Efficacy and Safety of Tianma Gouteng Decoction in the Treatment of Intracerebral Hemorrhage: A Systematic Review of Randomized Controlled Trials

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Abstract: Objective: To systematically evaluate the efficacy and safety of Tianma Gouteng Decoction (TMGTY) in the treatment of intracerebral hemorrhage (ICH). Methods: Eight databases, including CNKI, Wanfang, VIP, China Biomedical, PubMed, Cochrane, EMBASE, and Web of Science, were searched up to February 25, 2023. Two investigators independently screened articles, extracted data, evaluated quality, and performed a systematic review or meta-analysis. Results: 11 randomized controlled trials with 977 patients were included. Compared with conventional treatment alone, the combination of TMGTY with conventional treatment improved NIHSS scores (MD=-3.86, 95% CI: -6.42, -1.31, P=0.003), treatment efficiency (RR=1.19, 95% CI: 1.13, 1.26, P<0.00001), and Barthel Index scores (MD=11.48, 95% CI: 9.71, 13.24, P<0.00001), while reducing complication rates (RR=0.24, 95% CI: 0.13, 0.45, P<0.00001), IL-6 (MD=-11.20, 95% CI: -13.84, -8.57, P<0.00001), and TNF-α levels (MD=-13.88, 95% CI: -16.73, -11.02, P<0.00001). Conclusion: Current clinical evidence suggests that TMGTY combined with conventional treatment is safe and effective in the treatment of ICH, more high-quality randomized controlled clinical trials are needed to validate and support the findings.

***Keywords*:** traditional Chinese medicine, Tianma Gouteng Decoction, intracerebral hemorrhage

1. Introduction

Intracerebral hemorrhage (ICH) is bleeding caused by the rupture of a nontraumatic blood vessel in the brain parenchyma. ICH accounts for 10-20% of total stroke incidence in Western populations and is higher in Asian populations (Tsai et al., 2017)[1]. Although ICH incidence is lower than ischemic stroke, its mortality and disability rates are significant (Xu et al., 2017)[2]. ICH can lead to sequelae such as cognitive impairment, seizures, and psychiatric disorders, imposing mental, quality of life, and financial burdens on patients (Pinho et al., 2019)[3]. Current treatment focuses on blood pressure control, coagulation correction, hematoma removal, and complication prevention, but challenges remain, especially in clinical prognosis (Garg and Biller, 2019; Hostettler et al., 2019; Montaño et al., 2021)[4]. There is great societal value in continuing to seek effective drugs for ICH treatment.

Recent studies have demonstrated the efficacy of traditional Chinese medicine (TCM) in treating intracerebral hemorrhage (ICH). TCM exerts therapeutic effects in both the acute and recovery phases of ICH by inhibiting inflammation, reducing cerebral edema, and decreasing oxidative stress (OS), thereby reducing brain damage and promoting recovery from consciousness, cognitive, mental, and motor impairments associated with ICH (Duan et al., 2022; Yao and Zou, 2022)[5]. Tianma Gouteng Decoction (TMGTY) is a well-known TCM formula utilized clinically for hypertension, cerebrovascular disease, dizziness, and Parkinson's disease (Chen et al., 2018; Jiang et al., 2020; Tang et al., 2021)[6]. TMGTY contains various compounds with therapeutic effects on ICH, such as gastrodin with potent anti-inflammatory, antioxidative stress, and apoptosis-inhibiting properties, and isorhynchophylline with strong antioxidative stress effects (Chik et al., 2013; Liu et al., 2020; Zhao et al., 2021)[7].

Currently, comprehensive and systematic evidence to guide the clinical treatment of ICH with TMGTY is still lacking. Therefore, this study aimed to perform a systematic review and meta-analysis to evaluate the clinical efficacy and safety of TMGTY in the treatment of ICH.

2. Methods

This study was conducted under the PRISMA 2020 guidelines (Page, et al.,2022)[8], and has been registered with

PROSPERO under registration number CRD42023401629.

2.1 Search strategy

Two researchers searched the China National Knowledge Infrastructure (CNKI) database, Wanfang Database, VIP Database, China Biomedical Literature Database, PubMed, Cochrane Library, EMBASE, and Web of Science from database establishment to 25 February 2023. The search terms used were ("cerebral hemorrhage" OR "hemorrhagic stroke") AND "Tianma Gouteng". There were no language or publication status restrictions.

