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Original Research Article

Randomised controlled clinical study to evaluate the efficacy of IV injection of caroverine and intratympanic steroid injection in the treatment of cochlear synaptic tinnitus with sensorineural hearing loss

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ABSTRACT

Background: Cochlear synaptic tinnitus with sensorineural hearing loss (SNHL) is the most common type of subjective tinnitus. Many therapies were tried, but nothing is well proven to cure this. Hence, our present study aims to assess the efficacy of intravenous (IV) injection of caroverine and intratympanic steroid injection in treatment of cochlear synaptic tinnitus with SNHL.
Methods: This study was carried out at the ear, nose and throat (ENT) department with 60 patients (22 male, 38 female) between the ages of 20 and 70 who had idiopathic tinnitus. Patients who met inclusion criteria were randomized by simple randomization and divided into two groups. The study group receives intratympanic dexamethasone, twice weekly for total three weeks and stat dose of IV caroverine. The control group receives an intratympanic isotonic solution with an IV caroverine placebo. Tinnitus handicap index (THI) score and pure tone averages (PTA) were done before treatment and in the first week, first month, and six months after completing the study protocol.
Results: In the study group, pre-treatment results, and post-treatment first, sixth month THI scores, PTA results were different to a significant extent, whereas in the control group, the same scores were not different significantly. The THI scores between the groups revealed considerably lower scores in the first and six months for the study group. Successful treatment was defined as a decrease in PTA by 10 dB or more after six months.
Conclusions: The effect of the intratympanic injection of dexamethasone along with IV injection of caroverine on the efficacy of treatment of tinnitus severity and improving hearing was statistically significant.

Keywords: Intratympanic injection, Caroverine injection, Tinnitus

INTRODUCTION

By definition, tinnitus is the perception of sound without an external stimulus it affects 12–14% of adults. The prevalence of subjective tinnitus increases typically with aging, and it is clearly associated with hearing loss.[1,2] Among various tinnitus types, subjective non-pulsatile tinnitus is by far the most common type of tinnitus, representing an estimated 90% of all tinnitus referrals seen in an otolaryngology practice. The cochlea is the most common site for subjective tinnitus but other auditory pathway disorders may also be responsible. The most common diagnosis for cochlear tinnitus is presbyacusis, followed by noise-induced hearing loss and endolymphatic hydrops. The anxiety can exacerbate the discomfort caused by tinnitus and whether or not the tinnitus is disturbing is determined through further central auditory processing of the "signal" and psychological validation of tinnitus. Tinnitus impacts the patient's quality of life severely. Different methods had been developed for managing tinnitus, but none of them offered a permanent cure. Thus, it has become one of the most challenging tasks faced by

otolaryngologists. Hence the main objective of our study is to assess the efficacy of IV injection of caroverine and intratympanic steroid injection in treatment of cochlear synaptic tinnitus with sensorineural hearing loss (SNHL).

METHODS

This is a randomised case control study, carried out at the otorhinolaryngology department following the study protocols approved in Katuri Medical College and Hospital. Duration of study is one year from March 2019 to March 2020.

The patients with tinnitus for more than six months and diagnosed to have cochlear synaptic tinnitus were enrolled for the study, with each patient providing informed written consent. A total of 60 patients (22 male, 38 female) between the ages of 20 and 70 were selected by simple randomization technique to receive intratympanic dexamethasone along with IV injection of caroverine or the same amount of isotonic solution along with IV injection of caroverine placebo. We recorded the age, sex, religion, socio-economic status, occupation, and address of patients. The symptoms of the patients were recorded in a chronological fashion. The history of the present episode or previous such episodes were recorded. The past history of systemic disorders, ototoxic drug use was recorded. The familial and personal history, including the occupational work conditions, drug abuse (including tobacco), headphone use, and life style were also inquired. A complete clinical examination was carried out, which included a complete general examination and a complete otorhinolaryngological examination.

All the patients were subjected to pure tone audiometry (PTA), impedance audiometry, tinnitus matching in terms of frequency and intensity, magnetic resonance imaging (MRI) of brain and temporal bone. The tinnitus handicap inventory questionnaire (THI) scoring of the patients was done before and after the study. The results were compiled and analyzed statistically by using students' T test with p value <0.05 as a significant value.

