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Therapeutic role of Vitamin B12 in patients of chronic tinnitus: A pilot study

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Abstract

True tinnitus is a phantom auditory perception arising from a source or trigger in the cochlea, brainstem, or at higher centers and has no detectable acoustic generator. The most accepted is the famous neurophysiologic model of Jastreboff, which stresses that tinnitus, is a subcortical perception and results from the processing of weak neural activity in the periphery. The aim of this study is to determine the role of Vitamin B12 in treatment of chronic tinnitus. In this randomized, double-blind pilot study, total 40 patients were enrolled, of which 20 in Group A (cases) received intramuscular therapy of 1 ml Vitamin B12 (2500 mcg) weekly for a period of 6 weeks and Group B (20) patients received placebo isotonic saline 01 ml intramuscular. The patients were subjected to Vitamin B12 assay and audiometry pre- and post-therapy. Of the total patients of tinnitus, 17 were Vitamin B12 deficient that is 42.5% showed deficiency when the normal levels were considered to be 250 pg/ml. A paired *t*-test showed that in Group A, patients with Vitamin B12 deficiency showed significant improvement in mean tinnitus severity index score and visual analog scale (VAS) after Vitamin B12 therapy. This pilot study highlights the significant prevalence of Vitamin B12 deficiency in North Indian population and improvement in tinnitus severity scores and VAS in cobalamin-deficient patients receiving intramuscular Vitamin B12 weekly for 6 weeks further provides a link between cobalamin deficiency and tinnitus thereby suggestive of a therapeutic role of B12 in cobalamin-deficient patients of tinnitus.

Keywords: *Audiometry*, *neuropathy*, *tinnitus*, *tinnitus matching*, *Vitamin B12*

Introduction

Tinnitus has plagued the human civilization since time immemorial and has been described in the Egyptian papyri (6000 BC). Tinnitus is experienced as ringing, roaring, or buzzing in the ears. They all originate, in one way or the other, from inside the head, and they are all known as tinnitus. In some cases, tinnitus exists because there is actually a source of acoustic energy located somewhere in the head and neck area – vascular anomalies, myoclonus, a clicking jaw, respiratory or cochlear otoacoustic emission, etc., – that can also be heard by a second person, with or without the aid of special devices. However, true tinnitus is a phantom auditory perception arising from a source or trigger in the cochlea, brainstem, or at higher centers and have no detectable acoustic generator. Tinnitus is classified as either primary or secondary. Primary tinnitus is used to describe tinnitus that is idiopathic and may or may not be associated with sensorineural deafness. Secondary tinnitus is tinnitus that is associated with a specific underlying cause (other than sensorineural deafness) or an identifiable organic condition. It is a symptom of a range of auditory and nonauditory system disorders that include simple cerumen impaction of the external auditory canal; middle ear diseases such as otosclerosis or Eustachian tube dysfunction; cochlear abnormalities such as Meniere's disease; and auditory nerve pathology such as vestibular schwannoma.

Although the exact mechanism of tinnitus still eludes us, the most accepted is the famous neurophysiological model of Jastreboff, which stresses that tinnitus, is a subcortical perception and results from the processing of weak neural activity in the periphery. The tinnitus-related neural activity occurring usually near the periphery of the system undergoes processing in subcortical auditory pathways and finally perceived at a conscious level as sound. The loudness and pitch of tinnitus depend on the strengths and pattern of electrical activity arriving at the cortex of the temporal lobe after subcortical signal detection, and pattern matching has occurred, the process being the same as for any neural activity generated by the external sounds by the cochlea.