2.2 Inclusion criteria

The inclusion criteria were: 1) Study type: Randomized controlled trials (RCTs) and semi-RCTs; no language restrictions. 2) Research subjects: Hospitalized patients with a definite ICH diagnosis. 3) Interventions: Control group received conventional treatment (oxygenation, water-electrolyte balance maintenance, cerebral edema/intracranial pressure control, hypertension control, hypoglycemia and lipid regulation, complication prevention like infection/stress ulcers/seizures/central hyperthermia, cerebral circulation improvement, minimally invasive tube placement and drainage, physiotherapy, etc.). Experimental group received TMGTY plus conventional treatment. 4) Outcomes: a. Neurological function: NIHSS, MMSE, and GCS scores; b. Clinical efficacy: treatment efficiency, TCM syndrome score, complication rate, etc.; c. Biomarkers: hs-CRP, IL-6, TNF-α, MDA, and SOD levels; d. Quality of life: GOS and BI scores, etc.; e. Safety evaluation: adverse drug reactions.

2.3 Exclusion criteria

The exclusion criteria were: 1) Non-RCT designs such as animal studies, literature reviews, clinical experience studies, and correlation analyses; 2) Literature with incomplete raw data; 3) Noncompliant selection of diagnostic criteria, interventions, and outcome indicators; and 4) Duplicate reports.

2.4 Data extraction and methodological quality evaluation

Two researchers independently searched, selected and included articles. Disagreements were resolved by discussion with a third researcher. The following data were extracted: publication date, authors, sample size of each group, age, sex, intervention type, treatment duration, outcomes and adverse drug reactions.

According to the risk of bias tool recommended by the Cochrane Handbook of Systematic Reviews, risk of bias was assessed for randomized sequence generation, allocation concealment, blinding of participants, personnel, and outcome assessments, incomplete outcome data, selective reporting and other biases.

2.5 Statistical analysis

RevMan 5.4 software (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) was used for meta-analysis.

Relative risk (RR) ratios are used as the effect value for count data, and the mean difference (MD) are used as the effect value for measurement data, with each effect size expressed as the 95% confidence interval (CI). Heterogeneity between studies was tested by the chi-squared test. If statistical homogeneity existed among the included studies ($P>0.10$, $I2<50\%$), a fixed-effects model was used; if heterogeneity existed among the included studies ($P \leq 0.10$, $I2 \geq 50\%$), a random-effects model was used, and the sources of heterogeneity were analyzed.

2.6 Publication bias

Evaluation metrics for the inclusion of ≥10 papers produced funnel plots to determine the presence of publication bias.

3. Results

3.1 Search results

The main databases were searched, and a total of 163 studies were retrieved; of these studies, 90 were excluded due to duplication, 44 were excluded after title and abstract screening, and 18 were excluded after reading the full text.

Ultimately, 11 studies (Dong JP,2013; Fu JF, et al.,2021; Li Q, et al.,2020; Li Y, et al.,2020; Mao ZM,2013; Wang HF, et al.,2021a, 2021b; Xu HJ,2021; Xu XZ,2020; Zhang CJ, et al.,2021; Zheng T, et al.,2019)[9] were included in the study. Figure 1 shows the screening process, and Table 1 lists the basic characteristics of the included studies.

