Effectiveness and safety of moxibustion for vascular dementia
A systematic review and meta-analysis

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Abstract

Background: Vascular dementia (VD) is the only type of dementia that can be prevented and treated. Compared to conventional treatment methods, moxibustion therapy is more effective for VD. This study evaluated the effectiveness and safety of moxibustion in the treatment of VD through a meta-analysis, to provide a complete overview to the advantages of traditional Chinese medicine and provide guidance for clinical application.

Methods: Clinical trials on the therapeutic effects of moxibustion or moxibustion combined with acupuncture on VD were retrieved from the VIP information database, Wanfang, CNKI, PubMed, EMBase, and other resources. The included studies were conducted from January 2000 to October 2020. Among the retrieved studies, the content met the standards upon being collated and extracted, and RevMan5.3 was used for meta-analysis.

Results: Thirteen randomized controlled trials (RCTs) were included with 997 patients. The RevMan bias risk assessment revealed that the quality of the studies was generally low. The meta-analysis showed that compared to conventional treatments, moxibustion therapy in terms of effective rate, posttreatment Hasegawa Dementia Scale, Mini-Mental State Examination (MMSE), Activity of Daily Living Scale (ADL), Somatostatin (SS), Arginine Vasopressin (AVP), and Syndrome Differentiation Scale of VD were more favorable, and the difference in efficacy was statistically significant. Furthermore, no adverse events were observed in either group. Sensitivity analysis showed strong homogeneity and stable results, whereas funnel plot analysis revealed no significant publication bias.

Conclusions: Moxibustion is effective and safe in the treatment of VD, but more high-quality evidence from further studies is required to support this.

Abbreviations: AD = Alzheimer disease, CI = confidence interval, OR = odds ratio, RCTs = randomized controlled trials, RR = risk ratio, SMD = standardized mean difference, TCM = Traditional Chinese Medicine, VD = Vascular dementia.

Keywords: clinical trials, moxibustion, meta-analysis, vascular dementia

1. Introduction

Vascular dementia (VD) refers to dementia caused by ischemic or hemorrhagic cerebrovascular diseases and acute and chronic hypoxic encephalopathy. Its clinical features are the localization damage of nervous system, accompanied by difficulties in memory, intelligence, orientation, calculation, emotion and behavior.[1-2] Epidemiological investigation shows that with the development of aging and the rising incidence of cerebrovascular diseases, VD has become the second most common dementia after Alzheimer disease, which not only affects patients’ quality of life and self-care ability, but also brings a heavy burden to families and society.[3] At present, the diagnosis of VD has made great progress, but the treatment progress is slow, and there is no specific medicine for treating VD in western medicine.[4] Therefore, it is an urgent problem to seek safe and effective treatment.

VD belongs to the category of “apoplexy” and “foolish syndrome” in traditional Chinese medicine (TCM), which divides vascular dementia into “foolish disease, foolish syndrome” and so on. “Forgetting after a stroke” was recorded as early as “The Origin of Miscellaneous Diseases, Fluffy Candle Stroke”, which shows that Chinese medicine has already had a certain understanding of “vascular dementia”.[5] Modern clinical practice

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shows that TCM has its unique advantages in treating this disease, especially acupuncture and moxibustion have prominent effects in the treatment process. As a TCM therapy, moxibustion is more and more accepted by patients. Relevant evidence-based medicine shows that moxibustion may be a safe and effective therapy, but the outcome indicators are scattered, and some conclusions are inconsistent.

Therefore, this study focuses on moxibustion therapy. By searching the literatures of clinical randomized controlled trials of moxibustion for VD in the database for Meta-analysis, it provides high-quality reference evidence for the effectiveness of moxibustion for vascular dementia from the perspective of evidence-based medicine.

