200 ± 37.8				

Table 3: Distribution of patients' groups as per Visual Analogue Score (VAS) at different time intervals

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Groups	Time Interval(min)						
	On extubation	40 min	60 min				
Group Placebo	2.56 ± 0.13	2.60 ± 0.26	2.32 ± 0.42				
Group 1 mg	2.59 ± 0.61	2.40 ± 0.36	2.06 ± 0.44				
Group 4 mg	2.56 ± 1.01	2.20 ± 0.44	2.06 ± 0.34				
Group 8 mg	2.67 ± 0.18	2.26 ± 0.40	2.12 ± 0.12				

DISCUSSION

Many medications given to participants under anesthesia care are also known to cause QTc prolongation, such as inhaled anesthetics, propofol, thiopental, succinylcholine, and neuromuscular blocker antagonists. Most currently available antiemetics also cause QTc prolongation, including phenothiazines, antihistamines, and $5 \rm HT_3$ antagonists such as Ondansetron. In our study, QTc changes were monitored at different time intervals and it was observed that, among the three groups of participants receiving inj. Ondansetron (1 mg, 4 mg, 8 mg), a maximal QTc prolongation was recorded in 8 mg recipient participants at 3 min post administration period (0.47 \pm 0.02).

In one study it was observed that, a 2.7-3.5% QT prolongation recorded at 5 min after injection of preinduction medications was equal to 11.3 \pm 24.3 ms with 1.25 mg droperidol alone, 9.9 \pm 34.7 ms with 4 mg Ondansetron alone.^[8]

Another comparative study between droperidol (0.75 mg IV) and Ondansetron (4 mg IV) on 85 adults with PONV showed that the maximal QT prolongation with droperidol was 17±9 ms, occurring at 2 min after administration. Maximal prolongation with Ondansetron was 20±13 ms, occurring 3 min after drug administration. [9]

No volatile agent is completely safe. Therefore, intraoperative management should continue to focus on prevention of excessive sympathetic activity and avoidance of factors that can prolong the QTc interval. Non-invasive monitoring should commence before the induction of

Table 4: Percentage distribution of participants who required first rescue anti-emetic medication at different time intervals

Groups	Time Interval (min)					
	1-20	20-40	40-60	60-120	120-240	240-360
Group Placebo	0	94	5	1	0	0
Group 1 mg	0	0	0	28	63	9
Group 4 mg	0	0	0	22	74	4
Group 8 mg	0	0	0	07	57	36

Table 5: Distribution of patients' groups as per changes in QTc (mm) interval at different time intervals

Groups	1 min	3 min	5 min	10 min	15 min	20 min	40 min	60 min	120 min	240 min	360 min
Group	0.34 ±	$0.34 \pm$	$0.35 \pm$	$0.36 \pm$	$0.36 \pm$	0.36 ±	0.38 ±	0.34 ±	$0.34 \pm$	$0.35 \pm$	0.34 ±
Placebo	0.02	0.02	0.01	0.01	0.02	0.02	0.02	0.02	0.01	0.01	0.02
Group	$0.36 \pm$	$0.36 \pm$	$0.35 \pm$	$0.36 \pm$	$0.36 \pm$	$0.36 \pm$	$0.38 \pm$	$0.34 \pm$	$0.34 \pm$	$0.35 \pm$	$0.34 \pm$
1 mg	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.01	0.02	0.02
Group	$0.36 \pm$	$0.36 \pm$	$0.46 \pm$	$0.44 \pm$	$0.42 \pm$	$0.40 \pm$	$0.38 \pm$	$0.36 \pm$	$0.36 \pm$	$0.34 \pm$	$0.36 \pm$
4 mg	0.02	0.01	0.01	0.02	0.02	0.02	0.02	0.01	0.02	0.02	0.01
Group	$0.38 \pm$	$0.47 \pm$	$0.44 \pm$	$0.44 \pm$	$0.42 \pm$	$0.38 \pm$	$0.36 \pm$	$0.36 \pm$	$0.36 \pm$	$0.36 \pm$	$0.34 \pm$
8 mg	0.03	0.01	0.02	0.01	0.02	0.10	0.03	0.02	0.04	0.03	0.02

anesthesia and ideally should include ECG monitoring of more than one lead, as short bursts of torsades de pointes may be difficult to distinguish from monomorphic ventricular tachycardia, when only one lead is available for analysis.