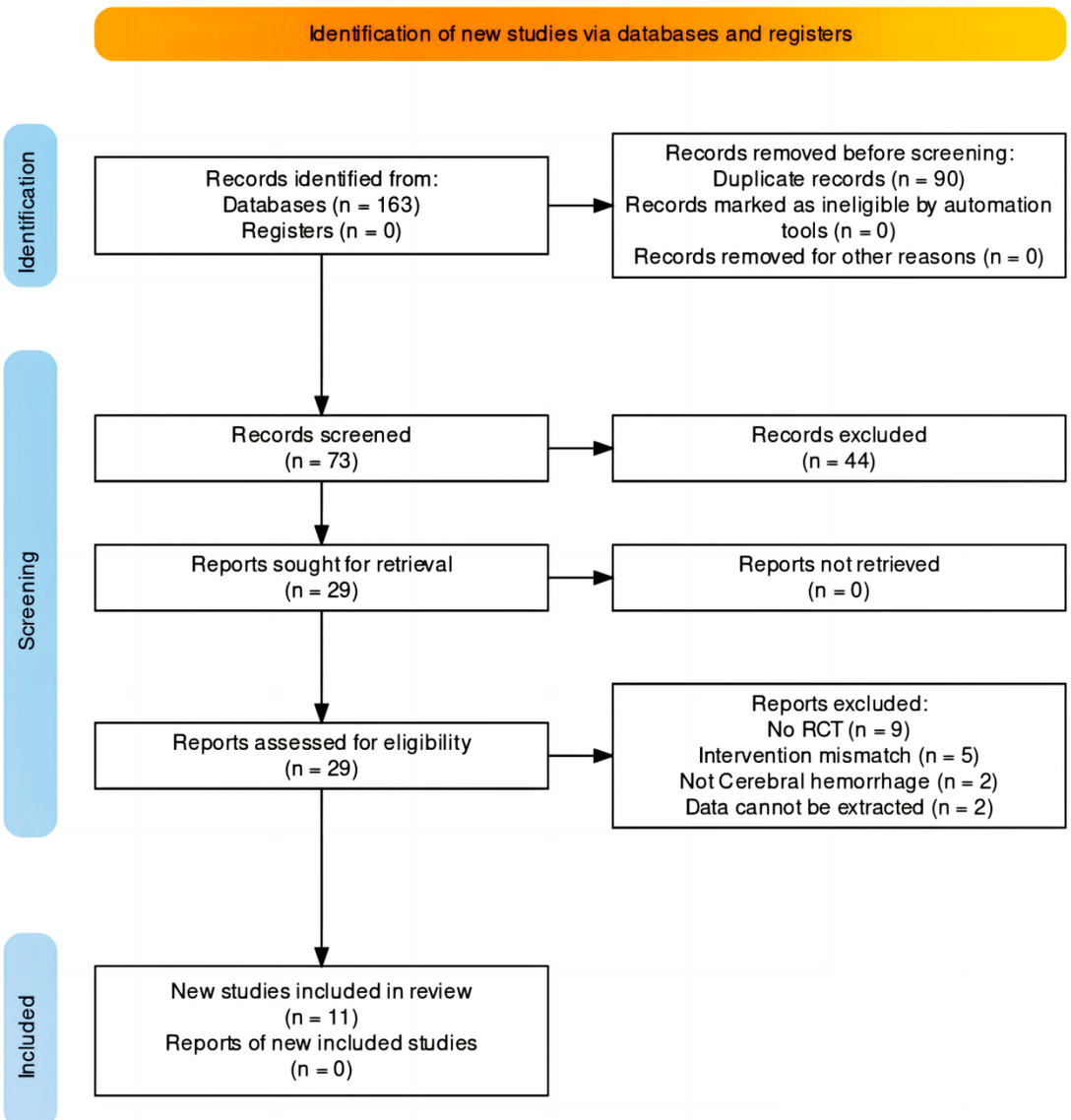

Figure 1. Study selection process for the Meta-analysis.

Table 1. Characteristics of the included studies in meta-analysis.

Literature	Sample size (T/C)	Age		Male/female ratio		Interventions		Treatment duration	Outcomes
		T	C	T	C	T	C		
Li 2020	48/48	63.48±7.19	65.34±6.42	22/26	27/21	TMGTD plus CT	CT	1 month	a,b,c,d
Xu 2020	33/33	56.15±6.41	55.94±6.33	23/10	22/13	TMGTD plus CT	CT	2 weeks	a,b,c
Li and Guo 2020	51/48	53.4±12.7	53.1±12.6	30/21	28/20	TMGTD plus CT	CT	2 weeks	b,c
Zheng 2019	49/49	70.18±3.21	68.75±8.56	31/18	29/20	TMGTD plus CT	CT	2 weeks	b,c,e
Dong 2013	20/18	50-71	51-68	not reported	not reported	TMGTD plus CT	CT	20 days	b
Wang and Li 2021	80/80	58.30±4.39	57.39±4.80	42/38	52/28	TMGTD plus CT	CT	1 month	b,c,d
Zhang 2021	60/60	54.5±3.3	54.3±3.3	40/20	38/22	TMGTD plus CT	CT	6 weeks	a,b,c,d
Xu 2021	35/35	65.34±2.1; 63.74±2.10	65.59±3.20; 62.84±2.20	20/15	18/17	TMGTD plus CT	CT	20 days	a,b
Fu 2021	35/35	66.31±5.37	65.35±5.61	20/15	22/13	TMGTD plus CT	CT	4 weeks	b,d
Wang 2021	50/50	65.20±1.50	65.30±1.40	30/20	28/22	TMGTD plus CT	CT	4 weeks	b,d
Mao 2013	30/30	54.5±6.54	53.8±6.87	18/12	20/10	TMGTD plus CT	CT	1 month	b