2. Methods

2.1. Search strategy

This systematic review and meta-analysis were carried out according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) Statement. The protocol of the present study was registered and approved by PROSPERO under the registration number of CRD42021227641. We searched through Chinese National Knowledge Infrastructure (CNKI), VIP information database, Wanfang Data Information Site, PubMed and EMBASE, etc. The retrieval time was from January 2000 to October 2020, without language restriction. In order to collect all related studies, the combination of subject words and free words were used to carry out a comprehensive search, and a search expression was established using OR and AND. The search terms used in both Mandarin and English were as follows: moxibustion, acupuncture, vascular dementia, dementia, randomized, controlled, trial, and clinical.

2.2. Inclusion and exclusion criteria

2.2.1. Inclusion criteria.

(1) Type of study: RCTs, no language restriction;
(2) Subjects met the diagnostic criteria for VD, regardless of gender, age, or nationality;
(3) Intervention measures: the experimental group used any form of moxibustion (no limitation on material, acupuncture points, and course of treatment), or moxibustion combined with Chinese drugs and western medicine was used. However, moxibustion was the only variable, and the matching groups were western medicine, Chinese drugs, acupuncture other therapies;
(4) Outcome indicators: clinical efficacy evaluation indexes included effective rate, Hasegawa Dementia Scale (HDS) score, Mini-Mental State Examination (MMSE) score, Activity of Daily Living Scale (ADL) score, Somatostatin (SS) level, Arginine Vasopressin (AVP) level, Syndrome Differentiation Scale of VD (DSVSD) level after effective treatment.

2.2.2. Exclusion criteria.

(1) do not conform to inclusion criteria;
(2) animal studies;
(3) improper statistical methods or descriptions;
(4) duplicate publications or incomplete data.

2.3. Data extraction

Two professionals read the title and abstract of studies, combined with the full text, selected the final included RCTs according to the preset inclusion and exclusion criteria. The study was screened and the information extracted according to Cochrane 5.3 standards, including basic information of the literature, study methods, quality evaluation characteristics, study object characteristics, intervention measures and outcome indicators, etc. Office software was used to collate the data. For any disputes that arose, 2 evaluators were appointed to interpret and negotiate the results, with the possibility of the intervention of a third evaluator to navigate dissension.

2.4. Quality assessment

The quality assessment of all studies included in this review was independently evaluated by 2 reviewers according to the quality evaluation standard recommended by Cochrane Reviewer Handbook 5.3. The following 6 criteria were applied: (1) random sequence generation, (2) allocation concealment, (3) whether to implement blind method, (4) integrity of data, (5) incomplete outcome data, and (6) other bias. Make a low risk, high risk and unclear judgment on the above 6 criteria, and finally show it as the risk graph of bias. Then, the improved Jadad scale was used to score the generation of random sequences, randomize hidden and blind methods, and the specific scoring criteria are appropriate (2 points), unclear (1 point) and inappropriate (0 point). Withdrawal and exit are divided into 1 point and 0 point according to the number of descriptions and reasons. The total score is 7 points, among which 1 to 3 points are of low quality and 4 to 7 points are of high quality.

2.5. Statistical analysis

2.5.1. Therapeutic effect index. Effective rate: According to the clinical practice, the research group unified the key information such as effectiveness and obvious effectiveness into effectiveness; In addition, that was being invalid, they also compared and integrated the data and then put into the effectiveness of the study groups accordingly.

2.5.2. Meta-analysis. The RevMan 5.3 software was used for meta-analysis, and risk ratio or odds ratio (OR) were used for counting data, and standardized mean difference (SMD) used for measuring data. Also, a confidence interval (CI) of 95% was used as efficacy analysis statistics.

2.5.3. Heterogeneity analysis. If the result is I^2 < 50%, it indicates good homogeneity and fixed-effect model is adopted. If I^2 > 50%, the heterogeneity is statistically significant, and then the random effect model is applied. If heterogeneity still exists, subgroup analysis or sensitivity analysis should be performed according to clinical heterogeneity.

