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Original Research Article

First Line Treatment of Meniere's Disease: A Randomized Controlled Trial

Anup Acharya,[a,d] Madan Mohan Singh,[b,d] Arati Shrestha[c,d]

ABSTRACT:

Introduction: There is no consensus on the first line medical treatment of Meniere disease to produce symptomatic improvement and slow the disease progress. Dietary salt restriction, diuretics, and vasodilators like betahistine are among the first line drugs that have been used for long. There is lack of evidence due to paucity of quality studies to support their effectiveness and advocate their use. This study is done to evaluate the effectiveness of three first line treatment of Meniere disease i.e. salt restriction, oral diuretics, and betahistine. **Methods**: Double blind randomized controlled trial was carried out in out-patient clinic of Ear Nose and Throat department of Lumbini Medical College Teaching Hospital. Cases were randomized into three groups; dietary salt restriction, diuretics as amiloride and furosemide, and vasodilator as betahistine. Pre and post treatment evaluation was done in terms of number and severity of vertigo, tinnitus, and hearing outcome. **Results**: There were a total of 97 cases with F:M ratio of 1.1:1. Mean age of patients was 47.86 yr (*SD*=12.7). Twenty-nine (30%) were treated with dietary sodium restriction alone (Group A), 35 (36%) were treated with diuretics (Group B) and the rest 33 (34%) were treated with vasodilator (betahistine, Group C). There was no significant difference in hearing outcome in any group. Tinnitus was significantly improved in Group B. Number of vertigo attack was significantly decreased in Group B and Group C. Severity of vertigo was significantly decreased in Group B. **Conclusion**: Dietary salt restriction alone was not effective in controlling any aspect of the disease whereas diuretics were effective in reducing tinnitus and number and severity of vertigo. Betahistine was effective in reducing the number of vertigo attacks but not effective on other aspects of the disease.

Keywords: betahistine • dietary sodium chloride • diuretics • meniere disease • randomized controlled trial

INTRODUCTION:

Meniere disease is the disease of inner ear characterized by endolymphatic hydrops. Clinically, the patients with this disease presents with characteristic features of episodic vertigo, ear fullness, tinnitus and fluctuating hearing loss. The disease is idiopathic. When the disease is secondary to a number of disorders, it is referred to as Meniere syndrome.[1]

No treatment has been so far found to stop the disease process. There is no consensus on the first line medical treatment to produce symptomatic improvement and slow the disease progress. Various treatment has been tried with different outcome in several studies. Dietary salt restriction is one of the first line treatment for Meniere disease. Some advocate mild rather than harsh restriction. Sodium restriction is thought to lower pressure in the inner ear which in turn reduces the chances of membrane rupture. Sodium restriction also helps to lower systemic hypertension which is regarded as a vascular risk factor.[2-4] Diuretics is another first line treatment for Meniere disease. Diuretics are believed to work by reducing the volume (and therefore also the pressure) of the inner ear fluids.

a - Assistant Professor
b - Associate Professor
c - Medical Officer
d - Department of Ear Nose Throat, Head and Neck Surgery
Lumbini Medical College, Palpa, Nepal

Corresponding Author:
Dr. Anup Acharya
e-mail: anupent@gmail.com

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Despite the lack of high quality evidence, some studies have reported an improvement in patients' vertigo with diuretics.[5] Oral betahistine is the most widely accepted treatment in Europe.[6-8] Betahistine has a structural similarity to histamine and has a weak agonist effect on H_1 and H_2 receptors, but a strong antagonist effect on H_3 receptors. It may have a beneficial effect upon endolymphatic hydrops by altering the microcirculation of organ of corti.[6] A recent systematic review however, concluded that there is no evidence that betahistine is effective in patients with Meniere disease or syndrome.[9] The second line treatment of Meniere disease includes the Meniett device, endolymphatic sac decompression, and intratympanic gentamicin injections.[10]

This study is done to evaluate the effectiveness of three first line treatment of Meniere disease i.e. salt restriction, oral diuretics, and betahistine in terms of hearing outcome, number and severity of vertigo attacks, and tinnitus.

