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A randomized control trail on the effectiveness of (Tricyclic antidepressant) Amitriptyline 10 mg bedtime in patients suffering from Meniere's disease

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ABSTRACT

Background: Meniere's disease is one of the most common causes of chronic recurrent vertigo in general population. Meniere's disease is closely associated with migraine and migrainous vertigo/ vestibular migraine. Amitriptyline has been classically used in management of Vestibular migraine. This randomized control trail examines the effectiveness of (Tricyclic antidepressant) Amitriptyline 10mg bedtime in patients suffering from Meniere's disease using a Randomized control trial. This was a randomized, double-blinded, placebo-controlled trial, cross over type with a power of 80% at 5% significance level.
Methods: One hundred five patients with definite Meniere's disease were randomized and assigned to either placebo or trial arm. Trial arm were given Amitriptyline 10 mg bedtime and placebo arm were given a generic Vitamin B-complex tablet. Visual analogue score and standard questionnaires were used to assess the improvements in vertigo, imbalance, dizziness and disease-specific quality of life before and after use of Amitriptyline vs. placebo for period of 10 days each.
Results: Amitriptyline 10mg at bedtime (10mg H.S), produces significant improvement in the vertigo in patients suffering from Meniere's disease compared to placebo. Chronic imbalance and hearing levels are not affected by the use of the above drug regime. Daytime sedation and weight gain are the most troublesome adverse effects of Amitriptyline at 10mg per day dose. No other serious adverse effects were observed in this research.
Conclusions: Low dose bedtime Amitriptyline 10mg appears to be safe and produces improvement in vertigo and disease-specific quality of life in Meniere's disease patients.

Keywords: Amitriptyline, Vertigo, Meniere's disease, Tricyclic antidepressant, Randomized control trial

INTRODUCTION

Meniere's disease is a chronic disease which is characterized by episodes of Vertigo, fluctuant hearing loss and tinnitus.[1] Vertigo attacks tend to occur in clusters over several weeks. Meniere's disease has been associated with Migraine and many patients with Meniere's Disease have increased risk of development of Migraine.[2] An important differential diagnosis of Chronic episodic vertigo is vestibular migraine also known as Migrainous vertigo (MV) for which a commonly used drug is Amitriptyline.[2] This randomized control trail examines the effectiveness of (Tricyclic antidepressant) Amitriptyline in patients suffering from Meniere's disease.

Objective

To evaluate the benefit of Amitriptyline 10mg at bedtime (10mg H.S) in the management of Meniere's disease using a Randomized control trial.

METHODS

Patients who were suffering from Definite Meniere's Disease patients were selected from our pool of Vertigo clinic, Department of Otorhinolaryngology, B.K.L Walawalkar Medical college Hospital. The study was carried out from July 2017 to Dec 2017 (half year). Written and verbal consent was obtained before inclusion in trail. Children less than 14 years and adults over 65 years were excluded from the study. Diagnostic inclusion criteria were based on Committee on Hearing and Equilibrium of the American Academy of Otolaryngology-Head and Neck Surgery (1995) guidelines for defining a definite case of Meniere's Disease.[3]

Definite Meniere's Disease- Inclusion criteria[3]

- 2 definitive spontaneous episodes of vertigo 20 minutes or longer pure tone Audiometry documented hearing loss on at least 1 occasion
- Tinnitus or aural fullness in the treated ear
- All other possible causes excluded

Written consent was obtained from all cases. Patients' were given University of Virginia Vestibular and Balance centre Dizziness Questionnaire.[4]Routine Complete blood count, Serum creatinine, Serum Alkaline phosphatase, Alanine Transaminase and Aspartate Transaminase assay was done and ascertained to be normal for inclusion candidacy in trail.

