



## Cross-sectional Study

Investigation role of ondansetron on long QT interval among non-cardiac patients<sup>☆</sup>Shahrouz Tabrizi<sup>a,b,\*</sup>, Shaghayegh Heidari<sup>a</sup>, Hooman Rafiei<sup>a</sup><sup>a</sup> Department of Emergency Medicine, Kermanshah University of Medical Science, Imam Reza Hospital, Kermanshah, Iran<sup>b</sup> Clinical Research Development Center, Imam Ali and Taleghani Hospital, Kermanshah University of Medical Science, Kermanshah, Iran

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## ABSTRACT

**Background:** Ondansetron is one of the commonly prescribed anti-emetic in emergency department however, high dose of the drug is associated with prolonged QT interval. This study was designed to evaluate the effect of ondansetron on prolongation of QT interval among patients referred to our emergency department.

**Methods:** In this cross-sectional study patients referred to the emergency department of Imam Reza hospital from June 2019 to December 2019 were included. Before the administration of ondansetron 12-lead electrocardiography was performed in all the patients. 4 mg of i.v. ondansetron was administered to these patients and ECG was obtained again. QT interval was calculated automatically from the system from these electrocardiographs. Demographic data of these patients along with QT interval findings was recorded in the questionnaire and analyzed statistically using SPSS software.

**Results:** A total of 55 patients were included with the mean age of  $58 \pm 13$  years, where 36 were females (65.5%) and 19 were males (34.5%). The mean QT interval before and after injection of 4 mg intravenous ondansetron was not statistically significant,  $p$ -value = 0.073. Similarly, QT interval before and after the administration of the drugs was also not significantly different among females and males,  $p$  = 0.479 and  $p$  = 0.078, respectively. The age of the patients was also not associated with prolonged QT interval,  $p$  = 0.948.

**Conclusions:** The findings of our study indicated that 4 mg i.v. administration of ondansetron among non-cardiac patients referred to emergency department is not associated with QT interval prolongation.

## 1. Introduction

Vomiting is controlled by emesis center in mid-brainstem that receives input signals from vagus nerve, splanchnic afferent nerves, cerebral cortex, and the vestibular apparatus in ear. Histamine, 5-hydroxytryptamine type 3, muscarinic and dopamine receptors are involved in emesis. Nausea and vomiting are among the significantly leading complaints in patients referred at emergency department, which is reported approximately among 4 million patients annually in the United States [1].

5-hydroxytryptamine type 3 (serotonin) receptor antagonists like ondansetron are known for their antiemetic effects and are used to treat nausea and vomiting due to chemotherapy and radiation therapy, gastrointestinal problems, pregnancy and anesthesia [2–4]. A number of studies have indicated that QT interval prolongation is one of the significant side effects of ondansetron and increases the risk of torsade de

pointes. Furthermore, cases of cardiac arrhythmias have been reported with the administration of serotonin receptor inhibitors [5]. Administration of ondansetron increase 330 folds in the United State of America from 38,000 doses to 12.6 million doses. In 2011, Food and Drug Administration disseminated the warning that high dose of ondansetron can be associated with fatal arrhythmias. Thereby, it is contraindicated among patients with arrhythmias, cardiac ailments, prolonged QT syndrome and electrolyte disturbances [6]. Following clinical studies, in 2012, 32 mg dose of ondansetron was proved to lead to serious cardiac events and is therefore no longer marked. Intravenous ondansetron is also known to cause prolonged QT interval in dose-dependent manner. However, discrepancies in these findings are seen from different researches [7].

The aim of this study was to evaluate the effect of 4 mg intravenous (i.v.) dose of ondansetron among emergency department patients referred to our center with no heart-related abnormalities.

<sup>☆</sup> The design was approved by the Ethics Committee of Kermanshah University of Medical Sciences.

\* Corresponding author. Kermanshah University of Medical Science, Kermanshah, Iran.

E-mail address: [md.sh.tabrizi@gmail.com](mailto:md.sh.tabrizi@gmail.com) (S. Tabrizi).

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## 2. Methods

In this cross-sectional study, conducted at (XXX) from June 2019 to December 2019, patients presented to the emergency department was included, aged between 20 and 50 years in who 4 mg of i.v. ondansetron was administered. Written consent form was obtained from all the patients before the participation in the study. Our exclusion criteria included patients with: cardiovascular disease, critically ill patients, gastrointestinal ailments who use ondansetron, pregnancy, heart defects, electrolyte abnormality, ventilation requirements and dissatisfaction to participate in the study.

12-lead electrocardiography was used to obtain ECG of patients before and 5 min after the administration of intravenous ondansetron and QT interval was automatically read by the machine. All the ECGs were performed by a trained technician teamed with research personnel. A questionnaire comprising of demographic data of all the patients along with QT interval before and after the administration of the drug was filled for all the patients.

