Meta analysis of treatment efficacy for posterior circulation ischemic vertigo using therapy for elevating Yang

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Abstract: Objective: To evaluate the clinical efficacy of TCM therapy for elevating Yang in the treatment of posterior circulation ischemic vertigo. Methods: all clinical randomized controlled trials of therapy for elevating Yang’s posterior circulation ischemic vertigo were screened by computer searching Chinese databases such as CNKI, Wanfang database, VIP Chinese science and technology and the Cochrane Library, PubMed, EMBASE and other English databases from the time the library was built to October 2020, and relevant references were manually reviewed. Patients in the control group were treated with western medicine, while those in the experimental group were treated with either Elevating Yang recipe (decoction) or Elevating Yang recipe (decoction) combined with western medicine. The Review Manager 5.3 software was used to conduct a meta-analysis on the clinical effective rate, TCM syndrome scores, vertebrobasilar blood flow velocity, and adverse reactions. Results: Eleven articles were finally included, covering a total of 1049 patients, including 522 cases in the observation group and 527 cases in the control group. The clinical effective rate of patients in the experimental group is higher than that in the control group [RR=1.22(1.16,1.28)], the vertebral-basilar artery blood flow velocity in the experimental group includes left vertebral artery (LVA) [MD = 4.88, 95%CI(3.30, 6.46)], right vertebral artery (RVA) [MD = 4.87, 95%CI(2.85, 6.88)], and basilar artery (BA) [MD = 5.17, 95%CI(4.55, 5.78)], TCM symptom scores significantly improved in the experimental group [MD = -4.17, 95%CI(-4.66, -3.67)], the difference was statistically significant. Conclusion: The results of this meta-analysis indicated that Therapy for Raising Yang had good therapeutic effects on CI after treatment, in that it could effectively improve the clinical efficiency, promote the blood flow velocity of vertebrobasilar artery, and reduce TCM symptom scores. However, it still needs to be further confirmed by large sample size and high quality RCTs.

Keywords: Posterior circulation ischemic vertigo, therapy for elevating Yang, Meta analysis, Randomized controlled experiment

1. Introduction

Posterior circulation ischemia is a common ischemic encephalopathy, which is mainly caused by atherosclerosis [1], including posterior circulation transient ischemic attack and cerebral infarction [2], and the incidence rate accounts for about 20% of the total incidence of ischemic stroke [3]. Vertigo is the most common clinical symptom, mainly due to the insufficient blood supply to the corresponding areas caused by blood circulation disorder of the vertebrobasilar artery system, which produces a series of symptoms [4], mainly manifested as dizziness and blurred vision, accompanied by visual rotation, cold sweated limbs, nausea and vomiting, and tinnitus. The disease is characterized by a long course of disease, difficulty in radical correction, and easy repetition [5], which has brought great pain to patients. In clinical western medicine, such measures as nerve protection, plaque stabilization, lipid lowering, and anti-platelet aggregation are often adopted to comprehensively intervene with the patients with posterior circulation ischemic vertigo, which can alleviate the clinical symptoms of the patients to a certain extent. However, there is a large gap between the overall efficacy and clinical expectations [6]. Studies have shown that prolonged treatment of posterior circulation ischemic vertigo will lead to the onset of cerebral infarction and seriously affect the life safety of patients [7]. Therefore, the treatment of integrated traditional Chinese and western medicine is very helpful for the posterior circulation ischemic vertigo.
Syndrome differentiation is often made based on the etiology and pathogenesis in traditional Chinese medicine, and the treatment is often effective. Meanwhile, more experience has been accumulated in the treatment of this aspect [8]. In this study, the clinical randomized controlled trials of circulating ischemic vertigo after treatment with Traditional Chinese Medicine therapy for Electing Yang were collected and the Meta-analysis was conducted on the clinical efficiency, clinical symptoms in traditional Chinese medicine, vertebrobasilar artery blood flow velocity, and adverse reactions, aiming to objectively analyze and evaluate the clinical efficacy of circulating ischemic vertigo after treatment with therapy for Electing Yang and provide an evidence-based basis for clinical promotion of therapy for Electing Yang.

