Efficacy and safety of mecobalamin combined with vestibular rehabilitation training for acute vestibular neuritis: a systematic review and meta-analysis

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Background: This study aimed to investigate the efficacy and safety of mecobalamin combined with vestibular rehabilitation training in acute vestibular neuritis and to improve the clinical therapeutic effect in vestibular nerve disease.

Methods: We performed a literature search of the PubMed, Medline, China National Knowledge Infrastructure (CNKI), and other databases from the date of establishment of the database until the present. The search terms included "mecobalamin", "vestibular rehabilitation training", "vestibular rehabilitation therapy", and "vestibular neuritis". References of the comparative study of vestibular rehabilitation training and vestibular rehabilitation training combined with mecobalamin were screened. Boolean logic retrieval was adopted, and Review Manager software was employed.

Results: Meta-analysis was conducted on a total of four studies with a low risk of bias. The activities specific balance confidence scale (ABC) scores of the two groups were heterogeneous (Chi^2=8.56, I^2=88%, P=0.003), and a fixed-effect model (FEM) analysis indicated that there were no significant differences in the ABC between the groups after treatment (Z=0.67, P=0.50). It may be that mecobalamin combined with vestibular rehabilitation training effectively alleviated the symptoms of vestibular neuritis in the experimental group, thereby reducing the canal paresis (CP) value. In addition, there was no heterogeneous dizziness handicap inventory (DHI) between the groups after treatment (Chi^2=20.75, I^2=86%, P=0.0001); finite element method (FEM) analysis showed that the DHI of the experimental group after 6 months of treatment was notably lower compared to that of the control group (Z=3.20, P=0.001).

Discussion: Mecobalamin combined with vestibular rehabilitation training can effectively improve vertigo and other symptoms of acute vestibular neuritis patients, with high effectiveness and safety.

Keywords: Mecobalamin; vestibular rehabilitation training; vestibular neuritis; vertigo

Introduction

Vestibular neuritis is a sudden vertigo disorder caused by acute damage to one of the vestibular nerves. When inflammation of the anterior vestibular nerve occurs, the balance model generated by the inner ear and the position information generated by the head cannot be normally transmitted to the brain, leading to acute or persistent vertigo in patients (1). Patients in the acute and convalescent phases exhibit different clinical symptoms; the acute phase manifests as persistent and severe dizziness, accompanied by nausea, vomiting, and other symptoms. During the recovery period, the vertigo symptoms of patients disappear, and at this time, the condition manifests as non-rotating dizziness, instability, and temporary vertigo after head movement. Also, patients can walk independently and deviate to one side, and the direction of deviation is related to the state of vestibular compensation (2,3). The most common cause of vestibular neuritis is viral infection of the vestibular nerve (measles, influenza, herpes zoster, varicella virus, etc.). Other causes include ischemia (acute ischemia of the vestibular and labyrinthian nerves) and bacterial infection (4,5). Treatment of vestibular neuritis includes specific treatment (glucocorticoids, antiviral therapy, etc.), symptomatic treatment, and vestibular rehabilitation training in the acute phase (6). In the acute phase, hormones (methylprednisolone, prednisone, etc.) are generally chosen to improve vestibular function, and antiviral therapy is required for viral infection (7,8). Mecobalamin, also known as methyl vitamin B12, is a neurotrophic drug. It can provide necessary substances for nerve repair by promoting the synthesis of protein, phosphoric acid, and phospholipid, and has a good therapeutic effect on vestibular neuritis and other diseases (9). After usage of mecobalamin, adverse reactions such as headache, fever, sweating, rash, blood pressure drop, and dyspnea may occur, and timely treatment measures should be taken when adverse reactions occur. For patients with vestibular neuritis, in addition to taking mecobalamin, diphenhydramine can also be used for sedation and hydrogen binding effect. In addition, it can relieve symptoms and patients' discomfort.

Vestibular rehabilitation therapy (VRT) is a non-pharmacological, non-traumatic, and physical therapy for the treatment of disorders of central and peripheral balance (10,11). Patients with vestibular dysfunction were treated with train-based therapy to improve their ability to coordinate and control balance by vestibular position, vision and proprioception, and to mobilize the compensatory function of the central nervous system (12,13). Vestibular rehabilitation training can accelerate the recovery of patients with acute vestibular neuritis and reduce the disability degree of patients with permanent vestibular injury. It has a certain positive effect on the long-term recovery of patients as well as the recovery of balance function (14,15). Training methods mainly include fixation stability visual tracking training, static and dynamic posture stability training, and functional activity training (16).

