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Meta-analysis of Acupuncture Combined with Cognitive Rehabilitation Training in the Treatment of Cognitive Impairment after Stroke

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Abstract: To systematically review the clinical efficacy and safety of acupuncture combined with rehabilitation training in the treatment of post-stroke cognitive impairment (PSCI). Chinese and English databases such as CNKI, Wanfang database, CBM, PubMed, Embase and The Cochrane Library were searched for randomized controlled trials of acupuncture combined with rehabilitation training in the treatment of PSCI. RevMan 5.4 was used to evaluate the quality of the literature and Meta analysis. Publication bias was determined by Egger test and funnel plot. A total of 30 RCTS were included with 2506 participants. The results of Meta-analysis showed that acupuncture combined with rehabilitation training was superior to the single treatment group in improving the effective rate, increasing the Montreal cognitive assessment (MoCA) score and BI index, reducing P300 delay and increasing P300 amplitude. Acupuncture combined with rehabilitation training has significant clinical effect in the treatment of PSCI, and the combination of the two has synergistic effect, and it is worthy of further study and discussion.

1. Introduction

Stroke is the chief reason of death and disability worldwide, with an epidemiological survey showing a global prevalence of 101 million people [1]. Post-stroke cognitive dysfunction (PSCI) refers to a clinical syndrome that reaches the standard within 6 months after the occurrence of cerebrovascular accidents, and is mainly manifested as visuospatial, orienting, calculating, memory and other disorders [2].There is data reports that about 1/3 of stroke patients had cognitive dysfunction [3], and the prevalence of PSCI was as high as 40% [4] and PSCI could also induce

stroke recurrence [5] .Since PSCI is the result of multiple factors, single therapy can not achieve satisfactory curative effects so the multi-mode intervention strategy has received special attention.

With people's attention to combined therapy, a good deal of clinical studies about acupuncture combined with cognitive training have appeared in recent years. Previous studies have found that compared with single treatment, acupuncture combined therapy has the advantages of alleviating adverse reactions , high patient compliance, good long-term efficacy and cost saving [6,7]. Although a Meta study [8] showed that acupuncture combined with cognitive training had better efficacy than acupuncture alone, it was published a long time ago, and there were few studies included, with limited reference value. Based on this, we hope to analyze the efficacy of acupuncture combined with cognitive training in the treatment of PSCI through statistical methods, further provide the latest evidence-based medical evidence and provide reference for clinical treatment.

2. Materials and Methods

2.1. Inclusion and Exclusion Criteria

The inclusion criteria were as follows: (1)type of studies: RCTs;(2)patients with clinically diagnosed PSCI;(3)The experimental group received acupuncture combined with cognitive training, while the control group received acupuncture or cognitive training alone, and the basic drugs of the two groups must be similar.(4)The main outcome measurements:included effective rate, MoCA;Secondary outcomes included Auditory Event-related Potential (P300) and Barthel index.

The following exclusion criteria were applied: (1) Intervention methods include moxibustion, traditional Chinese medicine, cupping, eye acupuncture, ear acupuncture and other therapies; (2) republished studies, full text unavailable or incomplete data; (3) Studies with unclear diagnosis or no relevant outcome indicators; (4) Mechanism studies, cases, reviews, guidelines and other non-clinical randomized controlled trials; (5) Study grouping was inappropriate, or cognition impairment caused by other diseases except for stroke.

2.2. Identification of Eligible Trials

We searched the Embase, PubMed, CBM,CNKI, Wanfang, VIP, and Cochrane Library in English and Chinese published on or before November , 2021.The search terms included "stroke", "cognitive impairment", "cerebrovascular accident," "cerebrovascular apoplexy," "brain vascular accident," "cognitive dysfunction ", "Mild Neurocognitive Disorder", "acopuncture", "Electroacupuncture", "scalp acupuncture ", etc.

2.3. Risk of Bias

For the included studies, RevMan 5.4, a risk bias assessment tool of the Cochrane Collaboration Network, was used for bias assessment. The relevant contents are as follows: (1) Random method; (2) allocation concealment; (3) blinding of participants ;(4)blinding of outcome assessment;(5) whether the result data is complete; (6) Selective reporting;(7)other bias. If there is disagreement in the evaluation process, the third researcher will be consulted to make a decision. The findings were classified as high, low, or undefined risk of bias.

2.4. Data Extraction

Two researchers independently screened the results according to the inclusion and exclusion criteria. If there is a dispute, a third researcher will participate in the discussion until a consensus is

reached. A self-designed data collection table was used to extract information from the final included studies, authors, publication time, diagnostic criteria, outcomes, course of treatment, adverse events, weighted.