There has been no promising treatment for tinnitus until date mainly because the etiology of tinnitus is still not clear. The generation of tinnitus has been attributed to the auditory system and neighboring anatomical regions, but at present, no test can identify these regions accurately.[1] Current consensus is that tinnitus results from aberrant neural activity in the auditory system, generally of excitatory nature.[2] New drugs have been emerging frequently which claim to play a role in managing tinnitus. Shemesh *et al*. in the year 1993 found Vitamin B12 deficiency in tinnitus patients, and its supplementation was found to help these patients.[3] The aim of this study is to determine the role of Vitamin B12 in the treatment of tinnitus. One of the mechanisms believed to be at play in Vitamin B12 deficiency neuropathy is hypomethylation in the central nervous system. Cochlear function is dependent on adequate vascular supply and the normal functioning of nerve tissue. B12 deficiency is associated with axonal degeneration, demyelination, and subsequent apoptotic neuronal death. Vitamin B12 deficiency may cause the demyelination of neurons in the cochlear nerve, resulting in hearing loss.[4,5,6] In addition, low levels of Vitamin B12 and folate are associated with the destruction of the microvasculature of the stria vascularis, which might result in decreased endocochlear potential and in hearing loss and tinnitus.[7] The objective of the study was to assess the prevalence of Vitamin B12 deficiency in chronic subjective tinnitus patients in Indian population and therapeutic effect of Vitamin B12 injection on tinnitus.

Methods

This pilot study was conducted at Era's Lucknow Medical College from August 2012 to August 2013. The study design was a randomized, double blinded, placebo-controlled prospective study. All the adult patients attending the ENT outpatient department aged 18-60 years with chronic subjective tinnitus were included in the study. Chronic tinnitus being defined as tinnitus lasting more than 6 month's duration with frequent occurrence and sufficiently severe that the patients turned to the clinic for treatment.

Inclusion criteria

- Adult patients aged 18-60 years with chronic subjective tinnitus with or without sensorineural hearing loss of more than 6 months duration.
- No gender bias, normal intelligence level.

Exclusion criteria

1. Patients of objective (pulsatile) tinnitus.
2. Patients suffering with any congenital anomalies which may lead to any otological problem will be excluded from the study.
3. Patients suffering from any infective otological problem will be excluded from the study.
4. Patients suffering from any psychiatric illness.
5. Patients suffering from any otological problem other than tinnitus and sensorineural hearing loss will be excluded from the study.
6. Patients with acute acoustic trauma or chronic noise exposure.
7. Patients suffering from systemic diseases such as anemia, hypertension, diabetes mellitus, and hypothyroidism which may lead to otological problems will be excluded from the study.
8. Patients using any other drugs for last 4 weeks which is known to have an effect on tinnitus such as steroids, cyclendalate, and vasodilators.
9. Patients who have undergone ear surgery or having tinnitus after head injury or any other organic illness in head and neck region.

This being a randomized, double-blind pilot study, total 40 patients were enrolled, of which 20 were in Group A (cases) and 20 in Group B (control). Group A patients (20) enrolled randomly received parenteral intramuscular therapy of 1 ml Vitamin B12 (2500 mcg) weekly for a period of 6 weeks. Group B (20) patients were given placebo isotonic saline 1 ml intramuscular in a similar manner for 6 weeks. The patient and the examiner were blinded about the treatment given. The observations were recorded by the examiner. The investigator analyzed the observations.

Patients with chronic subjective tinnitus more than 6 months duration underwent audiometry, tinnitus matching (pitch and loudness), Vitamin B12 assay (premedication and postmedication) by chemiluminescence method and a self-report by tinnitus severity index questionnaire[8] after detailed history and examination. The patients were followed for a period of 1 month after

6 weeks of interventional therapy. They were again subjected to tinnitus severity index testing, Vitamin B12 assay, tinnitus matching, Vitamin B12 assay, pure tone audiometry, and a self-report on tinnitus questionnaire.

Statistical analyses of data were conducted using the SPSS version 21.0 (IBM, Chicago, IL, USA) and MS EXCEL version 7. Proportion was calculated for a categorical variable, whereas mean and standard deviation was calculated for continuous variables. Chi-square test was used to check the association between categorical variables and the student *t*-test was used to check the significance difference for continuous variables. The $P < 0.05$ was deemed statistically significant. The statistical model used considered gender (male, female), age group (Group 1: 17-29, Group 2: 30-49, Group 3: 50-66 age), tinnitus status (tinnitus present/no tinnitus, normal), response to treatment (yes/no), tinnitus duration, Vitamin B12 level (low/normal), and frequency.

