OTOLOGY

Treatment of central and sensorineural tinnitus with orally administered Melatonin and Sulodexide: personal experience from a randomized controlled study

Il trattamento degli acufeni mediante somministrazione orale di Melatonina e Sulodexide: esperienza personale

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SUMMARY

Since very little is understood about the exact aetiology of tinnitus, this has made treatment of the condition difficult. Even though ~10-15% of the general population suffer from tinnitus, only 2% consider it serious enough to warrant any treatment. The main problem arising from tinnitus is the disturbance it causes not only in day to day life but also in sleep, leading to fatigue and general discomfort. The present study focused on the effect of Melatonin in conjunction with Sulodexide as a treatment method for tinnitus. Overall, 102 patients suffering from tinnitus were evaluated in a prospective randomised controlled study conducted in a tertiary care ENT department. After randomisation, 34 patients were treated with Melatonin and Sulodexide, another 34 were treated with Melatonin alone, while the remaining 34 (control group) were managed without treatment in order to evaluate spontaneous variations in the quality of tinnitus. Patients were assessed prospectively with the Tinnitus Handicap Inventory and Acufenometry, both pre- and post-treatment. Among the patients studied, better results with both Tinnitus Handicap Inventory and Acufenometry were found in the group who received Melatonin and Sulodexide compared to those receiving Melatonin alone. No improvement was observed in the control group. In conclusion, Melatonin in combination with Sulodexide is, in our opinion, a viable treatment option for patients suffering from central or sensorineural tinnitus.

KEY WORDS: Tinnitus • Hearing Loss • Medical treatment • Melatonin • Sulodexide • Tinnitus Handicap Inventory • Acufenometry

RIASSUNTO

Il trattamento degli acufeni si presenta particolarmente difficoltoso, anche a causa del fatto che si conosce molto poco riguardo all'esatta eziologia del problema. Nonostante circa il 10% della popolazione soffra di acufeni, solo il 2% richiede un trattamento specifico. Il problema principale determinato dagli acufeni è non solo il discomfort diurno, ma soprattutto il disturbo del sonno che porta ad una condizione di generale affaticamento. Il presente studio è centrato sull'effetto della Melatonina associata alla Sulodexide nel trattamento degli acufeni. Un totale di 102 pazienti affetti da acufeni sono stati valutati in uno studio prospettico randomizzato condotto presso la nostra Divisione ORL. Sulla base della randomizzazione 34 pazienti sono stati trattati con Melatonina e Sulodexide, 34 pazienti con la sola Melatonina e i restanti 34 (gruppo di controllo) non hanno ricevuto nessun trattamento, allo scopo di verificare la spontanea evoluzione degli acufeni. I pazienti sono stati sottoposti a Tinnitus Handicap Inventory e ad Acufenometria, sia prima che dopo il trattamento. Tra i pazienti studiati, si sono evidenziati risultati migliori nel gruppo trattato con Melatonina e Sulodexide, in confronto a quelli trattati con la sola Melatonina. Nessun miglioramento è stato invece evidenziato nel gruppo di controllo. In conclusione, a nostro avviso, la Melatonina associata alla Sulodexide rappresenta un'opzione valida di trattamento dei pazienti affetti da acufeni sia di origine centrale che neurosensoriale.

PAROLE CHIAVE: *Acufeni • Ipoacusia • Terapia medica • Melatonina • Sulodexide • Tinnitus Handicap Inventory • Acufenometria*

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Introduction

Tinnitus is defined as a perceived sound that cannot be attributed to an external source [1]. Epidemiologic data show that 10-15% of the general population are affected by tinnitus, but only 2% consider it to be an important problem that exerts profound influence on the sense of well-being and quality of life (QoL) [2].

Tinnitus is classified into two main categories, namely, subjective and objective tinnitus. The latter represents only 1% of all tinnitus cases. Subjective tinnitus is again subclassified into: conductive, sensorineural and central [1].

