The effects of ondansetron versus dexamethasone on electrocardiographic markers of ventricular repolarization in children undergoing cochlear implant

Reza Safaeian[a], Valiollah Hassani[a], Alimohamad Asghari[b], Masood Mohseni[a,*], Haleh Ashraf[c], Zahra Sadat Koleini[a]

[a] *Department of Anesthesiology, Iran University of Medical Sciences, Tehran, Iran*
[b] *Skull Base Research Center, The Five Senses Health Research Institute, Iran University of Medical Sciences, Tehran, Iran*
[c] *Cardiac Primary Prevention Research Center (CPPRC), Sina Hospital, Tehran University of Medical Sciences, Tehran, Iran*

ARTICLE INFO

ABSTRACT

Introduction: Congenital hearing loss is associated with cardiac rhythm disturbances namely long Q-T syndrome. This study was designed to investigate the effect of anti-emetic doses of ondansetron and dexamethasone on ECG recordings in children undergoing cochlear implant surgery.

Methods: Sixty-three pediatric patients scheduled for elective cochlear implantation were enrolled in the study. Two patients were excluded as their baseline ECG showed long QT syndrome. Anesthesia was induced with fentanyl, propofol and atracurium and maintained with propofol. Dexamethasone 0.1 mg.kg^{-1} or ondansetron 0.2 mg.kg^{-1} was randomly administered for the participants approximately 30 min before the end of surgery. ECG recording was performed 15 min after induction of anesthesia and 15 min after dexamethasone/ondansetron administration. RR interval, QRS duration, QT interval, and Tp-e interval were measured by a blinded cardiologist.

Results: Ondansetron resulted in no significant changes in RR, JTc and QTc intervals; while prolonged Tp-e interval. Multivariable logistic regression analysis showed that use of ondansetron was an independent predictor of QTc prolongation after adjustment for age, gender and baseline QTc (OR = 17.94, CI 95% 1.97–168.70, p = 0.011). The incidence of postoperative retching/vomiting in ondansetron group was significantly lower than dexamethasone group. (3.2% vs. 26.7%, p = 0.011).

Conclusion: The risk of arrhythmias with the use of ondansetron in otherwise healthy candidates of cochlear implant is very low. However, the drug may induce significant changes in ECG parameters. The clinical significance of these changes in patients with cardiac conduction abnormalities should be investigated in further studies.

1. Introduction

Nowadays, many children are admitted for cochlear implant for early onset inherited hearing loss [1]. One common complication of the surgery is post-operative nausea and vomiting (PONV) due to manipulation of the inner ear [1–3]. Common groups of antiemetic dugs including dopamine receptor antagonists like droperidol, 5HT3R receptor antagonists like ondansetron and corticosteroids such as dexamethasone may provoke the risk of QT prolongation [4,5]. Long QT interval is partly because of delayed repolarization of the ventricles that might lead to arrhythmias such as ventricular tachycardia and torsade de point [6]. The frequency of long QT syndrome (LQTS) in children

among all patients with congenital deafness is thought to be less than 1 in 50,000. However, patients with congenital sensorineural hearing loss including Jervell and Lange-Nielsen syndrome are already at increased risk of sudden cardiac death, even being asymptomatic before [7]. This necessitates ECG screening and a safe plan of anesthesia considering the potential for arrhythmogenicity of medications.

New electrical markers, including the interval between the peak and the end of the T wave (T p-e), stand out due to their ability to suggest the presence of refractory transmural dispersion, with potential application in the stratification of arrhythmogenic risk in different populations [8–12]. The JT interval is more effective for ventricle repolarization as it has been described more specific for arrhythmia prognosis

---

in patients with QRS duration more than 120 ms. It has been also described as an independent risk factor for sudden death in patients with coronary artery disease. However, little is known about the behavior of these markers in children undergoing anesthesia. This study was conducted to investigate the effect of anti-emetic doses of ondansetron and dexamethasone on QTc, Tp-e and JTc intervals in children undergoing cochlear implant surgery.