2. Materials and methods

2.1 Literature retrieval strategy

CNKI, Wanfang Data Knowledge Service Platform, VIP and other Chinese databases and The Cochrane Library, PubMed, EMBase and other English databases were retrieved by computer. Chinese term: vertigo, posterior circulation ischemic vertigo, elevating Yang, traditional Chinese medicine and traditional Chinese medicine, and English term: rising Yang method, traditional Chinese medicine and Chinese herb. The search time was from the database establishment to October 2020, and the references were manually reviewed by the self.

2.2 Criteria for inclusion and exclusion of literature

2.2.1 Document inclusion criteria

(1) Type of study: Randomized controlled clinical trials; (2) Subjects: patients with posterior circulation ischemic vertigo who met the diagnostic criteria of posterior circulation ischemic vertigo in the Chinese Experts Consensus on Posterior Circulation Ischemia [9], Criteria for Diagnosis and Therapeutic Effect of Diseases and Syndromes in Traditional Chinese Medicine [10], Neurology [11] and Practical Neurology [12], without limitation in age, gender and syndrome type; (3) Intervention measures: Patients in the control group were treated with western medicine; Patients in the experimental group were treated with either Elevating Yang recipe (decoction) or Elevating Yang recipe (decoction) combined with western medicine, and the prescription (decoction) treatment law of patients in the experimental group clearly stating “elevating Yang” was not limited to the formulation, dose and course of treatment of the prescription used in the study. (4) Outcome indicators: clinical efficiency, TCM syndrome score, blood flow velocity of vertebrobasilar artery (including left vertebral artery (LVA), right vertebral artery (RVA), and basilar artery (BA)), and adverse reaction.

2.3 Literature screening and data extraction

The literature database was independently and manually retrieved and screened by the two researchers in strict accordance with the criteria for literature inclusion and exclusion to eliminate all articles that did not meet the requirements of this study. If there were two researchers with divergent views, a third researcher would be asked to assist in the decision. Literature retrieval contents included publication time, article title, first author, intervention method, and outcome index.

2.4 Quality evaluation

In this study, the recommended risk assessment tool for bias in Cochrane Evaluation Manual Version 5.1.0 was used to evaluate the quality of included articles, including 7 items including whether random allocation was adopted, whether allocation concealment was adopted, whether the researchers and subjects were blinded, who evaluated the study results, whether the data of test results were complete, whether study results were selectively reported, and whether other bias sources were available. The risk of bias was rated as “high, medium, and unclear”.

2.5 Statistical method

The extracted data were subjected to meta-analysis using Review Manager 5.3 software. The enumeration data were combined with RR statistics, and the measurement data were expressed as effect quantity by MD. The confidence intervals (95%CI) were calculated using both methods. The difference was statistically significant when P<0.05. I² was used to test the heterogeneity between the data. When
If $I^2 \leq 50\%$ and $P > 0.1$, there was no significant statistical heterogeneity between the data. A fixed-effect model (TEM) was used for Meta-analysis. $I^2 > 50\%$ and $P < 0.1$ indicated high statistical heterogeneity among the articles, and the source of heterogeneity should be examined by sensitivity analysis or subgroup analysis. If the source of heterogeneity could not be found, the random effect model (REM) was used for Meta-analysis. If the data in outcome measures are more than 7, funnel plot can be used to evaluate publication bias.