Clinical studies found that the proportion of patients with acute vestibular neuritis returning to normal after treatment is about 60%, and the recurrence rate is high. Patients with vestibular neuritis have a high risk of recurrence of vertigo symptoms and are often accompanied by refractory benign paroxysmal positional vertigo (17). Therefore, we performed a meta-analysis to systematically evaluate the efficacy and safety of mecobalamin combined with vestibular rehabilitation training for acute vestibular neuritis. We present the following article in accordance with the PRISMA reporting checklist (available at https://apm.amegroups.com/article/view/10.21037/apm-21-3171/rc).

Methods

Literature search

Documents were searched using Boolean logic retrieval. We performed an electronic literature search of the PubMed, Medline, Embase, Chinese Biomedical Literature Database, CNKI, and Google Scholar databases. The search terms included "mecobalamin", "vestibular rehabilitation training", "vestibular rehabilitation therapy", and "vestibular neuritis". The list of references for all included reviews was traced to find references that were not indexed. The retrieval time was up to October 30, 2020, and evaluation was performed using RevMan 5.2 in the Cochrane system. A variety of terms were searched in free combination, multiple retrieval was performed to determine the literature, and the literature trace was recorded by the search engine. In addition, contact was made with researchers to ascertain the most recent research progress.

Inclusion and exclusion criteria

The included articles were required to meet all of the following criteria: (I) studies involving patients with confirmed acute vestibular neuritis without pathological type restriction; (II) intervention measures for patients in the control group were vestibular rehabilitation training (including static balance connection, vestibular eye reflex

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training, and vestibular neck reflex training) without mecobalamin intervention; (III) patients in experimental group received mecobalamin intervention combined with vestibular rehabilitation training; and (IV) randomized clinical trials (RCTs), as well as prospective cohort and case-control studies.

Literature was excluded according to the following criteria: (I) studies involving subjects with serious infectious diseases; (II) literature without randomized controlled trials (RCTs); (III) articles without valid data or missing literature; (IV) cases involving overlapped data or subjects; and (V) repeatedly published articles and those with small sample selections.

After three pre-experiments, two experts independently read the titles, abstracts, and full texts. Disagreements were resolved by consultation or arbitration by a third expert. Other disagreements were also addressed according to the method mentioned above.

Quality assessment

The Newcastle-Ottawa Scale (NOS) from the Cochrane Collaboration was used to assess the pathological control studies. The subjects' results, case comparisons, and inter-group comparisons were evaluated by the star system, with nine stars representing a full score. Seven stars or above was considered as high quality; that is, a low risk of bias. Meanwhile, articles with ≤one star were considered low quality (high bias), and studies with two–six stars were considered medium quality (medium bias). After three pre-experiments, two experts independently assessed the article quality.

Data extraction

Using a unified Excel table, the experts independently extracted the following data after three pre-experiments: (I) the first author and the year of publication; (II) the case numbers of the two groups; (III) grouping and intervention of the two groups; and (IV) recovery indicators, such as activities-specific balance confidence (ABC) scale and the Dizziness Handicap Inventory (DHI) score, before and after treatment.

Statistical methods

In Review manager 5.3, the mean difference (MD) and 95%

CI (confidence interval) indicated efficacy analysis statistics for continuity variables. The heterogeneity test (Q test) was performed initially, followed by the risk bias evaluation using the bias risk assessment map in the software. Each effect was expressed with a 95% CI. A fixed effects model (FEM) was employed if P>0.1 and I^2<50%; otherwise, a random effects model (REM) was used for processing.

Results

Summary of literature collection results and NOS scale rating

As shown in *Figure 1*, 526 references were obtained. Of these, 226 were excluded after reading the abstracts and titles of the articles, and 296 were excluded after reading the full texts of the articles. Finally, four references were included. The excluded articles involved subjects with primary acute and chronic cardiopulmonary dysfunction and mental diseases (100 articles), animal experiments (44 articles), repetitive subjects (36 articles), missing data (50 articles), no hematopoietic stem cell transplantation or killer cell therapy (40 articles), and lack of original data (26 articles). *Table 1* shows the major data, covering the period from 2005 to 2020. The NOS scale rating is illustrated in *Figure 2*; 25% of the included studies had ≥seven stars, 50% had two–six stars, and 25% had >two stars, all of which were over medium quality.

