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Difference In Effectiveness Of Fixed Combination Of Cinnarizine 20 Mg And Dimenhydrinate 40 Mg With Betahistine Dihydrochloride 16 Mg In Patients With Meniere's Disease

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ABSTRACT
Meniere's disease (MD) is a disorder of the inner ear characterized by hearing loss , tinnitus , and vertigo . In most cases , the disease is slowly progressive and has a significant impact on the social functioning of the affected individual. Hearing loss , tinnitus , and vertigo is common symptomatic complaints with many potential causes , but Meniere's disease is actually quite rare and is essentially a diagnosis of exclusion . This research uses a literature review method by tracing the results of scientific publications in the time period between 2012 and 2024 using 3 databases , namely : Google Scholar , PubMed , and ScienceDirect . A search strategy based on PICO suggests that the fixed combination of cinnarizine and dimenhydrinate is a safe and possibly better treatment options for patients . a combination of cinnarizine and low dose dimenhydrinate is a good choice for treatment . Dimenhydrinate has been proven to be effective in reducing the DHI score and sub- score of GVP sufferers , meaning that combination drugs administration is considered more effective for treating Meniere's disease when compared to monotherapy .

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INTRODUCTION

Meniere Disease (MD) is a disorder of the inner ear characterized by hearing loss, tinnitus , and vertigo . In most cases, the disease is slowly progressive and has [a] significant impact on the social functioning of the affected individual. Hearing loss, tinnitus , and vertigo are common symptoms with many potential causes, but Meniere's disease is actually quite rare and is essentially an exclusionary diagnosis 1 .

Meniere's disease is generally caused by the accumulation of endolymph in the cochlea and vestibular organs in the temporal bone. Excess production of endolymph , and/or decreased absorption mechanisms in the inner ear will cause hydrops. endolymphatic . This will result in distension of the endolymphatic space due to increased endolymphatic volume . The etiology of this disorder is uncertain and several factors may play a role in its

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pathophysiology such as genetic and environmental factors. Several autoimmune diseases are associated with this disease, including; lupus erythematosus systemic , ankylosing spondylitis , and rheumatoid arthritis [2]. In a study conducted by Robert Gürkov et al. , found that most patients do not experience auditory symptoms when vertigo attacks. Having symptoms such as nausea, vomiting, sweating, urge to defecate, urge to urinate, phosphenes , headache, photophobia , phonophobia , and transient loss of consciousness. About a quarter of patients experience vertigo attacks in less than 20 minutes, and subjective hearing loss precedes vertigo attacks during the course of the disease. Hearing loss in audiometry has the highest diagnostic value at a frequency of 1 kHz . Migraine and autoimmune disorders are not significantly associated with hydropic ear disease ; a positive family history is present in about 4% of cases [3].

Meniere's therapy are to reduce the number and intensity of vertigo attacks , preserve hearing and vestibular function , and prevent disease progression. Meniere's therapy is different for each patient, depending on the cause and symptoms. In Meniere's patients , a variety of therapies have been used, including dietary and lifestyle changes, surgery, use of hearing aids, and pharmacological treatments such as diuretics , betahistine , benzodiazepines , and intratympanic injections . Meniere's therapy is based on the patient's symptoms. Vertigo is the main symptom of acute attacks, followed by nausea, vomiting, sweating, and sometimes diarrhea. Suppressants vestibular drugs , which include antihistamines, anticholinergics , and benzodiazepines , are commonly used in the treatment of acute attacks.

Antihistamines work reduce severity vertigo with mechanism inhibition stimulation vestibular And decline function cochlear through effect central anticholinergic . Common antihistamines used to treat vertigo attacks in Meniere's is meclizine 25-50 mg every 4-6 hours and dimenhydrinate 50 mg every 4-6 hours.