3. RESULT

3.1 Retrieval results

A total of 207 articles were initially detected, and 11 articles were finally included according to the literature inclusion and exclusion criteria [13-23]. The literature screening process is shown in Fig. 1. The 11 included articles totally included 1,049 patients, including 522 cases in the observation group and 527 cases in the control group. The basic conditions of the included articles are shown in Table 1.
Table 1: Basic information of incorporated literature

<table>
<thead>
<tr>
<th>Literature</th>
<th>Sample size</th>
<th>Intervention measure</th>
<th>Outcome indicator</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Test team</td>
<td>Control group</td>
<td></td>
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<tr>
<td>Zhangfengling2009[13]</td>
<td>40</td>
<td>Sibiling capsules + phlegm and anti vertigo drinking</td>
<td>①②③④</td>
</tr>
<tr>
<td></td>
<td>46</td>
<td>Sibiling capsules + plain vertigo capsules</td>
<td></td>
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<tr>
<td>Guojingjuan2013[14]</td>
<td>30</td>
<td>Flunarizine Hydrochloride Capsules + elevating Yang Huoxue Tang</td>
<td>①②③④④⑥</td>
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<td></td>
<td>30</td>
<td>Flunarizine hydrochloride capsule</td>
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<tr>
<td>Li Jie2015[15]</td>
<td>45</td>
<td>Flunarizine hydrochloride capsule + elevating Yang Huoxue decocion</td>
<td>①②③④⑥⑨</td>
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<td></td>
<td>45</td>
<td>Flunarizine hydrochloride capsule</td>
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<tr>
<td>Wangchangde2015[16]</td>
<td>50</td>
<td>Flunarizine hydrochloride capsule + Fengxuan Ningfang</td>
<td>①②③④</td>
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<tr>
<td></td>
<td>50</td>
<td>Flunarizine hydrochloride capsule</td>
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<td>Dongbaojie2015[17]</td>
<td>33</td>
<td>Intravenous drip of gastrodin injection + modified rhizoma alismatis decocion</td>
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<td></td>
<td>34</td>
<td>Intravenous drip of gastrodin injection</td>
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<td>Shen Shan2016[18]</td>
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<td></td>
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<tr>
<td>Qi Wenchao2018[19]</td>
<td>57</td>
<td>Flunarizine hydrochloride capsule + elevating Yang Huoxue decocion</td>
<td>①②③④⑤</td>
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<td>Flunarizine hydrochloride capsule</td>
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<tr>
<td>Qinchengxi2019[21]</td>
<td>49</td>
<td>Flunarizine hydrochloride capsule + Zishen Pingxuan Decocion</td>
<td>①②③④⑥</td>
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<td></td>
<td>49</td>
<td>Flunarizine hydrochloride capsule</td>
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<tr>
<td>Zhengxiaorang2020[22]</td>
<td>60</td>
<td>Routine Treatment in Western Medicine+Spleen-Strengthening elevating Yang Decocion</td>
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<td>60</td>
<td>Conventional treatment in western medicine</td>
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<td>Gaoxuna2020[23]</td>
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<tr>
<td></td>
<td>42</td>
<td>Betahistine mesylate tablet</td>
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Notes: ① Clinical effective rate; ② Mean blood flow velocity of the left vertebral artery; ③ Mean blood flow velocity of the right vertebral artery; ④ Mean blood flow velocity of basilar artery; ⑤ TCM syndrome score; ⑥ Adverse reactions.

3.2 Quality evaluation

Random allocation: Six studies adopted random number table [16-19,22,23], while the remaining five studies mentioned randomization but did not describe the specific method [13-15,20,21]. Allocation concealment and blind method: All articles failed to mention allocation concealment, and only one study adopted blind extraction method. Completeness of outcome data: No omissions were mentioned in the literature outcome data; Selective reporting of study results: 11 studies did not selectively report study results; Other sources of bias: The other sources of bias for the 11 studies were not known, as shown in Fig. 2.

3.3 Meta analysis

3.3.1 Clinical effective rate

The 11 articles covered a total of 1,049 patients [13-23]. As for the evaluation of clinical effective rate, there was no significant statistical heterogeneity between the articles (P=0.31, I²=14%), so the fixed-effect model was used for Meta-analysis. The results showed that the clinical effective rate of patients in the experimental group was higher than that in the control group, and the difference was statistically significant [RR=1.22, 95%CI(1.16, 1.28), Z=7.60, P < 0.0001, see Fig. 3].