METHODS:

This double blind randomized controlled trial was carried out in the out-patient clinic of Ear Nose Throat (ENT) department of Lumbini Medical College Teaching Hospital from May 2014 to July 2016. In the last three months, follow-up evaluation was done and no new patients were enrolled. Ethical clearance was taken from the ethical and research committee of the College.

Patients were diagnosed according to AAO-HNS 1995 guidelines.[1] All the new cases or those diagnosed before but have not taken medicine for last three months were included in the study. The patients were evaluated clinically and, when indicated, with the investigations to rule out possible causes of Meniere syndrome. Special attention was given towards syphilis, thyroid disorders, auto-immune disorders like lupus and rheumatoid arthritis.

Patients who did not consent to study, could not come for follow up within three months, or those who were lost to follow up and could not be traced by various means were excluded from the study.

All the patients were then evaluated for the number of vertigo attacks in the preceding three months, severity of vertigo attack and tinnitus rating according to visual analogue score with maximum score of 10 (VAS). We followed the same staging system as James et al. for evaluation of severity of vertigo.[11] Vertigo was defined as mild when it was not accompanied by either nausea or vomiting with score of one, as moderate when it was accompanied by nausea but no vomiting with score of two and as severe when accompanied by vomiting with score of three. Hearing improvement was evaluated on basis of perceived improvement by the patients.

The patients were randomly assigned into one of the three groups according to computer generated random numbers. Group A were given a tablet of vitamin B complex daily as a placebo and advised to reduce the salt intake in their diet. Group B were given a combination tablet of amiloride five mg and furosemide 40 mg to be taken every morning. They were not advised anything about the intake of salt. Group C were given a tablet of betahistine 24 mg at bedtime daily. They were also not advised anything about the salt intake. All patients were called for follow-up at six weeks to check if they were taking medicine regularly and had any problems, and then at next six weeks for re-evaluation. The persons involved in re-evaluation was blinded such that they were unaware to which group the patient belonged to.

RESULTS:

There were a total of 97 participants. Forty six (47.4%) were male and 51 (52.6%) were female with F:M ratio of 1.1:1. Assuming equal proportion of male and female in the population, this difference was not statistically significant ($X^2[N=97, df=1] = 0.26$, $p=0.6$). Group-wise gender distribution is shown in Table 1. There was no significant difference of gender in any treatment group.

Table 1*: Gender distribution in treatment group.*

Group	Male	Female	statistics
A	14	15	$X^2=0.3$, $p=0.85$
B	15	20	$X^2=0.7$, $p=0.4$
C	17	16	$X^2=0.3$, $p=0.86$

Mean age of the patients was 47.86 yr (*SD*=12.7). Mean age in Group A was 47.34 yr (*SD*=11.9), Group B was 45.77 yr (*SD*=13.2), and Group C was 50.5 yr (*SD*=12.7). This difference of age among the three groups was not statistically significant ($F[N=97, df=2] = 1.2$, $p=0.3$). These data and statistics show that the patients were evenly distributed for age and gender among the three groups.

Of the total 97 patients, 29 (30%) were treated with dietary modification alone (Group A), 35 (36%) were treated with diuretics (Group B)

and the rest 33 (34%) were treated with vasodilator (betahistine, Group C).

There was no significant difference in hearing outcome in any of the groups as shown in table 2.

Table 2: Hearing outcome

	Hearing Outcome		
Group	worse	same	better
A	6	21	2
B	13	20	2
C	7	23	3
Total	**26**	**64**	**7**

p=0.55 by Fisher Exact Test (FET)

A Wilcoxon signed rank test was used to examine the pre-treatment and post-treatment tinnitus score in each treatment group. There was no significant difference in tinnitus score in Group A (z = -0.5, p=0.6) and Group C (z = -1.1, p=0.26). However, there was a significant decrease in tinnitus score in post-treatment group in Group B (z = -2.2, p=0.03). Hence, tinnitus score was likely to be decreased significantly only by diuretics.

