

Comparison of the safety and efficacy of caroverine and betahistine in patients of subjective tinnitus

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ABSTRACT

Background: Owing to lack of any established treatment and handicap assessment methods, subjective tinnitus can be a debilitating disorder. This study was carried out to compare the safety and efficacy of caroverine and betahistine in patients of subjective tinnitus.

Methods: A total of 60 patients of subjective tinnitus were randomized into two groups and followed-up for 12 weeks using tinnitus handicap inventory (THI) questionnaire. One group received 8 mg betahistine tablet TDS for a month whereas the other group was given supervised intravenous (IV) infusion of 160 mg of caroverine dihydrochloride. Data for the safety were also recorded.

Results: Both the drugs showed significant improvement in severity of symptoms at 1 week, 4 weeks and 12 weeks individually as assessed by the THI scores. The response to caroverine was significant up to 4 weeks, but it was not significant at 12 weeks; whereas the response to betahistine was significant up to 12 weeks. A total of 28 adverse drug reactions (ADRs) were reported (53.6% with caroverine, 46.4% with betahistine). 24 ADRs were mild and 4 were moderate in intensity. There was no serious adverse event.

Conclusions: Both the drugs are safe and efficacious in reducing the handicap of subjective tinnitus. A single IV infusion of caroverine may suffice for 4-6 weeks, so it may be repeated after 6 weeks to maintain the relief.

Keywords: Caroverine, Betahistine, Subjective, Tinnitus, Tinnitus handicap inventory

INTRODUCTION

Tinnitus is defined as “the conscious experience of a sound that originates in an involuntary manner in the head of its owner, or may appear to him to do so.”¹ It may be the first or the most prominent symptom of various disease processes that threaten the patient’s physical health and well-being. Two types of tinnitus are described as subjective (heard by the patient only) and objective (even the examiner can hear it with a stethoscope).² For those affected, it can be a debilitating disorder, and there is growing evidence to support that tinnitus can be linked to anxiety, depression, and insomnia.³ Betahistine and caroverine, both have shown efficacy in treating tinnitus⁴ and vertigo in some studies.

Despite all these encouraging findings, no controlled clinical study has examined the effect of betahistine or caroverine in patients with disabling subjective tinnitus. Further, no study until date has examined self-reported tinnitus severity before and after administration of these two drugs. Hence, this study was undertaken to compare the safety and effectiveness of these drugs in the domains of a tertiary care hospital in a rural area of Himachal Pradesh.

METHODS

This was a prospective randomized comparative clinical trial approved by Scientific Advisory cum Protocol Review Committee and Institutional Ethics Committee.

Sample size calculation

$$\text{Total sample size} = \frac{4 \times (a + b)^2 \times (\text{SD})^2}{(u_1 - u_2)^2}$$

Where

a = conventional multiplier for alpha (taken to be 0.05) = 1.96

b = conventional multiplier for power of the study (for power to be taken as 0.90) = 1.282

$u_1 - u_2$ (The difference we wish to detect is the average difference between two consecutive grades) = 20

Standard deviation (SD in the study conducted in the past)⁵ = 21.8.

Substituting the above values, the total sample size came out to be 49.95. Taking into consideration, some losses on follow-up and other reasons, 60 patients with subjective tinnitus presenting in the Department of Otorhinolaryngology and willing to participate in this study were included and follow-up of all these patients was done for 3 months. The participants were randomized into two groups (30 participants each).

Inclusion criteria

- Age of the patient between 18 and 60 years
- Unilateral or bilateral tinnitus
- Tinnitus handicap inventory (THI) basal score more than 20 points
- Willing to give a written consent.

Exclusion criteria

- Masticatory movements influencing subjective tinnitus sensation
- Patient not giving written consent
- Pregnancy
- Meniere's disease
- Blast injury of ear
- Excessive consumption of alcohol, drugs or nicotine
- Intolerance to interventional drugs
- Medical therapy of tinnitus within 1 week of enrolment.

The participants to be included in the study were explained about the study protocol in their local language and their informed written consent was obtained before enrolment. A complete medical history was obtained and recorded on a prescribed performa from all the participants and they were allowed to undergo a complete general physical examination and detailed ear, nose and throat examination. The pre-treatment investigations included complete blood count, liver, kidney and thyroid function tests, fasting blood glucose, urine: routine and microscopic examination, lipid profile, electrocardiogram, immunological screening, pure tone audiometry, relevant radiological examination and any other relevant etiological investigation. Record of abnormal investigations was also made.

