Flunarizine versus betahistine in vertigo: a systematic review

SYSTEMATIC REVIEW

ORIGINAL ARTICLE BY

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ABSTRACT

OBJECTIVE
To compare the efficacies of flunarizine and betahistine in patients with vertigo.

METHODS
We systematically searched electronic databases from the Cochrane Library, PubMed, Trip Database and Scopus. The other resource that we searched included web directory (google scholar). We also made hand searching. We included the previous randomized controlled trials (RCTs) regarding the efficacy of flunarizine comparing with betahistine. Our primary outcome was vegetative symptoms improvement after 2 months and the secondary outcome was vegetative symptoms improvement after 1 month, free attack of vertigo, gastrointestinal (GI) disorders, and drowsiness.

RESULTS
It showed that the percentage of patients with improvement of vegetative symptoms after 2 months was significantly higher in flunarizine 10 mg once a day than in betahistine 8 mg three times a day (65% vs. 43.9%; relative risk (RR), 0.62; 95% confidence interval (CI), [0.41 to 0.94]. There were similar percentages of patients with improvement of vegetative symptoms after 2 months in those using flunarizine 10 mg once a day and betahistine 16 mg three times a day (52.0% vs. 61.4%; RR, 1.24; 95% CI, [0.74 to 2.08]; I^2=25%). There were also a similar proportion of patients with improvement of vegetative symptoms after 1 month in those using 10 mg of flunarizine and in any doses of betahistine (40.2% vs. 40%; RR, 1.08; 95% CI, [0.62 to 1.88]; I^2=70%). The rate of free attack of vertigo was significantly higher in 10 mg of flunarizine than in any doses of betahistine (73.6% vs. 41.2%; RR, 0.49; 95% CI, [0.25 to 0.94]; I^2=64%). There was no significant difference between flunarizine and betahistine in rate of GI disorders (5.7% vs. 15.3%; RR, 1.06; 95% CI, [0.80 to 1.42]; I2=87%) but rate of drowsiness was significantly higher in flunarizine group than in betahistine group (23.0% vs. 7.1%; RR, 0.70; 95% CI, [0.25 to 1.99]; I2=94%).

CONCLUSION
Among patients experiencing vertigo, flunarizine and betahistine did not significantly reduce vegetative symptoms after 2 months.

INTRODUCTION

Vertigo is a type of dizziness with an illusion or hallucination of movement, usual rotation of environment either or around oneself.[1,2] It can be caused by vestibular disorders e.g., Ménière's disease and migraine that symptom disturbs patient's quality of life.[1,3-4] It is usually treated by flunarizine, one of calcium channel blocker.[5-9] Moreover, it is also can be treated with betahistine which is a strong histamine-3 antagonist and a weak histamine-1 agonist.[10-17] However, the efficacy of flunarizine and betahistine are still controversy. For instance, there was a randomized controlled trial in 1988 comparing 10 milligrams (mg) of flunarizine once a day with 8 mg of betahistine three times a day revealed that flunarizine was more effective than betahistine in the improvement of vegetative symptoms.[18] However, the second and the third trials in 1991 and 2003 which comparing 10 mg of flunarizine once a day with 16 mg of betahistine three times a day found that betahistine was more superior than flunarizine in an improvement of vegetative symptoms.[19-20] Thus, it is still a debate in efficacy between flunarizine and betahistine in vegetative symptoms improvement. Hence, we conducted a systematic review of RCTs to compare benefits of flunarizine and betahistine.

METHODS

SEARCH STRATEGIES

We systematically searched to identify all RCTs, electronic databases from their inception to January 2016: totally four resources are the Cochrane Library, PubMed, Trip Database, and Scopus. We used Medical Subject Headings (MeSH) for Pubmed and the Cochrane Library searching; (("Vertigo"[Mesh]) AND "Flunarizine"[Mesh]) and other databases, we used the following keywords: vertigo, flunarizine, and betahistine. We also perform hand searching as well as searching through web directory i.e., google scholar.

STUDY SELECTION

We independently searched and screened the titles and abstracts to exclude irrelevant articles then relevant articles were read the full text to select studies into the systematic review. Any disagreement among the authors resolved by consensus and discussion. After that, we exclusively reviewed the remain full-text papers and chose some qualified studies.

INCLUSION CRITERIA

STUDY DESIGN

We included all randomized controlled trials that compared the efficacies of flunarizine and betahistine in patients with vertigo.

PARTICIPANTS

Participants are any ages of patients with clinical diagnosis of vertigo.