Diagnosis of cochlear synaptic tinnitus

Investigations to confirm cochlear synaptic tinnitus: audiometry (0–16,000 Hz) - high frequency loss and sensorineural hearing loss are consistent with cochlear synaptic tinnitus diagnosis; impedance audiometry - should be within normal range to exclude middle ear pathologies; acoustic reflex (ipsilateral and contralateral) - in cochlear synaptic tinnitus the acoustic reflexes will be present at comparatively lesser sound intensity levels due to loudness recruitment; reflex decay - to exclude retro cochlear pathology, abnormal decay of acoustic reflex is indicative of retrocochlear pathology; tinnitus matching - has prognostic value and; BERA is dependable in assessing the nature of pathology, whether conductive or cochlear or retrocochlear.

Selection of cases

Inclusion criteria

The following criteria was included in the study: patients of age group 20 to 70 years; diagnosis of tinnitus, unilateral or bilateral; cochlear hearing defect; reflex audiometry confirming cochlear-synaptic tinnitus and excluding middle ear tinnitus; and written consent after explanation by consultant in charge.

Exclusion criteria

Patients not willing to give written consent after receiving due instructions; reasonable doubts as to the patient's cooperation; severe secondary disorders (i.e. any acute/chronic illness); contraindication for caroverine therapy (e.g. severe hypertension); pregnancy or plan for having children; Meniere's disease; retrocochlear hearing defect; blast injury; status post psychiatrist therapy; status post-operation of the middle ear; and excessive consumption of alcohol, drug or nicotine were excluded from the study.

A total of 60 patients (22 male, 38 female) between the ages of 20 and 70 with a mean age of 42.5 years who had idiopathic tinnitus were included in this prospective study. Patients were selected by simple randomization technique to receive intratympanic dexamethasone along with IV injection of caroverine or the same amount of isotonic solution along with IV injection of caroverine placebo. The intratympanic injections were administered twice a week for three weeks and a stat dose of IV injection caroverine given. The control group receives intratympanic isotonic solution in the doses with stat IV injection caroverine placebo. The study group composed of 30 patients (16 male, 14 female); ages ranging between 20 and 70 with a mean of 42.43 (±14.3) years and the control group composed of 30 patients (13 male, 17 female); ages ranging between 40 and 70 with a mean of 43.28 (±13.3) years. The patients were evaluated using the THI scoring.[14] THI is a very highly reliable test, which is not influenced by age, gender, or hearing loss. The test gives clear results and can be applied to the patient easily. There are three options available for each question in the THI: "yes," "no," and "sometimes" with points 4, 0, and 2, respectively (Figure 1). The purpose of these questions is to identify problems that the tinnitus is causing to the patient.

THI was performed before treatment and at the first week, first month, and six months after the completion of the study protocol. The audiometric tests were performed before treatment and six months after treatment. Study group patients were administered 0.5-ml intratympanic injections of 4 mg/ml dexamethasone. Following xylocaine spray application to achieve topical anaesthesia, the patients were made to lie down in supine position with their heads turned 45° to the opposite side. Using a 26-gauge needle, the assigned solution was injected through

the anteroinferior quadrant of the tympanic membrane, and the patients stayed in the same position for about 10 minutes. Along with first dose of intratympanic injection of dexamethasone study group patients were infused with a single dose of intravenously 160 mg/5 ml of caroverine in 100 ml of physiological saline at the rate of 2 ml/min. A total of six injections of intratymapnic dexamethasone and single injection of IV caroverine were given to study group patients and pre-treatment and post-treatment THI scores and PTA results were compared.

Patient Name: _____ Date: _____

INSTRUCTIONS: The purpose of this questionnaire is to identify difficulties that you may be experiencing because of your tinnitus. Please answer every question. Please do not skip any questions.

