Eur Arch Otorhinolaryngol
DOI 10.1007/s00405-012-2179-0

OTOLOGY

Ondansetron in patients with tinnitus: randomized double-blind placebo-controlled study

Shervin Taslimi · Hamed Vahidi · Ali Pourvaziri · Amirhossein Modabbernia · Arezoo Yeke Fallah · Nasrin Yazdani · Negin Taslimi · Mostafa Hosseini · Masoud Motesadi Zarandi

Received: 17 April 2012 / Accepted: 6 September 2012

Abstract The aim of this study was to assess the effect of ondansetron on symptoms of patients with subjective tinnitus accompanied by sensorineural hearing loss or normal hearing. Sixty patients with a chief complaint of tinnitus (with duration of more than 3 months) were equally randomized to ondansetron or placebo for 4 weeks. The dose of ondansetron was gradually increased from 4 mg/day (one tablet) to 16 mg/day (4 tablets) during 12 days and then continued up to 4 weeks. The exact number of tablets was prescribed in the placebo group. Patients underwent audiologic examinations and filled questionnaires at baseline and after 4 weeks of treatment. Our primary outcomes were changes in Tinnitus Handicap Inventory questionnaire (THI), Tinnitus Severity Index (TSI) and visual analog scale (VAS) scores. Our secondary outcomes were the changes in depression and anxiety based on Hospital Anxiety and Depression (HADS) questionnaire, side effects, tinnitus loudness matching, tinnitus pitch matching, pure tone audiometry and speech recognition threshold (SRT). In the ondansetron and placebo groups, 27 and 26 patients completed the study, respectively. The changes in VAS ($P = 0.934$), THI ($P = 0.776$), anxiety ($P = 0.313$) and depression ($P = 0.163$) scores were not different between the groups. TSI score decreased significantly in the ondansetron compared with the placebo group ($P = 0.004$). Changes in tinnitus loudness matching ($P = 0.75$) and pitch matching ($P = 0.56$) did not differ between the two groups. Ondansetron, but not placebo, decreased the SRT threshold (right, $P < 0.001$; left, $P = 0.043$) and mean PTA (right, $P = 0.006$; left, $P < 0.001$). In conclusion, ondansetron reduces the severity of tinnitus hypothetically through cochlear amplification.

Keywords Tinnitus · Ondansetron · Alpha9–alpha10 receptor · Cholinergic receptor · Nicotinic receptor

Introduction

Tinnitus is a perceived sound that cannot be attributed to an external sound [1]. The prevalence of tinnitus has been reported from 3 to 30 % [2, 3]. This wide range can be explained by numerous types of tinnitus, which are all grouped under the same name. Tinnitus may give rise to considerable distress and represents a great burden to sufferers and thereby the society [4]. About 5–10 % of tinnitus sufferers have severe symptoms that interfere with their quality of life [3].

Chronic tinnitus has divergent etiologies and generally is divided into subjective and objective categories. The etiology of objective tinnitus can usually be identified and treatment usually addresses the main etiology. Sometimes, subjective tinnitus might be caused by an identifiable etiology (infection, mass lesions, particular ear disease and

S. Taslimi · H. Vahidi · A. Pourvaziri · A. Y. Fallah · N. Yazdani · N. Taslimi · M. M. Zarandi
Otorhinolaryngology Research Center,
Tehran University of Medical Sciences, Tehran, Iran

S. Taslimi · M. Hosseini
Department of Epidemiology and Biostatistics,
School of Public Health, Tehran University of Medical Sciences,
Tehran, Iran

S. Taslimi (✉)
Otorhinolaryngology Research Center, Amir Aalam Hospital,
North Saadi Ave, Tehran, Iran
e-mail: taslimi@razi.tums.ac.ir

A. Modabbernia
Department of Psychiatry, Roozbeh Psychiatric Hospital,
Tehran University of Medical Sciences, Tehran, Iran

Published online: 22 September 2012

psychiatric problems) and in such circumstances treatment can be targeted to the identified etiology [5]. However, patients with identifiable etiologies account for only a small proportion of subjective tinnitus cases. Besides the aforementioned tinnitus cases, most cases of subjective tinnitus are associated with hearing impairment. Subjective tinnitus secondary to conductive hearing loss can be completely or partially alleviated with surgical interventions targeted at the cause of the hearing loss. In such cases of tinnitus related to conductive hearing loss, restoring hearing by means of surgery is indeed frequently effective in alleviating tinnitus [6]. In contrast, tinnitus which is associated with sensorineural hearing loss (SNHL) or normal hearing is still a great therapeutic challenge. Despite large expectation for an effective and safe drug to treat tinnitus, many drugs which have been used for this disturbing condition are either ineffective or have major side effects [7].

