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Original Research Article

Comparison of oral versus intranasal methylcobalamin in patients of tinnitus

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ABSTRACT

Background: Tinnitus is perception of sound in the absence of an external auditory stimulus. It is an experience that originates from a cause or trigger in the cochlea, brainstem or at higher centres.
Methods: A randomized, double-blinded pilot study was conducted, wherein a total of 64 patients were enrolled. Of which 32 were considered as Group A (oral methylcobalamin was administered) and 32 in Group B (intranasal methylcobalamin was administered). Group A patients enrolled randomly received oral methylcobalamin therapy (tablet methylcobalamin 500 mcg tablet once a day for a period of 6 weeks). Group B patients enrolled randomly received intranasal methylcobalamin treatment (nasal spray 500 mcg per day) for aperiod of 6 weeks.
Results: A sum of 19 patients of the total patients included in the study were found to be Vitamin B12 deficient that is 42.1% were considered to be Vitamin B12 deficient when the normal levels wereconsidered to be 250 pg/ml, which could be considered to be a significantly high prevalence. Patients having Vitamin B12 deficiency showed improvement in visual analogue scale score after vitamin B12 therapy.
Conclusions: Supplementation of Vitamin B12 in vitamin B12 deficient patients having tinnitus has shown symptomatic improvement. However, no significant improvement in visual analogue scale scores in patients without B12 deficiency was observed. There was improvement in VAS in cobalamin-deficient patients receiving Vitamin B12 weekly for 6 weeks.

Keywords: Methylcobalamin, Treatment, Tinnitus

INTRODUCTION

True tinnitus, the perception of sound in the absence of an external auditory stimulus. It is a phantom acoustic experience that originates from a cause or trigger in the cochlea, brainstem or at higher centres. Its prevalence is estimated to be between 10 and 15% in the adult population as per study conducted by Baguley et al in 2013.[1] The Jastreboff neurophysiologic hypothesis, which emphasises that tinnitus is a subcortical perception and originates from the processing of weak neuronal activity in the periphery, is the most widely recognized theory.[2] Tinnitus has had its origin in the human civilization since time immemorial, dates back to 6000 BC. Tinnitus is experienced as ringing, roaring, or buzzing in the ears. It is believed to result as a source of oto-acoustic energy located somewhere in the head and neck region caused as a result of vascular anomalies, myoclonus, a clicking jaw, cochlear otoacoustic emission etc., even present in the absence of a reasonable/desirable trigger. The prevalence of tinnitus accentuates with advancing age.[3] 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 while secondary tinnitus is usually associated with a specific underlying pathology (other than sensorineural deafness) or an identifiable organic condition. It could result from a vast multitude of causative factors namely simplecerumen 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.[4] Although the exact mechanism of tinnitus has not been ascertained, the most accepted theory is the famous neurophysiological model of Jastreboff, which emphasises that tinnitus, is a subcortical perception that results from the processing of weak neural activity in the periphery which gets processed in the subcortical auditory pathways and is perceived by conscious brain as a buzzing sound.

Other theories that have been postulated in tinnitus causation are the auditory plasticity theory, the crosstalk theory that involves an interplay between the somatosensory system, and the limbic and autonomic nervous systems causing tinnitus.[5] Many aspects of this condition remain incomprehensible, including its pathophysiology, ultimately hindering the development of a treatment plan. Current consensus is that tinnitus results from aberrant neural activity in the auditory system, generally of excitatory nature.[6] New drugs have been emerging frequently which claim to play a role in managing tinnitus. Shemesh et al in the year 1993 discovered relation of Vitamin B12 deficiency in tinnitus patients, and its supplementation was found to benefit patients of tinnitus.

