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ORIGINAL ARTICLE

Antioxidant therapy in the elderly with tinnitus☆,☆☆

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Tinnitus;
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Abstract
Introduction: Several approaches have been tried for the treatment of tinnitus, from cognitive-behavioral therapies and sound enrichment to medication. In this context, antioxidants, widely used in numerous areas of medicine, appear to represent a promising approach for the control of this symptom, which often is poorly controlled.
Objective: To evaluate the effects of antioxidant therapy for tinnitus in a group of elderly patients.
Methods: Prospective, randomized, double-blinded, placebo-controlled clinical trial. The sample consisted of 58 subjects aged 60 years or older, with a complaint of tinnitus associated with sensorineural hearing loss. These individuals completed the Tinnitus Handicap Inventory (THI) questionnaire before and after six months of therapy. The treatment regimens were: *Ginkgo biloba* dry extract (120 mg/day), α-lipoic acid (60 mg/day) + vitamin C (600 mg/day), papaverine hydrochloride (100 mg/day) + vitamin E (400 mg/day), and placebo.
Results: There was no statistically significant difference between THI by degree ($p = 0.441$) and by score ($p = 0.848$) before and after treatment.
Conclusion: There was no benefit from the use of antioxidant agents for tinnitus in this sample.

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PALAVRA-CHAVE
Zumbido;
Antioxidantes;
Idoso

Efeito da terapia com antioxidantes sobre o zumbido em idosos

Resumo
Introdução: Uma série de abordagens terapêuticas tem sido empregada no tratamento do zumbido, desde terapias cognitivo-comportamentais e de enriquecimento sonoro até terapias medicamentosas. Nesse contexto, os agentes antioxidantes, amplamente utilizados em diversas áreas da medicina, parecem representar uma perspectiva promissora para o controle desse sintoma, que muitas vezes tem um controle clínico insatisfatório.
Objetivo: Avaliar os efeitos da terapia com agentes antioxidantes sobre o zumbido em um grupo de pacientes idosos.
Método: Ensaio clínico prospectivo, randomizado, duplo-cego e controlado por placebo.A amostra composta de 58 indivíduos com 60 anos ou mais, com queixa clínica de zumbido associado à perda auditiva, do tipo neurossensorial, em graus variados. Esses indivíduos foram submetidos ao questionário THI (*Tinnitus Handicap Inventory*) antes e após 6 meses de uso da medicação. Os esquemas terapêuticos foram os seguintes: extrato seco de *Ginkgobiloba* (120 mg/dia), ácido α-lipóico (60 mg/dia) + vitamina C (600 mg/dia), cloridrato de papaverina (100 mg/dia) + vitamina E (400 mg/dia) e placebo.
Resultados: O THI após o tratamento foi estatisticamente igual ao THI antes do tratamento, tanto em graus (p = 0,441) quanto em escores (p = 0,848).
Conclusão: Não se verificou benefício estatisticamente significativo com o uso de agentes antioxidantes para o zumbido dos indivíduos avaliados.

Introduction

Tinnitus, whose prevalence is estimated at approximately 10% of the adult population, has repercussions and an impact on quality of life of the affected individuals, that varies from a slight perception without discomfort to an extreme compromise in quality of life.[1]

For those whose tinnitus has significant clinical impact, a number of therapeutic approaches have been described and employed, from cognitive-behavioral therapies and sound enrichment, to drug approaches. Some studies have shown favorable results, while others did not result in benefits.[2] Various substances have been used and tested as drug treatments. Among them, antioxidants have appeared promising.[2] Antioxidants encompass a wide range of substances whose primary function is the neutralization and clearance of free radicals, that is, because of their molecular configuration, result in being toxic and harmful to cells and tissues. With respect to the auditory system, the action of free radicals in cochlear physiology has been demonstrated experimentally.[3–6] In the case of auditory disorders, antioxidants have been used in sudden deafness, to try to prevent ototoxicity, and for acute acoustic trauma,[7,8] as well as in the approach to presbycusis, sometimes with conflicting results.[9,10] In cases of tinnitus, probably the substance most widely used and studied currently is *Ginkgo biloba*, an herbal antioxidant. Associations of antioxidants, vitamins, and phospholipids administered to patients diagnosed with idiopathic tinnitus demonstrated relief of this condition and decreased serum levels of free radicals in a case series study.[11]

Thus, it was decided to test the effects of antioxidants on tinnitus in a group of elderly patients in a controlled clinical study.