INTERVENTIONS

Medical treatments of our interest were flunarizine and betahistine regardless their dosing.

OUTCOMES

The primary outcome was the improvement of vegetative symptoms in 2 months. The secondary

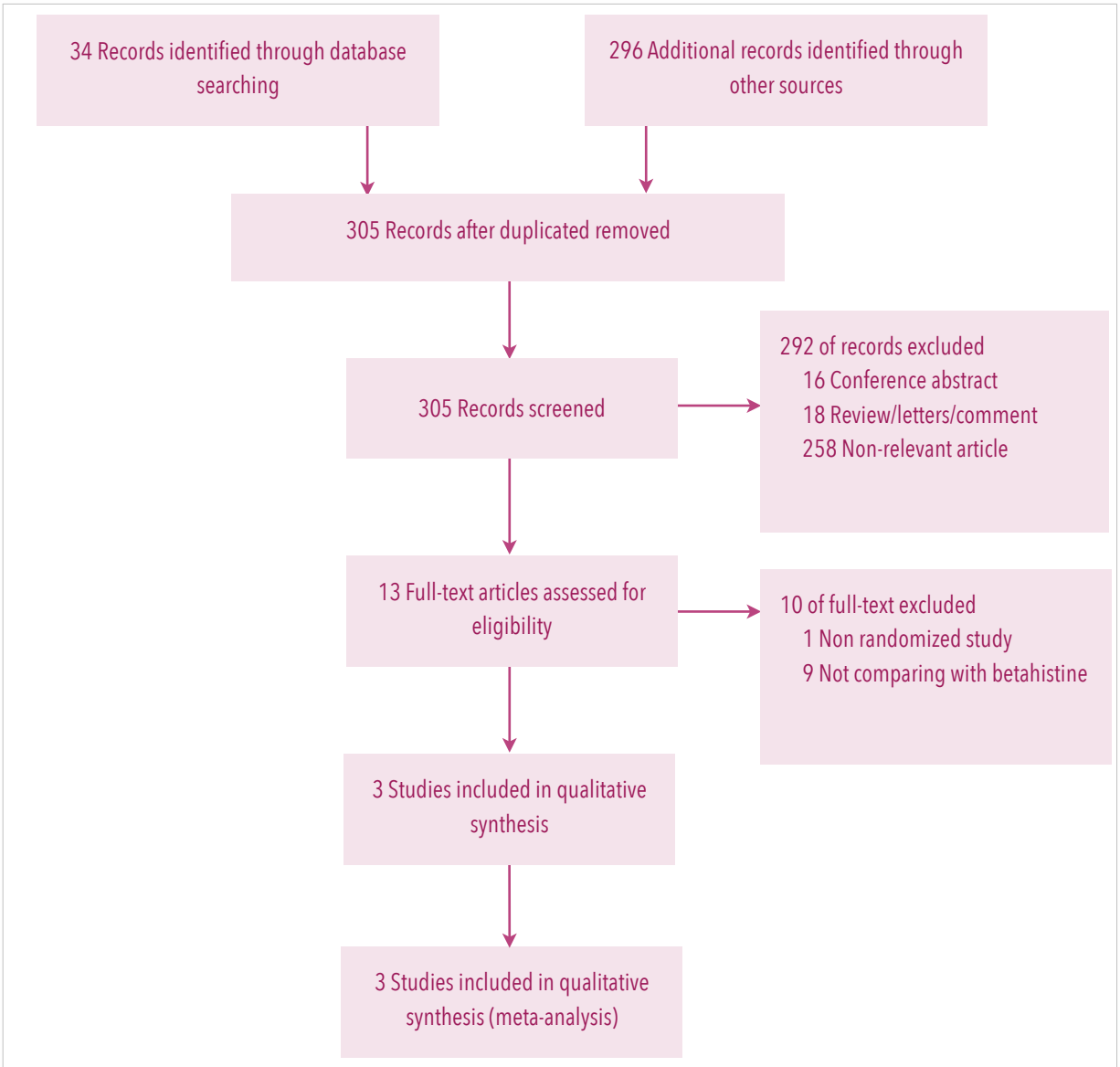

Figure 1. Study flow diagram

outcome was the improvement of vegetative symptoms in 1 month, free of vertigo attack in 2 months, adverse events in GI disorders and drowsiness.

EXCLUSION CRITERIA

We have no specific exclusion criteria.