In addition to antihistamines, administration of betahistine on therapy Meniere's very popular in Europe, Japan, and Australia. Betahistine is an antagonist $_{H3}$ receptors and have a weak partial agonist effect on the H3 receptors. H $_{1}$ and H $_{2.}$ Mechanism of action of betahistine on Meniere'scovering improvement circulation on system vestibular And cochlea as well as inhibition activity core vestibule Which impact on decline pressure endolymph . Barriers on core vestibule affects afferent nerve sensory input and neurotransmitter release so that it has an impact on the balance of afferent nerve activity. Variation in betahistine dosage based on frequency And the severity of vertigo attacks in patients. The initial dose of betahistine to be able to gives an effect of 48 mg per day and can be increased to 480 mg. mg per day for patients with severe Meniere's and not providing response to low doses.

RESEARCH METHODS

This study uses a literature review method by tracing the results of scientific publications in the time span between 2017 and 2024 using 3 databases, namely: Google Scholar , PubMed , and ScienceDirect . The search strategy is based on PICO.

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Table 1. PICO Summary

Component	Information
Population/problem	Meniere disease
Intervention	Cinnarizine
Comparison	Dimenhydrinate
Outcomes	Nausea in Meniere's patients disease

To assess eligibility, these articles were screened using the Critical Appraisal Skills Program (CASP) and the Center for Evidence-Based Medicine (CEBM). In addition, the quality of the articles was effectively screened and assessed using the Cochrane risk of bias tool recommended by Cochrane Handbook for Systematic Reviews of Interventions.

RESULTS AND DISCUSSION

No.	Journal Name	Title	Method	Writer	Conclusion
1	European Journal of Clinical Pharmacology (2019)	Cinnarizine/ betahistine combination vs. the respective monotherapies in acute peripheral vertigo: a randomized triple-blind placebo-controlled trial	This study used a random sampling method. It was conducted on 162 patients who were divided into 3 groups. Group 1 was given cinnarizine tablets 25 mg 3 times a day, group 2 was given betahistine tablets 8 mg 3 times a day, and group 3 was given a combination of betahistine 8 mg and cinarizin 25 mg 3 times a day. The therapy was given for 7 days.	Asadi et al.	Study This show superiority cinnarizine/ betahistine combination compared to monotherapy respectively APV treatment
2	Annals of Otology, Rhinology & Laryngology (2019)	The Impact of Betahistine versus Dimenhydrinate in the Resolution of Residual Dizziness in Patients with Benign Paroxysmal Positional Vertigo:	This study used a double-blind randomized clinical trial. Patients with canal-type BPPV posterior semicircularis were randomly assigned to one group for 1 week given betahistine , dimenhydrate or placebo . All patients were asked to describe their subjective characteristics. Then the results were	Jalali et al.	Data analysis shows that use betahistine more influential in repair symptom

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No.	Journal Name	Title	Method	Writer	Conclusion
		A Randomized Clinical Trial	analyzed using SPSS 19.0		
3	Tadulako Medic (2019)	effectiveness dimenhydrinate lower Dizziness handicap inventory scores and sub scores in patients disturbance vestibular peripheral	Study intervention , *pretest and posttest design.* GVP patients filled out DHI *pre-test* questionnaire to be continued giving dimenhydrinate 50 mg/ 8 hours. After 2 weeks giving drug done filling DHI *post test* score . Comparative test analysis using the paired t-test .	Nayoan R	Dimenhydrinate proven effective lower DHI scores and sub scores of GVP patients .
4	International journal of environmental research and public health (2021)	Efficacy and Pharmacological Appropriateness of Cinnarizine and Dimenhydrinate in the Treatment of Vertigo and Related Symptoms	This is a prospective study. This study involved 120 adults—70 men and 50 women. Respondents came from light work environments such as office workers, senior executives, and other jobs that are not exposed to noise.	Plescia et al.	The fixed combination of cinnarizine and dimenhydrate is effective against central, peripheral and combined central and peripheral vertigo .
5	Clinical Drug Investigation (2019)	Efficacy and Safety of a Fixed Combination of Cinnarizine 20 mg and Dimenhydrinate 40 mg vs Betahistine Dihydrochloride 16 mg in Patients with Peripheral Vestibular Vertigo: A Prospective, Multinational, Multicenter , Double - Blind,	This study used a prospective clinical trial method which was carried out in outpatients at the ENT clinic. Respondents were given a fixed combination of cinarizine 20 mg or dimenhydrinate 40 mg and betahistine 16 mg for 4 weeks.	Scholtz et al.	Combination still cinnarizine 20 mg and dimenhydrinate 40 mg improved peripheral vestibular vertigo more Good than betahistine 16 mg.

