A PROSPECTIVE COMPARATIVE STUDY ON EFFICACY OF CINNARIZINE AND BETAHISTINE IN PATIENTS WITH PERIPHERAL VERTIGO

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Abstract

Background: Peripheral vertigo is described as dizziness most often associated with loss of hearing, ringing in ears and difficulty focusing vision. Dizziness affects 15%-20% of adults yearly in large population-based studies where one in four cases represents vertigo. 12-month prevalence being 5% and annual incidence being 1.4%, vertigo remains an issue to be addressed.

Methods A therapeutic decision which corresponds to optimal therapy in this regard is of prime importance. We compared the efficacy of two commonly prescribed drugs in peripheral vertigo to ease the therapy for vertigo. The primary objective of this study was to assess the relative efficacy of Cinnarizine and Betahistine in patients with peripheral vertigo.

Results: The mean Unterberger- Fukuda Test (UFT) score for anteroposterior displacement between the two groups at 2 weeks showed significant difference (52.38 vs 66.6; *P*=0.01). Similarly, UFT score for angular deviation also showed positive results supporting Betahistine therapy (31.4 vs 38.57; *P*=0.03).

Conclusion: Group I who received Betahistine showed better results when compared to group II who received Cinnarizine. The results indicate that Betahistine can be considered as predominant and more effective medication than Cinnarizine for peripheral vertigo.

Key Words: Betahistine, Cinnarizine, Vertigo, Anteroposterior Displacement, Angular deviation

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BACKGROUND

The vestibular system can be categorized into peripheral and central components. The peripheral system consists of three semicircular canals such as posterior, superior, lateral and otolithic organs such as saccule and utricle. A body's sense of position and balance is maintained when rotational head movement is detected by semicircular canals while to linear acceleration and gravity is responded by utricle and saccule, respectively. The excitation of symmetrically tonic activity of the vestibular organs results to the stimulation of central vestibular system.

Further, the central vestibular pathways (e.g., vestibular nuclei) process this information, along with proprioceptive and ocular input, and maintain the body's sense of balance and position [1].

"Dizziness" can be referred as either to an unpleasant disturbance of spatial orientation or to the erroneous perception of movement, which is more specifically known as "vertigo." A person having vertigo can experience a perceived movement, such as swaying or rotation of his/her own body, of the environment, or both [2].

Approximately 80% of vertigo is diagnosed as peripheral vertigo which may be caused due to any disturbances in vestibular system of inner ear which in turn is due to any viral infections such as Herpes Zoster or labrynthitis or vestibular neuritis post viral infection.

Majorly peripheral vertigo is Benign Paroxysmal positional Vertigo which is caused due to displacement of otolith and calcium deposits in the inner ear [3]. Dizziness appears as a clinical manifestation for various disease conditions such as intraocular pressure [4], diabetes [5,6] various neurological conditions [7] and as an adverse effect of chemotherapy [8-10] and antidepressants [11].

Betahistine anti-vertiginous effect depends mainly on improvement of microcirculation in the inner ear [12]. Betahistine 8mg is primarily used in the treatment of peripheral vestibular disorders [13]. Betahistine improves microcirculation which leads to vertigo reduction and decline in concomitant symptoms. But this effect seems to be relatively slow in onset [14].

The mechanism of action of betahistine precisely is not completely known, but the benefit of betahistine in different types of peripheral vertigo was demonstrated in clinical experience [15].

Cinnarizine is a medicine comes under the category of anti-histaminic medications. It can be used to treat problems associated with the inner ear and balance such as dizziness and it also helps reduce the feelings of vertigo and sickness.

By affecting local calcium ion flux, Cinnarizine 25mg predominantly acts on the peripheral vestibular labyrinth [16-18]. On structures which are involved in pathogenesis of vertigo and vegetative symptoms, it acts symptomatically [14]. Similarly, like betahistine, in cinnarizine increase in blood flow in compromised intra- and extracranial areas were shown [19]. The analogue of histamine, Betahistine have weaker agonistic effect on histamine H1 receptors and stronger effect on histamine H3 receptors. On the other hand, Cinnarizine is more effective on H1 receptors [20].

The purpose of the study is to find more effective drug by comparing the efficacy measures, Vertigo Symptom Scale (VSS) and European Evaluation of Vertigo Scale (EEV) used in the study. Clinically, the more effective drug can be preferred over the less effective drug except as an alternative in case of preferred medication's shortage.