Tinnitus can be viewed as resulting from an imbalance between excitation and inhibition processes at various levels of auditory pathways [8]. The outer hair cells (OHC) are key cells for providing feedback to external sounds and cochlear amplification. The medial olivocochlear (MOC) bundle plays an important role in the physiological regulation of OHCs. The activation of MOC fibers leads to inhibition of OHCs through a unique nicotinic cholinergic receptor, the $\alpha 9\alpha 10$ receptor. This results in decreased amplification and sensitivity of the cochlea [9]. Overall, in physiological conditions, olivocochlear efferent neurons allow the central nervous system to control the processing of sounds in the auditory periphery [10] by offering the potential to increase sensitivity to detect background sounds, selectively concentrate on particular signals [11] and protect the peripheral auditory system from overly loud noises [12].

Chronic tinnitus characteristically escapes the auditory system and is perceived by centers in CNS [13]. However, administration of a drug with potential effects on the periphery may be justified by the fact that in patients in whom tinnitus is associated with hearing loss, tinnitus is expected to be softened after drug-induced hearing improvement [14]. Ondansetron, besides its well-known 5-HT3 antagonistic effects which makes it an effective antitussive drug, is able to block $\alpha 9\alpha 10$ receptors [15]. We hypothesized that ondansetron by blocking $\alpha 9\alpha 10$ receptors may increase amplification and sensitivity of the cochlea to external stimuli and consequently alleviate the tinnitus [16].

Materials and methods

Design and settings

This study was a randomized double-blind placebo-controlled parallel-group trial conducted in the outpatient tinnitus clinic of Amir Alam Hospital, Tehran, Iran from May to November 2011. Other physicians dealing with tinnitus patients in all other major university affiliated hospitals in Tehran were requested to refer patients with chronic tinnitus to our clinic.

Ethics

This trial conformed to the Declaration of Helsinki and subsequent revisions and approved by the Institutional Review Board of Tehran University of Medical Sciences. The study was explained to the participants and written informed consent was obtained from all patients before entering the study. All patients were told that they could withdraw from the study at any time.

Participants

Patients aged 18–70 years with a chief complaint of tinnitus for at least 3 months with SNHL or normal hearing were enrolled in the study.

Patients with the following characteristics were excluded from the study: (a) cerumen impaction (unless tinnitus remained after cerumen removal); (b) pulsatile tinnitus; (c) worsening of tinnitus with head and neck movements; (d) pregnancy or lactation; (e) severe illness including liver, kidney and heart problems that might interfere with the drug; (f) psychiatric problems needing psychiatric therapy; (g) CNS tumors such as acoustic neuroma or brainstem tumor (MRI obtained from all of the patients).

Randomization and allocation concealment

Sixty patients were equally randomized to ondansetron or placebo using block permuted randomization with block size of four. The eligibility criteria were evaluated by an expert otolaryngologist and eligible patients were referred to an assigned secretary for receiving the tablets. The randomization sequence was concealed in sequentially numbered, opaque and sealed envelopes. All recordings regarding the type of medication remained secret till the end of study.

Study protocol

One expert audiologist was appointed for audiologic assessments during the time of the clinic. Audiologic tests were: (1) pure tone audiometry up to 12 kHz, (2) maximal comfortable level (MCL), (3) uncomfortable level (UCL), (4) speech recognition threshold (SRT), (5) speech discrimination, (6) loudness matching (dB) and pitch matching (kHz) of tinnitus and (7) tympanometry with acoustic reflex. All audiologic tests were done at baseline and those

related to outcome measures were performed after 4 weeks of treatment.

Patients filled baseline characteristics questionnaire on the day of randomization. All patients were requested to fill several questionnaires before and after 4 weeks of treatment. The questionnaires included: (1) Tinnitus Handicap Inventory (THI), (2) Tinnitus Severity Index (TSI), (3) Hospital Anxiety and Depression Scale (HADS) and (4) visual analog scale (VAS).