2.5. Statistical Analysis

The Cochrane Review Manager version 5.4 software was used for evaluate the quality of the literature and Meta analysis. Measurement data were presented as weighted mean differences , and count data were presented as risk ratio, meanwhile $P < 0.05$ was considered significant. When $I^2 \leqslant 50\%$, the studies will adopt fixed-effects model. If $I^2 > 50\%$ significant heterogeneity was considered among the studies and random-effects model was adopted. When the number of articles is more than 10, we will use funnel chart to analyze the publication bias.

3. Results

3.1. Eligible Studies

The workflow of literature screening and inclusion is shown in Figure 1. According to the search strategy, a total of 2571 literatures were obtained from seven databases, and 1570 literatures remained after duplication removal. After initial screening, 1481 articles were excluded. 89 studies were excluded because they did not meet inclusion criteria, 55 articles were deleted after browsing the full text. Ultimately 30 RCTS were included with a total of 2506 patients, aged between 35 and 80 years.

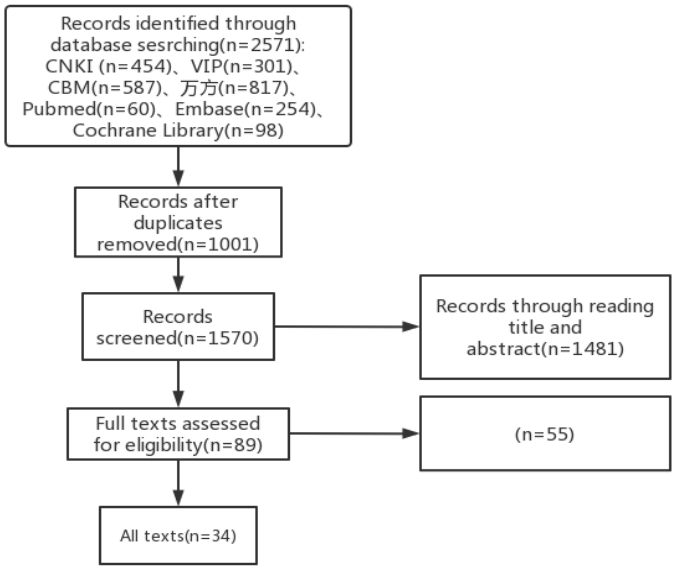

Figure 1. Literature screening flow diagram

3.2. Assessment of Risk of Bias

The 30 studies included all referred to "random assignment", but nine of them did not report the method of generating the randomized sequence in detail, so they were considered to be high-risk. Only 2 studies mentioned the implementation of allocation concealment using opaque sealed envelopes, so they were low risk. Two studies were blinded to the subjects and five studies were

blinded to the assessors and thus were low risk. All studies did not state whether there was selective reporting of results and other sources of bias, and were considered low risk Figure 2.

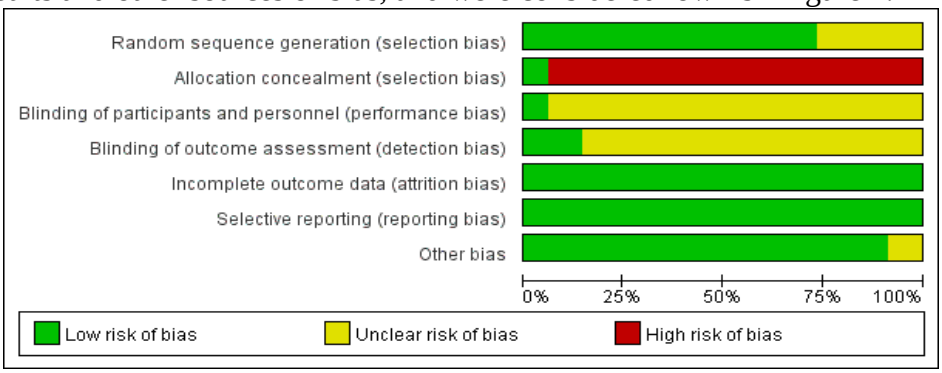

Figure 2. Risk of bias graph and summary

3.3. Effective rate

A total of 15 studies reported effective rates,As heterogeneity test I^2 =0%, fixed effects model was adopted.The results suggested that acupuncture combined with cognitive training was superior to single therapy in the treatment of PSCI(RR=1.23, 95% CI:1.17 to 1.30], *P*<0.05, I^2 =0%).

3.4. MoCA

17 studies used MoCA to assess overall cognitive function, involving 1,431 patients.Heterogeneity test I2 =78%, so we chose the random effect model, the results suggest that acupuncture combined with cognitive training is better than single therapy in the treatment of PSCI(WMD=2.96, 95%CI:2.28 to 3.63, P<0.05,I2 =78%）.In five aspects of attention, orientation, visuospatial and executive function, and language ability, the analysis of 4 studies showed that acupuncture combined with cognitive training was superior to single therapy, but for abstraction, there was no significant difference between the two (Figure 3).

