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Ozone Therapy in Auditory System Alterations

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Abstract

Introduction: Ozone therapy is a term that describes a number of different practices in which oxygen, ozone and hydrogen peroxide are administered by gas or water in order to eliminate diseases caused by micro-organisms, improve cell function and promote the healing of damaged tissue. Currently ozone therapy is indicated in pathologies of vascular and infectious etiology such as: peripheral arterial diseases, cerebrovascular diseases, ocular diseases and pathologies of the inner ear including sensorineural hearing loss, tinnitus, peripheral vertigo syndrome, sudden deafness and chronic suppurated otitis.

Objective: Through a literature review, we intend to study which pathologies and symptoms of the auditory system can be treated with ozone therapy, verifying its benefits in the short, medium and long term.

Methodology: The following databases were consulted: Academic Search Complete (EBSCO); Pubmed, Elsevier-Science Direct; Web of Science, Wiley, B-on., using the keywords, Ozone, Ozonotherapy/Ozone therapy, Deafness, Ménière disease, Inner ear and Tinnitus. After applying the inclusion criteria, five articles were considered for analysis. The selected articles studied the application of ozone therapy in auditory system alterations, particularly in cases of sudden deafness and tinnitus. Each pathology/symptom was analysed separately, analysing the methodology of each study and evaluating the results obtained in each one.

Conclusion: Ozone therapy is an alternative treatment for sudden deafness, with a high recovery rate. However, it has been found that this technique is not effective in treating tinnitus. It is a very safe technique, with no side effects or other complications during or after treatment.

Keywords: Ozone therapy; Sudden deafness; Tinnitus

Introduction

The first mention of ozone appeared in scientific literature in 1785 by the Dutch physicist Mak Van Marumom. In 1840, Cristian Frederick, a professor at the University of Basel in Switzerland, related changes in the properties of oxygen to the formation of a particular gas, which he called ozone [1].

Ozone (O_3) is usually presented as a gas formed by three oxygen atoms with a cyclic structure [2]. The gas is colourless, acrid in odour and explosive in its liquid or solid form. It has a half-life of forty minutes at twenty degrees centigrade and about one hundred and forty minutes at zero degrees centigrade [3]. There are numerous scientific evidences related to the clinical usefulness of ozone, which are supported by the various mechanisms of action of this gas. The modulation of the oxidant and antioxidant systems of the body is one of the fundamental biological effects of the application of ozone therapy and consists in the normalisation of the balance of the levels of oxidation products and the antioxidant defence system [1]. Ozone began to be used for

medical purposes in 1987 as a means of treating abscesses, acne, AIDS, allergies, hepatitis, rheumatism, herpes or high cholesterol.

As the years progressed, this form of treatment began to be applied to many other pathologies, using new forms of treatment. In 1988 ozone therapy began to be applied in cases of diabetes, atherosclerosis, ulcers, burns and other inflammations. It was also in this year that ozone began to be applied in the form of aqueous mixture, mixture with oil, or ozone baths, for disinfecting the skin and treating eczema. The following year a positive influence of ozone therapy on cancer treatment was observed and its immunostimulant activity was evaluated through a significant increase in immunoglobulin levels. In the 1990s, ozonation of blood was performed for the purpose of treating viral diseases, and the germicidal activity of ozone was discovered through its use in rhinoplasty, with the finding that its use significantly decreases postoperative complications [3].

Currently ozone therapy is indicated in circulatory disorders such as: peripheral arterial diseases, cerebrovascular diseases, ocular diseases and diseases related to blood circulation in the inner ear (sensorineural hearing loss and tinnitus).

This form of treatment is also indicated in angiopathies, viral diseases, hepatitis B and C, herpes simplex, herpes zoster, immunodeficiencies, and as a complementary therapy in asthenia, geriatrics and environmental medicine. Ozone therapy is also a complementary concept in chronic inflammatory processes in oncology, orthopaedics and rheumatology [4]. Ozone therapy has a great impact on the oxygenation of the inner ear, since the auditory hair cells (internal and external), and the peripheral fibres of the external auditory nerve are sustained by O_2 by diffusion through the perilymph. Taking sudden deafness as an example, ozone therapy can be used if there is: vascular alteration, ischaemia and anoxia of the cochlea, decreased oxygen transport, or alterations in the creation of electrical potencies [5].