The neuro-physiological model, first described by Jastreboff in 1990 [3], established that the connection between auditory pathways and the limbic system are responsible for tinnitus, its emotional response and its autonomous nervous system reactions such as: anxiety, depression, and sleep disorders, commonly observed in these patients [4]. One of the most common consequences of tinnitus is disturbance of sleep. The degree to which sleep is disturbed is directly proportional to the severity of tinnitus [5].

Many different treatment modalities have been proposed for central and sensorineural tinnitus, but none of them have demonstrated consistently good results in all patients. This difficulty encountered in treatment may be due to the different aetiology of tinnitus as well as to the inability to measure the perception of tinnitus. Part of the difficulty can also be attributed to the unknown mechanism of, and exact physiological processes involved in, tinnitus.

Recently, various studies have considered Melatonin in the treatment of tinnitus [2 6 7]. There are already numerous articles in the lay press concerning the use of Melatonin in the treatment of insomnia, depression, anorexia and jet lag [8]. This is a neurohormone secreted by the pineal gland at night. It acts at the level of the Central Nervous System modifying its activity and influencing circadian rhythms, promoting the regulation of the sleep-wake cycle [9]. The second agent, used in the current study, was Sulodexide, an oral anti-thrombotic agent.

Sulodexide, a glycosaminoglycan containing 80% heparin-sulphate and 20% dermatan-sulphate, is an enhancer of blood flow in the microcirculation and is usually used in vascular diseases. Sulodexide was included, in the present protocol as it has a relatively high affinity for endothelial cells that can preserve or improve blood flow in the inner ear microcirculation. This effect can enhance the action of Melatonin on tinnitus.

In this prospective randomised controlled study, an attempt has been made to compare the effects of oral Melatonin and Sulodexide (MS) combination against oral Melatonin (M) alone, on the perception of tinnitus in patients suffering from sensorineural and central tinnitus. The study was completed including a control group managed without any treatment. The discussion, in this report is restricted to subjective tinnitus secondary to sensorineural and central causes. Other causes of subjective tinnitus such as, for example, conductive hearing loss, vestibular schwannoma and other cerebellopontine-angle tumours (CPA), systemic vascular diseases, psychiatric diseases have not been included in this report.

Patients and methods

Overall, 102 patients were recruited for the study, from January 2006 through May 2006 when they attended the ENT Institute of the G. d'Annunzio University Chieti-Pescara. All patients underwent clinical (otologic) and audiological examinations Pure Tone Audiogram (PTA), Speech Discrimination Score (SDS) and Auditory evoked brainstem responses (ABR) to rule out organic causes of tinnitus. They also underwent Magnetic Resonance Imaging (MRI) and vertebral and carotid Doppler study, based on clinical suspicion and investigation results.

Only patients aged > 18 years, who had been suffering from tinnitus for a minimum period of one year and who did not present psychiatric or neurological diseases, were selected for the study. Excluded from the study were patients with: a) conductive or mixed hearing loss, b) pulsatile tinnitus, c) Meniere's disease, d) cerebro-vascular or diabetic disease, e) vestibular schwannomas or other cerebello-pontine angle tumours. Inclusion and exclusion criteria are outlined in Table I.

In accordance with the above-mentioned inclusion and exclusion criteria a total of 102 patients (45 male, 57 female), mean age 54.8 years (range 29-79) were eligible for the study.

Before commencing the study, QoL was evaluated in all patients as well as their subjective perception of tinnitus. For this purpose, the Tinnitus Handicap Inventory (THI) and acufenometry, respectively, were employed.

Table I. Inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria
Minimum age 18 years	CHL or MHL
Tinnitus for minimum of 1 year	Meniere's disease
Absence of psychiatric or neurological diseases	Systemic vascular or diabetic diseases
Noise-induced hearing loss	VS or CPA tumours
Cochlear and retro-cochlear damage	Pulsatile tinnitus

CHL: conductive hearing loss; MHL: mixed hearing loss; VS: vestibular schwannoma; CPA: cerebello-pontine-angle.