The effect of prolonging the QTc interval by a volatile agent may resemble the action of Class III antiarrhythmic agents that prolong the QTc interval. Sevoflurane which was least likely to produce any changes was used in this study. The concomitant presence of K+ and Mg+ serum level abnormalities (increased level) or existant endocrine dysfunction may alter QT interval.[14] Other researchers opined that prophylactic Ondansetron appeared to be more effective when administered at the end of surgery than prior to induction of anesthesia.^[15] In this study the study drugs were administered 30 min prior to anticipated extubation. As neostigmine is never given in isolation to reverse neuromuscular block, its true effect is unknown, but one would predict that the inevitable resultant bradycardia may prolong QT up to the extent of torsades, which would be undesirable.

Most research on the 5-HT3 receptor antagonists has been performed with Ondansetron, which has greater antivomiting than antinausea effects. Ondansetron 4 mg has an Number needed to treat (NNT) of approximately 7 in the prevention of nausea compared with placebo (0–24 h); the 8-mg dose has an NNT of approximately 6. For the prevention of vomiting (0–24 h), Ondansetron 4 mg has an NNT of approximately 6; the 8-mg dose has an NNT of approximately 5.^[4]

5-HT3 antagonists have become the first-line drug for management of PONV. These drugs are also known to prolong the QTc interval at high dosages.^[11]

Other researchers also concluded in their study that the treatment of PONV with ondansetron was more cost-effective than prevention in both a low-risk (30%) and a high-risk (60%) setting. The reason for this was the frequent success rate of treating established PONV, even with small doses of ondansetron (1 mg).^[16]

Strength of the study

Reversible transient changes in the, PR, QRS and QTc intervals have been consistently observed in noncomparative and comparative trials with Ondansetron. The present study showed stable and comparable hemodynamic parameters during the study period in all the groups, implicating a least association of contributory factors on QTc prolongation, other than the effects of the study drug in healthy adult participants.

Limitations of the study

The effects on QTc changes by different anesthetic agents could not be measured. Concurrent assessments of the QTc changes by the different anesthetic agents would have yielded better results for external validity.

Future directions of the study

There are many factors both related and unrelated to anesthesia that may influence PONV, such as age, sex, body weight, type and duration of surgery, type of induction and maintenance of anesthesia and the neuromuscular blocking agent used. This study was conducted in a homogenous group and with a single molecule in terms of age, sex, body weight, duration of anesthesia, and type of surgery. Emerging disparity among the 5-HT3 receptor antagonists suggests that the incidence and/or intensity of adverse events should not be regarded as a class effect. The side-effects of the supportive care are important particularly for those who are suffering from co-morbid conditions, such as cardiovascular disease and renal or hepatic impairment. Therefore it is very important to know whether the variation in the incidence of nausea and vomiting is related to the difference in agents used or not.

CONCLUSIONS

Postoperative nausea and vomiting continues to pose problems for surgical participants. Participants receiving Ondansetron in the doses of 4 mg and 8 mg were significantly better than those receiving placebo for prevention of emesis; the 8-mg dose prevented emesis longer than 1 mg or 4 mg dose; effect of 4 mg dose was not different from that of 1 mg. Therefore, 1 mg rather than 4 mg or 8 mg may be chosen as the optimal dose in preventing postoperative nausea and vomiting, because of having less propensity for inducing cardiac effects by prolonging the QTc, which along with other precipitating factors of surgery may precipitate the life-threatening torsades, despite the excellent overall safety profiles of this 5-HT, receptor antagonist. Therefore it may be concluded that Ondansetron in a dose of 1 mg in healthy adult participants can effectively prevent postoperative nausea and vomiting causing no or insignificant prolongation of QTc interval.

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