2.5.4. Publication bias detection. The latent publication bias was determined by the funnel plot.

3. Results

3.1. Searching results

There were 166 references retrieved in Chinese database and 6 references in English database. Among them, there were 90 from CNKI, 51 from Wanfang, 25 from VIP, 3 from PubMed, and 3 from EMBASE. Among the 166 Chinese studies, 78 of them were screened out of the research according to the titles and abstracts reviewed, and the remaining 88 were selected for consideration. After careful analysis, 10 articles were finally chosen as the references. According to the same procedure, 3 English studies were selected. Therefore, 13 studies were included in the quantitative synthesis meta-analysis,
which involved 997 patients, among which 496 patients were in the experimental group and 501 patients in the control group (Fig. 1).

3.2. Characteristics of included studies
Of the 13 included studies, all reported an effective rate and MMSE score;[9–21] 5 reported HDS score;[9, 12–14, 20] 11 reported ADL score;[9, 10–14, 18–19, 21] 2 reported SS level;[9, 14] 2 reported AVP level;[9, 14] and 2 reported SDSVD level.[10, 21] The thirteen references included RCTs were evaluated (Table 1).

3.3. Quality of the included studies
Among the thirteen included RCTs, “random” was adopted, 1 of them described random sequence generated by computer,[10] 1 mentioned allocation and hiding,[9] and twelve were shown in random number table method.[9, 11–21] One study implemented the blind method.[21] Eleven modified Jadad scores were of low quality studies,[10–17, 19–21] and 2 were of high-quality studies.[9, 18] The methodological quality of the included study was evaluated (Fig. 2).

3.4. Meta-analysis results
3.4.1. Effective rate. Thirteen RCTs (997 patients) reported effective rate.[9–21] The heterogeneity test analysis showed that the 13 RCTs were homogeneous (P = 0.99, I² = 0%). Therefore, the fixed-effect model is used to combine and for analysis. The meta-analysis results showed that the combined analysis effect of the VD effective rate in the experimental group was (OR = 3.31, 95%CI [2.36, 4.65], P < 0.00001), and the difference was statistically significant, revealing that the effective rate of the experimental group was higher than that of the control group (Fig. 3).

3.4.2. HDS score. Five RCTs (457 patients) reported HDS score.[9, 12–14, 20] The heterogeneity test analysis showed that the 5 RCTs were homogeneous (P = 0.77, I² = 0%), so that the...
fixed-effect model was adopted for the combined analysis. Meta-analysis results showed that the combined effect of HDS score after treatment with VD in the experimental group was \( \text{SMD} = 0.53, 95\% \text{CI} [0.34, 0.72], P < 0.00001 \), and the difference was statistically significant, indicating that the HDS score of the experimental group was better than that of the control group (Fig. 4).

3.4.3. MMSE score. MMSE score were reported in thirteen RCTs (997 patients).\(^{[9–21]}\) The heterogeneity test analysis showed that there was homogeneous among the 13 RCTs (\( P = 0.18, I^2 = 26\% \)), so that the fixed-effect model was used to combine the analysis. Meta-analysis results showed that the combined effect of MMSE score after treatment with VD in the experimental group was \( \text{SMD} = 0.66, 95\% \text{CI} [0.53, 0.79], P < 0.00001 \), and the difference was statistically significant, indicating that MMSE score of the experimental group was higher than that of the control group (Fig. 5).

3.4.4. ADL score. Eleven RCTs (769 patients) reported ADL score.\(^{[9–16, 18–19, 21]}\) The heterogeneity test analysis showed that the eleven RCTs had heterogeneity (\( P < 0.00001, I^2 = 90\% \)), so the random effect model was used to combine the analysis. Meta-analysis results showed that the combined effect of ADL score after treatment with VD in the experimental group was \( \text{SMD} = -0.29, 95\% \text{CI} [-0.75, 0.17], P = 0.21 > 0.05 \), and the difference was statistically insignificant. This illustrated that the ADL score of the experimental group was not necessarily better than that of the control group after treatment (Fig. 6).

