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Original Research Article

A meta-analysis of the efficacy of Buyang Huanwu decoction in the treatment of ischemic stroke

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Abstract

Purpose: *This meta-analysis was aimed at investigating the efficacy and safety of Buyang Huanwu decoction in the management of ischaemic stroke.*
Methods: *Randomized controlled trials (RCTs) on the clinical efficacy of Buyang Huanwu decoction for ischemic stroke patients were searched in PubMed, Cochrane Library, Embase, China Knowledge Infrastructure (CNKI), China Science and Technology Journal Database and Wanfang Database. The search period was from 1 January 2010 to 31 July 2023, and the parameters evaluated included efficacy, limb motor function score, National Institutes of Health Stroke Scale (NIHSS) score, and adverse drug reactions. Relevant data were extracted, assessed for quality, and analyzed using RevMan 5.2.*
Results: *The inclusion criteria were met by nine RCTs, encompassing a total of 883 participants. The meta-analysis revealed that Buyang Huanwu decoction significantly enhanced motor function recovery, reduced neurological impairment, decreased the incidence of adverse reactions, elevated ADL scores, and an overall increase in clinical effectiveness ($p < 0.05$). Additionally, there was a significant decrease and increase in TCM symptom scores and FMA scores respectively ($p < 0.05$).*
Conclusion: *Buyang Huanwu decoction improves clinical outcomes and motor functions in patients with ischaemic stroke. It is important to expand this study to include larger sample sizes, longer follow-up periods, and a broader scope of literature to validate its findings.*

Keywords: *Ischaemic stroke, Cerebral infarction, Buyang Huanwu decoction, Meta-analysis, Randomized controlled trials*

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INTRODUCTION

Stroke, often referred to in traditional Chinese medicine as a collective term for sudden cerebrovascular incidents, is primarily characterized by disruptions in cerebral blood flow leading to hemiparesis. Symptoms include abrupt loss of consciousness, difficulty speaking, facial asymmetry, and paralysis [1]. Strokes are categorized into hemorrhagic and ischemic types. Clinically, the progression of stroke is segmented into three stages based on the time elapsed since onset, and this includes; the acute phase (within two weeks), recovery phase (from two weeks to six months), and chronic or sequelae phase (beyond six months) [2,3]. As a result of the high mortality rate, disability, recurrence, and associated complications, stroke

is acknowledged as a fundamental public health challenge, ranking alongside cancer and coronary artery disease as a leading threat to global health [4]. *Buyang Huanwu* decoction, a traditional Chinese medicinal formula, is composed of seven ingredients namely; *Astragalus membranaceus*, *Angelica sinensis*, *Radix paeoniae* Rubra, *Ligusticum chuanxiong*, peach kernel, safflower, and earthworm [5]. This blend of seven distinct ingredients works synergistically to replenish vital energy, improve blood circulation, dissolve blood clots, and open the body's meridians [6]. Despite numerous randomized and semi-randomized controlled trials investigating its effectiveness and safety in aiding recovery from ischemic stroke, the varied metrics for evaluating efficacy and predominance of small-scale studies have led to questions regarding the reliability of these findings. This lack of comprehensive, systematic reviews has prompted the current meta-analysis of clinical trials on *Buyang Huanwu* decoction, aiming to provide a stronger, evidence-based foundation for its clinical use in treating ischemic stroke.

METHODS

Search strategy

Chinese databases such as China National Knowledge Infrastructure (CNKI), Wanfang Data, VIP database, China Biology Medicine Disc (CBMdisc) and English databases such as PubMed, Embase, and Cochrane Library were searched. The search terms were *Buyang Huanwu* tang, ischemic stroke, cerebral infarction, and randomized. The search was done between January 1, 2010 to July 31, 2023. According to different database conditions, subject words and free words were searched comprehensively to ensure systematization and completeness.

Inclusion criteria

Randomized controlled trials (RCTs) were included, in which participants were allocated to either treatment or control groups based on randomization criteria such as order of hospital admission, admission number, or date of birth. The studies varied in their methodology, encompassing those with and without concealment of allocation and blinding. Only trials published in Chinese or English were considered.