3.3.2 Mean blood flow velocity of left vertebral artery

Seven articles [13-16,19,21,22] were included, covering 668 patients in total. The mean blood flow velocity of the left vertebral artery was evaluated, and there was heterogeneity among the articles (P < 0.0001, I² = 81%), and the random effect model was used. They showed significant heterogeneity in the included studies. Sensitivity analysis was performed on the original articles, and the articles were excluded one by one. It was found that I² was still > 50%, and the results were consistent before and after, suggesting that the results were relatively robust. The results showed that the mean blood flow velocity of the left vertebral artery in the experimental group was higher than that in the control group, and the difference was statistically significant [MD = 4.88, 95%CI(3.30, 6.46), Z=6.04, P < 0.001, as shown in Fig. 4].
3.3.3 Mean blood flow velocity of right vertebral artery

Seven articles [13-16,19,21,22] were included, covering 668 patients in total. The mean blood flow velocity of the right vertebral artery was evaluated, and there was heterogeneity among the articles (P < 0.00001, $I^2 = 88\%$), and random effect model analysis was used. The included studies showed significant heterogeneity. Sensitivity analysis was performed on the original articles, and the articles were excluded one by one. It was found that $I^2$ was still $> 50\%$, and the results were consistent before and after, suggesting that the results were relatively robust. The results showed that the mean blood flow velocity of the right vertebral artery in the experimental group was higher than that in the control group, and the difference was statistically significant [MD = 4.87, 95%CI(2.85, 6.88), Z=4.74, P < 0.001, as shown in Fig. 5].

3.3.4 Mean blood flow velocity of basilar artery

Seven articles [13-16, 19-21] were included, covering a total of 650 patients. Mean basilar artery blood flow velocity was evaluated without significant statistical heterogeneity between articles (P = 0.07, $I^2 = 48\%$), and fixed-effect model analysis was used. The results showed that the mean basilar artery blood flow velocity in the treatment group was higher than that in the control group, and the difference was statistically significant [MD = 5.17, 95%CI(4.55, 5.78), Z=16.46, P < 0.0001, see Fig. 6].

3.3.5 Traditional Chinese medicine syndrome score

Three articles [19, 15, 23] were included, covering a total of 288 patients. TCM syndrome scores were evaluated, and there was no significant statistical heterogeneity between the articles (P = 0.34, $I^2 = 8\%$). The fixed-effect model was used for analysis. The results showed that the treatment group could significantly reduce the TCM symptom scores, and the difference was statistically significant [MD = -4.17, 95%CI(-4.66, -3.67), Z=16.55, P < 0.001, as shown in Fig. 7].

3.3.6 Incidence of adverse reactions

Four articles [14, 21-23] included in this study covered the adverse reactions, with a total of 362 patients. The results of heterogeneity test showed (P=0.63, $I^2=0\%$), and it was considered that there was no significant statistical heterogeneity between the articles. The fixed-effect model was used for analysis. The results of the meta-analysis showed that there was no significant difference in the incidence of adverse reactions between the treatment group and the control group [RR =1.33, 95%CI(0.48, 3.71), Z=0.55, and P=0.58, as shown in Fig. 8].