2. Methods

2.1. Study population

Sixty-one pediatric patients scheduled for elective one-sided cochlear implantation were enrolled in the study. The diagnosis of deafness in pre-lingual cases was confirmed with otoacoustic emission (OAE) and auditory brainstem response (ABR) tests. In post-lingual subjects, pure tone audiometry was done. For more evaluation temporal bone CT scan or MRI was done according to our cochlear implant center policy. The exclusion criteria were children with known cardiac disease including arrhythmias or conduction abnormalities, taking medicine known to induce conduction abnormalities, thyroid disease and abnormal serum electrolyte measurements. With the approval of the medical ethics committee of the university, the clinical trial was registered as IRCT number of IRCT2016122031487N1.

2.2. Protocol of anesthesia

The children were conducted to the waiting room 30 min before the surgery. They were premedicated with oral midazolam 0.4 mg kg^{-1} in 20 ml clear apple juice. After approximately 20 min a trace of ECG was taken to rule out long Q-T syndrome or other conduction abnormalities. For those with insufficient sedation to obtain ECG an intravenous access was applied and an additional dose of midazolam 0.05 mg.kg^{-1}was administered. Then the children were transported to the operating room. Children who required inhalation anesthesia to apply IV access and those who were not satisfactorily immobile to obtain ECG were excluded from study.

After standard monitoring, anesthesia was induced with fentanyl2ug.kg^{-1}, propofol 2 mg.kg^{-1}and atracurium 0.5 mg.kg^{-1}and maintained with propofol. Intubation was performed by an expert anesthesiologist for minimum sympathetic stimulation. Mechanical ventilation was conveyed with 50% oxygen/air to maintain normocapnia. Percutaneous temperature monitoring was applied intraoperatively. Forced warmed air with blanket was used to maintain normothermia.

2.3. Study protocol

Twelve lead ECG was taken fifteen minutes after induction of anesthesia. During this period the patients were only positioned, draped, and nerve monitoring was applied to minimize painful stimuli. The ECG recordings were obtained at the supine position with a paper speed of 50 mm/s and voltage of 10 mm/mV. Dexamethasone 0.1 mg.kg^{-1}or ondansetron 0.2 mg.kg^{-1}was randomly administered for the participants 30 min before the end of surgery. The randomization was conducted by a research assistant not involved in the study using computer generated random numbers which were allocated in sealed envelopes. The drugs were prepared in a 5 ml syringes diluted with normal saline. The second ECG was performed 15 min after the administration of dexamethasone/ondansetron. The occurrence of vomiting or retching of children at the recovery was also recorded by a blinded observer. Vomiting was objectively recorded but we could not find a validated nausea rating scale for very young children. Thus, we defined retching subjectively as facial expressions of furrowed brow, sweat and open mouth with head and neck movements usually seen before vomiting. These facial expressions have been validated earlier for older children.

2.4. Electrocardiography measurements

RR interval, QRS duration, QT interval, and Tp-e interval were measured manually. Tp-e/QT ratio and Tp-e/QTc ratio were calculated from these measurements. QT interval was defined as the time from the onset of the QRS complex to the end of the T wave. QTc interval was calculated by using the Bazett's formula (QT/√RR). QTc prolongation was defined as ≥ 470 ms for boys and ≥480 ms for girls. Clinically significant QTc prolongation was defined as QT interval more than 500 ms or 60 ms increase in QTc from baseline [13]. The JTc has been proposed as a more appropriate measure of ventricular repolarization than QTc when QRS duration is ≥ 120 ms.

Tp-e interval was measured from the peak of T wave to the end of T wave. The end of the T wave was defined as intersection of tangent to the down slope of T wave and isoelectric line. When the U wave is present T wave end was defined as the nadir between the T wave and U wave. The Tp-e interval was also expressed as a ratio to the duration of QT ([TpTe/QT] × 100%). Measurements of the Tp-e interval were performed in leads V2 and V5. The mean value of the measurements was used in the analysis. All measurements were performed by a blinded cardiologist.