Exclusion criteria

Exclusion criteria included studies with repeated publications or those presenting incomplete data, clinical studies that were not randomized controlled trials (RCTs), studies including patients who had serious complications, non-empirical literature such as reviews, theories, reports, case analyses, and animal experiments.

Research subjects

The participants were confirmed to have met established and reputable diagnostic standards for stroke, as defined by the World Health Organization [7]. Diagnosis of ischemic stroke was made within 2 weeks to 6 months after onset, verified through imaging techniques such as computed tomography (CT) and magnetic resonance imaging (MRI), with no restrictions on age or gender.

Intervention measures

Treatment group received *Buyang Huanwu* decoction, which was administered based on traditional Chinese medicine (TCM) syndrome differentiation. Conversely, control group was subjected to various alternative treatments, which included a placebo or no intervention at all.

Evaluation of parameters/indices

(NIHSS) score

Criteria for meta-analysis encompassed several key indicators which include National Institutes of Health Stroke Scale (NIHSS) score which assesses the severity of stroke symptoms.

Activities of daily living (ADL) scale

Activities of daily living (ADL) scale measures the ability of individuals to perform everyday tasks independently.

Adverse drug reactions

Adverse drug reactions such as nausea and retching that occur after medication were compiled.

Overall therapeutic effectiveness

Traditional Chinese medicine (TCM) symptom score was used in quantifying improvement in symptoms according to TCM principles.

Limb motor function score

Limb motor function score was obtained using the Fugl-Meyer Assessment (FMA) to evaluate recovery in motor function after stroke.

Literature screening and data extraction

Trained in evidence-based methodologies, researchers independently conducted literature screening, data extraction, and verification following the inclusion and exclusion criteria. Discrepancies in evaluations were resolved through discussion or by consulting an additional researcher for a decision. Extracted data include:

Study identification

This included the first author's name and year of publication.

Subject information

This includes the gender, age, and smoking status of the participants.

Disease inclusion criteria

The specific criteria used to include patients with stroke disease in the study.

Group data

Information on follow-up duration, sample size, interventions applied (treatment plans), and outcome measures that were assessed.

Literature quality evaluation

The Cochrane Handbook 5.1.0 bias risk evaluation tool was used to assess the integrity of randomized controlled trials [8]. This assessment covered various aspects, such as randomized sequence creation, allocation concealment, blinding of both participants and personnel, outcome data completeness, result reporting bias, and additional potential biases. Evaluators classified each aspect as either low risk of bias, high risk of bias, or unclear risk of bias. Studies that completely adhered to these criteria were deemed to have a low bias likelihood, receiving an A grade for quality. Those meeting the criteria to a lesser extent were considered to have a moderate bias risk, while studies failing to meet the criteria were viewed as having a high risk of bias, meriting a C grade for quality.

Statistical analysis

Analysis was conducted with RevMan 5.2 software, and heterogeneity was assessed using I^2 statistic and chi-square test. Significant heterogeneity was identified if $p < 0.05$ or I^2 statistic > 50 %, prompting the use of a random effects model for synthesis. Conversely, a fixed effects model was applied in the absence of significant heterogeneity. Study outcomes for categorical data were quantified using the risk ratio (RR) at 95 % confidence interval (CI). To verify the robustness of the findings, sensitivity analyses were undertaken by omitting specific studies for a subsequent re-evaluation. Furthermore, examination of funnel plots facilitated the assessment of potential publication bias.

RESULTS

Literature search outcomes

In the initial search, 512 articles were identified, with an additional 3 articles added through alternative methods, bringing the total to 515. Utilizing EndNoteX9 software, 78 articles were selected for closer examination. After reviewing titles, abstracts, and full texts, 69 articles were excluded for not meeting the inclusion criteria, leaving 9 articles for inclusion. Selection process and summaries of included studies are presented in Figure 1 and Table 1, respectively.

Risk of bias

Bias risk for included studies was evaluated using a table recommended in the Cochrane Reviewers' Handbook. Each of these studies was deemed to be of high quality, exhibiting low risk of implementation bias, measurement bias, and follow-up bias (Figure 2).

