Original Article

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Effect of Ondansetron on QTc Interval during Sevoflurane Anaesthesia: A prospective Randomized Double-Blind Study

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Abstract

Aim and objectives: Serious drug interactions are amongst the common problems encountered by the anaesthesiologists in their practice that compells them to understand the effects of individual drugs and their combinations. One such drug interaction is the effect of sevoflurane and ondonsetron on QT interval when administered individually and also when combined together.The aim of the study is toevaluate the effects of Ondansetron and Sevoflurane and theirpossible synergistic effectson QT interval. The effects on QT interval were observed whenOndansetron was administered on patients undergoing Sevoflurane anesthesia using corrected QT interval (QTc) by Bazett's formula.

Methodology: Our study was a prospective randomized double blinded study which was done to evaluate QTc interval in 150 patients, aged between 20-60 years. QT interval was corrected by using Bazett's formulato the heart rateand are noted at various interval period such as base line(Preoperative period), 10min, 15min, and 20 mins after the administration of ondansetron using 5 lead ECG in Lead II.

Results: There was significant prolongation of QTc interval in Sevoflurane + ondansetron group (477.92 ± 11.44) when compared with placebo (448.93 ± 8.21) with p value of <0.00001.

Conclusion: Ondansetron when administered with sevoflurane significantly prolonged theQTc intervalthat was not significant enough to produce arrhythmias. Though this combination seems to be safe, one must consider caution when administering these drugs to patients with long QT syndrome or any arrhythmia along with continuous ECG monitoring.

Keywords: Ondansetron; Sevoflurane; QT interval.

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Introduction

Anaesthesiologists administer medications routinely in combinations. It is a challenge to the anaesthesiologist to reach an optimal conditions and maintenance of anaesthesia while maintaining minimal side-effects during perioperative period.

In daily practice Anaesthesiologists encounter

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a variety of medications some of which can possibly cause arrhythmias and it is a prime responsibility to understand every detail of these medications. Some of the common drugs delivered to the patients such as antihistamines, antiemetics, inhalational agents and some antibiotics etc are arrhythmogenic individually and synergistic when combined causing significant morbidity and mortality perioperatively. One of the arrhythmias that are caused by these drugs is prolongation of QT interval which is more frequent than usually thought.

In 1920 drug induced syncope was encountered for the first time with Quinidine. Quinidine at that time was used as an antiarrhythmic. After that time occassional fatal syncopes were seen after the usage of other medications. Quinidine characteristic polymorphic arrhythmia was first observed by Dessertenne in a patient with atrio-ventricular block.[1] He reported his observations, changes in QRS complex around the isoelectric line on the surface ECG and coined the term "torsades de pointes".Since then there is an extensive research on understanding the mechanism of drug induced QT prolongation. QT prolongation may lead to polymorphic ventricular tachycardia known as "torsades de pointes" a fatal arrhythmia that can cause ventricular fibrillation and cardiac arrest. QT interval acts as a surrogate marker of proarrhythmic potential of the drugs used.

QT interval represents the Starting point of QRS complex that represents ventricular depolarization to the end of 'T" wave indicating ventricular repolarisation. It approximately estimates the duration of average ventricular action potential, a major part of the cardiac cycle. A smooth ventricular repolarisation is essential for the conductance of next electrical impulse along the myocardial fibres. QT interval prolongation can become a fatal life threatening polymorphic ventricular tachycardia which may lead to sudden cardiac death when associated with major risk factors such as electrolyte imbalance, congenital QT syndrome or associated with any medication which has the potential to increase QT interval. It is considered an independent risk factor for sudden death due to cardiac arrest especially in older adults and in general population.[2,3] It is the point where scrutiny should be highest and focused for further study.

Furthermore, situation of acquired QT prolongation is complicated by polypharmacotherapy used regularly in daily practice. It is relatively risky in patients receiving two or more drugs which might affect the QT interval.