Results

The mean age of the patients suffering from tinnitus was 38.37 (±12.40) years and the male to female ratio was 2:3. The mean duration of the complaints of tinnitus was 1.36 (±1.3) years [Table 1]. Tinnitus presented in both ears in 27.5% and unilaterally in 72.5% (right ear in 32.5% and left in 40% cases). Of the total patients of tinnitus, 17 were Vitamin B12 deficient that is 42.5% showed deficiency when the normal levels were considered to be 250 pg/ml. This is significantly high prevalence. In Group A patients, prevalence of Vitamin B12 deficiency was 50%, and Group B patients, it was 35% [Table 2]. A paired *t*-test showed that in Group A, patients with Vitamin B12 deficiency showed improvement in mean tinnitus severity index score after Vitamin B12 therapy which was significant ($t = 2.64$, $P = 0.016$, df = 18). However, there was no significant improvement in severity index scores of Group A patients without B12 deficiency and Group B patients receiving placebo [Table 3]. Furthermore, Group A patients with Vitamin B12 deficiency had a mean visual analog scale (VAS) of 3.34 ± 0.84 before therapy and 2.89 ± 0.47 posttherapy. The VAS showed a significant improvement with respect to tinnitus loudness ($t = 2.13$, $P = 0.04$, df = 18) after therapy. The results show favorable and encouraging outcome of Vitamin B12 therapy in vitamin deficient subjects. There was no significant improvement in other groups posttherapy. Subjective improvement was seen in six patients (30%) of Group A and four patients (20%) of Group B. The subjective improvement in tinnitus between the two groups was not statistically significant. The mean pitch (kHz) of tinnitus in patients with Vitamin B12 deficiency was 5.9 ± 2.3 (kHz) and in normal Vitamin B12 levels was 5.6 ± 2.7 (kHz). The mean loudness levels of tinnitus in Vitamin B12 deficiency patients were 4.2 ± 3.1 (db SL) and in normal B12 levels is 5.1 ± 2.9 (db SL) [Table 4]. There was no significant difference in the pitch and loudness levels of two groups asserting the insignificant role of Vitamin B12 levels on pitch and loudness. It was also observed that the mean hearing thresholds of Group A and Group B were almost similar [Table 5, $P > 0.05$]. Rest of the routine hemogram was normal in all patients. In the tinnitus severity questionnaire, patients reported maximum difficulty due to tinnitus in a quiet room, going to sleep, and difficulty in ignoring tinnitus.

Discussion

Epidemiologic studies have consistently reported that tinnitus prevalence in adults ranges from about 10% to 15% of the population worldwide.[9,10] In the Beaver Dam offspring study of more than 3000 adults between the ages of 21 and 84 years studied between 2005 and 2008,

10.6% reported tinnitus of at least moderate severity or causing difficulty falling asleep.[11] In patients with auditory neuropathy spectrum, the prevalence of tinnitus was found to be around 67%, mostly bilateral (89.5%), and seen more often in females (70.52%). The subjective pitch was low-pitched in individuals with low frequency hearing loss and the perceived pitch was high with a flat configuration of loss.[12]

The prevalence of frequent tinnitus in the US increased with increasing age, peaking at 14.3% between 60 and 69 years of age.[13] The prevalence of tinnitus increases with age.[14] Tinnitus has been found to affect men more than women.[15] However, in our study, it was found to be more prevalent in females (M:F = 2:3) Approximately, 25% of patients with tinnitus report an increase in severity over time.[9] Though exact data on the prevalence of tinnitus in India is not available, it is estimated that 4.5 millions of patients suffer from tinnitus (retrieved from www.tinnex.in). It is extrapolated that in India out of 1,065,070,607 people across the country an estimated population of 47,928,177 may have tinnitus. These prevalence extrapolations for tinnitus are only estimates, based on applying the prevalence rates from the US (or a similar country) to the population of India (retrieved from http://www.rightdiagnosis.com). [16]