The THI questionnaire consists of 25 items with three choice answers: [yes (4 point), sometimes [2], no (0)]. The THI questionnaire mainly evaluates the negative impact of tinnitus on the patient's life [17].

Tinnitus Severity Index questionnaire contains 12 questions which mainly evaluates the negative impact of tinnitus on the quality of life of the patients, as well as the magnitude of perceived annoyance by the patient. The answer to each question is through five possible choices: never (1 point), rarely (2), sometimes (3), usually (4) and always (5). The possible total scores range from 12 to 60 [18].

VAS score of the loudness of tinnitus was measured in standard fashion (with pencil and paper) in line with the consensus conference of IVth International Tinnitus Seminar, Bordeaux, 1991. The value of 0 corresponded to "no tinnitus" and 10 to "the worst imaginable tinnitus".

The HADS questionnaire consists of 14 questions. Items with even numbers evaluate depression and those with odd numbers evaluate anxiety. Each item is a four-point Likert-type scale (score range 0–3). A higher score on the questionnaire suggests a greater level of anxiety and/or depression [19].

The pitch and loudness of tinnitus were evaluated based on patient's reports of matched externally presented sound in pitch (kHz) (measured by presenting multiple octave and inter-octave tones) and loudness (dB) (measured in 1 dB steps) of the tinnitus [20, 21].

This is a type II clinical pharmacological study. The dose of ondansetron was gradually increased from 4 mg/day (one tablet) to 16 mg/day (4 tablets) during 12 days (4 mg increase every 3 days) and then continued up to 4 weeks. The exact number of tablets was calculated for placebo group.

Outcome

Outcomes of the present study were chosen based on the Regensburg consensus (July 2006) recommendations [22].

Our primary outcomes were change of THI, TSI and VAS scores. Our secondary outcomes were the changes in depression and anxiety based on HADS questionnaire, side effect, tinnitus loudness match, tinnitus pitch match, PTA and SRT.

Statistical analysis and sample size calculation

For detecting a large difference (effect size >0.4) in an ANCOVA analysis at the significance level of 0.05 and the power of 85 %, we needed a total sample size of 60. For baseline continuous variables, normality was tested using Kolmogrov–Smirnov (KS) test, skewness and its standard error (SE). If the normality was not markedly violated, *t* test was used for group comparison; otherwise, Mann–Whitney U test was applied. Moreover, if the normality assumption was not markedly violated, ANCOVA was applied for group comparisons. For comparing categorical variables (side effects), Chi-square test was used. To test the association of variables, Pearson's correlation coefficient was used. For analyzing the outcome measures, mean PTA was calculated by averaging the hearing threshold in 500, 1,000 and 2,000 kHz. For comparing the baseline characteristics, mean PTA was also calculated by averaging all the measured points. In the post hoc subgroup analysis, high-frequency hearing loss was defined as the average hearing loss more than the median of the placebo group. All analyses used two-sided test of significance. The level of significance was considered to be 0.05. Intention to treat analysis was applied in all analyses. Missing data were imputed based on baseline data using STATA software (version 11) [23].

Results

Three patients from the ondansetron group and four from the placebo group were lost to follow-up (Fig. 1). The baseline characteristics of the two groups were the same. Table 1 summarizes the baseline characteristics of the two groups. Of note, considerable proportion of our patients had a family history of tinnitus (33 % in ondansetron vs. 27 % in placebo).

Baseline mean PTA (calculated based on all measured points) was the same in both groups. The baseline data on UCL (right, $P = 0.77$; left, $P = 0.92$), MCL (right, $P = 0.44$; left, $P = 0.53$) and speech discrimination (right, $P = 0.16$; left, $P = 0.33$) did not significantly differ between the two groups. Tympanometry parameters were the same in the two groups at baseline.

The change in THI score did not significantly differ between the two groups ($P = 0.776$). Improvement of TSI score was significantly greater in the ondansetron group than the placebo group ($P = 0.004$). Loudness of tinnitus measured by VAS did not change differently in the two groups ($P = 0.934$) (Table 2).