Central indices (mean, median) and dispersion (standard deviation and standard deviation) and relative frequency were used to describe the data. Paired *t*-test was used to compare the mean length of QT interval before and after injection of ondansetron 4 mg intravenously. The relationship between age and QT was measured using Pearson correlation coefficient. Calculations were performed with SPSS software version 24 and a significance level of 0.05 was considered.

The study was approved by the board of ethical committee of (XXX). Unique identifying number is: researchregistry7145.

## 3. Results

A total of 55 patients were included in this study where 36 were females (65.5%) and 19 were males (34.5%). The mean of the patients was  $58 \pm 13$  years, [Tables 1 and 2](#).

The mean QT interval before and after injection of 4 mg intravenous ondansetron was  $0.4318 \pm 0.046$  and  $0.4420 \pm 0.042$ , respectively. Paired *t*-test showed no significant difference between before and after QT interval (*p*-value = 0.073) ([Fig. 1](#)).

Paired *T*-test was used to compare the relation of gender and QT interval among these patients. In females, QT interval before and after the administration of ondansetron was  $0.44 \pm 0.04$  s and  $0.44 \pm 0.036$  s. This difference was not statistically significant, *p* = 0.479. Similarly, among male patients, QT interval before and after the administration of the drug was  $0.416 \pm 0.039$  s and  $0.437 \pm 0.053$  s. The difference in QT among males patients before and after the administration of ondansetron was also not statistically significant, *p* = 0.078 ([Table 3](#)).

Pearson correlation coefficient was used to investigate the effect of age on QT interval. As seen in [Fig. 2](#), the age was not associated with QT interval in these patients, *p* = 0.948.

## 4. Discussion

The findings of our study determine that administration of ondansetron in emergency department doesn't not affect QT interval among patients without any cardiovascular disease. Furthermore, demographic factors like age and gender does not affect these findings too.

A prospective observational study was conducted by Li, Vo [8] to determine the effect of intravenous ondansetron on QT interval among patients referred to emergency department. A total of 20 patients were

**Table 2**

The average age of the patients.

	Count	Mean	Standard Deviation	Median
Age	55	58	13	60

included in the study where mean QT interval after the administration of 4 mg i.v. ondansetron was evaluated. The outcomes of the study reported that following the administration of the drug a significant increase of 16.2 msec of QT interval was seen in patients which was statistically significant. The findings of this study is not in parallel with our results.

In a study, Kim, Lee [9] evaluated the effect of prophylactic ondansetron on QT interval among patients undergoing laparoscopic cholecystectomy at different doses. The findings of this study reported that ondansetron at 0.3 mg and 4 mg dose does not significantly increase QT interval among these patients however, 8 mg dose of the drug significantly increases QT interval among these patients. Our study did not evaluate the dose-dependent effect of ondansetron however, similar to these findings, our study did not report the effect of 4 mg ondansetron on QT interval. A study by Trivedi, Schiltz [10] evaluated the effects of different doses of ondansetron on pediatric patients admitted in pediatric intensive care unit. The study reported an overall increase in QT interval following the administration of ondansetron irrespective of the dose administered however, 2 h following the administration, mean QT interval was not significantly different as compared to the baseline level. Multivariate analysis showed that this increase is more significant among patients with organ dysfunction, arrhythmias and electrolyte abnormality. On the contrary, Krammes, Jacobs [11] reported that among pediatric patients referred to emergency department, who were administered ondansetron for nausea and vomiting, QT interval was not significantly prolonged at 3-min of peak effect and 1-h of post-peak. Obal, Yang [12] reported that perioperative use of ondansetron during non-cardiac surgery is not associated with increased QT interval.

A study Charbit, Alvarez [13] evaluated the effects of ondansetron and droperidol on healthy adults. Prolonged QT interval was significantly greater in droperidol group and combination (droperidol and ondansetron) group, compared to ondansetron alone. Ondansetron alone led to prolonged QT interval following 4th, 7th, 8th and 11th of the administration. Discrepancies among these studies could be due to variation in the sample size, time at which QT interval was obtained, unknown or undiagnosed heart conditions among patients and the expertise of ECG technician.

## 5. Conclusion

Our study was also based on a small sample size, family history of heart disease and congenital diseases was not obtained, control group was not included in the study and QT interval was calculated at single time only. Therefore, further studies are required to evaluate the effects of ondansetron at different time intervals and dose and including control group with larger sample size.

The findings of our study conclude that 4 mg of i.v. ondansetron among emergency department patients do not prolong QT interval 5 min following its administration, compared to baseline QT interval. These findings are similar with respect to gender and age differences.

## Sources of funding

No funding was secured for this study.