National Institutes of Health Stroke Scale (NIHSS)

Nine studies presented data on NIHSS scores in patients treated with BYHWD in addition to standard therapy compared to standard therapy alone. Due to the heterogeneity test results between studies ($p < 0.001$, $I^2 = 95$ %), a random effect model was used. Results of the meta-analysis showed that NIHSS score of experimental group was significantly lower compared to control group (mean difference = -1.23, 95 % CI: -2.24, -0.22, $p < 0.05$) (Figure 3).

Adverse drug reactions

Adverse drug reactions (ADRs) after treatment were documented in five studies. Given the outcomes of heterogeneity tests among these studies ($p = 0.37$, $I^2 = 0$ %), indicating no significant heterogeneity, a fixed-effect model was applied for the analysis. The results showed that ADR in study group was significantly lower compared to control group (mean difference = 0.32, 95 % CI (0.11, 0.93), $p < 0.05$; Figure 4).

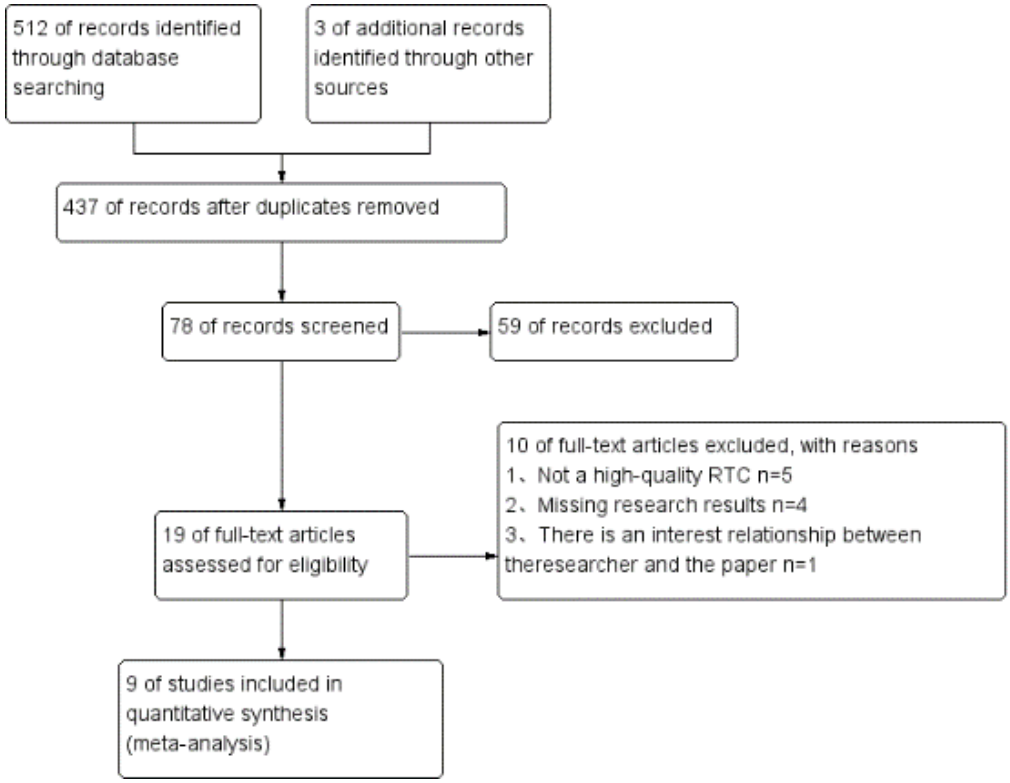

Figure 1: Flowchart of literature screening

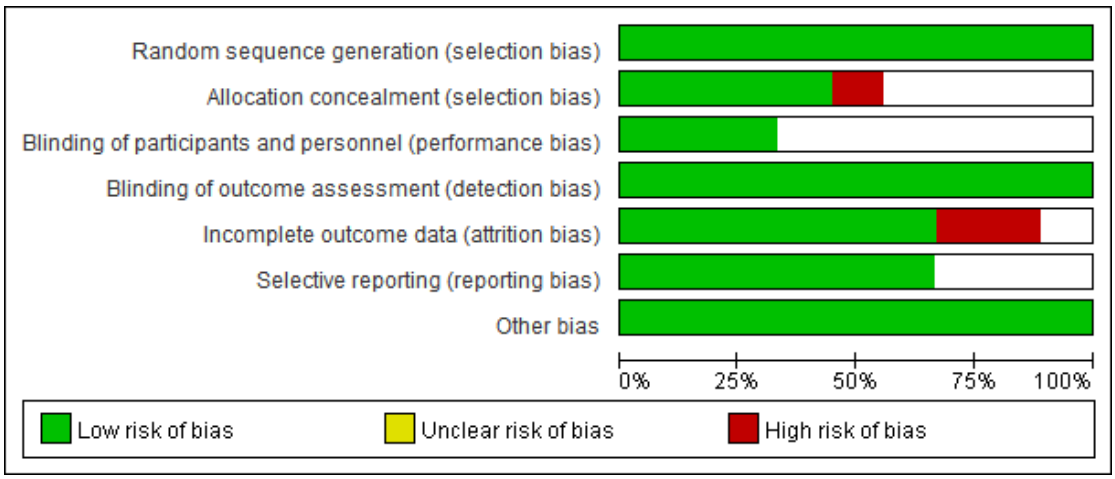

Figure 2: Summary of risk bias

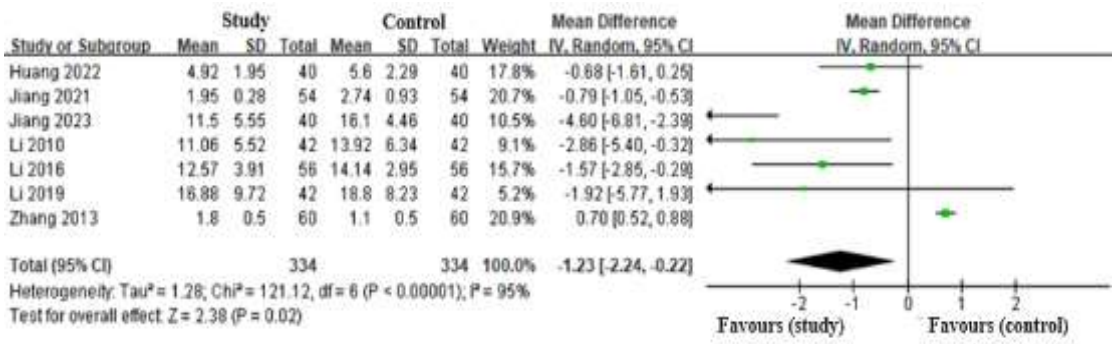

Figure 3: Forest plots of comparative reduction in NIHSS scores between study and control groups