2.5. Statistical analyses

Statistical analyses were performed with SPSS version 18 for windows (SPSS Inc., Chicago, IL, USA). Data were expressed as frequency (%), mean ± SD or Median (interquartile ranges). Comparison of variables between ondansetron and dexamethasone groups was done using independent T test for parametric and Mann-Withney U for nonparametric ones. Paired *t*-test was used for within group comparison of ECG parameters. We used multivariable logistic regression to assess the association between drugs used and the occurrence of QTc exceeding 500 ms. Age and sex of participants were considered as potential confounders. P values < 0.05 considered statistically significant.

3. Results

3.1. Baseline measurements

Seventy-two pediatric patients with the average age of 3 years old were included. Of those, nine patients were excluded because of insufficient sedation to obtain baseline ECG or inability to apply IV access without inhalation anesthesia. Two other participants were excluded as their baseline ECG showed QT interval more than 500 ms. Thirty one patients from the ondansetron group and 30 patients in the dexamethasone group included in analyses. The consort flow diagram has been provided Fig. 1. The median (range) age of patients in the ondansetron and in dexamethasone groups were comparable (38 (14–207) vs. 40 (21–150) months, p = 0.92). Sex distribution was comparable as well (male sex 67% in the ondansetron group versus 43% in the dexamethasone group, p = 0.05). The duration of anesthesia in ondansetron group was 91 ± 14 min and in dexamethasone group 84 ± 13 min (p = 0.3). Analyses of ECG parameters before antiemetic treatment showed similar results in two groups (Table 1, p > 0.05).

3.2. Within group comparisons

Table 1 shows ECG parameters before and after antiemetic treatments. In ondansetron group, there was no significant changes regarding heart rate, JTc and QTc intervals; while Tp-e interval increased by 10 ms on average following drug administration (p = 0.008). These indices showed no significant change after dexamethasone administration (Table 1). Seven patients in the ondansetron group and five patients in the dexamethasone group showed significant increase in QTc; defined as QT interval more than 500 ms or 60 ms increase in QTc
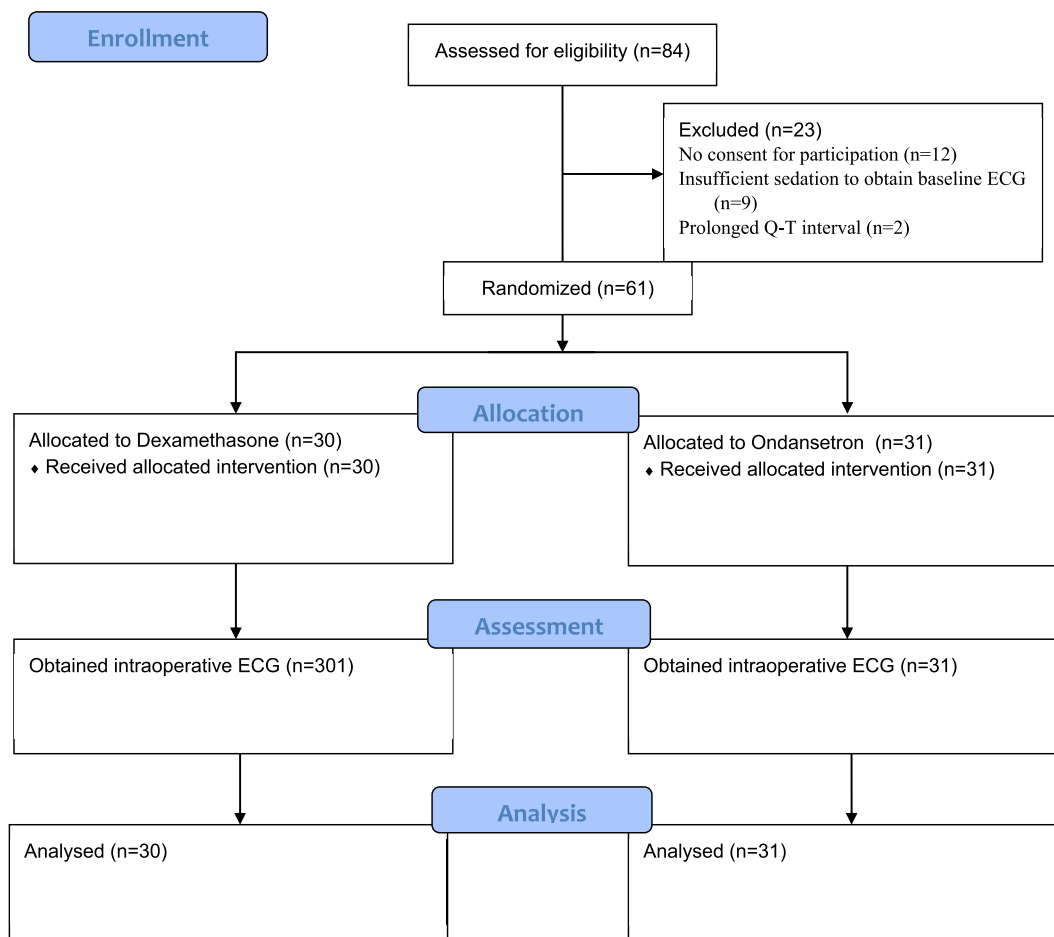
Enrollment