This Dizziness questionnaire has a Likert scale (Visual Analogue Scale) rating from 1 to 10 at the end of the section under the heading "influence of dizziness on your life".[4] Dizziness inventory handicap was also administered and used to quantify the effect of Vertigo on quality of life and related issues.[3,4] Data thus obtained by the questionnaire was used as a measure of vertigo and improvement following use of medication Amitriptyline 10 mg at bedtime (10 mg H.S). This is the literature recommended dose for treatment of migrainous vertigo.[5] Questionnaires were administered on first visit and then at the 10th day following start of medication.

Exclusion criteria

Patients with clinically demonstrable lesion in middle ear like middle ear effusion or tympanic membrane perforation were excluded. Ear endoscopy and pure tone audiogram was done in all patients. In addition, those at a high risk of toxicity like patients with history of seizures, cardiac diseases, and cardiac arrhythmias, urinary retention due to prostate hypertrophy, glaucoma, myocardial infarction, hepatic impairment, renal insufficiency, pregnancy, breast feeding and hyperthyroidism were excluded from thisstudy.[5, 6]

Study design, randomization and patient pool allocation[6]

The study design for this trail was as follows in the figure below. Double blinding was done as patients were unaware of the treatment given. Switch of arms over was done at the end of 10 days of therapy and hence patients acted as their own controls during half of the trail. 20 days was deemed to be the end stage of the trail. Common generic B-complex tablet containing folic acid 5 mg, riboflavin 10mg and pyridoxine 3 mg was used a placebo. It was ascertained that both test and control pills were of same colour, shape and size to prevent bias.[6]

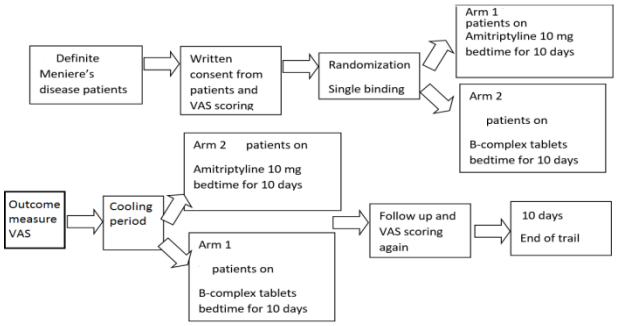

Figure 1: Study design of Randomized control trail with cross over design. Trail was deemed to have reached end at 20 days and visual analogue score questionnaire data was collected 3 times, on start, at end of first run lasting 10 days followed by the end of 2nd run lasting another 10 days.

Type of study

This is a type of Randomised, double-blinded, placebo-controlled trial with a power of 80% at the 5% significance level.[6]

Types of participants

Patients with Definite Meniere's Disease patients as defined by Committee on Hearing and Equilibrium of the American Academy of Otolaryngology-Head and Neck Surgery (1995) guidelines for defining a definite case of Meniere's Disease.[3]

Types of intervention

Amitriptyline 10mg at bedtime (10 mg H.S) for 10 days was compared with placebo.[5]

Main outcome measures

Improvements in vertigo, Imbalance, Dizziness and disease-specific quality of life.

Biostatistical analysis[7,8]

We used a cut-off of 5% level as the critical level (meaning 95% confidence in analysis) of significance in

our Biostatistical tests. Visual Analogue Score being a non-parametric (ordinal) variable was principally analysed using Mann-Whitney U test, Friedman two-way ANOVA, or Kruskal-Wallis one-way ANOVA test. Student's two-sample "t" test was also cautiously used to compare mean Visual Analogue Score data of Vertigo before and after Amitriptyline 10mg at bedtime (10mg H.S) use in same patient.[7] VAS data is non-parametric but can be subjected to Parametric testing like ANOVA and "t" test a fact supported by literature. The tests comprised the comparisons of the ratio of mean regression and mean residual sums of squares to an F distribution with appropriate degrees of freedom. Finally, an independent-samples chi-square test was applied to the data to analyse if difference was significant by more than what would be expected by chance alone.[8]

RESULTS

Baseline characteristics of population who completed the trail are illustrated by Table 1. One hundred five patients completed the study, and one hundred five patients with Meniere's disease were randomized and administered the Questionnaire at first visit, of which one hundred and five patients (100%) also completed the survey at second visit. The average age was 27.78 years (SD, 9 years), and the majority of suffering patients were female (68%). There were no observed statistically significant differences in age, sex across disease types.