Risk of bias of the included literatures

Figures 3,4 display the multiple risk bias evaluation results. RevMan was used to generate the bias risk assessment maps for each methodological feature included in the literature. Studies with random sequence generation (selection), assignment concealment (selection), blinding of outcome evaluation (measurement), incomplete data (follow-up), and selective reporting (reporting) were considered to be very low risk of bias. As for those with blinding bias (implementation) and other biases of both subjects and researchers are approximately 25%. The other literatures had a very low risk of bias, except for the references of Micarelli [2019] and Micarelli [2017].

DHI scores of the two groups of patients before treatment

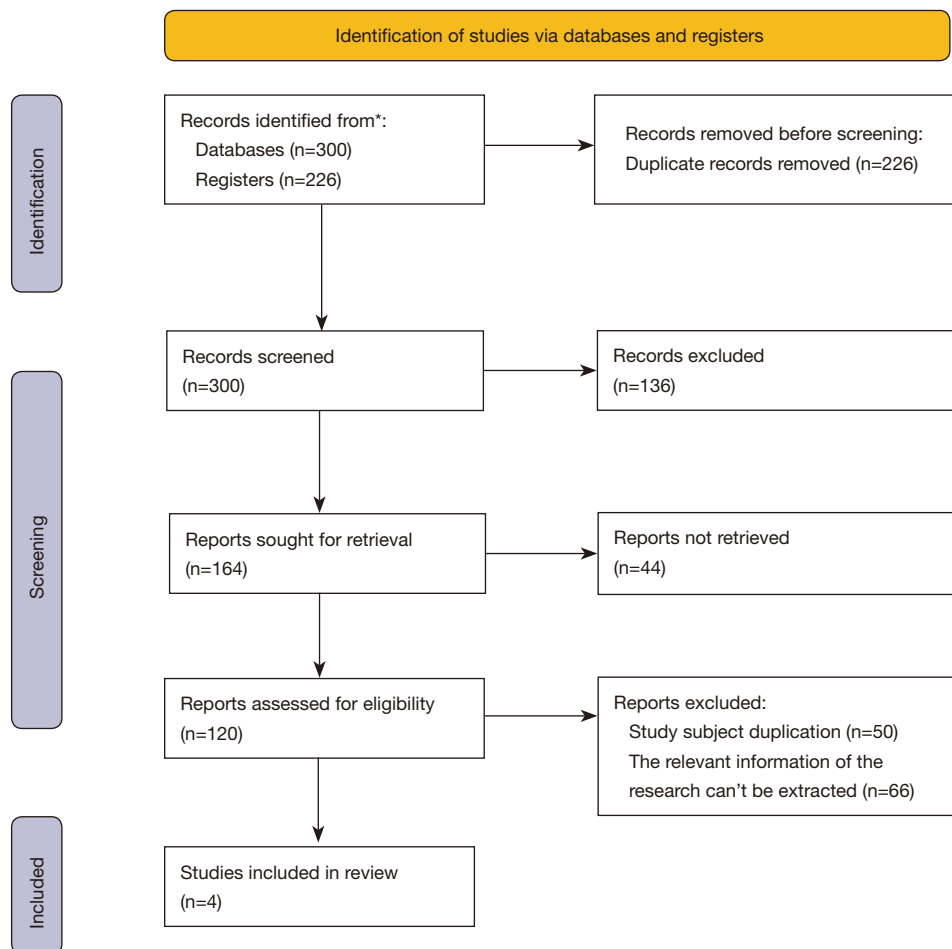*Figure 5* shows the DHI scores of two groups before treatment. The research results of Micarelli [2019] occupy

Figure 1 Screening process. *, databases and registers.