Assessed for eligibility (n=84)

Excluded (n=23)
No consent for participation (n=12)
Insufficient sedation to obtain baseline ECG
  (n=9)
Prolonged Q-T interval (n=2)

Randomized (n=61)

Allocation

Allocated to Dexamethasone (n=30)
♦ Received allocated intervention (n=30)

Allocated to Ondansetron (n=31)
♦ Received allocated intervention (n=31)

Assessment

Obtained intraoperative ECG (n=301)

Obtained intraoperative ECG (n=31)

Analysis

Analysed (n=30)

Analysed (n=31)

Fig. 1. Consort Flow Diagram

Table 1
ECG values at baseline and after ondansetron/dexamethasone administration.

Medication	ECG values	Before treatment	After treatment	P value
Ondansetron (n = 31)	Heart rate	110 (27)	115 (36)	0.37
	QTc (ms)	423 (40)	438 (67)	0.24
	JTc (ms)	327 (37)	342 (51)	0.22
	Tp-e (ms)	78 (16)	88 (20)	0.008
	TpTe/QTc	0.19 (0.04)	0.22 (0.13)	0.20
Dexamethasone (n = 30)	Heart rate	113 (25)	113 (40)	0.96
	QTc (ms)	424 (40)	409 (86)	0.37
	JTc (ms)	325 (31)	324 (69)	0.93
	Tp-e (ms)	80 (17)	79 (16)	0.66
	TpTe/QTc	0.19 (0.04)	0.22 (0.15)	0.23

Data presented as mean (SD).

from baseline.

3.3. Multivariable analysis

We used multivariable logistic regression to assess the association between drugs used and the fraction of postoperative QTc exceeding 500 ms. Analysis showed that the choice of anti-emetic medication is not an independent predictor of QTc > 500 ms.(OR = 4.89, 95% CI = 0.455–52.73, p = 0.19). However, when QTc prolongation was defined as > 470 ms for men and > 480 ms for women, administration of ondansetron was an independent predictor of QTc prolongation after adjustment for age, gender and baseline QTc (OR = 17.94, CI 95% 1.97–168.70, p = 0.011).

No clinically significant arrhythmias were reported in either group. The incidence of PONV in the ondansetron group was significantly less than the dexamethasone group (3.2% vs. 26.7%, p = 0.011).