3.4.5. SS level. Two RCTs (152 patients) reported SS level.\(^{[9, 14]}\) The heterogeneity test analysis showed that the 2 RCTs were homogeneous (\( P = 0.91, I^2 = 0\% \)), so the fixed-effect model was used to combine the analysis. Meta-analysis results showed that the combined effect of SS level after treatment with VD in the experimental group was \( \text{SMD} = 0.52, 95\% \text{CI} [0.19, 0.84], P = 0.001 < 0.05 \), and the difference was statistically significant, testifying that the SS level of the experimental group was possibly better than that of the control group after treatment (Fig. 7).

3.4.6. AVP level. Two RCTs (152 patients) reported AVP level.\(^{[9, 14]}\) The heterogeneity test analysis showed that the 2 RCTs were homogeneous (\( P = 0.95, I^2 = 0\% \)), so the fixed-effect model was used to combine the analysis. Meta-analysis results showed that the combined effect of AVP level after treatment with VD in the experimental group was \( \text{SMD} = 0.53, 95\% \text{CI} [0.34, 0.72], P < 0.00001 \), and the difference was statistically significant, indicating that the AVP level of the experimental group was better than that of the control group (Fig. 8).
results showed that the combined effect of AVP level after VD in the experimental group was (SMD = 4.45, 95%CI [3.84, 5.05], \( P < 0.00001 \)), and the difference between the 2 groups was statistically significant, certifying that the AVP level in the experimental group was possibly better than that in the control group (Fig. 8).

3.4.7. SDSVD level. SDSVD level were reported in 2 RCTs (136 patients).\(^{10, 21} \) The heterogeneity test analysis showed that the 2 RCTs were homogeneous (\( P = 0.23, I^2 = 32\% \)), so the fixed-effect model was used to combine the analysis. Meta-analysis results showed that the combined effect of SDSVD level after treatment of VD in the experimental group was (SMD = –1.05, 95%CI [–1.41, –0.69], \( P < 0.00001 \)), and the difference was statistically significant, indicating that the SDSVD level of the experimental group was possibly better than that of the control group after treatment (Fig. 9).

3.4.8. Sensitivity analysis. The effective rate was selected as the research object, and the sensitivity analysis of meta-analysis results was carried out for the 13 included RCTs, using article by article exclusion method. The results showed that, after the exclusion of each article, the effective rate difference was statistically significant (\( P < 0.00001 \)), and the OR of the combined effect of the calculation model is relatively stable, indicating that the homogeneity among studies is strong and the meta-analysis results are stable (Table 2).
Figure 5. Forest plot of meta-analysis of the MMSE scores in VD patients of the 2 groups.

Figure 6. Forest plot of meta-analysis of the ADL scores in VD patients of the 2 groups.

Figure 7. Forest plot of meta-analysis of the SS level in VD patients of the 2 groups.

Figure 8. Forest plot of meta-analysis of the AVP level in VD patients of the 2 groups.
3.4.9. Publication bias analysis. Most of the included trials were of poor quality, and many studies did not describe allocation concealment. Because of the special properties of moxibustion, it is very difficult for patients and practitioners to use blind study methods. Select the effective rate as the index to draw the inverted funnel plot (Fig. 10). As can be seen from the figure, the funnel plot shows that the scatter point distribution is basically symmetric, indicating that publication bias is not apparent. However, there were also some problems such as low methodological quality and unpublished negative result tests in the studies.

4. Discussion

“All diseases are blocked by qi and blood, and can not be publicized; Enlighten it with needles, and warm it with moxibustion.” Moxibustion or medicine is used as moxibustion materials, and fumigation moxibustion is carried out at acupuncture points or diseased parts to heat meridians, harmonizing qi and blood, eliminating pathogenic factors and strengthening body resistance. VD belongs to the category of “dementia” in traditional Chinese medicine. The etiology and pathogenesis of VD are mostly deficiency of blood stasis, which is the syndrome of deficiency of essence and excess. The treatment should focus on “removing blood stasis, dredging collaterals, replenishing essence and marrow.” Modern research has found that pressing moxibustion at important acupoints of cerebrovascular diseases can directly reach the brain, promote blood circulation, increase blood flow, improve blood vessel elasticity, and thus improve the blood supply of damaged brain. At the same time, moxibustion itself has antiinflammatory effects. It is found that it can play a role in the