ASSESSMENT OF STUDY QUALITY

Four review authors used the funnel plot and the Cochrane risk of bias tool to assess the methodological quality. We assessed every study that was included by concerning random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and

Table 1. Characteristics of studies included in systematic reviews

Study	Country	Study design	N	Participants	Intervention	Outcome
P.Elbaz et al. 1988	France	Randomised, double blinded controlled trial	117	patients with vertigo	60 patients with 10 mg of flunarizine tablet in the evening once a day compared with 57 patients with 8 mg of betahistine tablet three times per day	Flunarizine is more effective than betahistine in improving clinical symptoms (vertigo, feeling of instability, neurovegetative disorders, anxiety, auditory problems, tinnitus and headache, signs of disturbances of equilibrium and frequency of the attack.
B.Fraysee et al. 1991	France	Randomised, double blinded controlled trial	55	patients suffering from recurrent paroxysmal vertigo, with or without cochlear syndrome	27 patients with 10 mg of flunarizine tablet in the evening once a day and two doses of placebo taken at morning and noon compared with 28 patients with 16 mg of betahistine tablet three times per day	Betahistine is more effective than flunarizine in decreased frequency of attack, duration of attack, severity of attack, unsteadiness of attack, concomitant vegetative symptoms and cochlear symptoms and spontaneous vestibular dysfunction.
R.Albera et al. 2003	Italy	Randomised, double blinded controlled trial	52	patients aged 18-65 years with recurrent vertigo of peripheral vestibular origin	23 patients with 10 mg of flunarizine tablet in the evening once a day and two doses of placebo taken at morning and noon compared with 29 patients with 16 mg of betahistine tablet three times per day	Betahistine is significantly more effective than flunarizine in improving mean difference total DHI score, three subscores of DHI and vegetative or cochlear symptoms.

personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias) and other biases. We classified the study into low risk, high risk, and unclear risk. We discussed with our advisor when we had a disagreement if the discussion could not solve a disagreement, authors of original articles were contacted.

DATA EXTRACTION

Four reviewers extracted data from included trials, any disagreement was solved by discussion, and when necessary we contacted the authors of the studies. The reasons for excluding studies from the review were recorded. The following data was extracted, (i) characteristics of each study were country of study, study design, the number of participants in each group, intervention, and outcome (ii) baseline characteristics of participants were vegetative symptoms.

DATA SYNTHESIS

We measured the efficacy of the medication expressed as dichotomous data; ratio with 95% from RevMan, the programme provided by the Cochrane Collaboration. Then the systematic review was made by comparing parameters.

MEASURES OF TREATMENT

Data was double checked by four reviewers. We evaluated improvement of vegetative symptoms, free attack of vertigo, adverse events in GI disorders and drowsiness for synthesized data.

ASSESSMENT OF HETEROGENEITY AND SENSITIVITY ANALYSIS

Heterogeneity in the results was evaluated by means of the chi-square test and I^2 test. High heterogeneity was considered when $P<0.05$ in statistically the chi-square test and I^2 statistic more than 50%. A random effect model was used for the meta-analysis when heterogeneity was statistical significance and funnel plots were created to showing the standard error and the effect size to identify potential of publication bias. The chi-square test and I^2 test were calculated from Review Manager version 5.3 (Revman); The Cochrane Collaboration's software.

RESULTS

We systematically searched 330 studies from electronic databases, web directory and made hand searching. After excluding the duplicated the studies, there were 13 studies met the inclusion criteria. We excluded 10 studies; 1 observational study, 9 RCTs not compared with betahistine (Figure 1). Totally the final selection contained 3 studies for analysis.

STUDY CHARACTERISTICS

We included 3 RCTs with 224 participants experiencing vertigo. One study that compared 10 mg of flunarizine once a day with 8 mg of betahistine three times a day and two studies compared 10 mg of flunarizine once a day with 16 mg of betahistine three times a day (Table 1).

BIAS RISK ASSESSMENT

All studies were assessed quality by the Cochrane Collaboration's tool. For the Cochrane Collaboration's tool, one was assessed as having a low risk of bias.[20] Two were assessed as having an unclear risk of bias (Figure 2A).[19-20] The risk of bias graph was summarized in (Figure 2B).