It is a common practice in anaesthesiology to use multiple drugs. Drugs used in perioperative setup such as halogenated inhalational agents, antiemetics, anticholinergics etc. The drug that is used commonly for induction and maintenance of anaesthesiasuch as sevoflurane has the tendency to prolong the QT interval.[4,5] Moreover, the most commonly administered antiemetic, ondansetron also have the potential to cause increase in QT duration individually. Especially when administered in patients who are prone to long QT syndrome, it can cause torsade de pointes. There have been many reports of SCD (sudden cardiac death) in the intraoprative and postoperative period because of various ventricular dysrrhythmias in patients to whom ondansetron has been administered.[6,7] In addition when these drugs are used in combination they have collegial effect in increasing the duration of QT.We used corrected QT interval (QTc) using Bazett's formula[8] to measure the accurate QT interval which helps to compare the interval at different heart rates[9] and increses the identification of potential arrhythmias.

This study was done to analyze drug-drug interaction, betweenondansetron and sevoflurane on QT interval during intra-operative period.

Methods

This is a prospective randomized double blind comparative study conducted between May 2014 to May 2015 after institution Ethical committee approval in Vinayaka Mission's Medical College and Hospital, Karaikal, India. Written informed consent from all patients enrolled in our study was taken.

Sample size was calculated based on previous studies and 95% confidence level with a margin of error of 5% and 7.5 confidence interval using sample size calculator. We found out that the sample size required for our study is 124 patients and then we added 26 patients in order to cover the fallouts. 150 ASA I and II patients of both sexes, 20-60 years old, with BMI 21-26 kg/m2, undergoing elective surgery with expected duration of >90mins, were randomly divided into 2 groups (group 1, group 2) of 75 patients each. Randomized into groups using computer generated randomization (using rand between function on Microsoft Excel 2010).

Patients with baseline ECG abnormalities, who are on drugs implicated in prolonging QT interval, renal /hepatic dysfunction, severe cardiac disease, electrolyte abnormalities and who require change

in concentration of sevoflurane were excluded from the study.

Measuring QTc interval is an important aspect in our study. The most universally adopted method is Bazett's formula (QTc = QT/√RR in seconds) that provides an adequate correction for heart rate ranging anywhere between 60 and 100 beats/min. Nonetheless, it underestimates and overestimates the QT interval at low and high heart rates, respectively.

Based on Bazett's corrected QTc value, in adult males a QT interval greater than 450 ms is considered prolonged and between 430 and 450 ms is considered borderline. For females, a QT interval greater than 470 ms is considered prolonged and between 450 and 470 ms is considered borderline [Goldenberg et al. 2006].

All participants received Diazepam 5mg as anxiolytic premedication. Two syringes labelled A & B were prepared for the study by an investigator not involved in the drug administration or monitoring of the patients. The contents of syringe A were administered in the preoperative holding area, syringe B intraoperatively during sevoflurane anesthesia.

In group 1, syringe A contained ondansetron and syringes B contained normal saline placebo.

In group 2, syringe B contained ondansetron and syringes A contained normal saline placebo.

Patients were assessed one day before surgery and their ECGs taken,their QT intervals were calculated and corrected using Bazett's formula as it is widely used and accepted within the range of physiological heart rate.

A baseline ECG is obtained and the contents of syringe A were administered in the preoperative holding area for all patients. ECG was recorded after 10mins, 15 mins, 20 mins monitoring the QTc interval with a 5 lead ECG. The patients were then taken to the Operation theatre and induced with Inj. fentanyl 2.0 mcg/kg, propofol 2 mg/kg, vecuronium 0.1mg/kg and intubated with appropriate size ET tube and airway secured. Anaesthesia was maintained throughout the surgery using nitrous oxide (66%), oxygen (33%) and with 1 MAC concentration of Sevoflurane. After one hour of anaesthesia, patients received drug from syringe B and thereafter ECGs were recorded at 10 mins, 15mins and 20 mins. After the surgery the patients were reversed from the effect of muscle relaxant with neostigmine of 0.04mg/kg and glycopyrolate 0.01mg/kg. Hemodynamic changes were noted from the start of administration of syringe A to 4 hours after surgery.

All the ECG recordings obtained were immediately noted by using inbuilt QTc interval monitor, and recorded QTc interval as per study. Bazett's formula was used to correct the QT interval and the measured QTc interval was taken routinely a day before surgery and during the assessment period.