After obtaining informed consent, patients were randomised into 2 study groups and one control group.
The first study group (Group A) comprised 34 patients (24 M, 10 F), mean age 54.1 years (range 29-79) (Table II), managed with co-administration of MS taken *per os*, for 80 days. During the first 40 days of the trial, patients were given one capsule of Sulodexide (250 mg) each morning and evening and one capsule of Melatonin (3 mg) each evening before going to sleep.
After 40 days, Sulodexide was reduced to one capsule (250 mg) each morning (to avoid adverse effects, such as epigastric pain) but Melatonin was continued at the same dosage, for the remaining period.
The second study group (Group B) comprised of 34 patients (19 M, 15 F), mean age of 55.5 years (range 33-77) (Table III), were treated with Melatonin alone (3 mg capsules per os), one capsule each evening, for 80 days, before going to sleep.
The control group comprised 34 patients (14 M, 20 F), mean age 44.2 (range 25-68) (Table IV). These patients were managed without treatment in order to evaluate spontaneous time-related variations in tinnitus perception.
At the end of 40 and 80 days, all patients underwent THI and acufenometry evaluation.
Both the study groups (A + B) and the control group were followed-up for 40 days after completing the study. The audiological investigations were repeated at the end of this follow-up period with THI, acufenometry, PTA and SDS.
Subject characteristics were summarized by mean and standard deviation (SD) for continuous variables and by percentage for categorical variables. Differences in demographic and clinical characteristics between groups were evaluated using the t-test in the case of continuous variables. A p value of < 0.05 was considered statistically significant. All statistical analyses were performed with SPSS version 13 (SPSS Inc., Chicago, IL, USA).

Results

All 102 patients enrolled in this study and all subjects (100%) completed the entire study period of 80 days.
In Group A, the THI and acufenometry, at the end of the treatment period, showed an improvement. The initial THI mean was 41.1 (SD 21.9) and the final THI mean was 36.5 (SD 20.8); the initial acufenometry mean was 44.1 (SD 20.2) and the final acufenometry mean was 36.7 (SD 20.5). The differences between these mean values were statistically significant. Improvement in both examinations were observed in 27 patients (79.4%), while 6 patients (17.6%) showed no change in THI and Acufenometry. Tinnitus perception increased in only one patient (initial and final THI were 62 and 68, respectively and, initial and final acufenometry were 5dB and 15dB, respectively) at the end of the study.
In Group B, an improvement was observed in 20 patients (58.8%), after 40 and 80 days with an improvement in THI score: the initial mean THI was 46.3 (SD 19.0) and the final mean THI was 43.8 (SD 18.6). In this same group, a slight improvement was observed in acufenometry: the initial mean being 47.3 (SD 21.7) and the final mean 46.6 (SD 22.4). The differences between these means were not

Table II. Results in study Group A managed with co-administration of melatonin and Sulodexide

N. patients	Sex	Mean age (yrs)	Mean THI Pre	Mean THI Post (80 days)	Mean Acuf pre	Mean Acuf post (80 days)	Follow-up (120 days) THI/Acuf
34	24 M 10 F	54.1	41.1	36.5	44.1	36.7	36.4/36.7

THI: Tinnitus Handicap Inventory. Acuf: acufenometry. Pre: pre-therapy. Post: post-therapy.

Table III. Results in study Group B managed with Melatonin administration alone.

N. patients	Sex	Mean age (yrs)	Mean THI Pre	Mean THI post (80 days)	Mean Acuf pre	Mean Acuf post (80 days)	Follow-up (120 days) THI/Acuf
34	24 M 10 F	55.5	46.3	43.8	47.3	46.6	43.1/46.5

THI: Tinnitus Handicap Inventory. Acuf: acufenometry. Pre: pre-therapy. Post: post-therapy.

Table IV. Results in control group.

N. patients	Sex	Mean age (yrs)	Mean THI Pre	Mean THI Post (80 days)	Mean Acuf pre	Mean Acuf post (80 days)	Follow-up (120 days) THI/Acuf
34	14 M 20 F	44.2	40.6	41.1	42	41.1	41/40.2

THI: Tinnitus Handicap Inventory. Acuf: acufenometry. Pre: pre-therapy. Post: post-therapy.

statistically significant. In Group B, 14 subjects (41.2%) showed no change in tinnitus perception measured with THI and acufenometry.
No improvements were observed in the Control group.
Results are outlined in Tables II, III and IV.
At the end of this study (40 days after withdrawal of treatment), all study groups showed unchanged or only very slight variations in THI and acufenometry findings.
No improvement or deterioration in hearing loss was detected, during or after the treatment. PTA and SDS remained the same both at the initial and final evaluation. Furthermore, no adverse effects emerged either during the course of, or after completing, this study.