The changes in depression, anxiety and total HADS score were not different between the two groups ($P = 0.163$, 0.313 and 0.922, respectively). Tinnitus

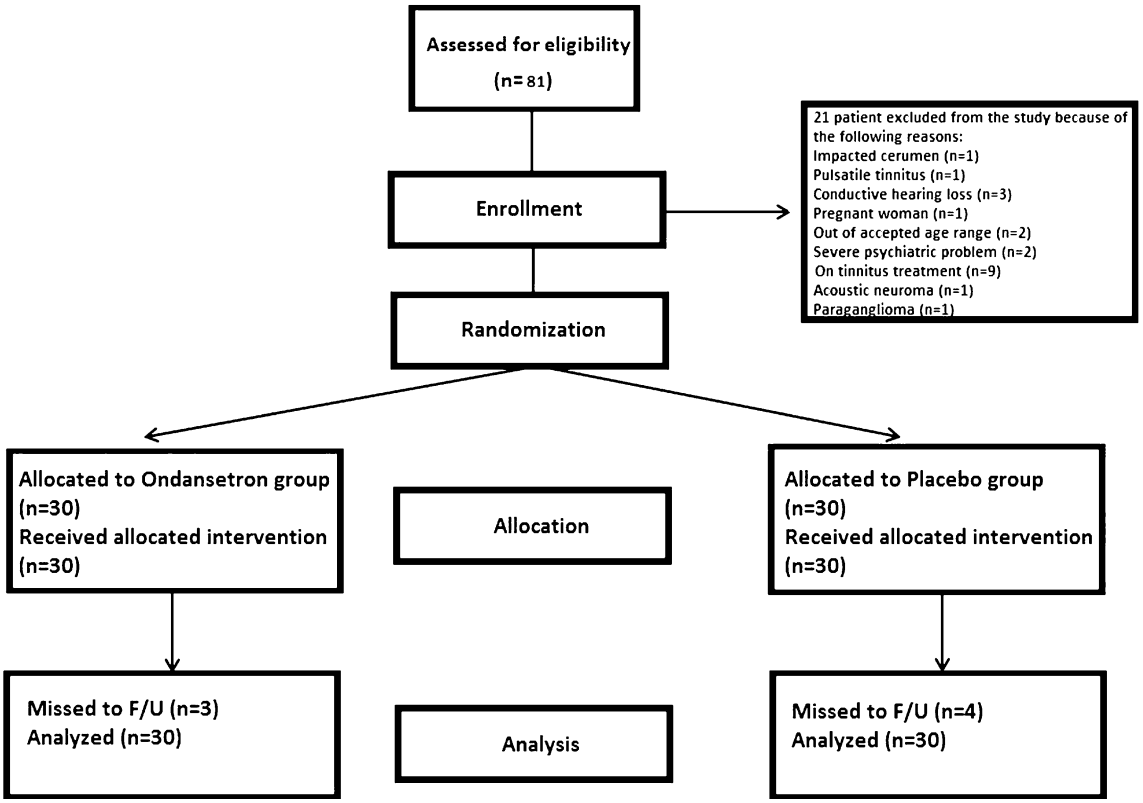

Fig. 1 CONSORT flow diagram

loudness (dB) and pitch matching (kHz) were not differently changed in the two groups. Both measures of hearing ability (mean PTA and SRT) significantly improved in the ondansetron group compared with the placebo group. Table 2 summarizes the change in primary and secondary outcomes in the ondansetron and the placebo groups.

Decease in the TSI score had a significant correlation with SRT and mean PTA change in the affected ear ($r = 0.52$, $P = 0.039$ and $r = 0.72$, $P = 0.006$, respectively) in the ondansetron group, but not in the placebo group ($r = 0.26$, $P = 0.25$ and $r = 0.33$, $P = 0.129$). In the placebo group, the change in the TSI score ($r = 0.498$, $P = 0.01$) and THI score ($r = 0.64$, $P < 0.001$) had significant correlation with depression change, but both changes in the TSI ($r = 0.26$, $P = 0.26$) and THI ($r = 0.35$, $P = 0.085$) scores were not correlated significantly with depression change in the ondansetron group.