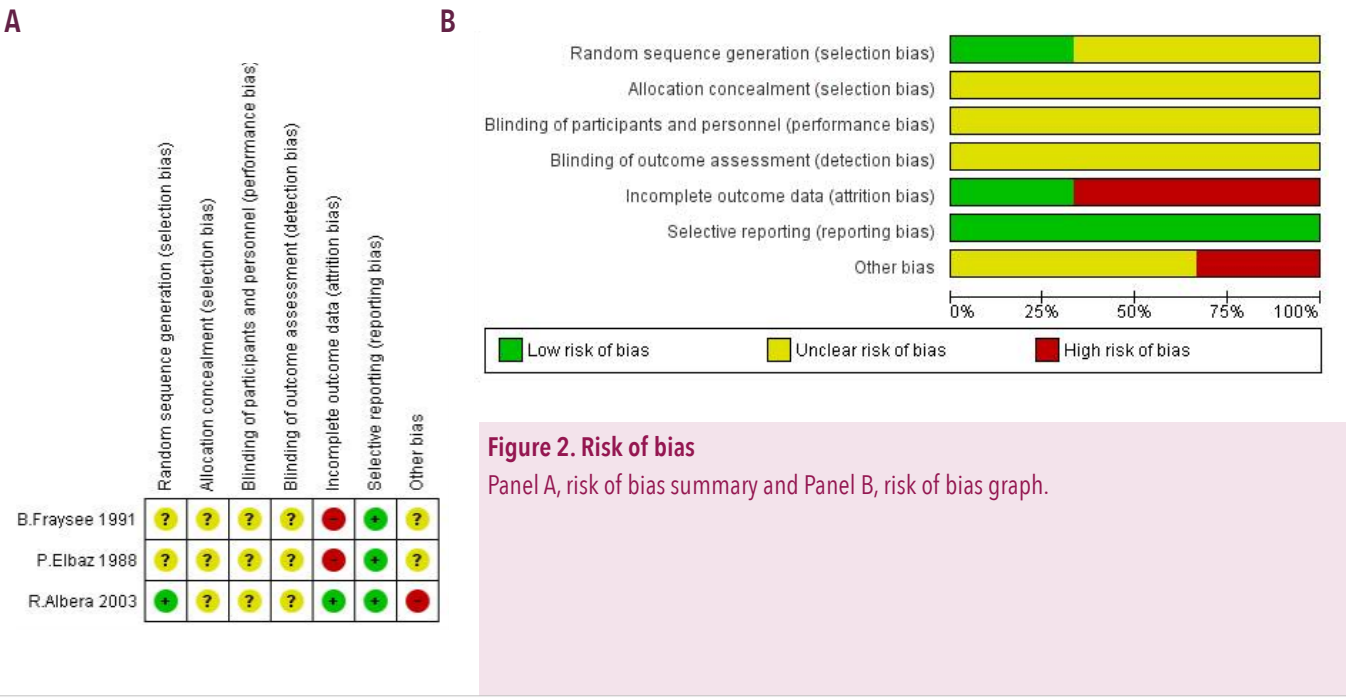

Figure 2. Risk of bias
Panel A, risk of bias summary and Panel B, risk of bias graph.

RANDOM SEQUENCE GENERATION

Two studies did not report the methods of generating a random sequence, while one study did and it was classified as "low risk".[18-20]

ALLOCATION CONCEALMENT

All included studies did not report details on allocation concealment and they were classified as "unclear risk".[18-20]

BLINDING OF PARTICIPANT AND PERSONNEL

All studies did not report details on blinding of participant and personnel and they were classified as "unclear".[18-20]

BLINDING OF OUTCOME ASSESSMENT

All studies did not report details on blinding of outcome assessment and they were classified as "unclear risk".[18-20]

INCOMPLETE OUTCOME DATA

One study were classified as "low risk".[20] Two studies were classified as "high risk".[18-19]

SELECTIVE REPORTING

All included studies properly described the adverse events and they were classified as "low risk".[18-20]

OTHER POTENTIAL SOURCES OF BIAS

One studies were supported by Solvay Pharma S.p.A and reported results as per-protocol thus it was classified as "high risk".[20] Two studies had no conflict of interest were classified as "low risk".[18-19]

OUTCOMES

IMPROVEMENT OF VEGETATIVE SYMPTOMS IN 2 MONTH

The systematic review of the three studies showed flunarizine 10 mg once a day had a higher