Table 1: Basic characteristics of the included literature (n = 9)

Studies	Number of people		Sex		Age		Treatment time	Treatment means	
	Groups		***Groups***		***Groups***			***Groups***	
	Study	*Control*	*Study*	*Control*	*Study*	*Control*		*Study*	*Control*
Jiang, 2021 [9]	54	54	30/24	32/22	75.23±5.64	75.39±5.72	12 weeks	BHD	Traditional Western medicine treatment
Huang, 2022 [10]	40	40	23/17	21/19	63.37±8.68	63.27±8.66	7 days	BHD	Traditional Western medicine treatment
Jiang, 2023 [11]	40	40	25/15	23/17	67.54±2.6	68.31±2.44	2 weeks	BHD+ acupuncture	Traditional Western medicine treatment, acupuncture
Tan, 2023 [12]	51	51	32/19	29/22	66.8±3.13	65.9±3.05	4 weeks	BHD+ acupuncture	Traditional Western medicine treatment, acupuncture
Wang, 2018 [13]	56	56	33/23	34/22	69.04±9.27	68.75±8.61	3 weeks	BHD+ Western medicine treatment	Traditional Western medicine treatment
Li, 2016 [14]	43	42	25/18	23/19	67.12±3.41	61.26±4.16	8 weeks	BHD	Traditional Western medicine treatment
Zhang, 2013 [15]	60	60	29/31	32/28	58.20±10.13	59.41± 9.84	6 months	BHD	Traditional Western medicine treatment
Li, 2010 [16]	56	56	31/25	30/26	59.1±5.1	57.9±6.5	30 days	BHD	Traditional Western medicine treatment
Li, 2019 [17]	42	42	23/19	24/18	54.34±8.22	4.52±8.16	4 weeks	BHD	Traditional Western medicine treatment