In terms of hearing improvement, patients with high-frequency hearing loss did benefit more from ondansetron compared with patients with low-frequency hearing loss (right ear: mean difference, 4.93; t(df), 2.45(25); $P = 0.021$; left ear: mean difference, 7.43; t(df), 2.45(25); $P = 0.004$), while this improvement was not different in the placebo group (right ear: mean difference, 0.72; t(df), 0.778(24); $P = 0.444$; left ear: mean difference, 2.9; t(df), 1.55(24); $P = 0.132$).

No serious adverse events were recorded during the course of the study. Three patients in the ondansetron group developed abdominal cramp during the first week of receiving the drug. In all of three patients, cramps subsided in a few days without any intervention.

Discussion

According to our results, ondansetron decreased TSI score and improved hearing ability although further clarification is necessary. We hypothesize that ondansetron improves tinnitus through hearing improvement. To the best of our knowledge, this is the first study which evaluated the application of ondansetron, a well-known anti-emetic agent, in patients with tinnitus.

Both THI and TSI questionnaires measure the tinnitus-related distress, disability and handicap [22]. In the present study, ondansetron decreased TSI, but not THI score significantly more than the placebo. So far, there is no consensus regarding the importance of several available questionnaires for the measurement of different aspects of tinnitus in clinical trials, although some suggestions have been made recently [22]. The THI questionnaire has been developed prior to development of TSI questionnaire and has been validated in more languages than the TSI

Table 1 Baseline characteristics of the patients

Variable	Ondansetron ($n = 30$)	Placebo ($n = 30$)
Sex, female (%)	8 (27)	12 (40)
Dominant hand, right (%)	19 (63)	21 (70)
PTA, right ear, mean (SD)	30 (14.3)	27 (8.7)
PTA, left ear, mean (SD)	34 (14.6)	33 (10.9)
Family history of tinnitus, no (%)	20 (67)	22 (73)
Onset, sudden (%)/gradual (%)	17 (57)/13 (43)	18 (60)/12 (40)
Cause, loud noise (%)/others (%)	7 (23)/23 (77)	9 (30)/21 (70)
Location, right (%)/left (%)[a]	12 (40)/18 (60)	11 (37)/19 (63)
Day to day variation (%)	21 (70)	20 (67)
Quality[b], sound (%)/ring (%)	7 (23)/23 (77)	12 (40)/18 (60)
Maskability[c] (%)	11 (37)	14 (47)
Exaggeration with loud noise (%)	14 (47)	18 (60)
Effect of sleep during daytime, change (%)/no change (%)	9 (30)/21 (70)	9 (30)/21 (70)
Effect of sleep at night, no (%)/yes (%)/don't know (%)	18 (60)/6 (20)/6 (20)	17 (57)/3 (10)/10 (33)
Effect of anxiety, worse (%)/better (%)/no change (%)	15 (50)/4 (13)/11 (37)	15 (50)/5 (17)/10 (33)
Hyperacusis[d], never or seldom (%)/ >sometimes (%)	15 (50)/15 (50)	11 (37)/19 (63)
Pain due to voices (%)	9 (30)	12 (40)
Headache (%)	8 (27)	11 (37)
Vertigo (%)	8 (27)	10 (33)
Pain in body (%)	12 (40)	13 (43)
Do you have hearing problem, yes (%)	15 (50)	11 (37)
Age, years, mean (SE)	52.06 (2.33)	52.4 (1.96)
Duration, median in month (range)	36.0 (3–480)	60 (3–360)
Percentage of awareness, median (range)	100 (20–100)	96 (50–100)
Percentage of nervousness, median (range)	50 (0–100)	50 (30–100)

[a] Left means only left or left domination, right means only right or right domination

[b] Patients were asked to state whether their tinnitus was more like a sound or a ring

[c] Exact question"Is your tinnitus reduced by music or by certain types of environmental sounds such as the noise of a waterfall or the noise of running water when you are standing in the shower?"

[d] Exact question"Do you often find too loud or hurtful sounds which other people around you find quite comfortable?"

questionnaire. Most of the questions of the TSI questionnaires consist of five-point Likert-type scale questions, whereas items of the THI questionnaire have only three choices. Because the questions of TSI questionnaire have more choices than the THI questionnaire, it seems that TSI has more power than THI in detecting the difference between different treatment groups.