3.3.7 Publication bias analysis

Eleven articles reported the clinical effective rate [13-23]. The funnel plot analysis of the effective rate as an outcome index showed that the funnel plot study was scatter-asymmetric, suggesting that there might be publication bias, as shown in Fig. 9. The sensitivity analysis was performed using the one-by-one elimination method, and the results showed no significant difference compared with those before, indicating that the results of the Meta-analysis for clinical effective rate were relatively robust.
Figure 4: Meta-analysis forest map of average blood flow velocity of left vertebral artery

Figure 5: Meta-analysis forest map of average blood flow velocity of right vertebral artery

Figure 6: Meta-analysis forest map of mean blood flow velocity of basilar artery

Figure 7: Forest plot of meta-analysis of TCM syndrome scores

Figure 8: Meta-analysis forest map of adverse reactions
4. Discussion

Posterior circulation ischemic vertigo belongs to the category of "vertigo" in TCM. It is located in the scalp orifices and is often closely related to the liver, spleen, and kidney. Vertigo refers to the general term of vertigo and vertigo; vertigo refers to the dim eyesight or blackness of the eye; vertigo refers to the sensation that the whole body rotates with external things or even stands instability; the two conditions often occur at the same time, which are collectively referred to as vertigo [24]. Successive physicians believed that the etiological mechanism of vertigo was Ben deficiency standard and that it was dominated by deficiency, and the main accounts of vertigo, such as Jiafeng, fire, phlegm, and stasis, can be traced back to the Yellow Emperor's Internal Classic [25]. As reported in Ling Shu Wei Qi: “Upper deficiency leads to dizziness”[26], Jing Yue book said: “vertigo caused by qi and blood deficiency; Most people with vertigo and qi and blood deficiency have this symptom, and very few people have hot phlegm symptoms at the same time.” "Su Wen · Yin Yang Ying Xiang Da Lun” said: “Qingyang out of upper orifices,” posterior circulation ischemic vertigo frequently attacking the middle-aged and elderly [27]. According to years of clinical experience, Professor Li Yan believes that for the middle-aged and elderly vertigo, the weakness of spleen and stomach and qi and blood deficiency are its pathogenesis basis [28], leading to the loss of orifices in qing dynasty and nourishing hair as vertigo. Therefore, the treatment of senile posterior circulation ischemic vertigo in traditional Chinese medicine emphasizes elevating Yang, which means that the yang qi will rise, the heaven will flourish in the brain, and the mind will be nourished. Thus, vertigo can be alleviated. The clinical efficacy is significant in the treatment, which can also reduce the recurrence rate and significantly improve the quality of life of patients. After western medicine treatment, the improvement of blood circulation in the brain is mainly used to promote the oxygen supply to the brain tissue, improve the functional blood status, and restore the normal function of the brain tissue [29]. Therefore, the combination of TCM therapy for elevating Yang and conventional western medicine treatment will greatly help to improve the symptoms of patients with posterior circulation.

In this study, the literature was collected, and the statistical software Rev Man 5.3 was used for the Meta-analysis of the 11 included articles. The results showed that compared with western medicine alone, the combination of traditional Chinese medicine and western medicine could significantly improve the clinical efficiency [RR=1.22(1.16,1.28)], and increase the verteobasilar blood flow velocity (including left vertebral artery (LVA) [MD = 4.88], 95%CI(3.30, 6.46); right vertebral artery (RVA) [MD = 4.87, 95%CI(2.85, 6.88)]; basilar artery (BA) [MD = 5.17, 95%CI(4.55, 5.78)], reducing TCM symptom scores [MD = − 4.17, 95%CI(-4.66, -3.67)]. Therefore, therapy for elevating Yang is effective in the treatment of posterior circulation ischemic vertigo, and worthy of clinical promotion. However, the quality of included articles and various factors affected the credibility of the Meta-analysis.

There existed the following shortcomings in this study: ① The specific random method and allocation concealment scheme were not explained in some included articles, and the blind method was
mentioned in only one article, with small sample size. ② Only four articles [19, 21-23] were included in the literature to report the adverse reactions, while no adverse reactions were reported in the other articles. ③ Articles included did not describe in detail whether the follow-up status of subjects dropped out or withdrew from the study. Therefore, the efficacy of therapy for elevating Yang in the treatment of posterior circulation ischemic vertigo still needs to be strongly supported by large sample size, multicenter, and high-quality clinical studies in the future.

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