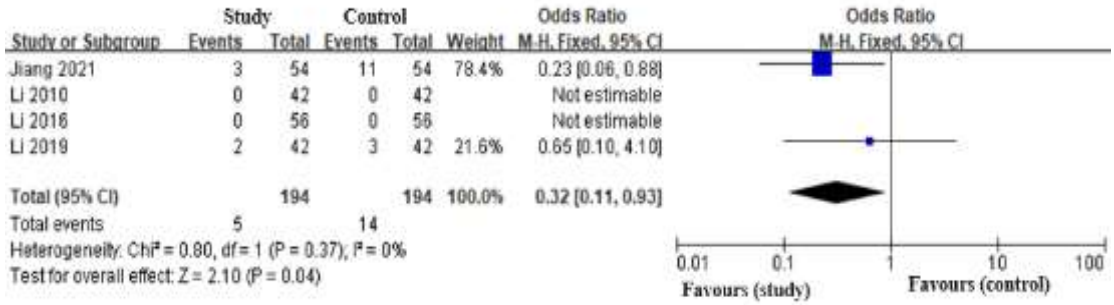

Figure 4: Forest plot demonstrating a significant reduction in ADRs in study group compared to control group

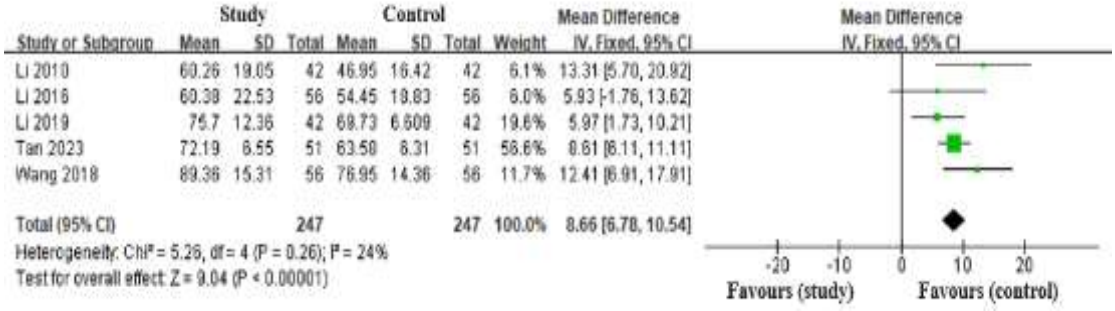

Figure 5: Forest plot illustrating the significant improvement in ADL scores in study group compared to control group

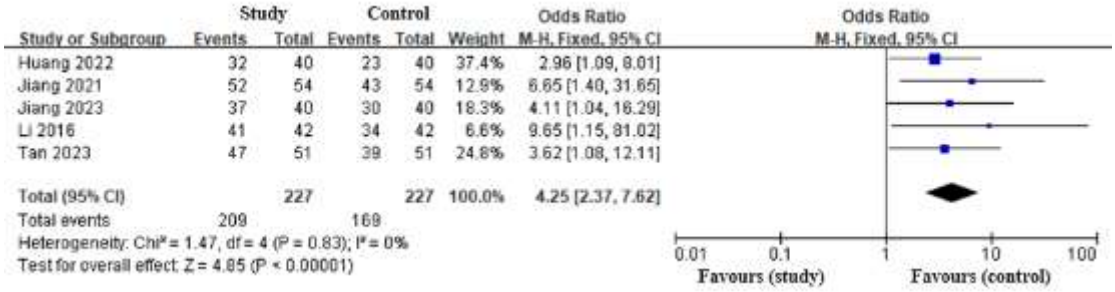

Figure 6: Forest plot displaying significantly higher clinical efficacy of study group compared to control group

Activities of daily living (ADL)

Seven research articles documented the scores of activities of daily living (ADL) after treatment. Given the moderate level of heterogeneity observed among these studies (p = 0.26, I^2 = 24 %), analysis was conducted using the fixed effect model. The results revealed that ADL scores in study group were significantly higher compared to control group (mean difference = 8.38, 95 % CI (6.63, 10.14), p < 0.001) (Figure 5).