1.	Because of your tinnitus, is it difficult for you to concentrate?	Yes	Sometimes	No
2.	Does the loudness of your tinnitus make it difficult for you to hear people?	Yes	Sometimes	No
3.	Does your tinnitus make you angry?	Yes	Sometimes	No
4.	Does your tinnitus make you feel confused?	Yes	Sometimes	No
5.	Because of your tinnitus, do you feel desperate?	Yes	Sometimes	No
6.	Do you complain a great deal about your tinnitus?	Yes	Sometimes	No
7.	Because of your tinnitus, do you have trouble falling to sleep at night?	Yes	Sometimes	No
8.	Do you feel as though you cannot escape your tinnitus?	Yes	Sometimes	No
9.	Does your tinnitus interfere with your ability to enjoy your social activities (such as going out to dinner, to the movies)?	Yes	Sometimes	No
10.	Because of your tinnitus, do you feel frustrated?	Yes	Sometimes	No
11.	Because of your tinnitus, do you feel that you have a terrible disease?	Yes	Sometimes	No
12.	Does your tinnitus make it difficult for you to enjoy life?	Yes	Sometimes	No
13.	Does your tinnitus interfere with your job or household responsibilities?	Yes	Sometimes	No
14.	Because of your tinnitus, do you find that you are often irritable?	Yes	Sometimes	No
15.	Because of your tinnitus, is it difficult for you to read?	Yes	Sometimes	No
16.	Does your tinnitus make you upset?	Yes	Sometimes	No
17.	Do you feel that your tinnitus problem has placed stress on your relationships with members of your family and friends?	Yes	Sometimes	No
18.	Do you find it difficult to focus your attention away from your tinnitus and on other things?	Yes	Sometimes	No
19.	Do you feel that you have no control over your tinnitus?	Yes	Sometimes	No
20.	Because of your tinnitus, do you often feel tired?	Yes	Sometimes	No
21.	Because of your tinnitus, do you feel depressed?	Yes	Sometimes	No
22.	Does your tinnitus make you feel anxious?	Yes	Sometimes	No
23.	Do you feel that you can no longer cope with your tinnitus?	Yes	Sometimes	No
24.	Does your tinnitus get worse when you are under stress?	Yes	Sometimes	No
25.	Does your tinnitus make you feel insecure?	Yes	Sometimes	No

Figure 1: Tinntus handicap inventory questionnaire.

Statistical analysis

The results were compiled and analysed statistically by using students' t test with p value <0.05 as significant value.

RESULTS

The demographic data and statistical results of the 60 patients are presented in Tables 1 and 2. The study group (IT steroid) comprised of 30 patients (16 male, 14 female); ages ranging between 20 and 70 with a mean of 42.43 (±14.3) years and the control group (IT saline) comprised of 30 patients (13 male, 17 female); ages ranging between 20 and 70 with a mean of 43.28 (±13.3) years. There is no age difference between the two groups (p>0.05) (Table 1).

Tinnitus duration in the study group ranged from 12 to 110 months with a mean duration of 36.28±21.67 months. Control group patients had tinnitus for a mean of 37.87±21.38 months (range 12-96 months). There is no differences in duration between the two groups (p>0.05) (Table 1).

The pre-treatment and post-treatment mean values at first week, post-treatment at end of first month, and post-treatment at end of sixth month THI scores of the study group were 58.33±24.9, 53±27, 48.93±27.62, and 46.13±28.79 respectively. The mean pre-treatment and post-treatment at end of first month and pre-treatment and post-treatment at the end of sixth month THI scores of the control group were 57.96±24.39, 58.04±22.73, 58.68±23.25, and 56.77±23.13 respectively. In the study group, pre-treatment and post-treatment THI scores at the end of first month and pre-treatment and post-treatment THI scores at the end of six months were different significantly (Table 2) whereas the same scores were not different significantly in the control group (Table 2). The THI scores compared between the control and study groups revealed significantly lower scores at the end of first and sixth months in the study group (p=0.05 and 0.037 respectively) (Table 2).

Table 1: Demographics, pre-treatment, and post-treatment THI scores of the study and control groups.