The observations of our study highlight the high prevalence of serum cobalamin deficiency levels in the North Indian population aged 18–60 years, i.e., 42.5% when the threshold value was taken as 250 pg/ml and 15% when the threshold was fixed at 150 pg/ml which are both significantly high. Despite poor serum cobalamin levels, there was no anomalous finding in the hemogram of such patients. Shemesh *et al*.[3] in the year 1993 found Vitamin B12 deficiency in tinnitus patients, and its supplementation was found to help these patients. The prevalence of cobalamin deficiency was 47% in the tinnitus with noise-induced hearing loss patients, whereas it was 27% in nontinnitus patients with noise-induced hearing loss. In an Indian study, the published prevalence of subnormal Vitamin B12 concentration in elderly varies from 3% to 40.5% depending on the cutoff used for defining deficiency of cobalamin level in serum.[17] Using 150 pmol/L as threshold, 67% men had low Vitamin B12-concentration (68% rural, 51% slum residents, and 81% urban middle-class) in India.[18] Plasma levels of Vitamin B12 were subnormal (<150 pmol/l) in 16% of the study population in India.[19] In this study, the prevalence of cobalamin deficiency in tinnitus patients was significantly high and similar (42.5%) to the result of Shemesh *et al*. and at 15% similar to Shobha *et al*. when cutoff was taken at 250 pg/ml and 180 pg/ml, respectively.

Stouffer and Tyler[9] reported that tinnitus was bilateral in 52% of cases, one-sided in 37% of cases, and localized in the cranium instead of the ear in 10% of cases; in 1% of cases, sounds were perceived as coming from outside the head. Berkiten *et al*.[20] reported 43% of the patients and 57% of the patients had bilateral and single-sided tinnitus, respectively. However, in this study, tinnitus presented more unilaterally in 72.5% (right ear in 32.5% and left in 40% cases) and in both ears in 27.5%.Though tinnitus severity was highest in Group A with normal cobalamin levels, the improvement in tinnitus severity levels were significant in cobalamin-deficient group. Tinnitus pitch and loudness levels were not found to bear any correlation with serum cobalamin levels.

Multiple theories have been put forward to account for tinnitus related to disturbances of the peripheral auditory system, the auditory nerve, and cochlea.

One of the mechanisms believed to be at play in Vitamin B12 deficiency neuropathy is hypomethylation in the central nervous system. Inhibition of the B12-dependent enzyme methionine synthase results in a fall in the ratio of S-adenosylmethionine (SAM) to S-adenosylhomocysteine;[4] the resultant deficiency in SAM impairs methylation reactions in the myelin sheath. The methylation of homocysteine to methionine requires both methylcobalamin (an active form of Vitamin B12) and the active form of folic acid (5-methyltetrahydrofolate).[21] Deficiency of Vitamin B12 leads to accumulation of homocysteine which is a neurotoxin and vascular toxin. Cochlear function is dependent on adequate vascular supply and the normal functioning of nerve tissue. B12 deficiency is associated with axonal degeneration, demyelination, and subsequent apoptotic neuronal death. Hcy has been implicated as a risk factor for vascular disease as well as brain atrophy.[22] Concentrations of Hcy above 11.9 μmol/L were associated with approximately 3-fold higher risk for white matter damage when compared to concentrations below 8.6 μmol/L.[23] Vitamin B12 deficiency may cause the demyelination of neurons in the cochlear nerve, resulting in hearing loss and tinnitus.[5,6] In addition, low levels of Vitamin B12 and folate are associated with the destruction of the microvasculature of the stria vascularis, which might result in decreased endocochlear potential and in hearing loss and tinnitus.[7] Martvnez-Vega *et al*.[24] in their study, demonstrated, for the first time, that the relationship between hyperhomocysteinemia induced by folate deficiency and premature hearing loss involves impairment of cochlear homocysteine metabolism and associated oxidative stress.