Table 1 Patients' baseline characteristics.

Participants demographics	
Characteristic	No. (%)
Female sex	67.62 (71 females+34 males)
Mean (SD) age (y)	27.78±9 years
Age (y)	
16-26	13 (12.38)
27-36	26 (24.76)
37-46	20 (19.04)
47-56	31 (29.52)
56-64	15 (14.30)
Education	
Uneducated	76 (72.38)
College graduate	16 (15.24)
High school	8 (7.62)
Junior	5 (4.76)
Years since Meniere's disease diagnosed, mean SD	Median 2 years 6 months (0 to 7.1 years range)
Symptoms	
Sensori-neural Hearing loss (Outside of attack)	56 (53.34)
Tinnitus	101 (96.19)
Aural fullness	72 (68.57)

Responsiveness to amitriptyline 10 mg at bedtime (10 mg H.S) for 10 days compared with placebo[5]

After 10 days of treatment with amitriptyline 10mg at bedtime (10mg H.S), there was a significant improvement in the Vertigo, as well as in each individual symptom ($p<0.001$) was significantly better than placebo in each patient.[5] The vast majority of patients (88.3%) also showed improvement in the disease-specific quality of life vs. placebo.

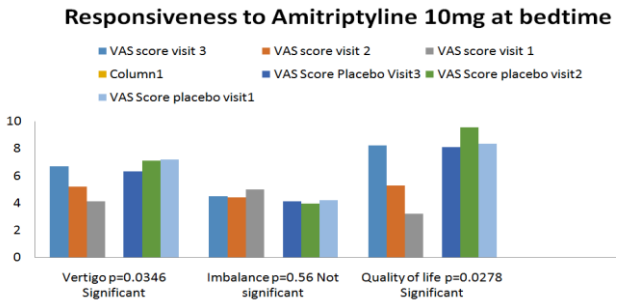

Figure 2: Response of Amitriptyline 10 mg at bedtime 10 mg HS in comparison to placebo. There was significant improvement in vertigo and quality of life. Imbalance was not significantly improved.

Adverse effects of Amitriptyline 10 mg at bedtime (10 mg H.S) for 10 days

Most patients reported daytime somnolence as the result of therapy. Patients were given Epworth sleepiness score, used to quantify day time somnolence in Obstructive sleep apnoea patients. Statistical analysis showed that Somnolence is a significant adverse effect in some cases. Few cases (<5 patients, p=0.732=Not statistically significant) also reported minimal Anticholinergic activity symptoms like dryness of mouth, constipation, fatigue, increases thirst, headache and tachycardia.[8] Weight gain was another troublesome symptom with a median weight gain of 570 (half kg) grams in a period of 10 days. These effects are more manifest at higher doses (60mg bedtime for instance) which are used when an Antidepressant action is desired.[8]

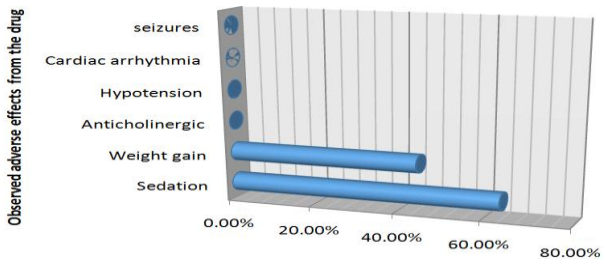

Figure 3: Observed adverse effects of amitriptyline 10mg at bedtime 10mg HS in comparison to placebo. There was statistically significant sedation, day time somnolence and weight gain in comparison to placebo. Patients gained approximately half kg (570 grams) within a period of 10 days.