Table 1 Basic data of the included studies

First author	Year of publication	Case numbers		Age		Means of intervention	Disease duration (month)
		Control group	Experimental group	Control group	Experimental group		
Micarelli (9)	2017	24	23	49.72±10.34	50.48±9.12	Medication combined with vestibular rehabilitation training	9.37±1.55
Micarelli (10)	2019	24	23	74.3±4.7	76.9±4.7	Medication combined with vestibular rehabilitation training	23.5±5
Krueger (11)	2011	25	25	60.1±5.44	60.0±3	Medication combined with vestibular rehabilitation training	29.2±40.6
Garcia (12)	2013	23	21	47.9±19	47.65±20	Medication combined with vestibular rehabilitation training	4–48

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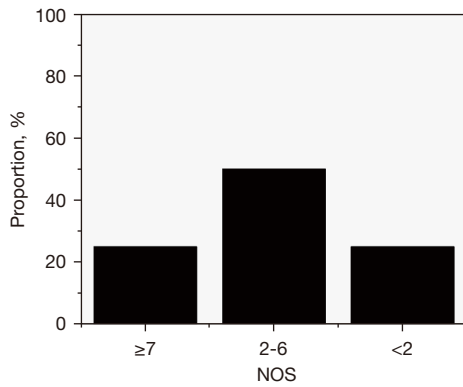Sun et al. Combined treatment of acute vestibular neuritis

Figure 2 NOS scale for quality rating. NOS, Newcastle-Ottawa Scale.

the highest percentage (81.9%), followed by Micarelli [2017] (6.5%) and Garcia [2013] (6.5%). In addition, the horizontal lines (HL) of the 95% CIs of most studies crossed the invalid vertical line (IVL). There were 96 control cases and 92 experimental cases in the four included articles. No heterogeneity was indicated in the DHI scores between the two groups before treatment (Chi^2=2.76, I^2=0%, P=0.43). The combined effect size, which is represented by a diamond block, crossed the IVL, and the Odds ratio (OR) value was 2.64 (95% CI: –0.58 to 5.86). FEM analysis indicated no considerable differences in the DHI scores between the groups before treatment (Z=1.61, P=0.11).
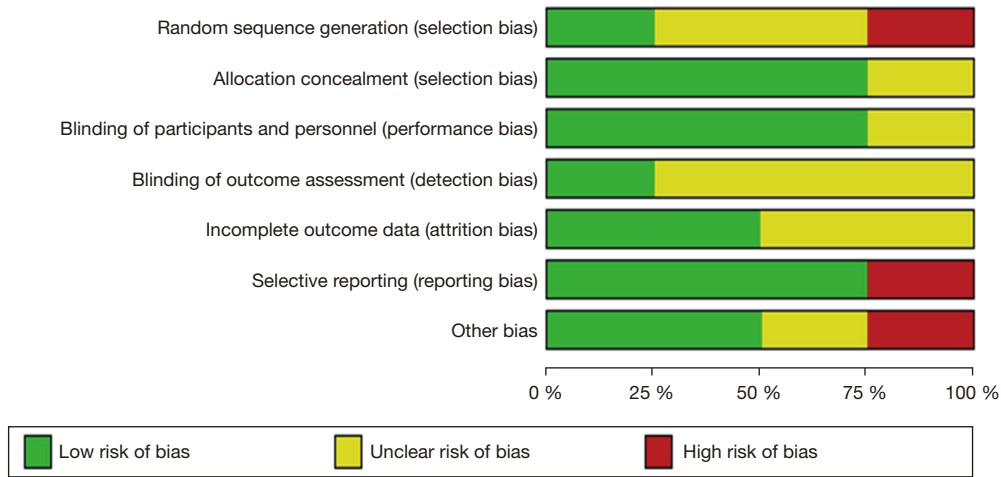
On both sides of the invalid midline are the circles, as

Figure 3 Risk of bias assessment.

Figure 4 Evaluation results of multiple risk bias.

Study or Subgroup	Experimental			Control			Weight	Mean Difference IV, Fixed, 95% CI
	Mean	SD	Total	Mean	SD	Total		
Garcia 2013	57.57	21.27	21	52.67	21.39	23	6.5%	4.90 [-7.72, 17.52]
Krueger 2011	41.8	18.5	25	50.1	31.2	25	5.1%	-8.30 [-22.52, 5.92]
Micarelli 2017	56.6	5.13	23	50.12	31.2	24	6.5%	6.48 [-6.18, 19.14]
Micarelli 2019	64	5.05	23	61.16	7.25	24	81.9%	2.84 [-0.72, 6.40]
Total (95% CI)			92			96	100.0%	2.64 [-0.58, 5.86]