## Ethical approval

All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration

**Table 1**

The average sex of the patients.

sex	Frequency	Percent	Valid Percent	Cumulative Percent
Female	36	65.5	65.5	65.5
Male	19	34.5	34.5	100.0
Total	55	100.0	100.0	

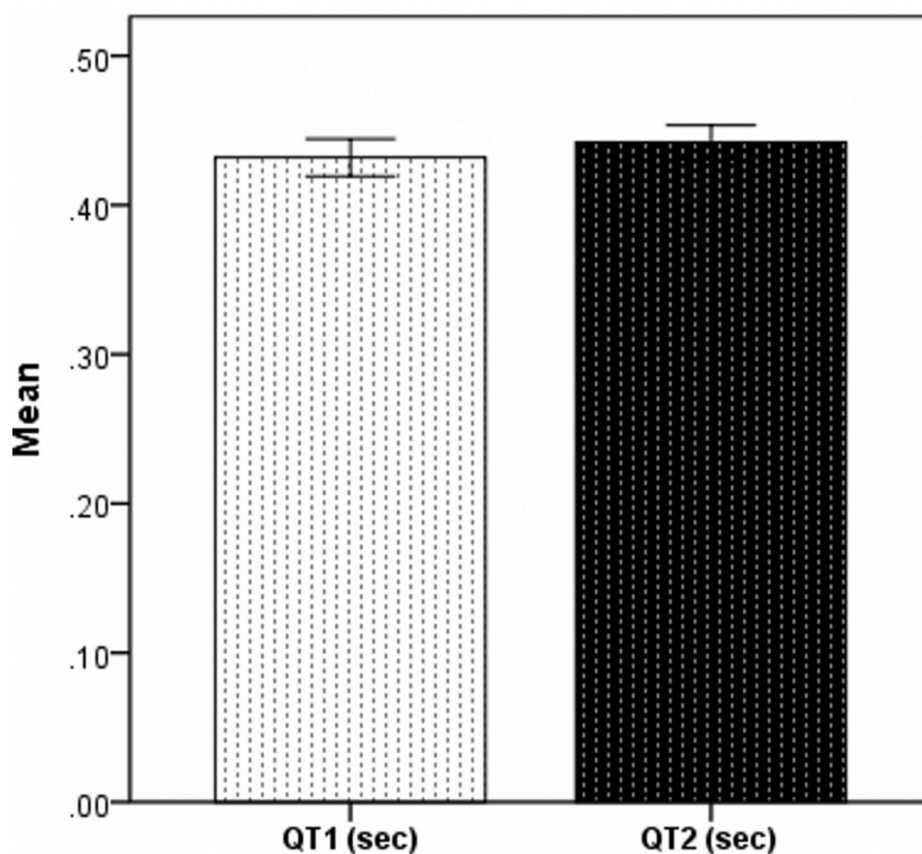


Fig. 1. Mean QT interval before and after ondansetron injection.

**Table 3**

Results of mean QT before and after in individuals.

Sex		Mean	N	Std. Deviation	Std. Error Mean	p-value
Female	QT1 (sec)	.4400	36	.04828	.00805	0.479
	QT2 (sec)	.4442	36	.03628	.00605	
Male	QT1 (sec)	.4163	19	.03905	.00896	0.078
	QT2 (sec)	.4379	19	.05339	.01225	

and its later amendments or comparable ethical standards.

#### Consent

Not applicable.

#### Author contribution

Dr. Shahrouz Tabrizi: conceptualized and designed the study, drafted the initial manuscript, and reviewed and revised the manuscript. Dr. Shaghayegh Heidari: Designed the data collection instruments, collected data, carried out the initial analyses, and reviewed and revised the manuscript. Dr. Hooman Rafiei Coordinated and supervised data collection, and critically reviewed the manuscript for important intellectual content.

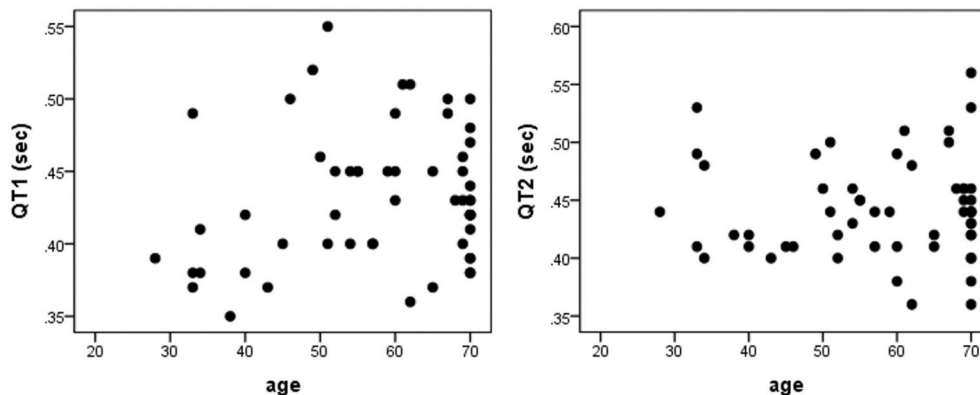


Fig. 2. Correlation between age and QT interval before and after injection.