Assessment of severity was done by the THI which is a self-administered questionnaire that is used to determine the degree of distress suffered by the tinnitus patient. Some studies have indicated that the minimum reduction in THI score of 6-7 points⁶ can be considered clinically relevant and in some other studies minimum reduction of 20 points⁷ is clinically significant. Grading based on THI has been presented below in a tabular form (Table 1).⁸

The data collected for each participant was recorded on Microsoft Excel sheet including THI scores at baseline and after 1, 4 and 12 weeks, grades of severity (pre and post-treatment) and the adverse events, if any.

Therapeutic procedure

1. Betahistine group (standard): Tablet betahistine dihydrochloride 8 mg p.o. 3 times a day for 1 month.
2. Caroverine group (test): One ampoule of caroverine dihydrochloride was diluted in 100 ml of normal saline solution. A single intravenous (IV) infusion was administered at the rate of 2 ml/min until relief in tinnitus was achieved or the total dose had been infused. The infusion was stopped if any adverse events occurred.

The primary outcome measures were comparisons of THI scores and severity grades at baseline and follow-up at 1 week, 4 weeks and 12 weeks' time. Participants were included in the primary analysis on the basis of intention to treat. Any participant showing a reduction in score by at least 20 points was considered to be a responder to the drug due to subjective improvement. Follow-up was done for 3 months for every participant. In other words, we can say that THI questionnaire was recorded on four different periods of time i.e. pre-treatment, at 1 week, 4 weeks and at 12 weeks' time.

Adverse drug events were evaluated and severity was graded on a three point scale as mild (awareness of sign and symptom but easily tolerated), moderate (discomfort sufficient to reduce or affect normal daily physical activity) and severe (causes inability to work or adverse drug reaction [ADR] is associated with hospitalization, permanent disability or is life threatening). Causality assessment of suspected adverse drug reactions was done by WHO probability scale.⁹

RESULTS

The mean value for pre-treatment THI scores in the sample was 56.37±11.64. The absolute scores ranged from 32 to 78. The mean value in caroverine group was 60.73±10.54 with a range of 34-78 and the mean value in betahistine group was 52±11.2 with a range of 32-74. The total number of participants in various pre-treatment severity grades were 4 in mild, 28 in moderate, 26 in severe and 2 in catastrophic. There was no participant in "slight" category

Table 1: Tinnitus severity scale.

Score	Grade	Description
0-16	Slight	Only heard in a quiet environment, very easily masked. No interference with sleep or daily activities
18-36	Mild	Easily masked by environmental sounds and easily forgotten with activities. May occasionally interfere with sleep but not daily activities
38-56	Moderate	May be noticed, even in the presence of background or environmental noise, although daily activities may still be performed. Less noticeable when concentrating. Not infrequently interferes with sleep and quiet activities
58-76	Severe	Almost always heard, rarely, if ever, masked. Leads to disturbed sleep pattern and can interfere with ability to carry out normal daily activities. Quiet activities affected adversely. There should be documentary evidence of the complaint having been brought to the general (or some other) medical practitioner (prior to any medico-legal claim). Hearing loss is likely to be present but its presence is not essential
78-100	Catastrophic	All tinnitus symptoms at level of severe or worse. Should be documented evidence of medical consultation. Hearing loss is likely to be present but its presence is not essential. Associated psychological problems are likely to be found in hospital or general practitioner records

as it was an exclusion criterion in our study. The mean value in caroverine group was 3.67 ± 0.66 . The mean in betahistine group was 3.2 ± 0.61 . The post-treatment severity grades compared with pre-treatment grades for each study group have been shown in Figures 1 and 2. The grades in caroverine group ranged from 1 to 3 i.e. from slight (1), mild (2) and moderate (3). There was no participant who remained at severe (4) or catastrophic (5) level even after treatment with caroverine. In the betahistine group, the post-treatment severity grades ranged from 2 to 4 i.e. from slight (1), mild (2), moderate (3) and severe (4). There was no participant who had catastrophic (5) severity grade even after treatment with betahistine. Finally, 93.3% of the participants in caroverine group responded to treatment whereas only 33.3% of the participants in betahistine group were responders. So out of total participants (n=60) enrolled in the study, only 63.3% of the participants responded to the treatment.