The THI and TSI questionnaires have been validated based on Beck Depression questionnaire [24]. Therefore, it is logical that the decrease in their scores may be correlated with decrease in depression scores. The decrease in the scores of both THI and TSI questionnaires were correlated with decrease in depression scores in the placebo group, but not in the ondansetron group. This suggests that mechanisms other than improvement of depression were responsible for improvement of TSI scores in the ondansetron group.

The definition of clinically significant difference in the score of THI and TSI questionnaires is not known yet [25]. In this study, decrease in the scores of THI and TSI questionnaires in the ondansetron group were in average 6.74 and 5.8 compared with 5.45 and 0.14 on the placebo group, respectively.

The decrease in hearing threshold in the affected ear had significant correlation with decrease in the score of the TSI questionnaire in the ondansetron group. nAChRs demonstrated high density in the cochlear base OHCs, but in less density in the low-frequency end of the cochlea [26]. Ondansetron improved hearing threshold in patients with high-frequency hearing loss more than ones with low-frequency hearing loss, while placebo did not change the hearing threshold differently in high-frequency and low-frequency hearing loss patients. Moreover, there were not any differences between the groups in the change in pitch

Table 2 Comparison of outcome measures between the two groups

	Ondansetron ($n = 30$)		Placebo ($n = 30$)		P value*
	Week 0	Week 4	Week 0	Week 4	
THI	53.20 (23.87)**	46.46 (22.42)	52.36 (25.6)	46.91 (24.0)	$F(1,57) = 0.08$, 0.776
TSI	39.70 (13.58)	33.90 (11.51)	35.56 (14.4)	35.70 (11.6)	$F(1,57) = 8.99$, **0.004**
Depression	5.66 (4.02)	4.40 (3.23)	5.76 (3.99)	5.36 (3.48)	$F(1,57) = 1.99$, 0.163
Anxiety	6.53 (2.88)	6.96 (3.96)	6.26 (3.92)	6.0 (3.46)	$F(1,57) = 1.03$, 0.313
HADS	12.20 (6.34)	11.36 (6.68)	12.03 (7.46)	11.36 (5.82)	$F(1,57) = 0.01$, 0.922
VAS	6.73 (2.35)	5.37 (2.52)	5.70 (1.76)	4.88 (1.90)	$F(1,57) = 0.007$, 0.934
Loudness matching (HL)[a]	59.53 (17.87)	54.75 (18.70)	60.63 (15.36)	56.26 (11.27)	$F(1,57) = 0.099$, 0.752
Pitch matching (kHz)[a]	10.48 (21.93)	10.31 (21.93)	7.70 (0.71)	7.14 (2.01)	$F(1,57) = 0.34$, 0.560
Mean PTA (right)	19.16 (9.71)	16.26 (7.07)	17.46 (6.27)	17.66 (6.47)	$F(1,57) = 8.1$, **0.006**
Mean PTA(left)	21.83 (13.25)	17.51 (8.38)	19.96 (9.44)	20.63 (8.17)	$F(1,57) = 19.6$, **<0.001**
SRT(right)	19.66 (8.41)	16.10 (6.48)	18.33 (7.11)	19.06 (7.04)	$F(1,57) = 18.8$, **<0.001**
SRT(left)	20.33 (12.39)	17.13 (8.01)	17.60 (7.34)	18.13 (5.61)	$F(1,57) = 4.28$, **0.043**

THI Tinnitus Handicap Inventory, *TSI* Tinnitus Severity Index, *HADS* Hospital Anxiety and Depression Scale (Total score), *VAS* visual analog scale, *PTA* pure tone audiometry, *SRT* speech recognition threshold

* All *P* values were derived from ANCOVA

** All data presented as mean (SD)

[a] Loudness matching and pitch matching of tinnitus

matching and loudness matching of tinnitus. These findings are in line with our hypothesis that ondansetron may exert its beneficial effects on tinnitus by blocking α9α10 nicotinic receptors in OHCs, which results in inhibition of MOC negative feedback on OHCs and subsequent increment in cochlear amplification. If this hypothesis turns out to be true, decreased severity of tinnitus with hearing improvement without any change in pitch (kHz) and loudness (dB) of tinnitus may be explained by reduction in the awareness of tinnitus and improvement in communication and probably neural plasticity [27].