Methods

The research project was submitted to the Ethics Committee on Institutional Research and approved under No. CEP 0723/10.

The research was registered with the International Clinical Trials platform of the World Health Organization at: http://apps.who.int/trialsearch/trial.aspx?trialid=ACTRN12610000667011.

The sample was composed of 58 male and female subjects aged 60 years or older with clinical complaints of tinnitus associated with a variable degree of sensorineural hearing loss confirmed by previous audiometric testing. These subjects were administered the Tinnitus Handicap Inventory (THI) questionnaire[12] before and after medication use. THI is a scale that measures discomfort caused by tinnitus, with questions related to everyday annoyances and losses attributed to the symptom, defining a different numeric value for each affirmative or negative answer, or for partial agreement. The final sum (score) is framed by a gradation (degree), from 1 (slight, only perceived in quiet environments) to 5 (catastrophic). In the sample selection, subjects with known allergy to any substance to be tested or with clinical contraindications to the use of these substances were excluded. Anticoagulant users or subjects with coagulopathy, as well as diabetics, were also excluded from the sample.

Table 1 Profile of individuals with complaints of tinnitus.

Gender		
Male	26	44.8%
Female	32	55.2%
Age (years)		
Mean	72.6	
Median	73.0	
Minimum	60.0	
Maximum	89.0	
Standard deviation	6.6	
Education		
Illiterate	1	1.7%
Literate	7	12.1%
Elementary school	38	65.5%
High school	10	17.2%
College	2	3.4%
Professional occupation		
Retired	49	84.5%
Unemployed	1	1.7%
Employed	8	13.8%
Smoking		
No	53	91.4%
Yes	5	8.6%
Alcohol consumption		
No	50	86.2%
Yes	8	13.8%
Number of medications		
None	4	6.9%
1	17	29.3%
2	17	29.3%
3	8	13.8%
4	6	10.3%
5	3	5.2%
6	2	3.4%
7	1	1.7%

Table 2 Distribution of the presence of comorbidities reported by patients with complaints of tinnitus.

Hearing aid use		
No	55	94.8%
Yes	3	5.2%
Systemic blood hypertension		
No	20	34.5%
Yes	38	65.5%
Dyslipidemia		
No	49	84.5%
Yes	9	15.5%
Heart disease		
No	58	100.0%
Yes	–	–
Hypothyroidism		
No	49	84.5%
Yes	9	15.5%
Osteoporosis		
No	49	84.5%
Yes	9	15.5%
Arthropathy		
No	52	89.7%
Yes	6	10.3%
Benign prostatic hyperplasia (among men)		
No	22	84.6%
Yes	4	15.4%
Other comorbidities		
No	38	65.5%
Yes	20	34.5%
Hearing loss time (years)		
Mean	6.7	
Median	5.0	
Minimum	1.0	
Maximum	25.0	
Standard deviation	4.9	
Hearing risk (exposure to occupational noise and to ototoxics)		
No	52	89.7%
Yes	6	10.3%
Otoscopy		
No distinctive factors	57	98.3%
Bilateral tympanosclerosis	1	1.7%

The entire group was interviewed in detail about their medical history, and the data were recorded. Then, participants were asked to give information about hearing loss duration, use (or not) of hearing aids, hypertension, dyslipidemia, heart disease, thyroid disease, and osteoarthropathy, and also in men, benign prostatic hyperplasia. The subjects were also asked about possible exposure to ototoxic substances or noisy environments, i.e., an exogenous auditory risk. In addition, a clinical exam was performed, focused on otoscopy.