Heterogeneity: Chi² = 2.76, df = 3 (P = 0.43); I² = 0%
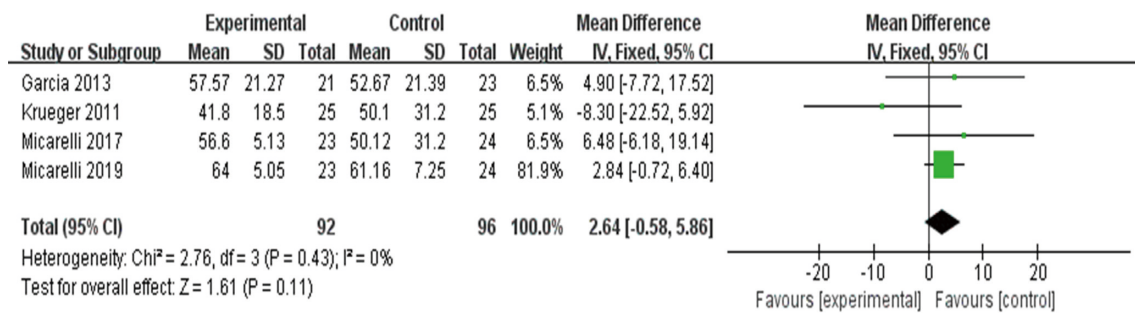Test for overall effect: Z = 1.61 (P = 0.11)

Figure 5 Comparison of DHI before treatment. DHI, Dizziness Handicap Inventory.
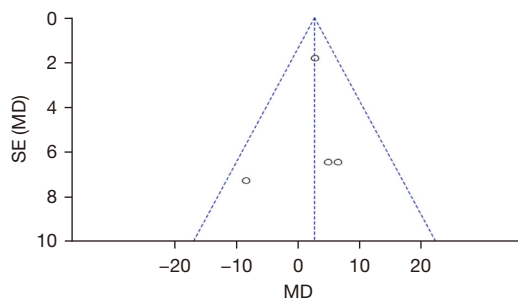

Figure 6 Funnel chart illustrating the DHI of the patients before treatment. DHI, Dizziness Handicap Inventory.

presented in *Figure 6*, which are uniform and symmetrical, indicating no obvious publication bias.

DHI scores of the two groups of patients after treatment

Figure 7 shows the DHI scores after 6 months of treatment. The results of Micarelli [2017] account for the highest percentage (33.0%), followed by those of Micarelli [2019] (32.4%). In addition, most 95% CI's HL fell to the left of the IVL, and only few research HLs crossed the IVL. Among the four studies, there were 96 subjects in the control group and 92 subjects in the experimental group. There was no heterogeneous DHI between the groups after treatment (Chi²=20.75, I²=86%, P=0.0001). The diamond block was on the left of the IVL, and the OR value was –10.56 (95% CI: –17.03 to –4.09). FEM analysis showed that the DHI of the experimental group after six months of treatment was remarkably lower compared to the control group (Z=3.20, P=0.001).

Figure 8 shows the DHI scores of the two groups after treatment. The circles are in the top area, indicating high accuracy. The circles are on both sides of the midline, which are symmetrical, signifying no obvious publication bias.

Comparison of the ABC scores between the two groups before treatment

Figure 9 shows the ABC scores of the two groups before treatment. The results of Micarelli [2019] occupied the highest percentage (51.9%). In addition, most of 95% CI's HLs were on the left of the IVL, and the research HL crossed the IVL. There were 48 subjects were in the control group and 46 cases in the experimental group. No statistical heterogeneity was suggested in the ABC scores of the two groups before treatment (Chi²=0.83, I²=0%, P=0.36). The diamond block was on the right side of the IVL, and the OR value was –1.37 (95% CI: –3.59 to 0.85). FEM analysis indicated no considerable differences in the ABC scores between the groups before treatment (Z=1.21, P=0.23).

Figure 10 shows that the circles are in the top area, indicating high accuracy. The circles are symmetrical, signifying no obvious publication bias.