## Registration of research studies

- 1 Name of the registry: N/a
- 2 Unique Identifying number or registration ID: N/A
- 3 Hyperlink to the registration (must be publicly accessible):

## Guarantor

Dr. Shahrouz Tabrizi.

## Human and animal rights

No animals were used in this research. All human research procedures followed were in accordance with the ethical standards of the committee responsible for human experimentation (institutional and national), and with the Helsinki Declaration of 1975, as revised in 2013.

## Consent for publication

Informed consent was obtained from each participant.

## Availability of data and materials

All relevant data and materials are provided with in manuscript.

## Provenance and peer review

Not commissioned, externally peer reviewed.

## Declaration of competing interest

The authors deny any conflict of interest in any terms or by any means during the study.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.amsu.2021.102971>.

[org/10.1016/j.amsu.2021.102971](https://doi.org/10.1016/j.amsu.2021.102971).

## References

- [1] A.E. Patanwala, R. Amini, D.P. Hays, P. Rosen, Antiemetic therapy for nausea and vomiting in the emergency department, *J. Emerg. Med.* 39 (3) (2010) 330–336.
- [2] M.P. Patel, S. Woodring, D.M. Randazzo, H.S. Friedman, A. Desjardins, P. Healy, et al., Randomized open-label phase II trial of 5-day aprepitant plus ondansetron compared to ondansetron alone in the prevention of chemotherapy-induced nausea-vomiting (CINV) in glioma patients receiving adjuvant temozolomide, *Support. Care Cancer* 28 (5) (2020) 2229–2238.
- [3] T.A. Zikos, L. Nguyen, A. Kamal, N. Fernandez-Becker, K. Regalia, M. Nandwani, et al., Marijuana, Ondansetron, and Promethazine Are Perceived as Most Effective Treatments for Gastrointestinal Nausea, *Digestive Diseases and Sciences*, 2020, pp. 1–7.
- [4] L.A. Michie, K.K. Hodson, Ondansetron for Nausea and Vomiting in Pregnancy: Re-evaluating the Teratogenic Risk, SAGE Publications Sage UK, London, England, 2020.
- [5] B. Charbit, P. Albaladejo, C. Funck-Brentano, M. Legrand, E. Samain, J. Marty, Prolongation of QTc interval after postoperative nausea and vomiting treatment by droperidol or ondansetron, *Anesthesiology* 102 (6) (2005) 1094–1100.
- [6] S.B. Freedman, E. Ulerik, M. Rumantir, Y. Finkelstein, Ondansetron and the risk of cardiac arrhythmias: a systematic review and postmarketing analysis, *Ann. Emerg. Med.* 64 (1) (2014) 19–25, e6.
- [7] S.A. Doggrell, J.C. Hancox, Cardiac safety concerns for ondansetron, an antiemetic commonly used for nausea linked to cancer treatment and following anaesthesia, *Expet Opin. Drug Saf.* 12 (3) (2013) 421–431.
- [8] K. Li, K. Vo, B.K. Lee, N. Addo, Z. Coralic, Effect of a single dose of i.v. ondansetron on QTc interval in emergency department patients, *Am. J. Health Syst. Pharm. : AJHP : official journal of the American Society of Health-System Pharmacists* 75 (5) (2018) 276–282.
- [9] S.-H. Kim, S.-M. Lee, Y.-K. Kim, S.-Y. Park, J.-H. Lee, S.-H. Cho, et al., Effects of prophylactic ramosetron and ondansetron on corrected QT interval during general anesthesia, *J. Clin. Anesth.* 26 (7) (2014) 511–516.
- [10] S. Trivedi, B. Schiltz, R. Kanipakam, J.M. Bos, M.J. Ackerman, Y. Ouellette, Effect of ondansetron on QT interval in patients cared for in the PICU, *Pediatr. Crit. Care Med.* 17 (7) (2016) e317–e323.
- [11] S.K. Krammes, T. Jacobs, J.M. Clark, R.E. Lutes, Effect of intravenous ondansetron on the QT interval of patients' electrocardiograms, *Pediatr. Emerg. Care* 34 (1) (2018).
- [12] D. Obal, D. Yang, D.I. Sessler, Perioperative doses of ondansetron or dolasetron do not lengthen the QT interval, *Mayo Clin. Proc.* 89 (1) (2014) 69–80.
- [13] B. Charbit, C. Alvarez Jean, E. Dasque, E. Abe, L. Démolis Jean, C. Funck-Brentano, Droperidol and ondansetron-induced QT interval prolongation: a clinical drug interaction study, *Anesthesiology* 109 (2) (2008) 206–212.