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No.	Journal Name	Title	Method	Writer	Conclusion
		Randomized, Non - inferiority Clinical Trial			
6	Clinical Drug Investigation (2022)	Efficacy and Safety of a Fixed - Dose Combination of Cinnarizine 20 mg and Dimenhydrinate 40 mg in the Treatment of Patients with Vestibular Vertigo: An Individual Patient Data Meta-Analysis of Randomized, Double - Blind, Controlled Clinical Trials	During four week , patient mature take care road given treatment combination fixed cinnarizine 20 mg and dimenhydrinate 40 mg, cinnarizine (20 mg, 50 mg), dimenhydrinate (40 mg, 100 mg), betahistine dimesylate (12 mg), betahistine dihydrochloride (16 mg), and placebo . Subtraction validated mean vertigo score (MVS) , which is a score combination of twelve individual vertigo symptoms rated by the patient on a scale five point visual analog , is point end efficacy main . Mean square least squares adjusted (LSM) with associated two - sided confidence intervals (CI) For difference MVS reduction between group treatment counted with use analysis adjusted covariance with baseline (ANCOVA) for analysis primary and secondary efficacy point end .	Scholtz et al.	analysis results This show that combination fixed cinnarizine and dimenhydrinate are choice safe and possible treatment more Good For patients suffering from central vestibular vertigo and/ or peripheral . This is different with choice treatment conventional given to patient such as cinnarizine, dimenhydrinate, or betahistine as monotherapy
7	Clin Drug Investigation (2012)	Comparison of the Therapeutic Efficacy of a Fixed Low-Dose Combination of	Sixty - two patients given cinnarizine 20 mg and dimenhydrinate 40 mg as combination still or betahistine 12 mg every day during four weeks . At baseline (t0), after 1	Scholtz et al.	results show that combination of cinnarizine and dimenhydrinate dose low is good choice For treatment

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No.	Journal Name	Title	Method	Writer	Conclusion
		Cinnarizine and Dimenhydrinate with Betahistine in Vestibular Neuritis	week (t1w), and after 4 weeks (t4w), vertigo and accompanying symptoms recorded by electronystagmography , which includes nystagmus spontaneous , calorie test bithermal , and rotational .		symptomatic unilateral VN. Within weeks First , the combination still produce significant improvements in vertigo and ADL, and after four week , recovery almost perfect . In case recovery calories , treatment four Sunday with combination still , compared with betahistine , no show signs impact negative . Test results neurotologist show No There is signs impact negative Power responsiveness and decline nystagmus consequence rotation .

According to the literature search that has been conducted, there is literature that specifically discusses the differences in effectiveness of a fixed combination of cinnarizine 20 mg and dimenhydrinate 40 mg with betahistine. dihydrochloride 16 mg in Meniere's patients Disease . Apart from that, there is also literature discussing betahistine , cinarizin and dimenhydrinate monotherapy .

In the first journal by Asadi et al (2019), stated that the results showed significant differences between groups on VAS (p = 0.001), MVS (p = 0.0001), and MCSS (p = 0.0001) at 1-week follow-up . Compared with monotherapy , the values of each group were significantly lower in the Cin . + Bet. group on the third day and 1-week follow-up period (p = 0.0001). During the study, no side effects were reported by patients. The results of this

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study indicate that the combination of cinnarizine / betahistine in the treatment of APV is better than each monotherapy [4].

In the second journal by Jalali et al (2019), it was stated that this study involved 117 patients aged 20 to 65 years. After the Epley maneuver , 88 participants had RD. 38 patients showed improvement in RD after the intervention. In all three groups, less than 50% of participants experienced mild to moderate dizziness disability. However, the mBBS scores of the groups before and after the intervention did not differ significantly. According to logistic regression, patients receiving betahistine were 3.18 times more likely than the placebo group to experience RD. The decrease in the likelihood of improving RD was associated with increasing age (P = 0.05) [5].