Student's *t*-test was applied for the analysis of data obtained for THI scores for subjective improvement of tinnitus by both the drugs administered. The mean±SD values obtained for both groups at various points of time like pre-treatment, at 1 week, 4 weeks and 12 weeks and the p values are shown in Table 2. It can be interpreted that the p values at each point of time obtained are statistically significant (≤ 0.05). Further, p values for analysis between both groups are also statistically significant (≤ 0.05) which means there is statistically significant improvement in THI scores at each follow-up with each drug. So, both drugs have some efficacy in management of subjective tinnitus.

Further, group-wise comparison for data at each point of time with other times in the same group was also done which revealed the values for each group shown in Table 3 and Figure 3. On analysis, it is seen that p values for each pair are ≤ 0.05 , which are statistically significant. Only pair comparing mean THI scores at 3rd and 4th week in caroverine

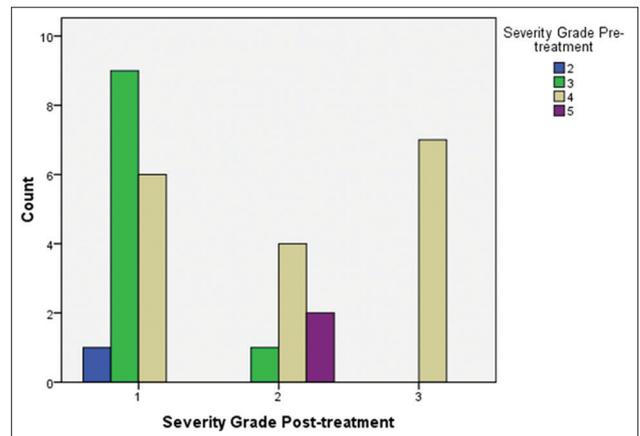


Figure 1: Post-treatment severity grades for caroverine group.

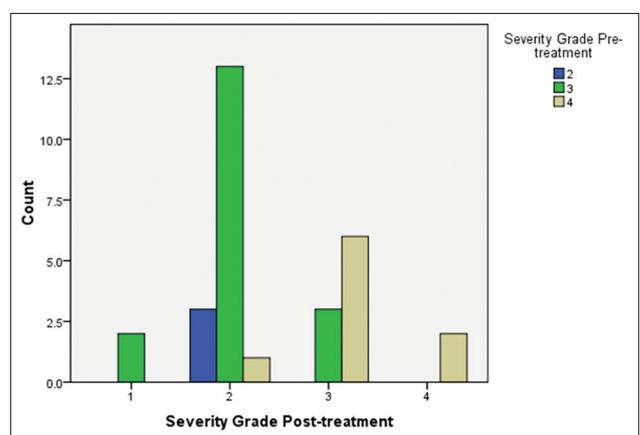


Figure 2: Post-treatment severity grades for betahistine group.

group has $p=0.079$, which is not statistically significant. Similarly pair-wise comparison for the same data was done between both the groups. The data have been shown in Table 4 where it is seen that p values for pairwise comparison

Table 2: Groupwise comparison of THI scores at various time intervals.

THI score	Caroverine		Betahistine		p value between groups
	Mean±SD	p value (pre-Tt)	Mean±SD	p value (pre-Tt)	
Pre-Tt	60.73±10.54	-	52.00±11.20	-	0.003
1 week	33.60±15.85	0.000	46.00±12.97	0.007	0.002
4 weeks	24.87±17.68	0.000	38.13±13.09	0.000	0.002
12 weeks	19.93±15.28	0.000	33.87±12.51	0.000	0.000

THI: Tinnitus handicap inventory

Table 3: Groupwise analysis of THI scores amongst various time intervals.

Group	Time (I)	Time (J)	Mean difference (I-J)	p value
Caroverine	1	2	27.13	0.000
		3	35.87	0.000
		4	40.80	0.000
	2	1	-27.13	0.000
		3	08.73	0.000
		4	13.67	0.000
	3	1	-35.87	0.000
		2	-08.73	0.000
		4	04.93	0.079
	4	1	-40.80	0.000
		2	-13.67	0.000
		3	-04.93	0.079
Betahistine	1	2	06.00	0.007
		3	13.87	0.000
		4	18.13	0.000
	2	1	-06.00	0.007
		3	07.87	0.000
		4	12.13	0.000
	3	1	-13.87	0.000
		2	-07.87	0.000
		4	04.28	0.000
	4	1	-18.13	0.000
		2	-12.13	0.000
		3	-04.28	0.000

THI: Tinnitus handicap inventory

between both groups are also statistically significant (≤ 0.05) in each pair, which means there is statistically significant difference in THI scores at all points of time.