Discussion

Despite numerous trials, no drugs have, so far, been approved by the Food and Drug Administration for the treatment of tinnitus [10]. Many of the current treatment options focus on symptomatic relief, since the pathophysiology of central and sensorineural tinnitus is largely unknown [10]. Eggermont [11] and Zenner and Ernst [12] proposed that, the high incidence of cochlear damage in patients with tinnitus suggests that most of the tinnitus arises in this organ.
According to some reports, sensorineural hearing loss leads to a reorganization of the pathways in the central auditory system [13-15]. These changes can occur rapidly and lead to abnormal interactions between auditory and other central pathways [13 16]. Analogous changes in the somatosensory system, linked to phantom pain, lead us to suggest that there are similarities between neuropathic pain and tinnitus [17 18].
Levine hypothesized that a reduction in auditory nerve input leads to disinhibition of the dorsal cochlear nucleus and an increase in spontaneous activity in the central auditory system, which is experienced as tinnitus [19]. This mechanism could explain the temporary ringing sensation that may follow exposure to noise, the effects of some drugs such as furosemide, and spontaneous tinnitus in subjects with normal hearing who are placed in a silent area [20].
Despite numerous hypotheses on the aetiopathogenesis of tinnitus, no treatment can, as yet, be considered well established in terms of reproducibility and long-term reduction of the tinnitus impact, in excess of placebo effects [21].
Among the various treatment strategies suggested, just to remember a few, there are: Lidocaine, Benzodiazepines, Ginkgo Biloba, acupuncture, tinnitus retraining therapy, masking devices, hearing aids and cochlear implants, microvascular decompression of auditory nerve, auditory nerve transaction [10].
One of the main consequences of tinnitus is disturbance of sleep. This led us to consider Melatonin as a potential aid in the treatment of tinnitus. Rosenberg et al., in 1998, showed that Melatonin is a useful device in the treatment of subjective tinnitus, especially in patients with high THI scores and difficulty in sleeping [8]. Megwalu et al., in 2006, demonstrated that Melatonin may be safe treatment for patients with subjective tinnitus, particularly in those with sleep disturbances [9]. Alpini et al., in 2006, treated patients with chronic disabling tinnitus with Citalopram and Melatonin and all demonstrated an improvement in tinnitus and QoL [2].
Melatonin (N-acetyl-5-methoxytryptamine) can be considered as a pharmacological option, even if it is commercialized as a diet integrator. It is a neurohormone produced by the pineal gland that regulates the sleep-wake cycle [7].
The most commonly proposed mechanism for Melatonin, to induce sleepiness, relates to its effects on the circadian clock. For example, it opens the sleep gate and also reduces body temperature which promotes sleep. Melatonin has been successfully used, with various degrees of effectiveness, to enhance sleep processes in elderly individuals with restless leg syndrome, Rapid Eye Movement (REM) sleep disorders, delayed sleep phase syndrome, in manic patients with insomnia and in patients with fibromyalgia [7]. Moreover, Rudin, in 1980, suggested that Melatonin may improve tinnitus by reducing labyrinthine pressure. He suggested this considering the fact that secondary endolymphatic hydrops has, clinically, been found to occur significantly in patients with a subjective idiopathic tinnitus of a severe disabling type [22].
Secondary endolymphatic hydrops is hypothesized to be a factor, not an aetiology, influencing the clinical course of subjective tinnitus [23]. This suggestion was supported by a recent study[24] where Melatonin has been considered as a potential antihypertensive treatment. It plays a role in blood pressure regulation and its night-time production has been shown to be reduced in hypertensive individuals. Melatonin may also improve endothelial function by increasing availability of nitric oxide, thereby exerting a vasodilatatory and hypotensive effect. It also appears to interfere with the peripheral and central autonomic system, with a subsequent decrease in tone of the adrenergic system and an increase in the cholinergic system. Furthermore, Melatonin may reduce blood pressure also via specific Melatonin receptors, localized in peripheral vessels or in parts of the central nervous system playing a role in blood pressure control [24].
In the present study, co-administration of Melatonin with Sulodexide was examined in 34 patients with tinnitus and compared to administration of Melatonin alone in another 34 patients suffering from the same disorder. A further 34 patients with tinnitus did not receive any treatment in order to estimate spontaneous time-related variations in the quality of tinnitus.
There is no evidence to date, in the English literature, concerning the use of Sulodexide in the treatment of tinnitus.
This therapeutic protocol was suggested, based on the observation that the inner ear has a termino-terminal micro-