The aim of this study is to determine the therapeutic role of vitamin B12 supplementation in the treatment of tinnitus. Hypomethylation in the central nervous system is believed to be a significant role in Vitamin B12 deficiency neuropathy.[7] Cochlear function results from adequate vascular supply and for the optimal functioning of nervous tissue. B12 deficiency is believed to cause axonal degeneration, demyelination, and subsequent apoptotic neuronal death.[8] Vitamin B12 deficiency is believed to cause demyelination of neurons in the cochlear nerve, resulting in hearing impairment. In addition, low levels of vitamin B12 and folate are associated with the destruction of the microvasculature of the stria vascularis, thereby resulting in decreased endocochlear potential, subsequently in hearing loss and tinnitus.[9] Tinnitus can be a troublesome condition on both individual and societal levels. It represents one of the most frequent and burdensome otologic problems, posing various somatic and psychological infirmities that adversely affect the quality of life.[10] Tinnitus may represent a heterogeneous disorder that can be caused by or exacerbated by many factors. Damage to the auditory system from illness, injury, surgery, or noise exposure may contribute to tinnitus. It is possible that inflammation and vascular damage may play a role in some cases.[11]

Aim and objectives

The objective of the study was to assess the prevalence of vitamin B12 deficiency in chronic subjective tinnitus patients in North Indian population and therapeutic effect of vitamin B12 on tinnitus. For outcome assessment, various tools have been developed and tested for quantifying tinnitus outcome, assessing how troublesome their tinnitus is and its influence on their daily activityand ability to function is assessed via visual analogue scale. Patients analyse in a graphic way the pitch and loudness of tinnitus using a visual analogue scale. The results of visual analogue scale are thus compared before and after treatment, which helps to objectively assess the therapy impact

METHODS

A pilot study was carried out at Era's Lucknow Medical College, between August 2022 and August 2023. It was a randomized, double blinded, placebo controlled prospective trial. Participants includedmen and women aged 18 to 60 from Northern India who had chronic subjective tinnitus with or without sensorineural hearing loss of Tinnitus that occurs frequently, lasts longer of more than 6 months' duration.

Inclusion criteria

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

Exclusion criteria

Participants were excluded if they had any of the following: objective (pulsatile) tinnitus, congenital anomaly that contributed to otological problems, infection, psychiatric illness, otological problems other than tinnitus, acute acoustic trauma or chronic noise exposure, systemic diseases such as anemia, hypertension, diabetes mellitus, and hypothyroidism, use of medications known to have an effect on tinnitus, such as steroids, cyclendalate, and vasodilators within 4 weeks prior to study start and history of ear surgery, tinnitus status post-head injury, or any organic illness in the head and neck region.

In a randomized, double-blinded pilot study, total 64 patients were enrolled, of which 32 were considered Group A (oral methylcobalamin was administered) and 32 in Group B (intranasal methylcobalamin was administered). Group A patients enrolled randomly received oral methylcobalamin therapy (tablet methylcobalamin 500 mcg tablet once a day for a period of 6 weeks). Group B patients enrolled randomly received intranasal methylcobalamin treatment (nasal spray 500 mcg per day, 1 Spray in each nostril for 6 weeks) for a period of 6 weeks. Patients with chronic subjective

tinnitus more than 6 months duration attending ENT, OPD were subjected to complete ENT examination. Patient selection was done on the basis of Inclusion and exclusion criteria after taking informed consent. Patients were further subjected to audiometry (pure tone audiometry and impedence audiometry), visual analogue scale (VAS) serum vitamin B12 assessment (premedication and postmedication) by chemiluminescence method. The effect of methylcobalamin treatment on hearing was examined using Audiometric tests and results were compared with a VAS before treatment, 2 and 6 weeks after treatment.