METHODS

Study design

A prospective comparative study was carried out in ENT department of a tertiary care hospital, Chennai, India from October 2019 to January 2020 and was approved by the Institutional Ethical Committee (IEC), School of Pharmaceutical Sciences, VELS Institute of Science Technology and Advance studies.

Study criteria

The inclusion criteria included: patients aged between 18– 70 and patients with peripheral vertigo.

The exclusion criteria included the following.

- Patients with Parkinson's disease (as Unterberger's test cannot be performed in such patients in normal set up.)
- Patients diagnosed with central vertigo (as they are not peripheral vertigo patients)
- Patients with ataxia (degenerative disease of nervous system)
- Patient's with alcohol abuse and convulsive disorders (alcoholic patients can drop out or

still be dependent on alcohol which could affect therapeutic efficacy)
- Convulsive disorder patients are excluded as they may require other computerized tests.
- Patients who had discontinued anti-vertiginous medication previously prior to the start of the treatment (No baseline could be noted from them)
- Pregnant women (Betahistine and Cinnarizine not recommended for them)
- Orthostatic Hypertension patients (not related to peripheral vertigo) were excluded from the study.

Study procedure

Patients satisfying the study criteria were recruited and informed consent was obtained from the patients. The demographic details were collected in the data collection forms.

Before initiation of therapy, the patient was given VSS scale to fill up. After filling up the scales the scores were added up initially as baseline.

In the efficacy measure, Unterberger's test (UFT), was determined and baseline on Anteroposterior Displacement (APD) and Angular Deviation (AD) were noted under the supervision of the physician.

In this open labeled study, a total of 42 patients were diagnosed with peripheral vertigo, out of which 21 patients were randomly assigned into two groups each. EEV scale was assessed by the physician for each patient and the scores were noted as baseline.

Group I was administered with Betahistine dihydrochloride tablet of 16mg twice a day orally and Group II were administered with Cinnarizine tablet of 25mg twice a day orally.

After the commencement of therapy, each patient was followed up first after 1 week and then after 2 weeks. During the follow up, efficacy measure, VSS and EEV were repeated to analyze the improvement in patients in both the groups,

Efficacy measures:

Vertigo Symptom Scale (VSS)

VSS is a patient-reported questionnaire designed to comprehensively evaluate vestibular-balance symptoms. Vestibular imbalance or ear imbalance can have a great impact in a patient's quality of life. By evaluating the frequency and duration of vestibular-balance symptoms and the severity of autonomic-anxiety symptoms using VSS, quality of life can be improved. The VSS consists of a five-point Likert scale:

0-Never, 1- a few times, 2- several times, 3- quite often [every week], and 4- very often [most days]. The total score ranges from 0 to 60. Higher the score, higher will be the frequency of symptoms [21].

European Evaluation of Vertigo Scale (EEV)

EEV is a validated physician- administered questionnaire which analyzes the symptoms of the vestibular syndrome such as, illusion of movement, duration of illusion, motion intolerance, neurovegetative signs, and instability. It can monitor the course of vertigo and assess the efficacy of anti-vertigo therapy [22].

Unterberger- Fukuda Test (UFT)

The material used for UFT was made with three concentric circles of radiuses of 50, 100, and 150 cm and angles of 30, 60, and 90 degrees.

This material was fixed to the floor of the examination room. The participants were instructed to stand in the center of the drawing with both the arms raised. Further, they were instructed to perform 50–100 steps [15].

The UFT results can be classified as either normal or altered. If the volunteer presented an anteroposterior displacement (APD) equal to or greater than 50 cm, or angular deviation (AD) equal to or greater than 30^{o}, then the result would be classified as altered [23].

This analysis usually enables four response modalities: AD and APD in the open-eyes test, and AD and APD in the closed-eyes test. But in this study, AD and APD have been only done with closed eyes.

STATISTICAL ANALYSIS

EEV score, VSS score and UFT score for angular deviation and anteroposterior displacement were obtained from each recruited patients who were newly diagnosed with peripheral vertigo before commencement of therapy and at week 1 and week 2 after the therapy.

EEV score, VSS score and UFT score being the statistical parameter was used as mean± standard deviation and statistical significance was analyzed using unpaired *t*-test. $P \leq 0.05$ was statistically significant. Comparison between mean baseline EEV score, VSS score and UFT scores were done

using unpaired *t*-test. All analyses were carried out using GraphPad prism with 95% confidence interval.