As ozone therapy is indicated in pathologies of vascular and infectious etiology, some studies evaluate the application of this form of treatment in patients presenting tinnitus, peripheral vertigo syndrome, sudden deafness, sensorineural deafness and chronic suppurated otitis. The results obtained depend on various factors, such as the route of administration, concentration, total dose, precision of the technique and treatment time. The use of this technique is contraindicated in cases of hyperthyroidism, spondylolisthesis and during pregnancy [6]. Ozone used for medical purposes is a mixture of pure oxygen (O_2) and pure ozone (O_3), which is produced using medical oxygen in a medical ozone generator [4]. Pure ozone is contraindicated in ozone therapy due to its toxicity [7]. From a therapeutic point of view, there are certain aspects to be considered in each application, namely that its concentration, dose and volume have different values depending on the form of administration, the purpose of the application and the characteristics of the individual undergoing treatment [4,6].

Through a literature review, we intend to study which pathologies and symptoms of the auditory system can be treated with ozone therapy, verifying its benefits in the short, medium and long term.

Methodology

This review of the literature included only original studies published in the last 15 years in which the sample presented pathologies or symptoms of the auditory system and ozone therapy was used, alone, to treat them.

The following databases were consulted: Academic Search Complete (EBSCO); Pubmed, Elsevier-Science Direct; Web of Science, Wiley, B-on., using the keywords, Ozone, Ozonotherapy/Ozone therapy, Deafness, Ménière disease, Ineer ear and Tinnitus and five articles were considered for analysis as we can see in Table 1.

Table 1: Summary of the articles included in this review.

Article	Objetive	Participants	Instruments	Results	Conclusions
Sönmez, et al. [2]	To evaluate the effectiveness of treatments with ozone and betahistine in cases of tinnitus.	68 Participants: 27 ozone treatment group; 26 betahistina treatment; group; 15 control group;	Tinnitus loudness; Tinntitus handicap inventory (THI)	No significant differences	The study results do not provide sufficient evidence to support ozone therapy as a treatment for tinnitus.
Sherief, et al. [10]	To evaluate the role of ozone therapy in the treatment of idiopathic tinnitus	40 Participants: 30 study group; 10 control group	Pitch matching; Loudness matching; Minimum level of masking; Residual inhibition	No difference between the groups	Ozone therapy is not a treatment of great importance in the treatment of idiopathic tinnitus.
Ragab, et al. [7]	To investigate the safety and efficacy of ozone therapy in adult patients with sudden sensorineural hearing loss	45 Participants: 15 control group, 30 study group	Pure tone audiogram; Speech perception threshold (SRT); Speech discrimination level; Subjective recovery rate	Significant recovery was observed in 23 patients (77%) receiving ozone treatment, compared with six (40%) patients receiving placebo (p , 0.05).	Ozone therapy, in patients with peripheral vestibulocochlear syndrome, is effective.
Menéndez. et al. [8]	To evaluate the efficacy of ozone therapy in the treatment of peripheral vestibulocochlear syndrome.	50 Patients: 4 with labyrinthitis, 2 with MPV, + acoustic trauma, 7 Menière´s disease, 3 MPV + otosclerosis	Romberg test, Babinsky Well Star, Osterhamser test, Measurement of nystagmus, the patient will be in Quick submission, Frenzel goggles, Pure tone audiogram; To measure tinnitus, a subjective evaluation was carried out	Patient improvements, according to vertigo, hearing loss, tinnitus and nystagmus, were of 90, 80, 65 and 100 %, respectively.	Patient improvements, according to vertigo, hearing loss, tinnitus and nystagmus, were of 90, 80, 65 and 100 %, respectively.