Efficacy

Five studies evaluated the clinical effectiveness of *Buyang Huanwu* decoction in treating ischemic stroke. Absence of significant heterogeneity among these studies (p = 0.83, I^2 = 0 %) warranted the use of a fixed effect model for the analysis. Findings indicated that study group showed significantly higher clinical effectiveness compared to control group (mean difference = 4.25, 95 % CI (2.37, 7.62), p < 0.001) (Figure 6).

Traditional Chinese medicine (TCM) symptom score

Two studies documented the traditional Chinese medicine (TCM) symptom scores after treatment. The heterogeneity test indicated considerable variability among the studies (p = 0.05, I^2 = 74 %), prompting the use of a random effects model for analysis. The result revealed that the TCM symptom score in study group was significantly lower compared to control group (mean difference = -3.92, 95 % CI (-6.50, -1.35), p < 0.05) (Figure 7).

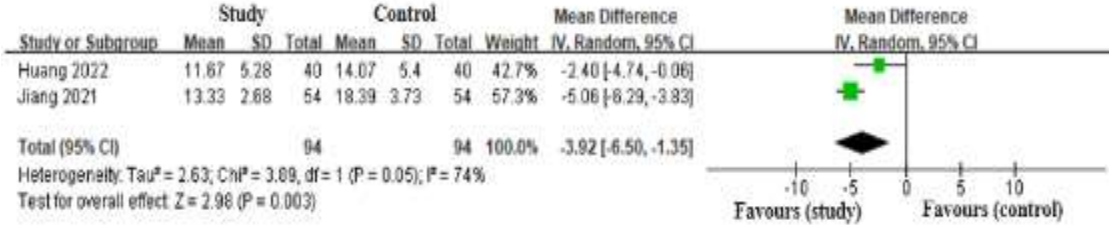

Figure 7: Forest plot results indicating significant improvement in TCM symptom scores study group compared to control group

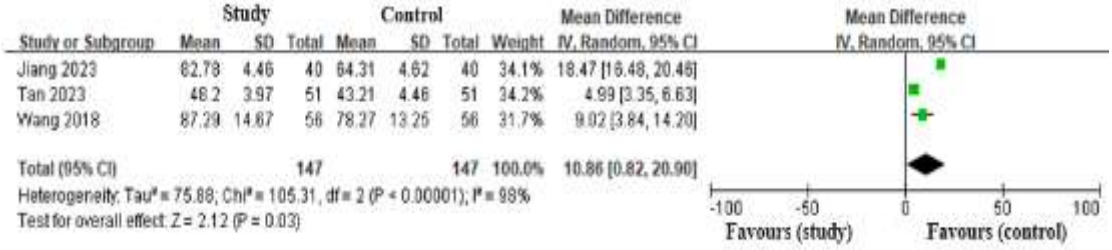

Figure 8: Forest plot results indicating significant improvement in FMA scores for study group compared to control group

Fugl-Meyer assessment (FMA)

Three studies reported FMA scores of patients after treatment. Due to heterogeneity between the studies ($p < 0.001$, $I^2 = 98$ %), the random effect model was used for the analysis. The results showed that study group had a significantly higher FMA score compared to control group (mean difference = 10.86, 95 % CI (0.82, -1.35), $p < 0.05$) (Figure 8).

DISCUSSION

Ischemic stroke is a significant global health challenge, posing a serious threat to human life and well-being. It remains a pivotal area of focus and complexity within medical research. As medical science evolves, the array of treatment options for ischemic stroke expands, with traditional Chinese medicine (TCM) playing a crucial role. Numerous studies have validated the efficacy of TCM in enhancing neurological and motor functions in ischemic stroke patients, thereby improving daily life quality and neuroprotection [18]. In TCM philosophy, the concepts of qi (vital energy) and blood are intricately linked; and proper circulation of qi ensures blood flow, while qi deficiency leads to impaired blood circulation, resulting in blood stasis. This stasis obstructs veins, disrupts the harmony of qi and blood, and directly impacts the brain, causing stroke through intracranial blood stasis or hemorrhage. The principles of traditional Chinese medicine focus on enriching qi, strengthening the body, promoting blood circulation, eliminating blood stasis, and clearing the meridians [19]. *Buyang Huanwu* decoction, a quintessential formula for augmenting qi and stimulating blood circulation, embodies these principles. It is extensively employed in both prophylaxis and therapy of ischemic stroke, recognized for its capabilities to fortify qi, invigorate blood flow, and unblock meridians [20].