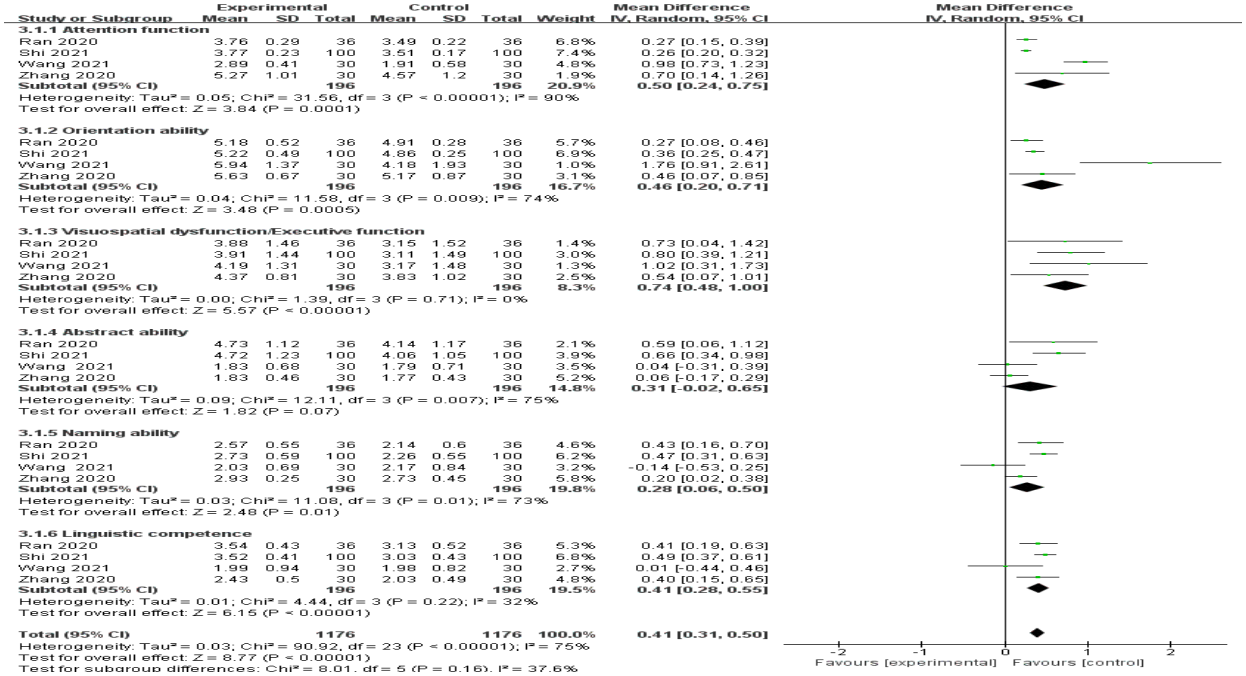

Figure 3. Forest plot of MoCA

3.5. Activities of Daily Living(ADL)

BI are widely used basic ADL measures with good reliability and validity, and can quantify functional changes after stroke rehabilitation [9,10]. 7 studies used BI involving 638 patients, meta-analysis showed WMD=7.43, 95% CI:6.21 to 8.66, $P<0.05$, $I^2= 67\%$. Sensitivity analysis was used to eliminate articles one by one, and it was found that the Xing study was the main cause of heterogeneity, which may be related to the short course of the included patients and the high risk of bias.

3.6. Auditory Event-related Potential (P300)

P300 is a mature and objective neurophysiological method, which is widely used in the assessment of cognitive function in patients with nervous system. The more severe the cognitive injury, the longer the latency, and the smaller the amplitude. A total of 3 studies documented changes in P300 latency and amplitude before and after treatment.Meta-analysis revealed that the latency (WMD=-13.75,95%CI:-24.91to -2.59,$P<0.05$, $I^2= 88\%$) and the amplitude (WMD = 0.91, 95% CI: 0.42 to 1.39, $P<0.05$,$I^2=53\%$) significantly differed between the acupuncture + cognitive training and control groups. These results indicated that acupuncture + cognitive training could effectively improve global cognition in patients with PSCI.

3.7. Publication Bias

The funnel plot of MoCA showed that most of the scattered points were in the middle and upper part, indicating that publication bias was small.And the Egger test on MoCA(P=0.72), which also confirmed the small possibility of bias(Figure 4).