RESULTS

Forty-two patients who were diagnosed with peripheral vertigo were recruited in the study and were assigned into 2 groups, 21 in each group. Demographics and baseline characteristics were recorded for all the patients before commencement of therapy [Table 1].

Table 1: Baseline characteristics

Characteristics	Group I (*n*=21)	Group II(*n*=21)	*P*-value (intergroup)
Age (years)	50.2±17.1	48±15.8	0.6673
Gender			
Female	9(42.8)	7(33.3)	
Male	12(57.1)	14(66.6)	
EEV Score	16.571 ± 2.13	15.38 ± 3.3	0.1723
VSS Score	56.66 ± 13.7	56.38 ± 11.4	0.9430
UFT Score (AD)	71.42 ± 20.07	71.42 ± 14.9	>0.999
UFT Score (APD)	119.04 ± 24.8	116.6 ± 24.15	0.7484

Data are shown as mean± standard deviation or number (%) as appropriate. Unpaired *t*-test was used to determine the *p*-value. Group I (Betahistine administered group). Group II (Cinnarizine administered group).

After the commencement of therapy, to monitor the effectiveness of betahistine and cinnarizine, first follow up was done after one week. During the first follow up, efficacy measures were repeated and reduction of vertigo symptoms were seen in both the groups. Further, after 2 weeks, during the second follow up, from efficacy measures it was assessed that there was an effective reduction in vertigo symptoms in betahistine administered group. In cinnarizine administered group the vertigo symptoms persisted.

EEV score and VSS score, both showed P<0.0001, statistically high significance in both the groups as indicated in Table 2. Unterberg Fukuda test indicated that, though both the results showed significant difference, Betahistine showed high significance (P=0.0003), than Cinnarizine (P=0.03). The effectiveness of both the drugs are demonstrated in UFT graph (Figure1 and 2).

Figure 1 UFT test's demonstration on displacement reduction

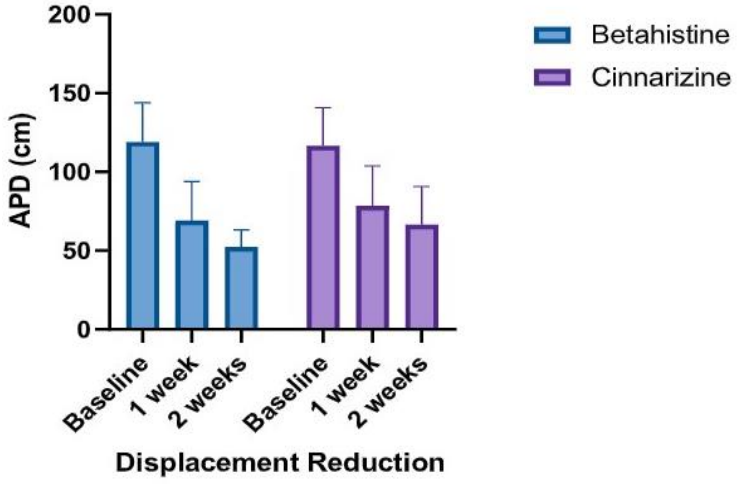

Fig 1: APD represents anteroposterior displacement and is measured in centimeter (cm)

Table 2: Efficacy outcomes

Parameter	Group I (*n*=21)	Group II(*n*=21)	*P*-value (intergroup)
EEV Score			
Baseline	16.571 ± 2.13	15.38 ± 3.3	0.1
1 week	8.714 ± 2.75	10.09 ± 1.78	0.06
2 weeks	0.857 ± 1.01	5.38 ± 2.5	<0.0001
P-value	<0.0001	<0.0001	
VSS score			
Baseline	56.66 ± 13.7	56.38 ± 11.4	0.9
1 week	22.23 ± 8.9	29.23 ± 9.7	0.01
2 weeks	10.28 ± 1.6	16.04 ± 5.7	0.0001
P-value	<0.0001	<0.0001	
UFT Score (AD)			
Baseline	71.42 ± 20.07	71.42 ± 14.9	1.0
1 week	45.7 ± 15.3	48.5 ± 14.9	0.5
2 weeks	31.4 ± 6.5	38.57 ± 13.8	0.03
P-value	0.0003	0.03	
UFT Score (APD)			
Baseline	119.04 ± 24.8	116.6 ± 24.15	0.7
1 week	69.04 ± 24.8	78.5 ± 25.3	0.2
2 weeks	52.38 ± 10.9	66.6 ± 24.15	0.01
P-value	0.007	0.1	

Data are shown as mean± standard deviation. Unpaired *t*-test was used to determine the significance. Group I (Betahistine administered group). Group II (Cinnarizine administered group).