A total of 28 ADRs were reported (Figure 4). Out of this, 53.6% were in caroverine group and 46.4% were in betahistine group. Dry mouth and nausea were most common ADR in caroverine group. Headache was the most common ADR in betahistine group. Out of total 28 ADRs, 24 were mild and 4 were moderate. There was no serious adverse event. Further, all the ADRs in caroverine group were mild. In the betahistine group, 69.2% ADRs were mild and 30.8% were moderate. Causality assessment classified all the ADRs

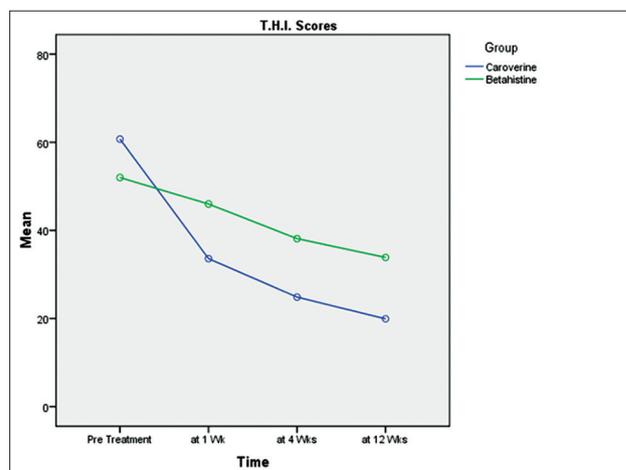


Figure 3: Profile plot for pairwise analysis.

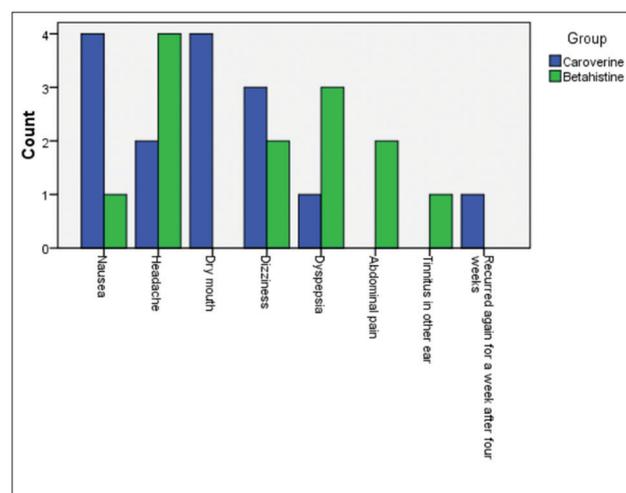


Figure 4: Frequency distribution of various adverse drug reactions.

into possible category. Among these, 53.6% were due to caroverine and 46.4% were due to betahistine.

DISCUSSION

Idiopathic subjective tinnitus is the most common form of tinnitus with a 5-year incidence of 3-5.7%.^{10,11} In addition to being a subjective phenomenon, assessment of outcome of tinnitus is the most difficult step in conducting clinical research. Various drugs have been tried from time to time for subjective tinnitus, but none has shown promising

Table 4: Pairwise analysis between different follow-up visits.

Time (I)	Time (J)	Mean difference (I-J)	p value
1	2	16.57	0.000
	3	24.87	0.000
	4	29.47	0.000
2	1	-16.57	0.000
	3	08.30	0.000
	4	12.90	0.000
3	1	-24.87	0.000
	2	-08.30	0.000
	4	04.60	0.000
4	1	-29.47	0.000
	2	-12.90	0.000
	3	-04.60	0.000

results.^{12,13} In the last decade, pharmacotherapy of tinnitus has become more rational due to knowledge of molecular or receptor pharmacology of tinnitus giving the patients a hope to alleviate their distress. This comparative prospective study was conducted to assess the safety and efficacy of caroverine and betahistine in patients of subjective tinnitus in a rural area.

The pre-treatment severity of grades of tinnitus in caroverine group had mean value of 3.67 ± 0.66 and in betahistine group, the value was 3.20 ± 0.61 . Both these values are on the higher side of grading toward moderate to severe and catastrophic, which shows that most of the participants were suffering from more severe forms of subjective tinnitus. Hence, they were expected to be more disturbed on psychosocial basis. The reason for this could be that only more severe cases are usually referred to a tertiary level institute where we had conducted our study. Another reason could be the lack of interest to seek medical care by rural population in milder illnesses.