VAS is a subjective tool wherein tinnitus assessment is done under 4 sub-categories namely VAS-L (Loudness), VAS-A (Annoyance), VAS-D (Distress), VAS-C (Coping) wherein they are assessed on how troublesome their tinnitus is and its influence on their daily activity and ability to function on a scale of 0 to 10 wherein 0 indicates absence of tinnitus and 10 indicates unbearable tinnitus which helps to subjectively assess and compare the therapy results. Statistical analyses of data were performed using the SPSS version 21.0 (IBM, Chicago, IL, USA) and MS EXCEL version 7. Calculation of mean and standard variables was done for continuous variables. Chi-square test was done to study the association between categorical variables and the paired *t*-test was done to check the significance difference for continuous variables, $p<0.05$ was found out to be statistically significant. The demographical data used considered gender (male, female), age group (Group 1: 18-28 years, Group 2: 29-39, Group 3: 40-49 years, Group 4: 50-59 years), duration of tinnitus (<1 year, 1-2 years, >2 years), vitamin B12 level (low/normal). Comparison of visual analogue scale scoring (VAS-A, VAS-C, VAS-D, VAS-L) was done for both Oral as well as intranasal methylcobalamin before therapy, 2 weeks post-therapy and 6 weeks post- therapy.

RESULTS

The mean age of the patients, recorded to suffer from tinnitus as per the study conducted, was 24.75 (±11.52) years (Table 1).

Table 1: Age profile of patients enrolled in study (n=64).

Age group (years)	N	%
18-28	12	18.75
29-39	25	38.06
40-49	16	25.07
50-59	11	17.18
Mean age±SD (range)	37.35±11.52, (40-49 years)	

Male to female ratio suffering from tinnitus was 1.37:1 (Table 2). The study revealed that the mean duration for which the complaints of tinnitus was reported was 1.35 (±1.3) years (Table 3). Tinnitus having bilateral representation in 28.12% patients and presented unilaterallyin 74.5% patients (right ear in 34.36% patients and in left ear in 37.52% patients) (Table 4).

Table 2: Gender profile of patients enrolled in study (n=64).

Sex	N	%
Male	37	57.8
Female	27	42.2
Sex ratio M:F	1.37:1	

Table 3: Distribution of patients according to duration of complaints (n=64).

Duration of tinnitus (years)	N	%
≤1	12	18.75
1-2	38	59.37
>2	14	21.8

Table 4: Presentation of tinnitus with respect to laterality of ear as per the study (n=64).

Tinnitus presentation	N	%
B/L ear	18	28.12
U/L right ear	22	34.36
U/L left ear	24	37.52

A sum of 19 patients of the total patients included in the study were found to be vitamin B12 deficient (29.68%) when the normal levels were considered to be 250 pg/ml, which could be considered to be a significantly high prevalence. In patients administered oral methylcobalamin, 8 patients were found to be Vitamin B12 deficient i.e. the prevalence of vitamin B12 deficiency was 42.1% and in patients administered intranasal methylcobalamin, 11 patients were found to be vitamin B12 deficient, the prevalence of vitamin B12 deficiency was 57.9% (Table 5).

Table 5: Distribution of patients with respect to vitamin B12 levels deficiency (n=64).

Groups	B12 deficient population	B12 sufficient population
Group A (oral methylcobalamin)	8	18
Group B (intranasal methylcobalamin)	11	27
Total	19	45

A paired t test demonstrated that in Group A, patients having vitamin B12 deficiency showed improvement in visual analogue scale score after vitamin B12 therapy which was significant ($t=2.56$, $p=0.012$, $df=16$). Also, in Group A patients having vitamin B12 deficiency, a mean visual analog scale of 3.24±0.64 before therapy and 2.76±0.46 post-therapy was noted. The VAS showed a significant improvement with respect to tinnitus ($t=2.14$,

p=0.04, df=16) in terms of all subtypes of VAS scoring namely VAS-A, VAS-C, VAS-D and VAS-L after therapy.

The results demonstrated positive outcome of vitamin B12 therapy in vitamin deficient subjects (Table 6). However, no significant improvement was noted in vitamin sufficient subjects post-therapy (Table 7). The subjective improvement in tinnitus amongst the two groups was not statistically significant (p>0.5). Man-Whitney test was used for comparison of effectiveness of oral and intranasal methylcobalamin therapy (Table 8). Friedman test was done for comparison in every subsequent follow-up visit to see the response to therapy.