Figure 2 UFT test's demonstration on reduction in angular deviation

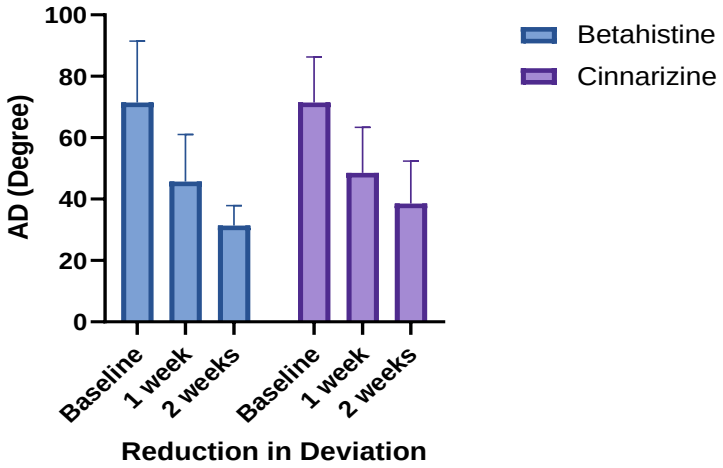

Fig 2: AD represents angular deviation and is measured in degree

The efficacy outcomes from UFT test were not like the results of EEV and VSS, because some symptoms still persisted in Cinnarizine administered patients when physically involved efficacy measure, UFT was performed.

In demonstration of VSS score graphically, Betahistine showed more effective reduction (0.81%) than Cinnarizine (0.71%) (Figure 3), though both the drugs showed significance (Table-2) in 2 weeks.

Figure 3 Demonstration of VSS Score

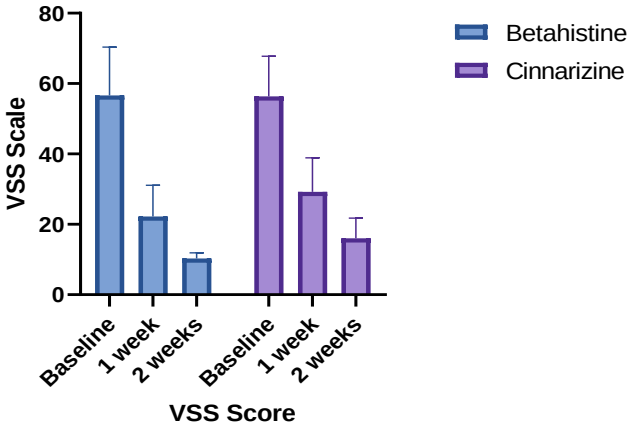

Fig 3: VSS represents Vertigo Symptom Scale

Cinnarizine administered patients responded positively to questionnaires as they experienced reduction in symptoms but still not completely and that is why they could only show partial success in UFT performance. Whereas Betahistine administered patients showed complete success in UFT performance. Group I showed 0.56% reduction in AD (UFT) whereas group II showed only 0.45% reduction in AD. Group I showed 0.55% reduction in APD (UFT) whereas group II showed only 0.42% reduction in APD (UFT) from baseline to endpoint result.

In case of EEV scale, when graphically demonstrated, it showed an effective reduction in symptoms of Betahistine administered patients (0.94%) than in Cinnarizine administered patients (0.65%) (Figure 4). Both the drugs showed significant difference in 2 weeks.

Figure 4 Demonstration of EEV Score

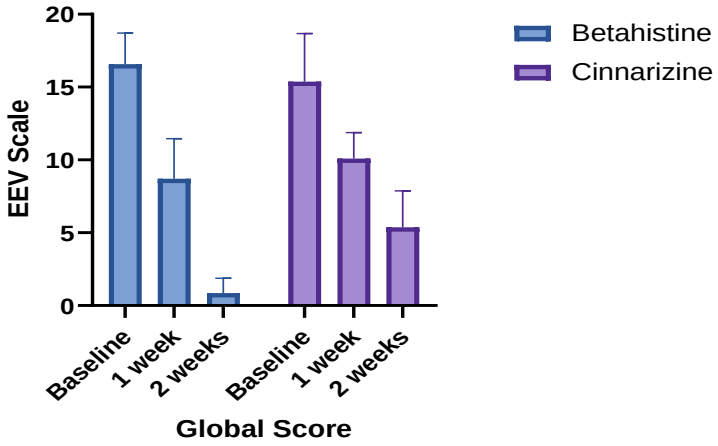

Fig 4: EEV represents European Evaluation of Vertigo Scale

DISCUSSION

Peripheral vertigo is mainly diagnosed with dizziness but often associates with the symptoms such as nausea, vomiting, hearing loss, tinnitus, difficulty in walking, sweating and nystagmus [24,25]. Treatment of vertigo in patients is often related to treat the symptoms and due to that different categories of drugs have been used. Many drugs have adverse effects in patients such as sedative effects and due to that they may discontinue or limit the use of dosages of drugs. Therefore, it is necessary to identify the drug with fewer side effects [26].