DISCUSSION

Amitriptyline is a traditional Antidepressant used in the management of depression. The mechanism of action is the inhibition of nor-epinephrine (nor-adrenaline) and serotonin reuptake (NSRI) at the neural junctions. This presumably causes increasing in noradrenergic and serotonergic neurotransmission. Frontal cortex of human brain is the seat of cognition and planning. Frontal cortex lacks dopamine transporters and thus enhanced noradrenergic transmission can increase cortical levels of dopamine. Amitriptyline has been classically used in management of Vestibular migraine or Migrainous vertigo, its use in management of Meniere's disease has been unexplored before.[8]

Amitriptyline is metabolized to an active metabolite nortriptyline, which is nor-epinephrine reuptake inhibitor. The plasma half-life is around 10–28 hours (about 1 day) allowing convenient once a day dosing. Drug is excreted is via cytochrome peroxidise i.e. CYP450 by the liver, hence is hepatotoxic at higher doses and cause liver failure.[9]

Most patients with Meniere's disease are managed by long term betahistine and vestibular sedatives.[13] Vestibular suppressant drugs are categorized as anticholinergics, antihistamines, sedatives and calcium channel antagonists. Amitriptyline is a drug with known anticholinergics, antihistamines, sedatives or sleep inducing property.[9] So it naturally follows that amitriptyline is found to be effective in control the symptoms of vertigo in Meniere's disease patients and is especially beneficial when the treatment has to be a prolonged one. Studies have shown that amitriptyline can be used safely for many years to prevent relapse of depression. In addition, the onset of therapeutic action in depression maybe delayed up to 2 to 4 weeks.[8]We utilized a lower dose of amitriptyline for a shorter duration in an attempt to preclude any possible antidepressant activity. Added advantage of lower dose is that there is no need for gradual dose reduction (tapering dose), for preventing withdrawal symptoms which usually appear within the first 2 weeks of discontinuation of a higher dose of amitriptyline.[10]

Significant weight-gain and day time somnolence was observed in most patients. Studies have shown that these effects wane with continued use of in most cases[11]. Serotoninergic syndrome is a serious toxic reaction to excessive Serotonin 5-HT in brain. This is characterized by high fever, myoclonus, chorea, confusion, fits and coma, this usually caused by combination of serotoninergic neuro-psychiatric drugs. This syndrome was tactfully watched for but fortunately not observed in any patient in this study.[11]

Literature is also clear that Amitriptyline is not habit forming with prolonged use. No Life Threatening adverse effects described in textbooks like, malignant hyperthermia, paralytic ileus, acute angle closure glaucoma, akathisia, seizures, orthostatic hypotension, electrocardiographic (E.C.G) QTc interval prolongation, Extra-pyramidal symptoms and hepatic failure were observed.[12]

Amitriptyline effectiveness in Vertigo control may be related to its effect on the sleep. Various studies have demonstrated that amitriptyline significantly improves sleep in a variety of neuro-psychological conditions. Vestibular sedatives, like diazepam which improve vertigo act by a similar mechanism, proving that the crux of problem lies in the abnormal sleep patterns in Meniere's disease sufferers.[13]

Amitriptyline 10mg at bedtime (10mg H.S), produces significant improvement in the Vertigo in patients suffering from Meniere's disease compared to placebo. Chronic imbalance and hearing levels are not affected by the use of the above drug regime.[14] Daytime sedation and weight gain is the most troublesome adverse effect of Amitriptyline at 10mg day dose. No other serious adverse effects were observed in this research.[15,16].

CONCLUSION

Low dose bedtime Amitriptyline 10mg appears to be safe and also produces improvement in vertigo and disease-specific quality of life in Meniere's disease patients. In addition, a lower dose of Amitriptyline can be tried for prolonged period of time for control/ prevention of vertigo in chronic recurrent or resistant cases.

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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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