In the present study, the patients were followed for 4 weeks after receiving treatment. The effect of ondansetron beyond this time is not yet clear. Moreover, there is a need to determine how long the beneficial effect of ondansetron on tinnitus patients can last once the drug is discontinued.

The baseline characteristics were the same between the two groups in our study. Because several subgroups of patients with different characteristics are known, similar baseline characteristics between the treatment groups are of paramount importance.

This study was able to show the beneficial effects of ondansetron on patients with tinnitus. Due to the method of sample size calculation, this study was underpowered to detect subgroup differences in terms of main outcomes of the study. As a result, we did not present subgroup data regarding the primary outcomes of the study. Since the effect of ondansetron on improving the hearing loss and tinnitus could probably be through modulation of the OHCs, a good subgroup analysis could be performed between patients with preserved and those with impaired function of OHCs. Another potential subgroup analysis in this regard could be between patients with normal and those with impaired hearing threshold levels. Moreover, usually low-tone tinnitus with low-frequency hearing loss responds better to treatments than high-tone tinnitus with high-frequency hearing loss, which mandates a subgroup analysis in this regard.

Calculated mean PTA using all points of measurements showed higher level of hearing impairment than calculated mean PTA using 500, 1,000 and 2,000 kHz measurements, reflecting that in our patients hearing loss was more prominent at higher frequencies. While addressing our secondary outcome measure, we calculated mean PTA based on the average of three mentioned points, since it is more compatible with speech recognition threshold and thus provides more practical assessment of hearing level [28]. In our study, the change in SRT and PTA in ondansetron was around 3 db. We think that since our patients had more hearing loss at higher frequencies than frequencies below 2,000 kHz, with our outcome measure we underestimated the hearing change which should be explicitly investigated in future studies.

This study had several limitations. Because of the nature of tinnitus, the outcomes of this study are subjective. Otoacoustic emission test (OAE) was not done to evaluate the function of OHCs. In the present study, we did not use a specific questionnaire for evaluating the response to treatment. Both THI and TSI questionnaire primarily developed

for screening and diagnostic purposes. Unfortunately, there was no specific questionnaire for evaluating the response to treatment prior to the commencement of the present study. Recently, a questionnaire for evaluating the response to treatment has been validated [29]. Because it is possible that some subgroups of tinnitus do not respond to ondansetron, we think some beneficial effects of ondansetron on tinnitus might have been diluted in this study.

In conclusion, ondansetron decreases the perception of tinnitus probably through improvement of the hearing threshold.

Acknowledgments This project was funded by the Tehran University of Medical Sciences, grant number 89-01-48-1045. The trial was registered in IRCT.ir (ID: IRCT201105185867N4). This project was MD-MPH thesis of the first author.

Conflict of interest The authors declare no conflict of interest.