This meta-analysis revealed that combining *Buyang Huanwu* decoction with acupuncture significantly enhances overall treatment effectiveness in patients with ischemic stroke compared to control group. Improvements were noted in neurological deficit scores, daily living abilities, adverse drug reactions, traditional Chinese medicine symptom scores, and limb motor function scores after treatment. The observed high heterogeneity among the studies might stem from variances in sensitivity of the instruments and methodologies applied by researchers, details of which were not thoroughly described in the original studies. As a result of this, further sub-group analyses were not feasible.

Meta-analysis of the total clinical efficacy rate indicated that *Buyang Huanwu* decoction significantly improved the overall clinical success rate in treating ischemic stroke patients. Additionally, the analysis revealed that *Buyang Huanwu* decoction significantly reduced neurological deficit scores. In the composition of *Buyang Huanwu* decoction, raw astragalus, with

its sweet and warm properties, is utilized to enhance vital energy, ensuring that qi flows vigorously to promote blood circulation, disperse blood stasis, and clear the meridians. Angelica root is known for its ability to stimulate blood circulation without harming the blood itself. Ingredients such as red peony, chuanxiong rhizome, peach kernel, and safflower are recognized for their roles in activating blood circulation and dissolving blood stasis. These components collectively contribute to inhibiting blood coagulation system, extending prothrombin time, safeguarding the blood-brain barrier, and minimizing cerebral infarction areas. This mechanism aids in alleviating neurological deficit symptoms and enhancing neurological functions [21].

Stroke often leads to varying degrees of limb motor dysfunction, and the Fugl-Meyer assessment (FMA) score is a comprehensive indicator of limb motor capabilities, known for its reliability and validity. This study revealed that study group showed significantly higher FMA scores compared to control group, suggesting that *Buyang Huanwu* decoction effectively enhances motor function in ischemic stroke patients. According to traditional Chinese medicine, post-stroke limb dysfunction primarily results from qi and blood deficiency, leading to circulation obstruction. The inclusion of astragalus in *Buyang Huanwu* decoction plays a crucial role in replenishing vital energy, thereby facilitating recovery of motor functions after stroke. Consequently, *Buyang Huanwu* decoction may be integrated with conventional Western medicine for the clinical management of motor dysfunction following an ischemic stroke.

Limitations of this study

Despite efforts to minimize the impact of statistical heterogeneity and ensure the stability and reliability of the findings, this study encountered several limitations due to clinical and methodological heterogeneity. The analysis was limited to published literature, potentially introducing publication bias. This could arise from delays in publication due to negative results or from the exclusion of studies published in languages other than those searched, leading to an incomplete dataset. Also, many of the studies included did not provide long-term follow-up data for patients with ischemic stroke. Considering the complexity and variability of stroke symptoms and the time required for recovery and stabilization of neurological deficits, a longer follow-up period is essential to comprehensively evaluate therapeutic effects on neurological recovery. The studies incorporated into this meta-analysis generally had small sample sizes, which may limit the generalizability and strength of the findings. Furthermore, for certain outcomes, the number of available studies was too limited, making it difficult to access original data for a more thorough analysis. These limitations highlight the need for caution when interpreting the results.

CONCLUSION

Buyang Huanwu decoction enhances clinical outcomes for patients with ischemic stroke, and improves neurological deficits and limb motor functions, with a favorable safety profile. There is therefore a pressing need for future research involving large-scale, high-quality clinical randomized controlled trials to offer more robust evidence for clinical practice. Such studies are essential to further validate the therapeutic benefits and safety of *Buyang Huanwu* decoction in the treatment of ischemic stroke.

DECLARATIONS

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Ethical approval

None provided.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them.

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