Table 6: Distribution of patients with respect to vitamin B12 levels deficiency (n=64).

Variables	Pre- therapy	Post-therapy 2 weeks	Post-therapy 6 weeks	P value
VAS (A)	8.8	8.4	8.0	<0.001
VAS (C)	7.8	7.5	7.2	<0.001
VAS (D)	7.5	7.2	6.8	<0.001
VAS (L)	8.0	6.8	7.5	<0.001

Table 7: Comparison of visual analogue scale before and after treatment (intranasal).

Variables	Pre-therapy	Post- therapy 2 weeks	Post-therapy 6 weeks	P value
VAS (A)	8.9	8.4	8.0	<0.001
VAS (C)	8.0	7.5	7.2	<0.001
VAS (D)	7.8	7.2	6.8	<0.001
VAS (L)	8.3	8.0	7.5	<0.001

Table 8: Comparison of visual analogue scale before and after treatment (between oral andintranasal).

Test groups	VAS scoring	Pre-therapy	Post- therapy 2 weeks	Post-therapy 6 weeks	P value (intra group)	P value (inter group)
Group A oral methyl-cobalamin	VAS (A)	8.8	8.4	8.0	<0.001	>0.05
	VAS (C)	7.8	7.5	7.2	<0.001	
	VAS (D)	7.5	7.2	6.8	<0.001	
	VAS (L)	8.0	6.8	7.5	<0.001	
Group B intranasal methyl-cobalamin	VAS (A)	8.8	8.4	8.0	<0.001	>0.05
	VAS (C)	7.8	7.5	7.2	<0.001	
	VAS (D)	7.5	7.2	6.8	<0.001	
	VAS (L)	8.0	6.8	7.5	<0.001	

DISCUSSION

Studies conducted worldwide have persistently showed that the prevalence of tinnitus ranges from about 10% to 15% amongst adult population. Beaver Dam offspring study, conducted between 2005 and 2008, that was carried out on 3000 adults between the age of 21 and 84 years, reported 10.6% population to be suffering from tinnitus of at least moderate severity or causing difficulty in falling asleep.[11] In patients having auditory neuropathy spectrum involvement, the prevalence of tinnitus was found to be approximately 67%, having mostly bilateral presentation (89.5%), and reported more often in females (70.52%).[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 is believed to increase with age.[14] Tinnitus was known to prevail more amongst men as compared with women.[15] In our study too, tinnitus was seen to affect more than women (M:F=1.37:1). In India, it is estimated that 4.5 millions of patients suffer from tinnitus (retrieved from www.tinnex.in). It is deduced that out of 1,065,070,607 people living across the subcontinent an estimated population of 47,928,177 is likely to be suffering from tinnitus.[16] In our study, the high prevalence of serum cobalamin deficiency levels in the North Indian population aged 18-60 years, i.e., 29.68% when the threshold value was considered as 250 pg/ml and 36.46% when the threshold was considered to be 150 pg/ml which are both considered to be significantly high. Despite poor serum cobalamin levels, the patients showed no other abnormality. Shemesh et al in the year 1993 established that supplementation of vitamin B12 in vitamin B12 deficient patients having tinnitus has shown improvement in tinnitus. In a study conducted in India, the prevalence of subnormal vitamin B12 concentration in elderly ranges from 3% to 40.5% depending on the cutoff which marks the 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. Plasma levels of Vitamin B12 were subnormal (<150 pmol/l) in 16% of the study population in India.[18] 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 study conducted by Shobha et al

when cutoff was taken at 250 pg/ml and 180 pg/ml, respectively. Stouffer and Tyler, in their study, estimated that tinnitus had bilateral presentation in 52% of cases while it had unilateral presentation in 37% of cases, also tinnitus was localized in the cranium instead of the ear in 10% of cases; and in 1% of cases, sounds were perceived as coming from outside the head.[19] In a study conducted by Berkiten et al it was found out that 43% of the patients had bilateral tinnitus while 57% of the patients had unilateral tinnitus, respectively.[20] However, in this study, tinnitus presented unilaterally in 72.5% cases (32.5% in right ear and 40% cases in left ear) and 27.5% cases in bilateral ears. The improvement in tinnitus severity levels was noted to be significant in cobalamin-deficient group post-therapy.