Betahistine is the commonly prescribed drug for balance disorders and is an anti-vertigo medicine. It is the first line pharmaceutic agent for vertigo and used for the symptomatic treatment [27]. Cinnarizine belongs to the category of anti-histamine which is mainly prescribed for nausea and vomiting, mainly in motion sickness and

chemotherapy. It also has its efficacy and safety in the treatment of peripheral vertigo [28,29].

Despite of the established therapies currently available in the market for vertigo, the disease is still symptomatically cured unless it does not have any underlying cause. Establishing a correct treatment for vertigo through trials is still essential in this regard. Moreover, there is a controversy existing with regard of randomized triple blind placebo control trial carried out by Asadi P*et al.* [19]. The trial reported that combination therapy of Betahistine and Cinnarizine is superior to the monotherapies. However, they haven't mentioned the patient acceptability, cost effectiveness and side effect profile of the combination therapy when compared to the monotherapies. The results demonstrate that betahistine is better in terms of efficacy when compared to cinnarizine. In a study performed in the year 2017, Motamed H *et al.* compared oral betahistine and injectable promethazine in patients with acute peripheral vertigo. The results concluded that oral betahistine is a safe and effective drug in treating peripheral vertigo [30]. In a study performed in clinical routine practice for vestibular vertigo also showed the efficacy of betahistine and it was well tolerated between the outpatients [31-33]. These results are comparable to our results proving the efficacy of betahistine in peripheral vertigo.

Both drugs do not show any serious side effect profile. The current study aimed at identifying more effective drug used in peripheral vertigo by comparing the efficacy measures in South Indian population. The results demonstrate betahistine as superior to cinnarizine in abating the symptoms of peripheral vertigo which is supported by the VSS scale, EEV scale and UFT scale.

One of the limitations of the study is the short duration of therapy. None of the patients showed any kind of side effect in 2 weeks of therapy. This drawback limits the study in assessing the long-term side effects associated if any. The efficacy measures were not determined with the combination therapy of betahistine and cinnarizine. This drawback limits the study in evaluating the patient acceptability and effectiveness of combination therapy when compared to monotherapy. It was a single-centered trial which was another limitation to the study. Multi-centered trials can be conducted in future in more diverse population for the determining the pharmacoepidemiologic variations in the therapy.

CONCLUSION

In the present study, after the completion of follow up and statistical analysis of efficacy measures, betahistine and cinnarizine, both the medications showed significant difference in vertigo symptom reduction. But as betahistine showed high significant difference in reducing vertigo symptoms, betahistine can be considered as predominant and more effective medication than cinnarizine.

LIST OF ABBREVATIONS

Histamine 1 (H1); European Evaluation of Vertigo Scale (EEV); Unterberger's Fukuda Test (UFT); Anteroposterior Displacement (APD); Angular Deviation (AD)

DECLARATIONS

Ethics approval and consent to participate

The protocol of this study was revised and approved by the Institutional Ethics Committee, VELS Institute of Science, Technology and Advanced Studies, Chennai, India- 600117. Ref: VISTAS-SPS/IEC/II/2019/09. Written informed consent was obtained from each of the study participants after briefing them about the study and that the obtained data will be published.

Consent for publication

Consent was obtained from the patients participated in the study for the publishing of the datas obtained during the study.

Availability of data and materials

All the above-mentioned data and results of statistical analysis are available with the authors and are ready to be shared with approved personnel upon request.

Competing interests

The authors declare that they have no competing interests.

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No funding was received through any funding agencies towards carrying this research work.

Authors' contributions

RFB and SS made the contributions in conception and design in conducting the study and approved the manuscript. MEJ, ASS, and RFB performed the study and drafted and revised the manuscript for intellectual content. RFB and SS gave

technical inputs in the acquisition of data and analysis. All authors have read and approved the final manuscript.

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