4. Discussion

We encounter a triangle to be broken. Candidates of cochlear implant may suffer from prolonged QT interval [14], they are prone to PONV [1], and many antiemetics are known to prolong QT interval [12,15].The results of this study showed minor changes in JTc, JT and QTc intervals, but only Tp-e as a predictor of torsadogenicity was significantly increased after ondansetron administration. Nevertheless, ondansetron provided better protection against PONV without producing clinically significant arrhythmias.

Serotonin receptors on the gastrointestinal tract, postrema, and nucleus solitarius are responsible for nausea and vomiting. Blockade of these receptors can reduce the incidence of nausea and vomiting. Ondansetron is a well-known 5HT receptor antagonist which is known for its anti-emetic properties. It blocks the human ether-a-go-go related gene (hERG) potassium channels and increases the action potential thus may prolong QT interval. Dexamethasone expresses its antiemetic properties with the mechanism of prostaglandin synthesis inhibitor. Increasing the permeability of the blood brain barrier may also contribute to its antiemetic properties [16–19]. Earlier reports have suggested that dexamethasone may suppresses long QT phenotype [20]. The possible explanation might be the potential of shortening the

ventricle action potential that has been addressed in animal models. Taken together, dexamethasone seems to be safe in candidates of cochlear implant. Its efficacy is the question to be answered.

Most of earlier studies have reported that ondansetron prolongs QT interval. It seems that this effect is dose-dependent [5,8,21], more common in females [6] and occurs about 15 min after drug administration [10]. However, reports of arrhythmias are rare [22] and usually limited to those patients with history of severe cardiac disease [7]. Few studies have measured Tp-e interval [4,5]. This interval indicates transmural dispersion of repolarization. Similar to our findings, prolonged Tp-e interval as a consequence of ondansetron administration was not associated with torsadogenicity or any clinically significant arrhythmias.

4.1. Study limitations

We excluded the patients with known cardiac rhythm disturbances. Thus, generalization of findings to this subgroup of patients is difficult. Another limitation of this study is that the half-life of ondansetron is 5–7 h and we did not evaluate the ECG recordings in this period of time. We could not find a validated scale to evaluate the severity of nausea in children with average age of three years. Thus, the reported incidence of retching/vomiting can roughly estimate this secondary outcome of the study.

4.2. Conclusion

Ondansetron more effectively prevents PONV and the risk of its arrhythmogenecity in otherwise healthy candidates of cochlear implant is very low. Thus, it seems to be a better choice than dexamethasone in patients with QTc < 470 ms. The clinical significance of prolonged Tp-e interval and arrhythmogenecity of ondansetron in patients with cardiac conduction abnormalities should be investigated in further studies.

Declaration of competing interest

None to disclose.

Acknowledgment

References

[1] A. Chakrabarty, V.K. Tarneja, V.K. Singh, P.K. Roy, A.K. Bhargava, D.K. Sreevastava, Cochlear implant: anaesthesia challenges, Med. J. Armed Forces India 60 (4) (2004 Oct) 351–356.

[2] 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 May) 421–431.

[3] 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 Jul) e317–e323.

[4] D. Mehta, S. Sanatani, S.D. Whyte, The effects of droperidol and ondansetron on dispersion of myocardial repolarization in children, Paediatr. Anaesth. 20 (10) (2010 Oct) 905–912.

[5] 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 Nov) 511–516.

[6] M.J. Hafermann, R. Namdar, G.E. Seibold, R.L. Page, Effect of intravenous ondansetron on QT interval prolongation in patients with cardiovascular disease and additional risk factors for torsades: a prospective, observational study, Drug Healthc. Patient Saf. 3 (2011) 53–58.

[7] P.J. Schwartz, L. Crotti, R. Insolia, Long QT syndrome: from genetics to management, Circ. Arrhythm Electrophysiol. 5 (4) (2012 Aug 1) 868–877.