The QTc changes with preoperative IV ondansetron were evaluated from ECG obtained from patients in group 1 after syringe A. ECG from Group 2 after syringe A provides data on saline placebo control for preoperative QTc.

The QTc changes with administration of ondansetron during sevoflurane anesthesia were obtained from group 2 patient's ECG, after administration of syringe B. ECG from Group 1 after syringe B provides data on QTc changes during sevoflurane anesthesia in patients on preoperative ondansetron.The primary outcome wassynergistic interactions between ondansetron and sevoflurane on QTc interval.

Statistical Analysis

The statistical analysis was performed using SPSS version17. As per Shapiro-Wilk test normality of the groups confirmed and both groups were comparable(Table1) .The continuous data with normal distribution was described as mean and 95% confidence interval for mean (95%C.I). The continuous variables were compared between the groups using Student t-test. Categorical data was compared using Chi-square test. The changes in the QTc from baseline were compared with ANOVA for repeated variables. A two-sided p value of < 0.05 was considered significant for all tests.

After administration of syringe A and syringe B in group 1 there was a significant increase in QTc comparing with base line mean 434.58(±8.45) ms at 10 min after ondansetron administration of intravenously mean 448.93(±8.21) and maximum difference is observed at 10 min after giving of ondansetran with the mean of 14.3466(±2.63) when compared to baseline (p=0.).

After administration of contents of syringe A and B in group 2 the change in QTc interval after 10min of ondansetron intra-operatively showed significant prolongation of mean 477.92(±11.44)ms compared with baseline mean 438.41(±8.99)ms with significant p=0.0018. The maximum raise of QTc (mean ± SD 39.46±5.96 ms) interval is seen at 10min after intravenous ondansetron during sevoflurane anesthesia in the intra-operative period.

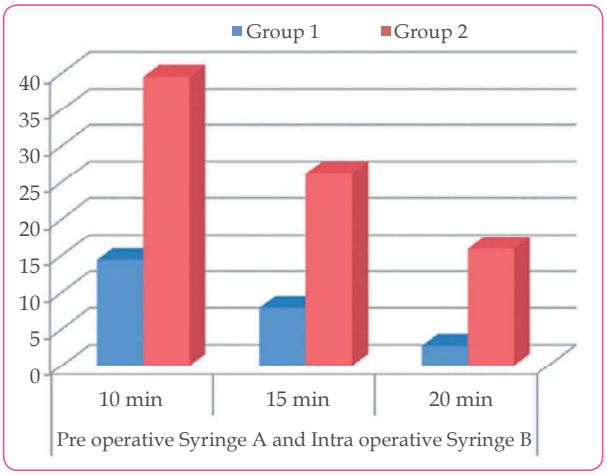
After administration of content of syringe B, patients receiving ondansetron intraoperatively during sevoflurane anesthesia (group 2) had a significant prolongation of QTc when compared to patients who are receiving ondansetron preoperatively (group 1). The mean QTc was more than 450 m sec immediately 10 mins after the drug administration and continued after 15 and 20 mins. The maximum (mean ± SD) difference between these groups are 25±12 ms with P value 0.00089.

Table 1: As per Shapiro-Wilk test normality is confirmed in the groups and both groups are comparable.

Parameter	Group I	Group II
Mean:	434.580	438.413
Standard Deviation:	8.45	8.996
Variance:	45.134	80.921
Kurtosis:	0.769	-0.354
Calculated Shapiro-Wilk statistic W:	0.910462	0.017746
Calculated Shapiro-Wilk p-value:	0.000059	0.01774
Critical value of W (5% significance level):	0.947	0.947
P value	0.00342	0.947

Table 2: Group 1 syringe A (ondansetron only) & Group 2 syringe B (ondansetron + sevoflurane)

Time	Group 1 A (ondansetron only)	Group 2 B (ondansetron + sevoflurane)	P value
Baseline	434.58±8.45	438.41±8.99	0.115(not significant)
10 min	448.93 ± 8.21	477.92 ± 11.44	0.0031 (significant)
15 min	442.44 ± 8.25	464.45 ± 10.32	0.0047 (significant)
20 min	436.97 ± 8.56	454.28 ± 9.30	0.007 (significant)



Graph 1: Observed QTc Prolongation after syringe B (ondansetron with sevoflurane) in Group 2 (intraoperative) compared with Syringe A (ondansetron only) in Group 1 (preoperative).