T/C, treatment group/control group; 2. TMGTD, Tianma Gouteng decoction or modified Tianma Gouteng decoction; 3. CT, conventional treatment (including oxygenation, maintenance of water-electrolyte balance, control of cerebral edema/intracranial pressure, control of hypertension, hypoglycemia and lipid regulation, prevention of complications including infection/stress ulcers/epileptic seizures/central hyperthermia, improvement of cerebral circulation, minimally invasive tube placement and drainage, physiotherapy, etc.); 4. a. Neurological function: National Institute of Health Stroke Scale (NIHSS), Mini-Mental State Examination (MMSE), and Glasgow Coma Scale (GCS) scores; b. Clinical efficacy: treatment efficiency, TCM syndrome score, complication rate, etc.; c. Biomarkers: high-sensitivity C-reactive protein (hs-CRP), interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), malondialdehyde (MDA), and superoxide dismutase (SOD) levels; d. Quality of life: Glasgow Outcome Scale (GOS) and Barthel Index (BI) scores, etc; e. Safety evaluation: adverse drug reactions.

3.2 Quality evaluation

All 11 trials were randomized. Four studies explicitly described a rational randomization method (Wang HF et al., 2021a; Xu XZ, 2020; Zhang CJ et al., 2021; Zheng T et al., 2019)[10], two used a grouping method by order of attendance (Dong JP, 2013; Mao ZM, 2013), one used a grouping method by number of inpatient beds (Xu HJ, 2021), and the remaining studies did not report a specific randomization method. None of the studies mentioned allocation concealment or blinding of participants, personnel, or outcome assessments. There were no missing data, and all studies fully reported the desired outcomes. There was insufficient information to determine other biases. Figure 2 shows the risk of bias assessment for the included literature.

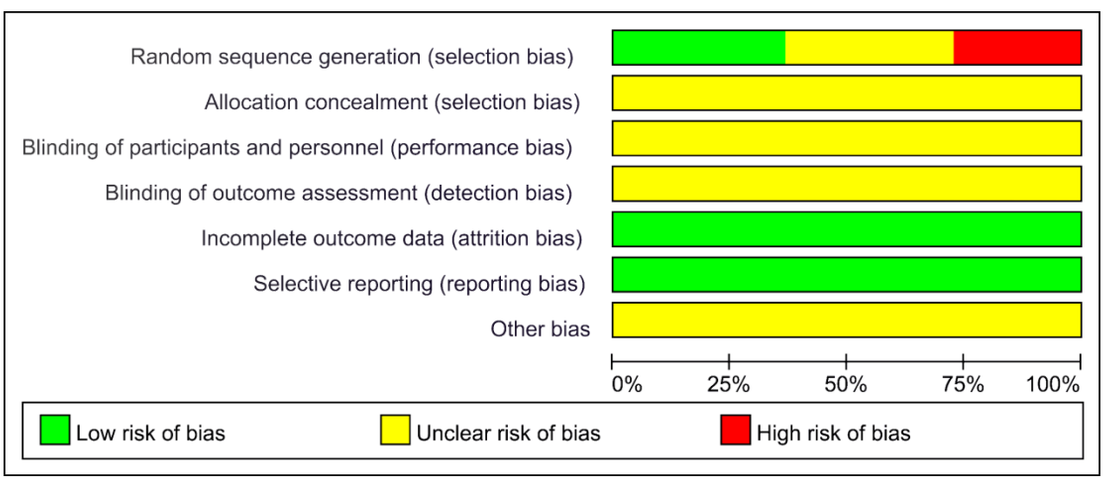

Figure 2. Risk of bias grap.

4. Analysis

4.1 Neurological function scores

4.1.1 NIHSS scores

Four studies reported the NIHSS scores of patients treated with combined TMGTY and conventional treatment versus conventional treatment alone for ICH (Li Q, et al.,2020; Xu HJ,2021; Xu XZ,2020; Zhang CJ, et al.,2021)[11]. There was statistical heterogeneity among the studies (P<0.00001, I2=97%), so a random-effects model was used. The results of the meta-analysis showed that the NIHSS score of the treatment group was lower than that of the control group (MD=-3.86, 95% CI: -6.42, -1.31, P=0.003) (Figure 3).