Table 2

Results of sensitivity analysis of the included literature for analysis of effective rates.

| Deleted literature | OR (95%CI)     | Z-value | P-value |
|-------------------|---------------|---------|---------|
| Wang 2010         | 3.35 [2.35, 4.77] | 6.70    | <0.0001 |
| Zhu 2013          | 3.38 [2.37, 4.62] | 6.72    | <0.0001 |
| Sheng 2017        | 3.35 [2.35, 4.77] | 6.71    | <0.0001 |
| Wang 2009 [2]     | 3.32 [2.34, 4.75] | 6.67    | <0.0001 |
| Wang 2009 [2]     | 3.36 [2.35, 4.81] | 6.64    | <0.0001 |
| Chen 2011         | 3.44 [2.39, 4.94] | 6.69    | <0.0001 |
| Wang 2020         | 3.26 [2.30, 4.62] | 6.62    | <0.0001 |
| Li 2010           | 3.36 [2.38, 4.76] | 6.84    | <0.0001 |
| Hao 2017          | 3.19 [2.25, 4.52] | 6.54    | <0.0001 |
| Wang 2017         | 3.24 [2.28, 4.61] | 6.58    | <0.0001 |
| Ma 2018           | 3.47 [2.44, 4.94] | 6.90    | <0.0001 |
| Kuang 2012        | 3.17 [2.23, 4.51] | 6.42    | <0.0001 |
| Wang 2018         | 3.20 [2.25, 4.56] | 6.45    | <0.0001 |

Figure 9. Forest plot of meta-analysis of the SDSVD level in VD patients of the 2 groups.

Figure 10. Funnel plot.
inflammatory cascade reaction of VD. Therefore, this study systematically evaluated the effectiveness and safety of moxibustion in the treatment of vascular dementia from the perspective of evidence-based medicine through literature excavation.

Meta-analysis showed that the RCTs of moxibustion for VD had high homogeneity in effective rate, HDS score, MMSE score, SS level, AVP level and SDSVD level, and the difference between the experimental group and the control group was statistically significant. This would suggest that moxibustion therapy for VD had better efficacy than traditional acupuncture, western medicine or Chinese drugs treatments alone. When analyzing the combined effect of ADL score, the included studies showed great heterogeneity. However, due to the clinical homogeneity of all the included studies, the difference between the 2 groups was statistically insignificant after the combination of the random effect model. These results suggest that ADL score was not necessarily significantly enhanced after treatment of VD patients with moxibustion. Because only 2 included RCTs mentioned SS level, AVP level and SDSVD level, moxibustion may not be superior to other treatments for VD at these levels, and it is necessary to expand the sample for study. Among the thirteen included RCTs, no adverse reactions were reported in either of the 2 groups, indicating a high safety factor for moxibustion treatment.

The quality of the studies included in this meta-analysis was uneven, but the funnel plot showed that the scatter point distribution was basically symmetrical, so it is believed that the study had low levels of bias, and in general had certain credibility for the meta-analysis results. The specific limitations of this study are as follows: (1) most of the included studies described the randomization method of research methodology and the implementation of distributive hidden and blind method were rough, so it is difficult to judge the risk of bias; (2) among the evaluated RCTs in this system, the inclusion criteria of VD patients is not unified, so that the VD patients studied in each RCTs are different; (3) only 2 of the included RCTs mentioned SS, AVP and SDSVD levels; (4) as there is no definite and standardized treatment for VD, the design scheme of the control group is not unified, and subsequently there is no recognized control scheme. Nevertheless, based on the current clinical evidence, the results of this study can still provide a certain reference for the clinical treatment of VD, and also the conclusion that moxibustion has a defined clinical effect on VD is scientifically established.

5. Conclusions
In this systematic review, we comprehensively evaluated the therapeutic effects of moxibustion, which was found to be more effective than Chinese drugs, western medicine and acupuncture in improving the symptoms of Vascular dementia (VD). However, due to the low quality of evidence and heterogeneity, this hypothesis needs to be confirmed by further studies.

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