vascular organization that may be influenced by a numerous causes [25]. Sulodexide has been used in the treatment of intermittent claudication, in vascular complications of diabetes, to attenuate myocardial ischemia-reperfusion injury and in the treatment of venous leg ulcers [26]. Alterations over time (i.e., delay in the homeostatic mechanism in normal function of the inner ear perilymph, endolymph, or cerebrospinal fluid) result in endolymphatic hydrops and interference with the normal function of the cochlea, resulting in cochlear complaints that may be presenting as tinnitus rather than vertigo [23].

Sulodexide is a standardized highly purified glycosaminoglycan containing 80% fast mobility heparin and 20% dermatan-sulphate. The fast mobility heparin fraction is defined based on its electrophoretic mobility. It differs from other glycosaminoglycans, such as heparin, by having a longer half-life and reduced effect on systemic clotting and bleeding [27]. It has thrombogenesis-inhibiting properties, fibrinolysis stimulating and anti-atherogenic activities. It also, has a relatively high affinity for endothelial cells that can preserve or improve blood flow in the microcirculation. These properties were also demonstrated following oral administration of single as well as repeated doses [26 27].

All these beneficial effects of this molecule, on the microvasculature and its haemodynamics, led us to suggest that Sulodexide may have similar beneficial effects possibly on the labyrinthine microvasculature and also its haemodynamics. Furthermore other drugs with antithrombotic activity, containing enoxaparin, showed positive results in the treatment of tinnitus [28].

Results of the present study revealed that the combination of M and S in the treatment of idiopathic tinnitus improves the QoL and subjective perception of tinnitus. The improvements were quantified with the use of THI, a reliable and valid questionnaire, employed by many tinnitus research workers, and acufenometry.

Acufenometry offers an instrumental and objective quantification of tinnitus. In the current world literature, changes in tinnitus, following Melatonin therapy, have been measured only with subjective questionnaires, for example THI, Pittsburgh Sleep Quality Index, Tinnitus Cognitive Questionnaire and Tinnitus Reaction Questionnaires [2 8 9]. In our opinion, it is important to obtain a subjective measure of tinnitus severity but, it is also important to evaluate whether the same results are reproduced with an instrumental evaluation.

When comparing our results, it showed that patients who received MS (Group A) had a consistent improvement in THI and acufenometry (79.4%). The outcome in Group B in which tinnitus was treated with Melatonin alone showed an improvement in QoL, when evaluated with THI and acufenometry in 58.8%.

Results of the present study, in agreement with previous studies [2 8 9], suggest that Melatonin is a useful aid in treating patients with sensorineural and central tinnitus.

This improvement correlates well with the effects of Melatonin on sleep quality. Moreover, the present results also showed that Melatonin and Sulodexide administration leads to better results in tinnitus treatment probably due to the beneficial effects of Sulodexide on microcirculation and, at the same time, increasing the effect of Melatonin on the microcirculation.

In conclusion, even though only 2% of tinnitus sufferers are affected, in their lives, when this occurs, it is a very distressing symptom. The fact that, as yet, there is no definitive therapy for this condition, it only makes matters worse for the suffering patient. Our study proposes a new approach in the treatment of tinnitus by adding Sulodexide together with Melatonin. This study provided very encouraging results thereby supporting our opinion.

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