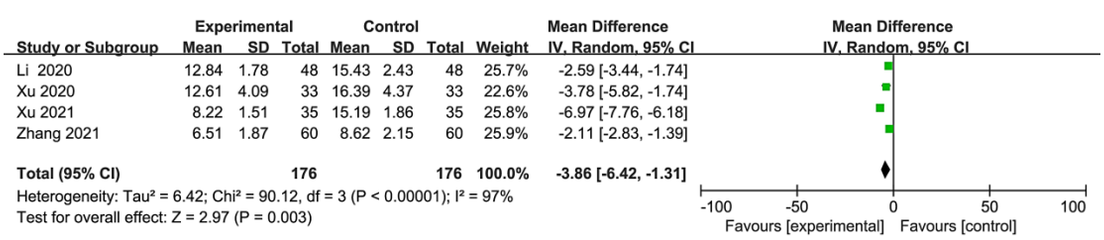

Figure 3. The NIHSS score of the treatment group was lower than that of the control group.

4.1.2 Other outcomes

Two studies each reported the GCS and MMSE scale scores of patients treated with combined TMGTY and conventional treatment versus conventional treatment alone for ICH (Li Q, et al.,2020; Xu XZ,2020)[12]. The results showed that the GCS and MMSE scale scores were improved compared to those of the control group.

4.2 Clinical efficacy

4.2.1 Treatment efficiency

Eleven studies reported the treatment efficiency of combined TMGTY and conventional treatment versus conventional treatment alone for ICH (Dong JP,2013; Fu JF, et al.,2021; Li Q, et al.,2020; Li Y, et al.,2020; Mao ZM,2013; Wang HF, et al.,2021a, 2021b; Xu HJ,2021; Xu XZ,2020; Zhang CJ, et al.,2021; Zheng T, et al.,2019)[13]. There was no statistical heterogeneity among the studies (P=0.25, I2=20%), so a fixed-effects model was used. The results of the meta-analysis showed that the treatment efficiency of the treatment group was higher than that of the control group (RR=1.19, 95% CI: 1.13, 1.26, P<0.00001) .

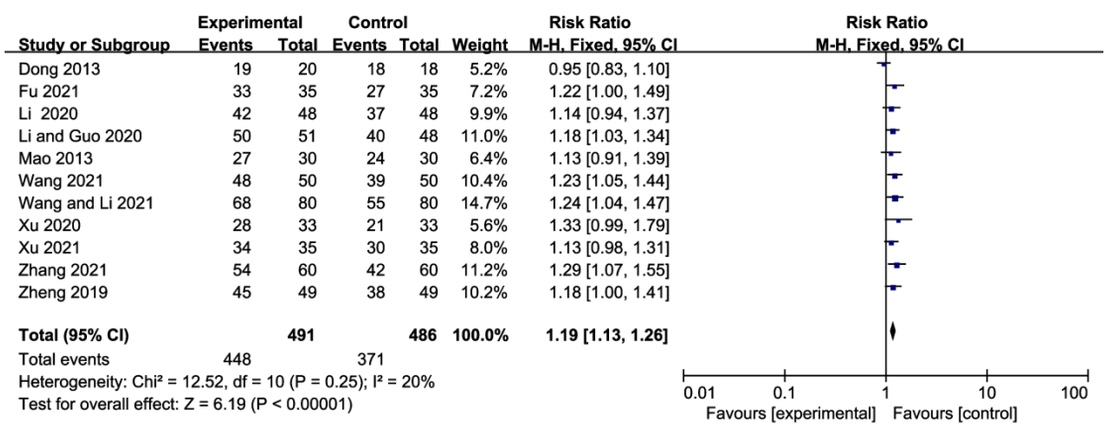

Figure 4. The treatment efficiency of the treatment group was higher than that of the control group.

4.2.2 Complication rate

Five studies reported the incidence of complications (e.g., rebleeding, hemiplegia, coma, pharyngeal dysfunction, pulmonary infection, upper gastrointestinal bleeding, hepatic and renal impairment, and stress ulcers) of combined TMGTY and conventional treatment versus conventional treatment alone for ICH (Li Y, et al.,2020; Fu JF, et al.,2021; Wang HF, et al.,2021a, 2021b; Zhang CJ, et al.,2021)[14]. There was no statistical heterogeneity among the studies (P=0.56, I2=0%), so a fixed-effects model was used. The results of the meta-analysis showed that the complication rate of the treatment group was lower than that of the control group (RR=0.24, 95% CI: 0.13, 0.45, P<0.00001)