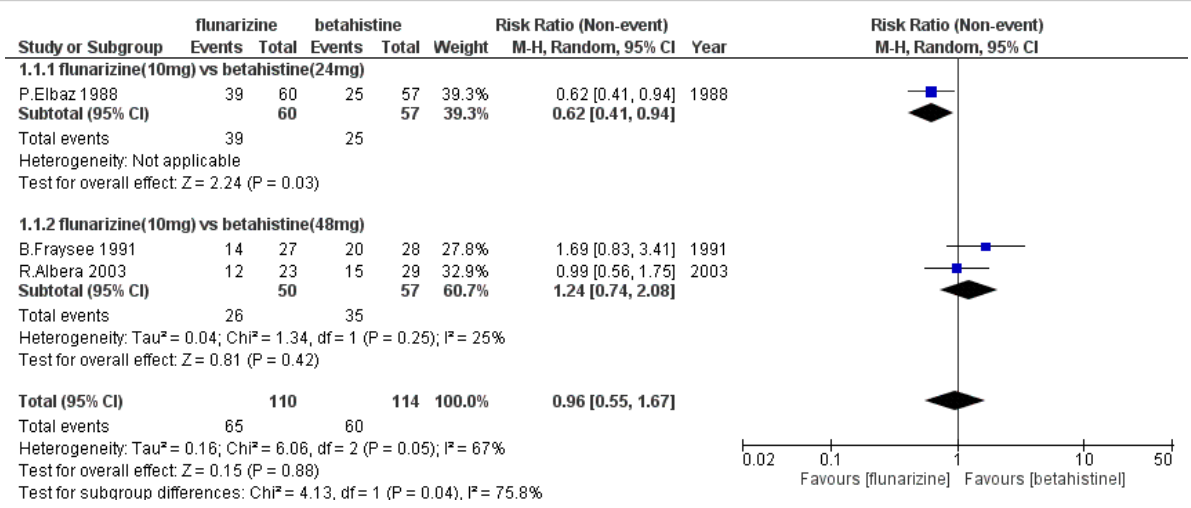

Figure 3. The forest plot of comparison: flunarizine 10 mg once daily versus betahistine 8 mg, 16 mg three times a day, outcome: the improvement of vegetative symptoms in 2 months

percentage of patients with improvement of vegetative symptoms after 2 months more than betahistine 8 mg three times a day (65% vs. 43.9%; RR, 0.62; 95% CI, [0.41 to 0.94]). The heterogeneity was not applicable due to 1 trial in this subgroup. There were similar percentages of patients with improvement of vegetative symptoms after 2 months in those using flunarizine 10 mg once a day and betahistine 16 mg three times a day (52.0% vs. 61.4%; RR, 1.24; 95% CI, [0.74 to 2.08]; I^2=25%) (Figure 3).

IMPROVEMENT OF VEGETATIVE SYMPTOMS IN 1 MONTH

The systematic review of the two studies showed a similar proportion of patients with improvement of vegetative symptoms after 1 month in those using flunarizine 10 mg and any doses of betahistine (40.2% vs. 40%; RR, 1.08; 95% CI, [0.62 to 1.88]). The heterogeneity was measured as having I^2 equal to 70% (Figure 4).

FREE VERTIGO ATTACK

The systematic review of the two studies showed the statistically significant difference improved rate of free vertigo attack compared 10 mg of flunarizine once a day with any doses of betahistine three times a day after 2 months (73.6% vs. 41.2%; RR, 0.49; 95% CI, [0.25 to 0.94]). The heterogeneity was measured as having I^2 equal to 64% (Figure 5).

ADVERSE EVENTS

The systematic review of two studies showed no statistically significant difference rate of adverse events compared flunarizine with betahistine after 2 months (14.4% vs. 11.2%; RR, 0.94; 95% CI, [0.78 to 1.15]). The heterogeneity was measured as having I^2 equal to 84%. There was no significant difference between flunarizine and betahistine in the rate of GI disorders (5.7% vs. 15.3%; RR, 1.06; 95% CI, [0.80 to 1.42]). The heterogeneity was measured as having I^2 equal to 87% but rate of drowsiness was significantly higher in flunarizine

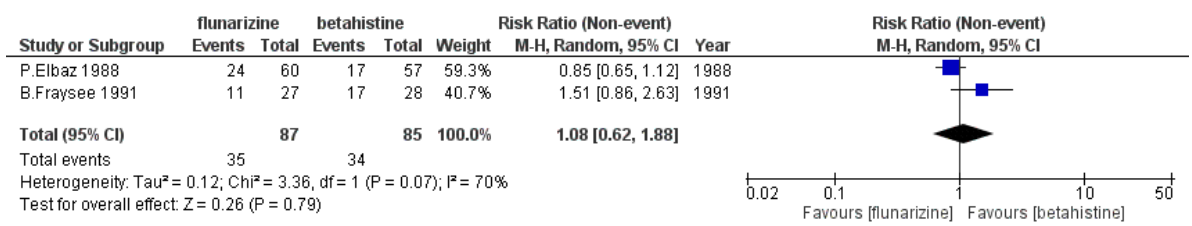

Figure 4. The forest plot of comparison: flunarizine 10 mg once daily versus betahistine 8 mg, 16 mg three times a day, outcome: the improvement of vegetative symptoms in 1 month