Comparison of the ABC scores between the groups after treatment

Figure 11 is a comparison of the ABC scores of patients after 6 months of treatment. Micarelli's [2019] results accounted for the highest percentage (50.1%). In addition, most 95% CI's HLs were on the right of the IVL, and the research HL did not cross the IVL. Among the included four studies, there were 48 controls and 46 experimental subjects. The ABC scores of two groups were heterogeneous (Chi²=8.56, I²=88%, P=0.003). The diamond was on the right of the IVL, and the OR value was 2.14 (95% CI: –4.13 to 8.42). FEM analysis indicated no considerable differences in the ABC scores between the groups after treatment (Z=0.67, P=0.50).

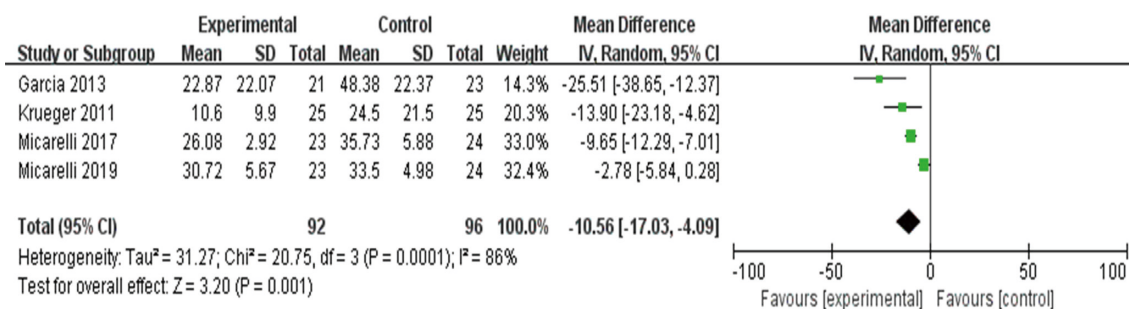*Figure 12* shows that the circles are on both sides of the midline and are symmetrical, suggesting no obvious

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Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Garcia 2013	22.87	22.07	21	48.38	22.37	23	14.3%	-25.51 [-38.65, -12.37]
Krueger 2011	10.6	9.9	25	24.5	21.5	25	20.3%	-13.90 [-23.18, -4.62]
Micarelli 2017	26.08	2.92	23	35.73	5.88	24	33.0%	-9.65 [-12.29, -7.01]
Micarelli 2019	30.72	5.67	23	33.5	4.98	24	32.4%	-2.78 [-5.84, 0.28]
Total (95% CI)			92			96	100.0%	-10.56 [-17.03, -4.09]

Heterogeneity: Tau² = 31.27; Chi² = 20.75, df = 3 (P = 0.0001); I² = 86%
Test for overall effect: Z = 3.20 (P = 0.001)

Figure 7 DHI scores of patients after treatment. DHI, Dizziness Handicap Inventory.
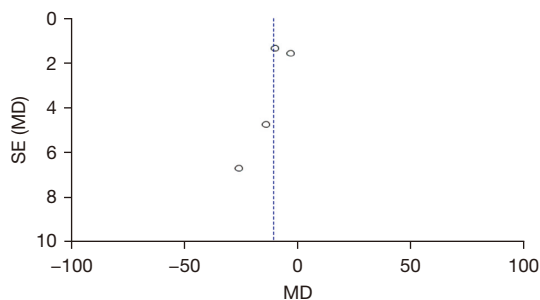
Figure 8 Funnel chart of the DHI of the patients after treatment. DHI, Dizziness Handicap Inventory.

publication bias.

Discussion

When inflammation of the anterior vestibular nerve occurs, the balance model generated by the inner ear and the position information generated by the head cannot be normally transmitted to the brain, leading to acute or persistent vertigo in patients, which is a sudden vertigo disorder caused by acute damage to one of the vestibular nerves. Patients in the acute and convalescent phases of vestibular neuritis exhibit different clinical symptoms. The acute phase manifests as persistent and severe dizziness, accompanied by nausea, vomiting, and other symptoms. During recovery, the vertigo symptoms of patients disappear, and at this time, the condition manifests as non-rotating dizziness, instability, and temporary vertigo after head movement. The patient can walk independently and deviate to one side, and the direction of deviation is related to the state of vestibular compensation. The most common cause of vestibular neuritis is viral infection of the vestibular nerve, including measles, influenza, shingles, and varicella.

The vestibular system has a strong compensatory ability.