[8] K.E. Trinkley, R.L. Page, H. Lien, K. Yamanouye, J.E. Tisdale, QT interval prolongation and the risk of torsades de pointes: essentials for clinicians, Curr. Med. Res. Opin. 29 (12) (2013 Dec) 1719–1726.

[9] J.E. Tisdale, H.A. Wroblewski, B.R. Overholser, J.R. Kingery, T.N. Trujillo, R.J. Kovacs, Prevalence of QT interval prolongation in patients admitted to cardiac care units and frequency of subsequent administration of QT interval-prolonging drugs: a prospective, observational study in a large urban academic medical center in the US, Drug Saf. 35 (6) (2012 Jun 1) 459–470.

[10] B. Obal, 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 Jun) 1094–1100.

[11] 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 Jan) 69–80.

[12] Arteyeva NV, Goshka SL, Sedova KA, Bernikova OG, Azarov JE. What does the T(peak)-T(end) interval reflect? An experimental and model study. J. Electrocardiol. 2013; 46: 296.e1-296.e8.

[13] J.N. Johnson, M.J. Ackerman, QTc: how long is too long? Br. J. Sports Med. 43 (9) (2009) 657–662.

[14] A. Khosravi, S. Amirsalari, M. Ajalloueyan, A. Honaramooz, R.I. Tafreshi, A. Saburi, The frequency of congenital long QT syndrome based on new formula in children with sensori-neural hearing loss, Indian J. Otol. 21 (2015) 114–118.

[15] C. Antzelevitch, A. Oliva, Amplification of spatial dispersion of repolarization underlies sudden cardiac death associated with catecholaminergic polymorphic VT, long QT, short QT and Brugada syndromes, J. Intern. Med. 259 (2006) 48–58.

[16] J. Hawthorn, D. Cunningham, Dexamethasone can potentiate the anti-emetic action of a 5HT3 receptor antagonist on cyclophosphamide induced vomiting in the ferret, Br. J. Cancer. 61 (1) (1990 Jan) 56–60.

[17] J.F. Smyth, R.E. Coleman, M. Nicolson, W.M. Gallmeier, R.C. Leonard, M.A. Cornbleet, et al., Does dexamethasone enhance control of acute cisplatin induced emesis by ondansetron? BMJ 303 (6815) (1991 Dec 7) 1423–1426.

[18] D.B. Smith, E.S. Newlands, O.W. Spruyt, R.H. Begent, G.J. Rustin, B. Mellor, etal, Ondansetron (GR38032F) plus dexamethasone: effective anti-emetic prophylaxis for patients receiving cytotoxic chemotherapy, Br. J. Canc. 61 (2) (1990 Feb) 323–324.

[19] P.J. Hesketh, W.H. Harvey, W.G. Harker, T.M. Beck, T. Ryan, L.J. Bricker, J.A. Kish, et al., A randomized, double-blind comparison of intravenous ondansetron alone and in combination with intravenous dexamethasone in the prevention of high-dose cisplatin-induced emesis, J. Clin. Oncol. 12 (3) (1994 Mar) 596–600.

[20] J.R. Winterfield, D.J. Milan, Dexamethasone suppresses long QT phenotype in patient with acute promyelocytic leukemia treated with arsenic, HeartRhythm Case Rep. 2 (4) (2015 Sep 8) 280–282.

[21] B. Charbit, J.C. Alvarez, E. Dasque, E. Abe, J.L. Démolis, C. Funck-Brentano, Droperidol and ondansetron-induced QT interval prolongation: a clinical drug interaction study, Anesthesiology 109 (2) (2008 Aug) 206–212.

[22] D. Zeltser, D. Justo, A. Halkin, V. Prokhorov, K. Heller, S. Viskin, Torsade de pointes due to noncardiac drugs: most patients have easily identifiable risk factors, Medicine (Baltimore) 82 (4) (2003 Jul) 282–290.