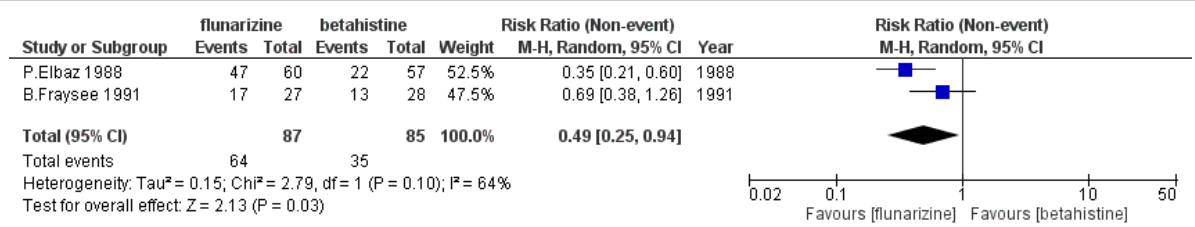

Figure 5. The forest plot of comparison: flunarizine 10 mg once daily versus betahistine 8 mg, 16 mg three times a day, outcome: free of vertigo attack in 2 month

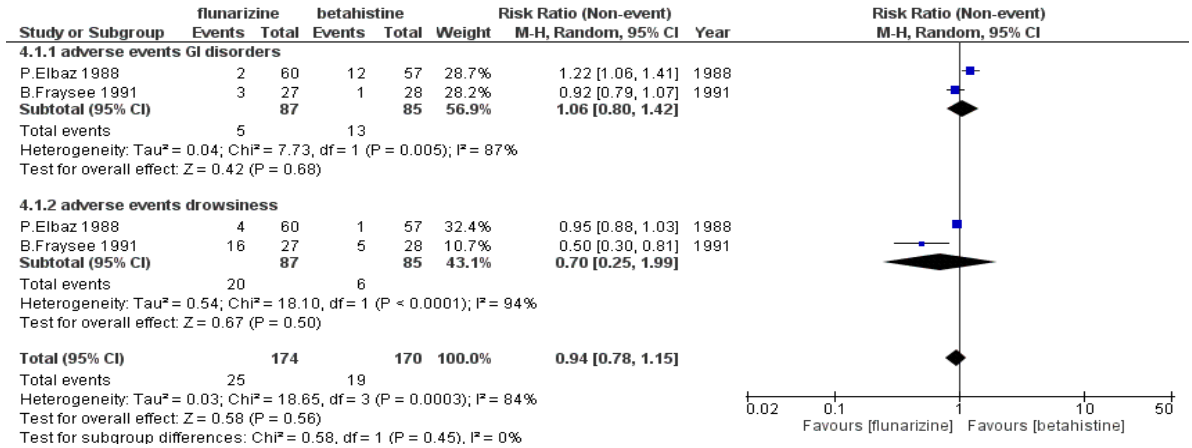

Figure 6. The forest plot of comparison: Flunarizine 10 mg once daily versus betahistine 8 mg, 16 mg three times a day, outcome: adverse events in GI disorders and drowsiness

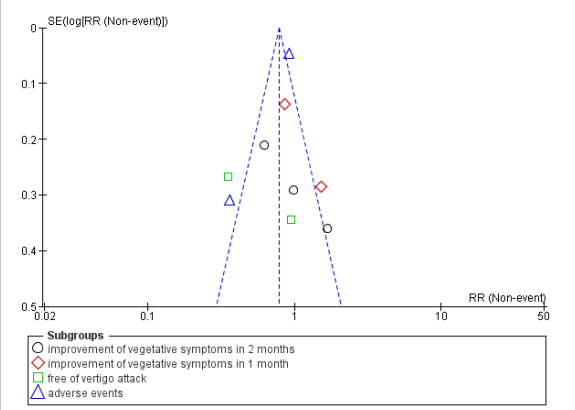

Figure 7. Funnel plot of comparison: Flunarizine 10 mg once daily versus betahistine 8 mg, 16 mg three times a day, outcome: the improvement of vegetative symptoms in 2 months, improvement of vegetative symptoms in 1 month, without attack of vertigo, adverse events

group than in the betahistine group (23.0% vs. 7.1%; RR, 0.70; 95% CI, [0.25 to 1.99]) The heterogeneity was measured as having I^2 equal to 94% (Figure 6).