References

1. Eggermont JJ (2003) Central tinnitus. Auris Nasus Larynx 30:7–12
2. Sanchez L (2004) The epidemiology of tinnitus. Audiol med 2(1):8–17
3. McFerran D, Phillips J (2007) Tinnitus. J Laryngol Otol 121(03):201–208
4. Vio MM, Holme RH (2005) Hearing loss and tinnitus: 250 million people and a US$10 billion potential market. Drug Discov Today 10(19):1263–1265
5. Chan Y (2009) Tinnitus: etiology, classification, characteristics, and treatment. Discov Med 8(42):133–136
6. Kleinjung T (2011) Surgical treatment: the ear. In: Moller AR, Landgrebe M, De Ridder D, Kleinjung T (eds) Text book of tinnitus. Springer, New York, p 663
7. Dobie RA (1999) A review of randomized clinical trials in tinnitus. Laryngoscope 109(8):1202–1211
8. Jos JE (2005) Tinnitus: neurobiological substrates. Drug Discov Today 10(19):1283–1290
9. Dallos P, Popper AN, Fay RR (1996) The cochlea. In: Springer handbook of auditory research, vol. 8. Springer, New York, pp 435–502
10. Zheng XY, Henderson D, McFadden SL, Ding DL, Salvi RJ (1999) Auditory nerve fiber responses following chronic cochlear de-efferentation. J Comp Neurol 406(1):72–86
11. Delano PH, Elgueda D, Hamame CM, Robles L (2007) Selective attention to visual stimuli reduces cochlear sensitivity in chinchillas. J Neurosci 27(15):4146–4153
12. Maison SF, Liberman MC (2000) Predicting vulnerability to acoustic injury with a noninvasive assay of olivocochlear reflex strength. J Neurosci 20(12):4701–4707
13. Eggermont JJ (2005) Tinnitus: neurobiological substrates. Drug Discov Today 10(19):1283–1290
14. Van de Heyning P, Vermeire K, Diebl M, Nopp P, Anderson I, De Ridder D (2008) Incapacitating unilateral tinnitus in single-sided deafness treated by cochlear implantation. Ann Otol Rhinol Laryngol 117(9):645–652
15. Rothlin CV, Lioudyno MI, Silbering AF, Plazas PV, Casati ME, Katz E, Guth PS, Elgoyhen AB (2003) Direct interaction of serotonin type 3 receptor ligands with recombinant and native alpha 9 alpha 10-containing nicotinic cholinergic receptors. Mol Pharmacol 63(5):1067–1074
16. Elgoyhen AB, Katz E, Fuchs PA (2009) The nicotinic receptor of cochlear hair cells: a possible pharmacotherapeutic target? Biochem Pharmacol 78(7):712–719
17. Newman CW, Jacobson GP, Spitzer JB (1996) Development of the Tinnitus Handicap Inventory. Arch Otolaryngol Head Neck Surg 122(2):143–148
18. Meikle M, Griest S, Stewart B, Press LS (1995) Measuring the negative impact of tinnitus: a brief severity index
19. Zigmond AS, Snaith RP (1983) The Hospital Anxiety and Depression Scale. Acta Psychiatr Scand 67(6):361–370
20. Henry JA, Zaugg TL, Schechter MA (2005) Clinical guide for audiologic tinnitus management II: treatment. Am J Audiol 14(1):49–70
21. Henry JA, Zaugg TL, Schechter MA (2005) Clinical guide for audiologic tinnitus management I: assessment. Am J Audiol 14(1):21–48
22. Langguth B, Goodey R, Azevedo A, Bjorne A, Cacace A, Crocetti A, Del Bo L, De Ridder D, Diges I, Elbert T, Flor H, Herraiz C, Ganz Sanchez T, Eichhammer P, Figueiredo R, Hajak G, Kleinjung T, Landgrebe M, Londero A, Lainez MJ, Mazzoli M, Meikle MB, Melcher J, Rauschecker JP, Sand PG, Struve M, Van de Heyning P, Van Dijk P, Vergara R (2007) Consensus for tinnitus patient assessment and treatment outcome measurement: tinnitus research initiative meeting, Regensburg, July 2006. Prog Brain Res 166:525–536
23. He Y (2010) Missing data analysis using multiple imputation: getting to the heart of the matter. Circ Cardiovasc Qual Outcomes 3(1):98–105
24. Langguth B, Kleinjung T, Fischer B, Hajak G, Eichhammer P, Sand PG (2007) Tinnitus severity, depression, and the big five personality traits. Prog Brain Res 166:221–225
25. Landgrebe M, Langguth B, Zeman F, Koller M (2011) Methodology of clinical trials for tinnitus. In: Moller AR, Landgrebe M, De Ridder D, Kleinjung T (eds) Text book of tinnitus. Springer, New York, pp 202–203
26. Simmons DD, Morley BJ (1998) Differential expression of the alpha 9 nicotinic acetylcholine receptor subunit in neonatal and adult cochlear hair cells. Brain Res Mol Brain Res 56(1–2):287–292
27. Del Bo L, Ambrosetti U (2007) Hearing aids for the treatment of tinnitus. Prog Brain Res 166:341–345
28. Gelfand SA (2009) Speech audiometry. In: Gelfand SA (ed) Essentials of audiology, 3rd edn. Thieme Medical Publisher, New York, p 241
29. Meikle MB, Henry JA, Griest SE, Stewart BJ, Abrams HB, McArdle R, Myers PJ, Newman CW, Sandridge S, Turk DC, Folmer RL, Frederick EJ, House JW, Jacobson GP, Kinney SE, Martin WH, Nagler SM, Reich GE, Searchfield G, Sweetow R, Vernon JA (2012) The Tinnitus Functional Index: development of a new clinical measure for chronic, intrusive tinnitus. Ear Hear 32(2):153–176