Parameter	Study group		Control group		
	Range	Mean±standard deviation	Range	Mean±standard deviation	P value
Age	20-70	42.43±14.31	20-70	43.28±13.3	0.734
Duration	12-110 months	36.28±21.67	12-96	37.87±21.38	0.721
Pre tx THI	10-98	58.33±24.9	12-98	57.96±24.39	0.877
Post tx1 wk THI	10-100	53±27	16-94	58.04±22.73	0.202
Post tx 1 mo THI	10-100	48.93±27.62	14-94	58.68±23.25	0.05
Post tx 6 mo THI	10-100	46.13±28.79	14-86	56.77±23.13	0.037

With regard to the 30 patients who received intratympanic steroid and IV injection caroverine treatment, in 13 patients, the PTA threshold improved more than 10 dB, in 17 patients there was no change greater than 10 dB, and no patients deteriorated more than 10 dB. When PTA done in the control group, none of the patients showed any change greater than 10 dB. The difference was statistically significant (P=0.002).

There were no complications like increased perception of tinnitus, vertigo, and tympanic membrane perforation during the course of the therapy and the follow-up period

Table 2: Statistical analysis of pre-treatment and post treatment THI in study and control groups at the end of 1st week, 1st month, and 6th month.

THI	Study group, P	Control group, P
Post tx1 wk THI	0.06	0.854
Post tx 1 mo THI	0.05	0.755
Post tx 6 mo THI	0.037	0.368

DISCUSSION

Subjective tinnitus, the phantom ringing or buzzing sensation that occurs in the absence of sound, affects 12–14% of adults; in some cases the tinnitus is so severe or disabling that patients seek medical treatment. The prevalence of subjective tinnitus increases typically with aging and it is clearly associated with hearing loss.[2] Various other factors associated with tinnitus are noise exposure, head trauma, middle ear pathologies, ototoxic drugs, and endolymphatic hydrops but idiopathic cases are the most prevalent group.[3]

Cochlea is the most common site for subjective tinnitus but other auditory pathway disorders may also be responsible.[3] Among cochlear pathologies, the most common pathology include presbyacusis followed by noise-induced hearing loss and endolymphatichydrops.[4] The central process anxiety, exacerbate the discomfort and whether or not the tinnitus is disturbing, is determined through further central auditory processing of the tinnitus "signal" and its psychological validation.

Tinnitus has a moderately negative impact on patient's quality of life. Different methods had been developed for managing tinnitus but none of them offered a permanent cure. Thus, it has become one of the most challenging tasks faced by the otolaryngologists. Hence, present study was undertaken to assess the efficacy of IV injection of caroverine along with intratympanic steroid injection in treatment of cochlear synaptic tinnitus.

Effect of treatment

Intravenous steroids

Steroids have anti-inflammatory and electrolyte modifying effects, are one of the most popular agents used for intratympanic treatment.[4] The mechanism of action of intratympanic drugs starts through round window by diffusion, annular ligament of oval window, capillaries, or through the lymphatics of the inner ear.

Intratympanic steroid injection for the treatment of tinnitus has been tried for over fifteen years. Sakata et al reported that in 75% of 3,978 ears showed improvement in tinnitus after four IT-steroid injections and in 68% showed improvement after 6 months.[5]

Cesarani et al reported 13.5% cure rate and 24% improvement rate 8 weeks after nine injections of intratympanic decadran. However, those studies were without controls single arm studies.[6]

The mechanism of action of steroid

Intratympanic steroids after diffusing into the round window, they show their anti-inflammatory and electrolyte modifying effects by the steroid receptors which have been demonstrated in animals and humans.[7,8] The mechanism of action of steroids in tinnitus is to decrease the inflammation caused by immunomediated/autoimmune dysfunction or a direct effect on the inner ear epithelium.[9] Cochlear blood flow increase also been suggested as another mechanism.[10,11] The main advantages of intratympanic steroid injections are the avoidance of systemic side effects providing high concentrations to the inner ear.

Cochlear damage from various causes involves hair cells and also striavascularis which can impair ion-homeostasis. Steroids maintains ion-homeostasis thus help in preventing cochlear damage by activating sodium potassium (Na^+K^+) ATPase, sodium chloride (Na^+/Cl^-) cotransporter and epithelial sodium and calcium channels of the striavascularis.