Tasdövena, et al. [9]	To evaluate the efficacy of hyperbaric oxygen therapy or ozone therapy in the treatment of idiopathic sudden sensorineural hearing loss.	106 patients with idiopathic sudden sensorineural hearing loss: 63 oral steroid only, 26 oral steroid + hyperbaric oxygen, 17 oral steroid + ozone	Speech Discrimination Scores (SDSs); Pure Tone Audiogram	The highest response rate to treatment was observed in the oral steroid + ozone therapy group (82.4%), followed by the oral steroid + hyperbaric oxygen (61.5%), and oral steroid groups (50.8%).	Ozone therapy significantly contributes to the recovery process in treatment of Idiopathic sudden sensorineural hearing loss

Discussion

The application of ozone therapy in alterations of the auditory system has been widely spread since its application in sudden deafness, acoustic trauma or even in individuals with tinnitus. In the work by Ragab and colleagues (2009) 45 adults with unilateral, acute onset hearing loss of greater than 30dB in more than three contiguous frequencies over more than three days, were selected who met the following inclusion criteria: individuals of both genders aged over 18 years, with no etiology that could explain the sudden deafness. The duration between the onset of hearing loss and the onset of treatment was less than one month [7].

Patients with bilateral sudden deafness were excluded from the study; patients where a medical comorbidity leading to contraindication of ozone therapy is present; individuals with a known cause of sudden deafness (such as M`nière's disease, perilymphatic fistula or vestibular Schwanoma); adults with hearing loss (of any degree) in the opposite ear; or subjects with co-morbidities such as hypertension or diabetes. The patients of this study had no identifiable cause of hearing loss, and had no cranial nerve defects. Of the 45 adults selected, fifteen were randomly chosen to constitute the control group. The remaining 30 patients were submitted to ozone therapy. Patients were instructed not to smoke or drink caffeinated beverages during the treatment course [7].

In the study group, the patients underwent ozone therapy using auto-haemotherapy. The procedure consisted of withdrawal of 100ml of blood from the patient and then immediate treatment of the blood, for at least 5 minutes, with a gaseous mixture of 1:1 volume oxygen and ozone. Three assessments were performed on each patient throughout the treatment: before it was started, after the 5th session, and at the end of the study (after the 10th and last treatment session) [7].

Throughout the treatment the following were evaluated: the average of pure tone audiometry, speech audiometry, the speech perception threshold, the speech discrimination level and the subjective recovery rate, in which the patient describes his or her recovery: complete recovery, significant improvements or no improvements. After ozone treatments, 23 patients (77%) showed significant improvements regardless of the type of hearing loss, with only 6 patients (40%) of the control group showing improvements not as significant as the study group. No effects were seen on the patients' tinnitus. During the treatment, no side effects were observed.

The effectiveness of ozone therapy is corroborated by other studies [8,9]. 50 adult patients, of both sex and different ethnic origins, that present a peripheral vestibulocochlear syndrome are eligible to participate in this study [8]. Of these 34 with diagnose of mild peripheric vertigo (MPV), 4 with labyrinthitis, 2 with MPV and acoustic trauma, 7 with Mènière´s disease and 3 patients with a MPV and otosclerosis. They presented hearing loss, tinnitus (lasting for more than 3 months), mild peripheric vertigo and nystagmus. Hearing loss is one of the important symptoms and it can be the expression of a lesion in the transmission apparatus or in the perception of the sounds. Tinnitus, frequently very annoying to patients even modifying their psyche, can be continuous or intermittent and of acute or grave tones. Vertigo is the sensation of moving around in space (subjective vertigo) or of having objects moving around the person (objective vertigo) and is a result of a disturbance of equilibratory apparatus. Nystagmus is mainly horizontal and inhibited by visual fixation [8].