Similarly, a Wilcoxon signed rank test was used to examine the number of vertigo attack in pre and post-treatment group in each treatment category. There was a decrease in number of vertigo attack in Group A which was not significant (z = -1.8, p=0.07). Number of vertigo was significantly decreased in Group B (z = 5.1, p<.001) and Group C (z = -4, p<.001). Hence, number of vertigo attacks were likely to be reduced by diuretics or vasodilators but not by dietary restriction of salt alone.

Again, a Wilcoxon signed rank test was applied to see the difference in severity of vertigo in pre and post treatment group. Severity of vertigo was decreased in Group A (z = -1.7, p=.08) and Group C (z = -1.8, p=.07) but was not significant. It was significantly decreased in Group B (z = -4.2, p<.001).

DISCUSSION:

Meniere disease is considered to be a disease of female. Alexender TH. et al. found that the F:M ratio of patients suffering from Meniere disease was 1.89:1.[12] Simo H. et al. found it to be 1.5:1.[13] We found the F:M ratio to be 1.1:1. Though there was a female preponderance in out study, the difference was small and not significant. We do not have explanation for this decrease in female preponderance. We did not find any similar study done in our country to compare our results from the similar demography.

Salt restriction has been mentioned as one of the first line of medical treatment of Meniere disease.[2,3,4] Luxford E. et al. found an improvement in the number and severity of vertigo with dietary modification containing low sodium diet.[14] Beneficial result of dietary sodium restriction has also been documented by Sheahan SL. et al. [15] Dietary sodium restriction has been advised by many clinicians as a first line treatment for Meniere disease.[16,17] In our study, we found no benefit by dietary salt restriction in terms of hearing improvement, number of vertigo, severity of vertigo and tinnitus score. Dietary restriction is highly variable and is patient dependent. We believe the role of dietary modification, if any, does not depend only on reducing the sodium content. It may have complex relationship between several components like water restriction, amount of caffeine and alcohol consumption etc.

Diuretics has been mentioned by many studies to be effective for the treatment of Meniere disease.[18,19] We found that diuretics were effective in significantly reducing the number and severity of vertigo and tinnitus score but were not effective in improving hearing outcome. Another study concluded that hydrops is not always associated with Meniere and should not to be considered its ultimate cause.[20] Diuretics are believed to work by reducing the volume (and therefore also the pressure) of the inner ear fluids. A study found no evidence of endolymphatic hydrops modification one hour after intravenously administered frusemide.[21] A Cochrane review of diuretics for Meniere disease failed to identify any trials that could be used to support their use.[5] Hence, diuretics may be effective in controlling the symptoms of Meniere disease by unknown mechanisms other than reducing the labyrinthine pressure.

Betahistine, as a vasodilator, has been one of the first line drug for control of Meniere disease.[6,7,8] We found that it was effective in significantly reducing the number of vertigo attacks but it did not improve hearing and did not reduce the severity of vertigo and tinnitus score. A recent meta-analysis supports the therapeutic benefit of betahistine on vertiginous symptoms.[22] Another meta-analysis, however, found no evidence that betahistine is effective in patients with Meniere disease or syndrome.[9] Generally a dose of up to 24 mg/day is used. High dose of betahistine from 144 mg/day to between 288 and 480 mg/day was well tolerated and found to be effective in

patients who did not sufficiently respond to lower dosages.[23,24]

It would have been better if the hearing outcome was assessed with audiogram. Many patients in our place do not come for follow up; we had to interview a few patients over phone to collect the data. Study of long term outcome with a larger study population would give more reliable knowledge about effectiveness of the treatment options.

CONCLUSION:

We conclude from our study that diuretics were effective in improving number and severity of vertigo and tinnitus score though it was ineffective in improving the hearing outcome. Betahistine as a vasodilator was effective in reducing the numbers of vertigo but not the severity of vertigo, tinnitus score, and hearing improvement. We found dietary sodium restriction to be ineffective in improving any of the parameters of Meniere disease.

Conflict of Interest: None declared.
Financial Interest: None declared.

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