Betahistine is being prescribed in the management of various vestibular disorders.¹⁴ Some studies have shown that it is very much effective in the management of Meniere's disease,¹⁵ but some other studies show that it does not have any effect on tinnitus when compared to a placebo.¹⁶ In our study also, only 33.3% of the participants given betahistine subjectively responded to the treatment. So, these findings are much more consistent with the earlier studies. But among the responders in this group, there was a statistically significant ($p \leq 0.05$) change in the THI scores between pre-treatment and each follow-up visit i.e. at 1 week ($p=0.007$), 4 week ($p=0.000$) and after 12 weeks ($p=0.000$) (Table 2). Further, pairwise analysis between different follow-up visits also shows a statistically significant ($p \leq 0.05$ in every pair) change in the THI scores (Table 3). So betahistine can be a useful option in alleviating the subjective handicap of tinnitus patients in a small sub-set of population who are very much distressed by it.

Caroverine has also been tried in patients of tinnitus in a placebo-controlled study.¹⁷ In the test group, 63% patients showed reduction in loudness of tinnitus immediately after treatment. There was no response in the placebo group. But these findings were not reproducible in a subsequent study following the same protocol.¹⁸ In our study, 93.3% of the participants given caroverine responded to the treatment. So, this response rate from our study is very much consistent with the first study. Among the responders in this group, there was a statistically significant ($p \leq 0.05$) change in the THI scores between pre-treatment and each follow-up visit i.e. at 1 week ($p=0.000$), 4 week ($p=0.000$) and after 12 weeks ($p=0.000$) (Table 2). This effect produced by a single caroverine injection could be explained by the pharmacological tuning of different inotropic glutamate receptors, which may re-establish physiological depolarization patterns.

Further pairwise analysis was also done between different follow-up visits which showed that there is a statistically significant ($p \leq 0.05$) change in the THI scores in each pair except in the last pair which compared change in THI score at follow-up visits between 4 weeks and 12 weeks (Table 3). This $p=0.079$ was statistically not significant. This implies that the response to caroverine therapy with a single injection is not sustained beyond 4 weeks, though the response rates are very much significant before 4 weeks. In other words, it can be suggested that caroverine might be re-administered after 4-6 weeks to produce a sustained response in the treatment of subjective tinnitus.

Out of 60 participants enrolled in our study, 28 ADRs were reported. Among these, 53.6% were in caroverine group and 46.4% were in betahistine group. There was no serious adverse event. Out of these, 4 ADRs were moderate in severity, rest all 24 ADRs were mild and required no treatment. Out of 4 participants with moderate ADRs, dyspepsia was noted in 3 cases and abdominal pain in a single case. All these were managed symptomatically. All these 4 participants were from betahistine group. All the ADRs seen in caroverine group were mild in severity. Causality assessment classified all the 28 ADRs into possible category as there was reasonable time relation to administration of the drug, but could also be explained by the concurrent disease.

In the caroverine group, dry mouth (4 cases) and nausea (4 cases) was the most common ADR reported (14.3% each). Other ADRs reported in this group were headache (2), dizziness (3) and dyspepsia in a single participant. Only one participant complained that his tinnitus had recurred after 1 month. But, it remained only for a week and then subsided. Primary literature review shows headache and epigastric discomfort as the possible adverse events arising from betahistine use.¹⁹ Findings in our study are very much similar to this as headache was the most common ADR reported in betahistine group (14.3%). Dyspepsia constituted 23.1% (3 cases) ADRs reported in betahistine group. Other ADRs reported in this group were nausea in a single patient only, dizziness and abdominal pain in two patients each. Only

one participant complained of having new onset of tinnitus in the other ear also. But, all of these ADRs were well-tolerated by all the participants and there was no incidence of discontinuation of participation by any member due to any ADR. Hence, these findings are supported by studies, which suggest that betahistine and caroverine are well-tolerated drugs in this regard.^{20,21}

CONCLUSION

Both the drugs are quite efficacious to reduce the handicap of subjective tinnitus. A single IV infusion of caroverine may suffice for almost 4-6 weeks. Hence, to maintain the relief, repeated administration of caroverine may be given after 6 weeks. Caroverine has the advantage as far as the compliance is concerned since the administration is supervised. Therefore, further studies should be conducted administering second dose after 6 weeks. Further, all the ADRs were well-tolerated by all the participants and there was no incidence of discontinuation of participation by anyone due to any ADR. Hence, both are safe drugs.

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