In the third journal by Nayoan (2019), it was stated that the number of research subjects was 20 people. The DHI score and DHI sub-score after the test were lower than the pre-test. test on dimenhydrinate group with significance value $p < 0.05$. Dimenhydrinate has been proven to be effective in reducing DHI scores and sub scores in GVP patients [6].

In the fourth journal by Plescia et al (2021) As a result, this study provides further details on the possible therapeutic effects of the fixed combination of cinnarizine and dimenhydrinate . This combination has been shown to be effective and well tolerated in the treatment of central, peripheral, and combined central/peripheral vertigo . Consequently, our findings strengthen and add to previous research evidence on the efficacy and appropriateness of prescribing cinnarizine and dimenhydrinate in the treatment of vertigo . Furthermore, our findings suggest that these medications may work in a gender-specific manner, which may allow for additional research. Using a gender-based approach to understand differences in vertigo symptoms may improve pharmacological treatment and the quality of medical care [7].

The fifth journal by Scholtz (2019), stated Three hundred and six patients, with a mean age of 53.5 years and approximately 60% female, were enrolled and randomized to the fixed combination group of cinnarizine / dimenhydrinate (n = 152) or betahistine (n = 154). 297 patients completed the study, and 294 of them (146 and 148, respectively) were valid for the per-protocol analysis, which was used for the non-inferiority analysis. The combination preparation was also more effective after the first week of therapy and received better patient assessments of overall efficacy and daily activity impairment. Both treatments were well tolerated. Only 12 patients (3.92%) reported that 13 patients did not experience serious problems. Adverse events: Two patients receiving cinnarizine or dimenhydrinate treatment discontinued the study prematurely due to adverse events. Compared with five patients receiving betahistine , the findings showed that the fixed combination of cinnarizine 20 mg and dimenhydrinate 40 mg was not only not inferior, but also better than betahistine 16 mg in improving vertigo. peripheral vestibular . In addition, given the good safety profile and slight benefit [8].

The sixth journal by Scholtz et al (2022), stated that of the 795 patients randomized, 779 were in the intention-to-treat (ITT) group, and 723 were in the per-protocol (PP) population. The ITT population had a mean age of 52.1 years, and 61% were female. The mean decrease in MVS from baseline to Week 4 in the cinnarizine / dimenhydrinate group

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(−1.10) was significantly greater than in the comparator group (−1.10). The LSM for the comparator compared with the fixed combination was 0.16 (95% confidence interval (CI) 0.03; 0.30, p = 0.017) for cinnarizine 20 mg and 0.60 (95% CI 0.42; 0.78; p < 0.001) for betahistine dimesylate 12 mg . After four weeks of treatment, 74 patients (or 24.7%) in the cinnarizine / dimenhydrinate group were completely symptom-free (MVS = 0), significantly more than in either of the comparison groups. Sensitivity analysis showed that baseline characteristics such as age, sex, duration of vertigo , and initial antivertigo treatment had only a very small and clinically irrelevant impact on the primary efficacy outcome of the drug. Subgroup analysis of the age groups below 65 years or above 65 years showed no significant differences in terms of primary efficacy. Differences in treatment effectiveness between the various options. All treatments were well tolerated. Nearly 95% of patients (cinnarizine / dimenhydrinate group : 97.9%) rated the tolerability of the study drug as “good” or “very good”. A total of 55 patients (6.9%) reported 75 non-serious adverse events (AEs), and 19 patients (2.4%) discontinued the study prematurely [9].

The seventh journal by Sholtz et al (2012), The results showed that the combination of cinnarizine and low-dose dimenhydrinate is a good choice for the symptomatic treatment of unilateral VN. It is also well tolerated. In the first week, the fixed combination resulted in significant improvements in vertigo and ADL, and after four weeks, recovery was almost complete. In terms of caloric recovery, four weeks of treatment with the fixed combination, compared with betahistine, showed no signs of negative impact. Neurological testing results showed No. signs of negative impact. responsiveness and decreased rotational nystagmus[10].

CONCLUSION

Based on the literature discussing the differences in effectiveness of the combination of cinnarizine and dimenhydrinate with betahistine dihydrochloride 16 mg in Meniere's patients disease it can be concluded that giving combination drugs is considered more effective for treating Meniere's disease when compared with monotherapy .

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