Exclusion criteria considered in this study [8] were: patients that present central vestibulocochlear syndrome, tumour of the acoustic nerve (schwannoma or neurinoma), tumors of the middle ear/inner ear/cerebellopontine angle, lesions of the brain stem, severe hypertension, severe septic conditions, multiple sclerosis, retinal disorders, liver/hematological/cardiovascular diseases, hypersensitivity to the medication that will be used, pregnancy or breast-feeding women, inability to cooperate with the requirements of the study, recent history of alcohol or drug abuse, abnormal laboratory values.

In this study [8], ozone was injected twice per week, for 20 sessions, at a concentration of 20mg/L and a volume of 5 mL, into the points localizable in the paravertebral muscle, corresponding to the cervical region C2-C3.

The evaluation criteria were based in the evolution of vertigo (by means of the evaluation of the static equilibrium and the behaviour of the march), nystagmus, hearing loss and tinnitus at the beginning, after fifth and tenth sessions and at the end of the treatment [8].

The evaluation criteria of vertigo, were the behaviour of the static equilibrium, measured by the Romberg test. For the behaviour of the march, Babinsky Well Star and Osterhamser tests were performed. The nystagmus was measured with the patient in decubitus or seated, in a room slightly illuminated, using Frenzel goggles for the elimination of the visual fixation. For the measurement of the hearing loss, pure tone audiogram (varying frequencies from 0.125kHz to 10kHz) were used. Finally, a subjective evaluation of tinnitus was performed [8].

The results of this study [8] showed that Tinnitus, nystagmus and hearing loss were present in 74, 88 and 68% of patients, respectively. All these symptoms were decreasing with following ozone treatments. After the 5th ozone treatment, tinnitus was still present in all patients; however, vertigo, hearing loss and nystagmus disappeared in 20, 6 and 52%, respectively. At the end of the treatment, symptoms and signs considered, the results according to vertigo, hearing loss, tinnitus and nystagmus were of 90, 80, 65 and 100%, respectively.

The efficacy of ozone therapy in the treatment of idiopathic sudden sensorineural hearing loss (ISSNHL) were studied by Tasdövena, and collaborators (2017) too [9], where patients were divided into three groups according to the treatment protocol received: oral steroid (Group A- 63 patients), oral steroid + hyperbaric oxygen therapy (HBOT) (Group B- 26 patients), and oral steroid + ozone (Group C- 17 patients).

The patients in the oral steroid + ozone group, in addition to receiving oral steroids according to the ISSNHL protocol, received medical ozone therapy using the major auto hemotherapy method. In this method, an anti-ozonant infusion set and 100mL blood drawn from the patient were mixed, under sterile conditions, with 99.5% oxygen and 0.5% of an ozone mixture obtained from an ozone generator. This blood mixture was again administered to the patient intravenously,

at least for a 5-min period. This therapy was performed in five sessions twice a week [9]. In this study [9], the results were evaluated considering changes in Speech Discrimination Scores (SDSs) and Pure Tone Averages at 500, 1000, 2000, and 4000Hz.

In this study [9], the steroid treatment group (Group A), was complete recovery in 14(22.2%) cases, partial recovery in 10(15.9%), weak recovery in 8(12.7%), and no recovery in 31 (49.2%). In the group administered ozone therapy in addition to steroid treatment (Group C), 3 cases (17.6%) had total recovery, 4 cases had partial recovery (23.5%), and 7 cases had weak recovery (41.2%); however, no recovery was observed in 3(17.6%) of the cases in this group. The highest response rate to treatment was in the steroid + ozone therapy group (Group C) (82.4%), followed by the steroid + HBOT group (Group B) (61.5%), and oral steroid group (Group A) (50.8%).

Changes in the auditory system can be the cause of tinnitus, a very prevalent symptom that can arise in isolation or related to hearing loss. The pathophysiology of tinnitus is unclear and no solid treatment with effective and consistent results is yet known. This fact has motivated the search for alternative treatment routes, also justifying the study by Sherief and colleagues (2007) with the aim of studying the effects of ozone therapy in the treatment of idiopathic tinnitus [10].