Discussion

The Surgical patients under general anesthesia with inhalational agents are simultaneously exposed to several intravenously administered drugs, several of which are known to cause QT prolongation.[10] Typical drug classes include antibiotics, antiemetic medications (ondansetron or droperidol) and antihistamines. In addition, conditions conducive for QT prolongation such as stress, hypothermia, and electrolyte disturbances, particularly hypokalemia and hypomagnesemia, are common during major surgery.

The introduction of the 5HT3 receptor antagonist, ondansetron, in the early 1990s was a significant breakthrough in treating nausea and vomiting. Apart from minor side effects like constipation, ondansetron is also known to cause major changes in electrical rhythm of heart (QT interval prolongation) especially when administered in patients who are prone to long QT syndrome, it can cause torsade de pointes in these patients.[11] There have been many reports of SCD (sudden cardiac death) in the intraoprative and postoperative period because of various ventricular dysrrhythmias in patients to whom ondansetron has been administered. FDA black label warning for its use with caution in patients with cardiovascular abnormalities has also been issued.

Sevoflurane, Halogenated volatile anaesthetic agent with low pungency, a non-irritant odour and a low blood: gas partition coefficient replaced many of the standerd inhalational agents for induction and maintainance of anesthesia. It can be rapidly and conveniently administered without discomfort, and its low solubility facilitates precise control over the depth of anaesthesia and a rapid and smooth induction of, and emergence from, general anaesthesia. Sevoflurane though considered as one of the best induction agents is also implicated in increasing the QT intervaland are sometime arrhythmogenic in susceptible individuals.

A number of studies were conducted on both sevoflurane and ondansetron for their effects on QT interval.[12] Most of the studies focused on the effect on QT interval prolongation of these drugs when administered independently but their possibility of interaction between the two drugs is not evaluated extensively.

It is important that the anaesthesiologists be aware of the potential arrythmogenicity that results from these drug-drug interactions perioperatively[13,14] and be prepared to manage the complications.[15] It

is seen from this study that two drugs which are in routine usage produce an additive or synergistic effect and produce a complication when least anticipated. Based on the findings of this study, it may be recommended against administration of ondansetron simultaneously with other potential arrythmogenic drugs like isoflurane, sevoflurane and halothane. The results of our study showed that significant prolongation of QTc interval that occurred following administration of ondansetron during sevoflurane anaesthesia even in the absence of potential arrhythmogenic conditions like electrolyte disturbances, metabolic abnormalities and hypothermia. These conditions occur more frequently towards the conclusion of the procedures which coincides with timing of administration of ondansetron. The timing of the ondansteron administration should be re-evaluated in the light of this potential complication.

It is imperative from our study that intravenous ondansetron in clinically administered doses for postoperative nausea and vomiting produces significant prolongation of QT interval. Sevoflurane anesthesia also results in small but statistically not significant prolongation of QT interval. The administration of ondansetron during sevoflurane anaesthesia results in greater prolongation of QTc when compared to either drug administered alone suggesting drug-drug interaction between sevoflurane and ondansetron.

Conclusion

Sevoflurane and ondansetron produce statistically significant prolongation of QTc. Significant number of patients receiving ondansetron along with sevoflurane had QTc exceeding the safe limit although none of the patients had life-threatening arrhythmias. The administration of ondansetron during sevoflurane anesthesia results in greater prolongation of QTc when compared to either drug administered alone suggesting drug-drug interaction between sevoflurane and ondansetron. Caution should be employed when ondansetron is administered in the presence of inhalational agents like sevoflurane. Further studies have to be done to evaluate the effects of these drugs as well as when combined with other commonly used drugs that have the potential to cause increase in QT interval.

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