The theoretical basis of vestibular functional rehabilitation is the brain's reintegration of visual, vestibular, and sensory systems, which strengthen the function of the visual proprioceptive system and replace the damaged part of vestibular function, thereby achieving a new balance (18). Amber *et al.* [2012] (19) found that the central nervous system of the human body has plasticity and adaptability to vestibular function damage. Through repeated training, the body can adapt to the asymmetrical information of the external anterior court. Vestibular training primarily helps patients improve their balance stability or visual compensatory ability through vestibular adaptation and substitution formed by long-term stimulation. The most common cause of vestibular neuritis is viral infection of the vestibular nerve (e.g., measles, influenza, shingles, varicella, etc.), while other causes include ischemia (acute ischemia of the vestibular and labyrinth nerves) or bacterial infection. In the acute stage of vestibular neuritis, the otolithostone and semicircular canal function of patients are simultaneously damaged. The addition of medication to conventional treatment can significantly improve the clinical prognosis of patients with acute preacoustic neuritis. The treatment of vestibular neuritis includes specific treatments (e.g., glucocorticoids, antiviral therapy, etc.) in the acute phase, symptomatic treatment, and vestibular rehabilitation training.

Among the 4 included literatures, nine were randomized controlled and grouped, and only one was a retrospective analysis, which introduced bias into the study; however, it had little influence on the results of the study. It was unstable to analyze single samples, so quantitative synthesis of each included article was implemented via meta-analysis, and sampling errors from different populations were avoided. Moreover, in terms of sample size, different
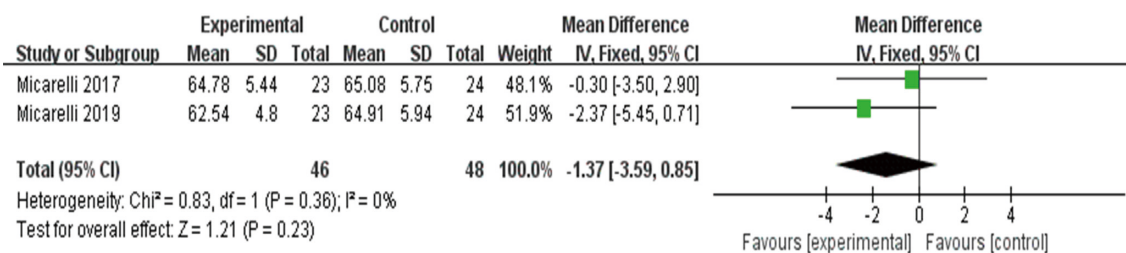
Study or Subgroup	Experimental			Control			Weight	Mean Difference IV, Fixed, 95% CI
	Mean	SD	Total	Mean	SD	Total		
Micarelli 2017	64.78	5.44	23	65.08	5.75	24	48.1%	-0.30 [-3.50, 2.90]
Micarelli 2019	62.54	4.8	23	64.91	5.94	24	51.9%	-2.37 [-5.45, 0.71]
Total (95% CI)			46			48	100.0%	-1.37 [-3.59, 0.85]

Heterogeneity: Chi² = 0.83, df = 1 (P = 0.36); I² = 0%
Test for overall effect: Z = 1.21 (P = 0.23)

Figure 9 Comparison of the ABC scores between the groups before treatment. ABC, activities-specific balance confidence.
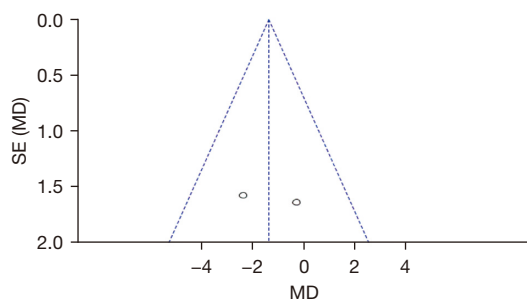
Figure 10 Funnel chart of the ABC scores before treatment. ABC, activities-specific balance confidence.

weights were assigned to the corresponding results. In this way, the sample size was expanded, and reliability of conclusion was guaranteed. The number of articles included in this study was limited, and thus, a large sample size is required to reduce bias.