Forty patients with the presence of tinnitus unrelated to another otologic symptom were selected. Subjects with pulsatile tinnitus, hormonal changes (in case of pregnancy or menopause), thyroid dysfunction, vitamin B_{12} deficit, favismus, treatment with ACE inhibitors or cases of thrombocytopenia or anaemia were excluded. Of the 40 patients selected, 30 constituted the study group and the rest formed the control group. The treatments were administered twice a week until ten treatment sessions were performed. Three assessments were made to each patient: before the treatment started, after the 5th session, and at the end of the study. Throughout the treatment, pitch matching, loudness matching, minimum masking level and residual inhibition were assessed. The use of ozone in the present study, revealed a high failure rate of 83%, with no statistically significant difference between the group submitted to ozone therapy and the control group ($p > 0.05$). It was suggested that the actions of ozone in the body have no effects on the treatment of idiopathic tinnitus and do not interfere with its pathophysiology [10].

In another study [2] the results also do not provide sufficient evidence to support ozone therapy as a truly effective treatment for tinnitus. Sönmez and colleagues (2013) [2] were evaluated the effectiveness of ozone and betahistine treatments in cases of tinnitus. The sample consisted of 68 patients aged between 18 and 75 years with perceived tinnitus for at least six months.

The frequency of tinnitus, the perception of its intensity (loudness of the tinnitus), and the Tinnitus Handicap Inventory (THI) scale were used before treatment and after three and six months respectively. Of the 68 adults selected, 27 were in the group treated with ozone (ozone therapy), 26 in the group treated with betahistine, and 15 in the control group. Two treatment sessions per week were administered until ten sessions were completed in all adults undergoing ozone therapy [2].

The comparison of loudness between the initial values, and the values obtained at the third and sixth months, did not reveal a significant difference in each of the three groups, $p=0.137$ in the group submitted to ozone therapy, and $p=0.794$ in the control group. Six out of 27 patients in the ozone group showed an improvement (of at least 15dB) in tinnitus loudness, while 4 out of 15 patients in the control group showed the same improvement. The comparison of the groups in terms of loudness improvement was not significant ($p=0.821$). The comparison of the groups, in terms of improvement in the THI scale, was not significant ($p=0.564$). No side effects were observed in the group submitted to ozone therapy, during the whole treatment [2].

Analysis of the articles reveals that the sample varies between 40 [10] and 106 [9] patients with auditory system alterations and that ozone therapy was applied in all studies, even though using different administration techniques. Sudden deafness and tinnitus are studied in most studies and the results support the thesis that ozone therapy is an effective and safe treatment for sudden deafness [7-9]. Regarding tinnitus, there is only one study [8] that reveals some benefit of this technique, with the other studies [2,10] showing little encouraging results in its application in cases of tinnitus.

Conclusion

This study discovered that ozone therapy can be beneficial for the treatment of sudden idiopathic deafness, presenting high recovery rates, regardless of the degree of deafness. However, it does not constitute an alternative therapy for the treatment of idiopathic tinnitus, given the absence of sufficient scientific evidence.

Despite the ineffectiveness of ozone therapy in treating this symptom - tinnitus, it showed no side effects on the patient, or negative effects on his hearing, proving to be a safe technique.

Notwithstanding these results, ozone therapy may be promising in the treatment of other alterations of the auditory system namely in the treatment of acoustic trauma, for which studies in animals already point it as a treatment with great potential [11].

Studies on the application of this technique in auditory system alterations are scarce and not very recent, which is a limitation to the present review. More studies are needed to prove the potential of this type of treatment in the recovery of auditory system alterations, especially in the context of tinnitus.

A greater scientific investment in this area is recommended so that we can understand the true potential of the clinical application of ozone therapy in all auditory system alterations even in those that due to lack of scientific evidence are not reported yet.

This study will help researchers to discover the critical areas for the application of ozone therapy, namely in the treatment of tinnitus, which many researchers have not been able to prove. Thus, a new theory about the clinical and effective application of ozone therapy in the auditory system alterations can be reached.

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