Patients were treated for a period of six months. They were allocated into four groups and treated with one of the following regimens: dry extract of *G. biloba* (120 mg/day), α-lipoic acid (60 mg/day) plus vitamin C (600 mg/day), papaverine hydrochloride (100 mg/day) plus vitamin E (400 mg/day), and placebo (starch capsules). The substances were not identified by name in the containers into which they were packed, but rather through symbols defined by a professional who did not participate in the research, as a way of blinding investigators and patients. For distribution and randomization of participants, the resources available at http://www.randomization.com were used.

The statistical tests used in the analysis included Pearson's chi-squared test, Fisher's exact test (or its extension), and analysis of variance with parametric and non-parametric repeated measures. In all conclusions reached through the inferential analysis, the significance level $\alpha = 5\%$ was used.

Results

The general epidemiological data of the sample are listed in Table 1.

Table 3 Distribution of Tinnitus Handicap Inventory (THI) by degree of subjects with complaint of tinnitus, for placebo (P), *Ginkgo biloba* 120 mg/day (GB), α-lipoic acid 60 mg/day plus vitamin C 600 mg/day (AA + VC), and papaverine hydrochloride 100 mg/day plus vitamin E 400 mg/day (PP + VE) groups, before and after treatment time points.

	P		GB		AA + VC		PP + VE	
THI degree – before								
1	7	53.8%	3	25.0%	3	23.1%	4	26.7%
2	2	15.4%	5	41.7%	5	38.5%	8	53.3%
3	1	7.7%	3	25.0%	1	7.7%	1	6.7%
4	3	23.1%	–	–	4	30.8%	1	6.7%
5	–	–	1	8.3%	–	–	1	6.7%
Total	13	100.0%	12	100.0%	13	100.0%	15	100.0%
THI degree – after								
1	7	53.8%	3	25.0%	4	30.8%	4	26.7%
2	3	23.1%	5	41.7%	5	38.5%	6	40.0%
3	1	7.7%	1	8.3%	–	–	3	20.0%
4	2	15.4%	2	16.7%	4	30.8%	1	6.7%
5	–	–	1	8.3%	–	–	1	6.7%
Total	13	100.0%	12	100.0%	13	100.0%	15	100.0%

The most significant general clinical data of the sample are listed in Table 2.

Table 3 lists the distribution of THI by degree for subjects with complaints of tinnitus, in the different groups and in the time points before and after treatment.

Table 4 lists the distribution of THI in scores for subjects with complaints of tinnitus, in the different groups and in the time points before and after treatment.

After statistical analysis, it was concluded that THI before treatment was statistically equivalent to THI after treatment, both by degree ($p = 0.441$) and by score ($p = 0.848$). Additionally, the inferential results revealed that the four treatment groups were statistically equivalent, both in THI expressed by degree ($p = 0.663$) and by score ($p = 0.715$).

Discussion

A number of antioxidants have been studied, showing positive effects in several clinical conditions.[13–15] In this study, the choice of the selected substances was based on the evidence and descriptions in the literature, both in clinical and experimental research, and also on their availability in this community. Briefly, *G. biloba* can be described as an herbal medicine whose active pharmacological groups are flavonoids with antioxidant and vasodilator action, and terpene lactones, which act as antiplatelet agents.[16] Originally, α-lipoic acid was considered as part of the vitamin B complex, but now is no longer considered as a vitamin, because there is evidence that this substance can be synthesized by the human body. α-Lipoic acid has an antioxidant effect and

Table 4 Distribution of Tinnitus Handicap Inventory (THI) by score of subjects with complaint of tinnitus, for placebo (P), *Ginkgo biloba* 120 mg/day (GB), α-lipoic acid 60 mg/day plus vitamin C 600 mg/day (AA + VC), and papaverine hydrochloride 100 mg/day plus vitamin E 400 mg/day (PP + VE) groups, before and after treatment time points.