DISCUSSION

MAJOR FINDINGS

In our study, we found that acetazolamide was not associated with the opening CSF pressure change, hypokalemia, and metabolic acidosis. However, opening CSF pressure at admission was associated with the opening CSF pressure change.

STRENGTHS AND LIMITATIONS OF THE STUDY

Our study is the first retrospective cohort design, that did in children and any causes of infectious meningitis.

Several limitations of this study should be mentioned firstly the sample size that the study required was 100 patients, but, in fact, ours was 85 patients, it was slightly different. Secondly, the medical records were not complete as some cases had no records of CSF pressure especially the record before discharge because in the case of improved clinical symptoms, the physician would not repeat LP for measuring CSF pressure and the patient would reject the procedure for those reasons the CSF pressure change could not access and it also was the one reason why we excluded some cases. Thirdly, the interval in each LP was varied. In addition, the LP technique, the measurement technique and the experiences of the practitioner were affected by the measure of the CSF pressure.

COMPARISON WITH PREVIOUS STUDIES

In our study, we found that adjunct acetazolamide to standard treatment in children with any causes of infectious meningitis and increased intracranial pressure had no difference in reduction of CSF pressure and adverse effects to standard treatment alone similar to the previous randomized single-blinded pilot study, from Uganda in 2005, the result showed no adverse effects and reduction in intracranial opening pressure.[16] However, the study performed in 18 AIDS adult patients with cryptococcal meningitis and increased intracranial pressure, which the intervention also combined with serial LP and the primary outcome was focused on clinical improvement. But one study that was affected by the adverse effects of acetazolamide, an RCT in 2002, comparing CSF pressure between

those using adjunct acetazolamide to standard treatment and those with standard treatment alone in 22 Thai patients, also studied in adults with cryptococcal meningitis and elevated intracranial pressure, was terminated as patients who were prescribed acetazolamide developed severe metabolic acidosis and hyperchloremia.[15] Anyway, there was a case series of 24 children, in 1979, suggested that repeated LP combined with acetazolamide adjunct to standard treatment could reduce the CSF pressure.[14] But there was no comparison group and performed in only children patients with tuberculous meningitis and communicating hydrocephalus.

On the other hand, in practice, acetazolamide is used as the main medical treatment for idiopathic
intracranial hypertension (IIH) for reduction of CSF production.[11,13] The evidence supports in this condition are the same as our condition that there are no studies to confirm the effectiveness of acetazolamide. Prior case series in children with IIH mentioned the success for improving symptoms of increased intracranial pressure and vision more than half patients.[26,27] Subsequently, the pilot RCT of 50 patients in United Kingdom, 2010, is difficult to practice due to poor recruitment and compliance.[28] And theirs limitation is the same as ours in the term of sample size. Later, in 2014, a multi-center, double-blinded, RCT of 86 patients in United States showed the improvement of visual field function but did not mention of other symptoms.[29]

CONCLUSION AND IMPLICATION

Adjunct acetazolamide to standard treatment had no difference in reduction of CSF pressure in children with meningitis and increased intracranial pressure. However, for better estimation effects of acetazolamide, larger sample size is needed. Multi-center retrospective cohort design should be conducted in settings where acetazolamide is of use for preliminary approximation effects of acetazolamide before conducting an RCT.

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COMPETING INTERESTS: This study has no competing on interest.
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REFERENCES