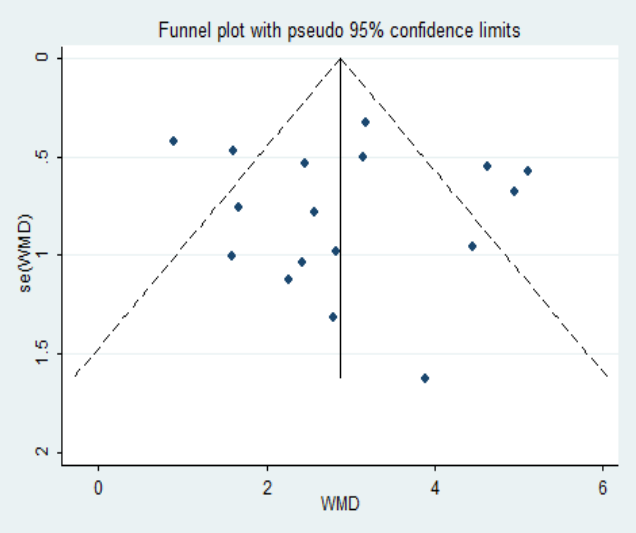

Figure 4. The funnel plot of MoCA

4. Discussion

Western medicine believes that the pathogenesis of PSCI may be related to direct damage of cognitive brain structures, neuroinflammation and cytotoxicity, damage of default and central executive network, and damage of cholinergic transmitter system [11,12].At present, the western medicine treatment of PSCI includes medicine, physical therapy, cognitive rehabilitation training and so on. The overall efficacy of drug and physical therapy is average, and there are problems such

as unclear treatment mechanism, poor safety, and high cost [13]. As a green and safe intervention, cognitive training is deeply loved by people.According to the cognitive rehabilitation theory, after a certain intense and repeated sensory stimulation and functional training, the surrounding normal brain tissue can compensate the damaged brain tissue, thereby promoting the rehabilitation of cognitive function in PSCI patients [14]. Traditional Chinese medicine believes that the occurrence of PSCI is related to the damage of brain collaterals after stroke, obstruction of meridians, loss of nourishing, and dysfunction of inherent spirit. The disease location is in the brain, and the disease character is virtual real , real isblood stasis and phlegm [15]. Acupuncture is the most common therapy with obvious advantages in improving intelligence, stimulating consciousness and enhancing memory and other cognitive fields. Modern studies have found that acupuncture can improve cognitive impairment after stroke by regulating signaling pathways [16], affecting the expression of related proteins [17], restoring vascular endothelial function [18,19], and increasing the functional connectivity of brain network [20]. Numerous studies [21-23] have shown that acupuncture combined with cognitive training has the best efficacy compared with acupuncture alone.

The results showed that the combined group was superior to the single treatment group in improving the total effective rate, increasing the score of MoCA, BI, and P300 amplitude, and reducing the delay of P300. And indicated that acupuncture combined with cognitive training had certain advantages over the single therapy in PSCI treatment, and also indicated that acupuncture and cognitive training were synergistic. Acupuncture and cognitive training may affect brain plasticity through different and complementary pathways, that is, acupuncture induces physiological changes (up-regulation of brain-derived neurotrophic factor and stimulation of hippocampal neurogenesis) , and in turn, promotes neuroplastic effects after cognitive training, thereby producing therapeutic effects on functional impairment in neurological diseases. But, some of the included studies exist interference factors. In terms of stroke type, all 12 studies involved ischemic stroke patients; 15 studies included patients with bleeding and ischemic stroke, and 3 studies included only post-stroke patients. In addition, there were differences in basic treatment, rehabilitation programs, education level and stroke period among different studies. However, the funnel plots of effective rate existence of publication bias, indicating that the objectivity of the data needs further discussion.

Our systematic review has the following limitations: (1) Although random allocation method was mentioned in all the included studies, the implementation process was not specifically described, and most of the studies did not implement allocation hiding and blind method1, which had a high risk of bias; (2) Insufficient sample size and lack of sample size estimation in the included study reduced the reliability of the conclusions of this study to some extent; (3) Many studies cannot be combined and analyzed due to differences in the degree of cognitive impairment, intervention programs and efficacy evaluation criteria included in the studies; (4) Acupuncture frequency, acupuncture depth, stimulation site, number of acupuncture points and basic treatment were different in different studies, and there was great clinical heterogeneity. (5)There is a lack of reliable data to support the long-term efficacy of the combined effect. It is hoped that more scientific evidence-based medical evidence can be provided in the future,including time after stroke occurrence, frequency of treatment, duration of treatment, and follow-up reports.

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If any, should be placed before the references section without numbering.

Data Availability

Data sharing is not applicable to this article as no new data were created or analysed in this

study.

Conflict of Interest

The author states that this article has no conflict of interest.

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