	P	GB	AA + VC	PP + VE
THI score – before				
n	13	12	13	15
Mean	28.2	32.8	38.8	28.0
Median	14.0	29.0	32.0	24.0
Minimum–maximum	2–72	12–80	4–76	2–96
Standard deviation	25.1	19.9	24.7	23.8
THI score – after				
n	13	12	13	15
Mean	24.2	34.8	32.5	30.4
Median	14.0	24.0	24.0	24.0
Minimum–maximum	0–64	6–80	0–72	2–96
Standard deviation	23.1	24.7	25.5	25.0

Pearson's chi-squared test ($p = 0.848$). THI before and THI after treatment, by score.

also an oxidative reduction effect on other antioxidants.[14] Vitamin E is an essential fat-soluble vitamin whose main function is related to the lipid stability of cell membranes against oxygen free radicals. This vitamin also has a modulating effect on cell growth, in response to oxidative stress, hence its positive effect on atherosclerosis and certain neoplasms.[17] Vitamin C or ascorbic acid is a water-soluble vitamin, critical for collagen and L-carnitine biosynthesis, for the conversion of dopamine to norepinephrine; it also improves iron absorption. Under physiological conditions, this vitamin also acts as a potent antioxidant.[18] Papaverine hydrochloride is a synthetic alkaloid that exerts a tissue protective effect correlated to antioxidants, because this substance promotes non-specific smooth muscle relaxation, leading to vasodilation.[19] Antioxidants act synergistically with other agents or in isolation, functioning in different ways, protecting cell membranes and also eliminating oxygen free radicals.[4,6]

The afflictions of the auditory apparatus are complex conditions that involve a number of physical phenomena, various tissues, and different topographies of the auditory pathway. Tinnitus appears to be caused by abnormal neural activity in cochlea–auditory cortex pathway.[20] There is a consensus in the literature that at least some of the changes found along the auditory pathway and related to auditory symptoms appear to be related to biochemical changes, inflammation, and injuries induced by free radicals.[8]

The main cause of tinnitus is damage to hearing sensory cells of the cochlea, with or without association to an injury of central auditory system structures, through several etiopathogenic mechanisms.[21] Subjects with normal hearing may also have tinnitus; however, patients with hearing loss may not have tinnitus. The sample of this study was entirely composed of subjects with tinnitus and sensorineural hearing loss.

With regard to the sample, anticoagulant users were excluded due to the chance of bleeding when these drugs are combined with *G. biloba*, which have an antithrombotic effect. Another group excluded was diabetics, due to the chance of glycemic imbalance when in combination with α-lipoic acid.[14] Given the authors' intention to test several substances in a very defined population group, the groups had a relatively limited number of subjects, but they were methodologically sound for this study and its statistical evaluation.

The substances chosen were processed in a compounding pharmacy, since the combinations used are not commercially available. This was also important in the blinding process, since the substances were packaged in identical capsules and identical bottles, but were identified by different symbols, so they could not be identified by the subjects or researchers. The person responsible for handling the substances was aware of this condition. The doses of substances used were based on what the literature recommends as an effective and clinically safe dose. In this study, there were no adverse effects with these substances during the study period and at the doses used. Moreover, according to the literature and pharmacological research, there are no reports on the associations of substances proposed in this study, nor information to indicate that, once associated, they could show decreased interaction or summation of their effects. This was corroborated by our results, since no modification of the researched symptom occurred after treatment.

The effects of antioxidant therapy for tinnitus were evaluated through THI,[12] a validated and widely used questionnaire to evaluate the influence of tinnitus on quality of life of the subjects tested. As described earlier, there was no observable effect of the antioxidants on tinnitus in the sample groups for a period of six months. Some reports indicate that the use of B-complex vitamins could be beneficial in controlling tinnitus. However, no controlled clinical trial has proven this hypothesis.[22] Regarding *G. biloba* in the treatment of tinnitus, a systematic review evaluating studies on the use of this substance (in its EGb 761 presentation) has demonstrated efficacy when compared to placebo.[23] Another Cochrane group review conducted in 2013 did not demonstrate efficacy of *G. biloba* in the treatment of tinnitus, irrespective of the form in which the plant extract was obtained.[24] The present study used compounded dry extract of *G. biloba*.

These findings also corroborate a recent international recommendation, against prescribing vitamin and dietary supplements for the treatment of patients with persistent and clinically relevant tinnitus.[25]

Conclusion

In the time interval and sample evaluated, we observed no statistically significant benefit from the use of antioxidants for tinnitus.

Conflicts of interest

The authors declare no conflicts of interest.

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