1. Baloh RW. Vertigo. The Lancet. 1998;352(9143):1841–6.
2. Hanley K, O'Dowd T, Considine N. A systematic review of vertigo in primary care. Br J Gen Pract. 2001;51(469):666–71.
3. Parnes LS, Agrawal SK, Atlas J. Diagnosis and management of benign paroxysmal positional vertigo (BPPV). CMAJ. 2003 Sep 30;169(7):681–93.
4. Furman JM, Cass SP. Benign paroxysmal positional vertigo. The New England Journal of Medicine. 1999 Nov 18;341(21):1590–6.
5. Holmes B, Brogden RN, Heel RC, Speight TM, Avery GS. Flunarizine. A review of its pharmacodynamic and pharmacokinetic properties and therapeutic use. Drugs 1984;27:6-44.
6. Haid T. Evaluation of flunarizine in patients with Ménière's disease - Acta Oto-Laryngologica, 1988; 460: 149-53.
7. Olesen J. Calcium Entry Blockers in the Treatment of Vertigo. Annals of the New York Academy of Sciences. 1988;522(1):690–7.
8. Schmidt R, Oestreich W. Flunarizine in the treatment of vestibular vertigo: experimental and clinical data. Journal of cardiovascular pharmacology. 1991;18:S27.
9. Wouters L, Amery W, Towse G. Flunarizine in the treatment of vertigo. The Journal of Laryngology & Otology. 1983;97(08):697–704.
10. Lacour M. Betahistine treatment in managing vertigo and improving vestibular compensation: clarification. J Vestib Res 2013;23: 139-51. 24177346
11. Aantaa E Treatment of acute vestibular vertigo. Acta Otolaryngol (Stockh). 1991;47944- 47
12. Mira E, Guidetti G, Ghilardi P, Fattori B, Malannino N, Maiolino L, et al. Betahistine dihydrochloride in the treatment of peripheral vestibular vertigo. Eur Arch Otorhinolaryngol. 2003 Feb;260(2):73–7.
13. Oosterveld WJ. Betahistine dihydrochloride in the treatment of vertigo of peripheral vestibular origin A double-blind placebo-controlled study. The Journal of Laryngology & Otology. 1984;98(01):37–41.
14. Canty P, Valentine J, Papworth SJ. Betahistine in peripheral vertigo. The Journal of Laryngology & Otology. 1981;95(07):687–92.
15. Lacour M, Sterkers O. Histamine and betahistine in the treatment of vertigo: elucidation of mechanisms of action. CNS Drugs. 2001;15(11):853–70.
16. Brandt T, Dieterich M, Strupp M. Vertigo and Dizziness: Common Complaints. Springer Science & Business Media; 2007. 155 p.
17. Rascol PO, Hain TC, Brefel C, Benazet M, Clanet M, Montastruc J-L. Antivertigo Medications and Drug-Induced Vertigo. Drugs. 2012 Oct 13;50(5):777–91.
18. Elbaz P. Flunarizine and betahistine. Two different therapeutic approaches in vertigo compared in a double-blind study. Acta Otolaryngol Suppl. 1988; 460: 143-8.
19. Fraysse B1, Bebear JP, Dubreuil C, Berges C, Dauman R. Betahistine dihydrochloride versus flunarizine. A double-blind study on recurrent vertigo with or without cochlear syndrome typical of Menière's disease. Acta Otolaryngol Suppl. 1991; 490: 1-10.
20. Albera R1, Ciuffolotti R, Di Cicco M, De Benedittis G, Grazioli I, Melzi G, Mira E, Pallestrini E, Passali D, Serra A, Vicini C. Double-blind, randomized, multicenter study comparing the effect of betahistine and flunarizine on the dizziness handicap in patients with recurrent vestibular vertigo. Acta Otolaryngol. 2003 Jun; 123(5): 588-93.
21. Deering RB, Prescott P, Simmons RL, Downey LJ. A double-blind crossover study comparing betahistine and cinnarizine in the treatment of recurrent vertigo in patients in general practice. Curr Med Res Opin. 1986;10(4):209–14.
22. Hahn A, Sejna I, Stefflova B, Schwarz M, Baumann W. A fixed combination of cinnarizine/dimenhydrinate for the treatment of patients with acute vertigo due to vestibular disorders: a randomized, reference-controlled clinical study. Clin Drug Investig. 2008;28(2):89–99.
23. Otto V, Fischer B, Schwarz M, Baumann W, Preibisch-Effenberger R. Treatment of vertebrobasilar insufficiency--associated vertigo with a fixed combination of cinnarizine and dimenhydrinate. Int Tinnitus J. 2008;14(1):57–67.
24. Cirek Z, Schwarz DM, Baumann W, Novotny M. Efficacy and Tolerability of a Fixed Combination of Cinnarizine and Dimenhydrinate versus Betahistine in the Treatment of Otogenic Vertigo. Clin Drug Investig. 2012 Aug 28;25(6):377–89.
25. Scholtz A-W, Steindl R, Burchardi N, Bognar-Steinberg DI, Baumann W. Comparison of the Therapeutic Efficacy of a Fixed Low-Dose Combination of Cinnarizine and Dimenhydrinate with Betahistine in Vestibular Neuritis. Clin Drug Investig. 2012 Dec 13;32(6):387–99.