Multiple theories have been put forth which have established that tinnitus results from disturbances of the peripheral auditory system, the auditory nerve, and cochlea.[21] One of the accepted theory states that Vitamin B12 deficiency neuropathy is thought to result from hypomethylation in the central nervous system.[21] Inhibition of the B12-dependent enzyme methionine synthase results in a failure of conversion of S-adenosylmethionine (SAM) to S-adenosylhomocysteine; the resultant deficiency in SAM prevents methylation reactions in the myelin sheath.[22] The methylation of homocysteine to methionine requires both methylcobalamin (an active form of Vitamin B12) and the active form of folic acid (5-methyltetrahydrofolate).[22] Deficiency of vitamin B12 leads to accumulation of homocysteine which is a neurotoxin and vascular toxin. Cochlear function is a measure of adequate vascular supply and the normal functioning of nervous tissue. Axonal degeneration, demyelination, and subsequent apoptotic neuronal death are believed to result from B12 deficiency. The role of homocysteine has been attributed as a pivotal marker for vascular disease as well as brain atrophy.[22]

Concentrations of homocysteine above 11.9 µmol/l are associated with increase in risk by approximately 3 times for white matter damage when compared to concentrations below 8.6 µmol/l.[22] Demyelination of neurons in the cochlear nerve may result from vitamin B12 deficiency, resulting in hearing loss and tinnitus.[23] In addition, low levels of vitamin B12 and folate result in the destruction of the microvasculature of the stria vascularis, which might result in decreased endocochlear potential and in hearing loss and tinnitus.[23] Martvnez-Vega et al in their study, proved, for the first time, that hyperhomocysteinemia that results from folate deficiency leads to premature hearing loss which results from impaired cochlear homocysteine metabolism and associated oxidative stress.[24] The high prevalence of vitamin B12 deficiency could possibly result from dietary habits such as vegetarianism, poor intake of milk and milk products, socioeconomic factors, and high prevalence of *H. pylori* neurological and hematological disorders may result as a consequence of cobalamin deficiency.[25] Tinnitus may result from a single to a vast multitude of factors, lays foundation for treatments for tinnitus ranging from different medications such as antipsychotics, vasodilators, herbs, neurotonics, cerebral cognition enhancers to tinnitus retraining therapy, psychophysiology treatment, and low- frequency repetitive transcranial magnetic stimulation.[25] In the hustle of a fast moving life and poor dietary habits, it is imperative to seek the pathophysiology of tinnitus and find means to overcome this debilitating condition that negatively influences the quality of life.[26] The study suggests an establishment of role of evaluation of 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 believed to have a therapeutic role in tinnitus though more studies with larger groups are required tosubstantiate and establish a direct relationship

Limitations

The limitations of this study are an unintentional bias encountered during data collection due to small sample size, lack of reliable data, lack of prior research studies and difficult follow ups.

CONCLUSION

Supplementation of vitamin B12 in vitamin B12 deficient patients having tinnitus has shown improvement in tinnitus. However, no significant improvement in visual analogue scale scores in patients without B12 deficiency was observed. Improvement in VAS in cobalamin-deficient patients receiving vitamin B12 weekly for 6 weeks thereby suggesting a correlation between cobalamin deficiency and tinnitus, a therapeutic role of B12 in cobalamin-deficient patients of tinnitus is suggested.

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