Four comparative studies of vestibular rehabilitation training and vestibular rehabilitation training combined with mecobalamin were meta-analyzed, which were retrieved according to the Boolean composite logic method, in order to investigate the efficacy and safety of mecobalamin combined with vestibular rehabilitation training for acute vestibular neuritis. The ABC scores of two groups were heterogeneous (Chi²=8.56, I²=88%, P=0.003), and FEM analysis indicated no considerable differences in the ABC scores between the groups after treatment. It may be that mecobalamin combined with vestibular rehabilitation training effectively alleviated the symptoms of vestibular neuritis in the experimental group, thereby reducing the canal paresis (CP) value. In addition, there was no heterogeneity in the DHI scores between the groups after treatment (Chi²=20.75, I²=86%, P=0.0001), and FEM analysis showed that the DHI scores of the experimental group after 6 months of treatment was notably lower than that of the control group (Z=3.20, P=0.001). These results

are similar to the findings of Tramontano *et al.* [2018] (20), indicating that mecobalamin combined with vestibular rehabilitation training can effectively improve vertigo and other symptoms in patients, with high effectiveness and safety. It was also found that 60% of patients returned to normal vestibular function after treatment, and the recurrence rate was high. Moreover, patients with cured vestibular neuritis exhibited a high risk of recurrence of vertigo symptoms, which are often accompanied by refractory benign paroxygenic positional vertigo. Vestibular rehabilitation training can accelerate the rehabilitation of patients with acute vestibular neuritis and reduce the disability degree of patients with permanent vestibular injury. It has a certain positive effect on the long-term recovery of patients and the recovery of balance function. Therefore, training should be performed, including fixation stability visual tracking training, static and dynamic posture stability training, and functional activity training.

Conclusions

In this study, meta-analysis is carried out on four comparative studies of vestibular rehabilitation training and vestibular rehabilitation training combined with mecobalamin, which were retrieved according to the Boolean composite logic method, in order to investigate the efficacy and safety of mecobalamin combined with vestibular rehabilitation training for acute vestibular neuritis. The results showed that mecobalamin combined with vestibular rehabilitation training could effectively improve the vertigo and other symptoms of patients, with high effectiveness and safety. However, confounding factors resulted in bias. The references selected were all case controls, and thus, survival bias existed. Moreover, multiple risk factors and indicators were not discussed, which affected the pooled effect size. Patients with acute vestibular neuritis will be considered in future research, so as to explore the impact of joint
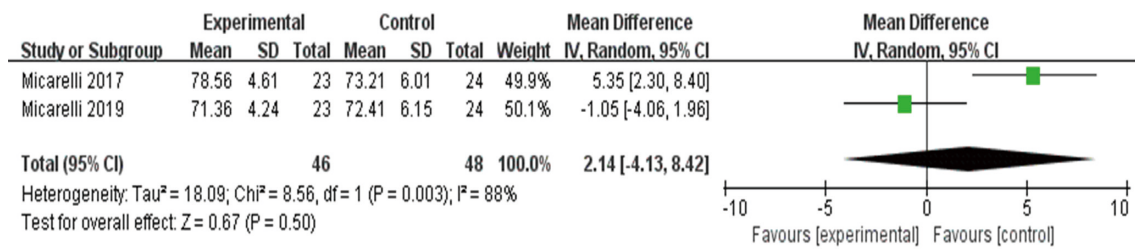
Figure 11 Comparison of the ABC scores. ABC, activities-specific balance confidence.
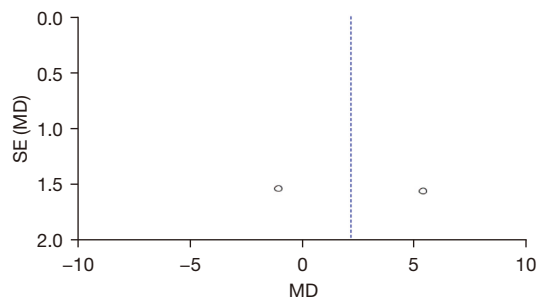

Figure 12 Funnel plot of the ABC scores after treatment. ABC, activities-specific balance confidence.

intervention in patients with acute vestibular neuritis. In conclusion, this research provides a treatment reference and related data for vestibular neuritis and other diseases.

Acknowledgments

Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at https://apm.amegroups.com/article/view/10.21037/apm-21-3171/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://apm.amegroups.com/article/view/10.21037/apm-21-3171/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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