The high prevalence of Vitamin B12 deficiency could be attributed to dietary habits such as vegetarianism, poor intake of milk and milk products, socioeconomic factors, and high prevalence of *Helicobacter pylori*. Cobalamin deficiency can manifest as neurological and hematological disorders. In view of the findings of this study, cobalamin deficiency could also present with tinnitus only in the absence of other manifestations and the authors suggest serum cobalamin determination in chronic tinnitus patients.

Just as myriad the etiology of tinnitus is equally expansive is the canvas of treatments for tinnitus ranging from different medications such as antipsychotics, vasodilators, herbs, neurotonics, cerebral cognition enhancers to tinnitus retraining therapy, psychophysiology treatment,[25] and low-frequency repetitive transcranial magnetic stimulation.[26] In the ever growing noisy world of fast life and poor dietary habits, it is imperative to seek the pathophysiology of tinnitus and find means to overcome this annoying malady. The results suggest role of evaluating serum Vitamin B12 levels in patients of chronic tinnitus in view of the significant prevalence of cobalamin deficiency in North Indian population. This pilot study sheds light on the relationship of deficient B12 levels and tinnitus and its supplementation playing a therapeutic role in tinnitus though more studies with larger groups are required to corroborate and establish a direct relationship.

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Conflicts of interest

There are no conflicts of interest.

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Figures and Tables

Table 1

Personal characteristics of the study subjects

Variable	*n* = 40
Age (in years)	38.37±12.40
Gender (male/female)	16/24
Tinnitus duration (in years)	1.36±1.3
Vitamin B_{12} deficiency (yes/no)	17/23

Table 2

Distribution of patients in Groups A and B

Group	With B_{12} deficiency	Without B_{12} deficiency
Group A (injection B_{12})	10	10
Group B (injection NS)	7	13

χ^2= 0.92, *P* = 0.33 and df = 1, df = Degree of freedom, NS = Normal saline

Table 3

Tinnitus severity scores of patient's pre- and post-therapy with Vitamin B_{12} injections

Group	Mean tinnitus severity index score		Significance *t*, *P* and df
	Pretherapy	Posttherapy	
Group A (injection B_{12})			
With B_{12} deficiency	36.50±7.6	28.30±6.2	*t*=2.64, *P*=0.016*, df=18
Without B_{12} deficiency	38.16±12.0	37.23±11.2	*t*=0.17, *P*=0.85, df=18
Group B (injection NS)			
With B_{12} deficiency	32.80±8.7	32.30±8.2	*t*=0.11, *P*=0.91, df=12
Without B_{12} deficiency	33.01±7.2	34.10±7.4	*t*=0.38, *P*=0.70, df=24

*Significant as $P < 0.05$ associated with paired *t*-test, df = Degree of freedom, NS = Normal saline

Table 4

Audiological measures of the tinnitus in patients with and without Vitamin B_{12} deficiency

Tinnitus parameters	Vitamin B_{12} deficiency	Normal Vitamin B_{12}	*t*, *P* and df
Tinnitus pitch (kHz)	5.9±2.3	5.6±2.7	0.36, 0.71,38
Tinnitus loudness (db SL)	4.2±3.1	5.1±2.9	0.94, 0.35,38

P-value using independent *t*-test, df = Degree of freedom

Table 5

Comparison of mean hearing threshold in Groups A and B

Group	With B_{12} deficiency (db)	Without B_{12} deficiency (db)
Group A (injection B_{12})	28.97±20.31	29.55±12.74
Group B (injection NS)	24.06±16.74	25.20±11.40
Significance (Group A vs. Group B)	*t*=0.83, *P*=0.26	*t*=1.13, *P*=0.26

P-value is calculated using independent *t*-test, NS = Normal saline