The striavascularis pumps K^+ over the blood-labyrinth barrier into the endolymph and then from the Henson cell and Claudius cell through the fibrocytes of spiral ligament to the striavascularis and recycling occurs. This mechanism maintains the endolymphatic potential of +80 mV for cochlear activity.

Pharmacokinetics of injection steroid into the middle ear cavity

Steroid administered to the middle ear through the round window membrane reaches perilymph in scala tympani, percolates to scalavestibuli via the Rosenthal's canal or spiral ligament, and finally reaches endolymph in scala media. In this delivery route, all of the cochlear inner structures (hair cell, spiral ganglion, striavascularis, etc.) can be exposed to steroid.

In our study intratympanic dexamethasone was administered twice a week for three weeks (total of 6 injections) in the anteroinferior quadrant of the affected ear. The maximum concentration of dexamethasone in perilymph was significantly higher via the intratympanic route versus oral administration or intravenous administration. The round window membrane thickness is approximately 70 μm in humans and consists of 3 layers with outer epithelial layer, middle connective tissue layer, and inner mesothelial layer. Penetration of drug through the round window membrane is mainly affected by drug factors such as molecular weight, concentration, electrical charge, and lipid solubility. Among all these, the molecular weight is the most important factor. The lower the molecular weight, the easier it would penetrate the membrane.

N-methyl-D-aspartate (NMDA) receptor antagonist

Caroverineisan spasmolytic and oto-neuroprotective agent having the antioxidant property also. It acts as an N-type calcium channel blocker, competitive α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor antagonist and non-competitive NMDA receptor antagonist has been shown to protect the inner ear from excitotoxicity and to be effective in the treatment of cochlear synaptic tinnitus. Spontaneous depolarisation of NMDA receptor canbe reversed to physiological polarization by antagonist property of caroverine. Glutamate is the main neurotransmitter and is excitatory to the cochlear afferents that is released on to the synaptic region of inner hair cells (IHC).

In conditions like, excessive noise exposure excessive glutamate release occurs with overload of intracellular calcium, this prolonged excitotoxic exposure could be a reason behind tinnitus. The glutamate receptors, e.g. NMDA at the synaptic region of inner hair cells can be blocked by their antagonists. Caroverine being a selective NMDA blocker can reduce tinnitus in a significant number of patients.

The NMDA receptors projecting from the medial geniculate body to the amygdala are hypothesized to be important in a pathophysiological model of tinnitus, in which the connections between the auditory, limbic, and autonomic nervous systems play an important role in the emergence of tinnitus.[12]

Caroverine, an antagonist of non-NMDA and NMDA receptors, has been considered as an effective drug for the therapeutic suppression of cochlear synaptic tinnitus by Denk et al.[13]

Pharmacokinetics of intravenous injection of caroverine – NMDA receptor antagonist caroverine is administered through intravenous route. One ampule containing 160 mg of caroverine was diluted in 100 ml of saline and was infused at the rate of 2 ml/min. The vitals of the patients like blood pressure, pulse rate and respiratory rate were measured before starting the infusion. Under close observation the infusion was given slowly.

The present study was conducted among a limited number of sixty patients and followed for six months period. Lack of long term follow up of patients and small sample size is a limitation of this study. The results of present study conclude that intratympanic injection of dexamethasone along with IV injection of caroverine is effective in the management of tinnitus. However, sparse data is available regarding the same.

Hence, further research should be undertaken towards the search of beneficial effect of combining intratympanic injection of dexamethasone and IV injection of caroverine in treatment of tinnitus with sensory neural hearing loss. Intravenous caroverine and intratympanic decadran could be a miracle medicine for cochlear synaptic tinnitus with sensory neural hearing loss. Thus, further studies with large sample size and long term follow up are required.

CONCLUSION

Through this study we would like to conclude that combination therapy of intratympanic injection of dexamethasone and IV injection of caroverine will provide better results in treating greater majority of patients suffering with cochlear synaptic tinnitus and sensory neural hearing loss.

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