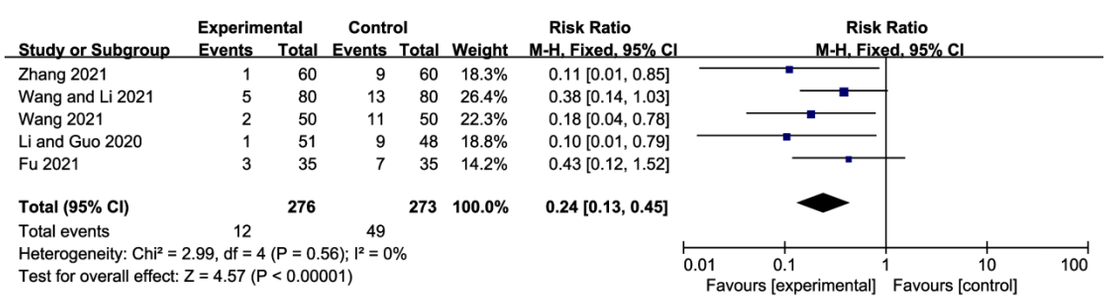

Figure 5. The complication rate of the treatment group was lower than that of the control group.

4.3 Biomarkers

4.3.1 IL-6

Four studies reported the IL-6 levels of patients treated with combined TMGTY and conventional treatment versus

those of patients receiving conventional treatment alone for ICH (Li Q, et al.,2020; Wang HF, et al.,2021b; Xu XZ,2020; Zheng T, et al.,2019)[15]. There was statistical heterogeneity among the studies (P=0.002, I2=79%), so a random-effects model was used. The results of the meta-analysis showed that the IL-6 levels of the treatment group were lower than those of the control group (MD=-11.20, 95% CI: -13.84, -8.57, P<0.00001) .

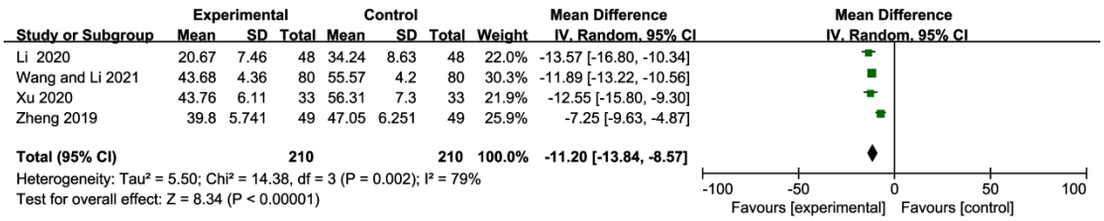

Figure 6. The IL-6 levels of the treatment group were lower than those of the control group.

4.3.2 TNF-α

Four studies reported the TNF-α levels of TMGTY combined with conventional treatment versus conventional treatment alone for ICH (Li Q, et al.,2020; Wang HF, et al.,2021b; Xu XZ,2020; Zheng T, et al.,2019)[16]. There was statistical heterogeneity among the studies (P<0.0001, I2=87%), so a random-effects model was used. The results of the meta-analysis showed that the TNF-α levels were lower in the treatment group than in the control group (MD=-13.88, 95% CI: -16.73, -11.02, P<0.00001) (Figure 7).

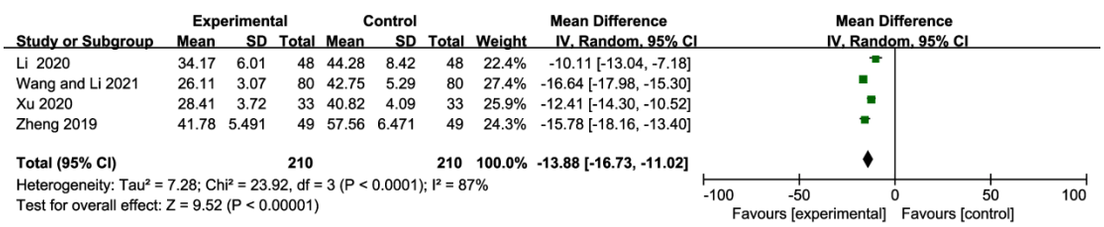

Figure 7. The TNF-α levels were lower in the treatment group than in the control group.

4.4 Quality of life (Barthel Index)

Three studies reported the BI scores of patients treated with combined TMGTY and conventional treatment versus those of patients receiving conventional treatment alone for ICH (Wang HF, et al.,2021b; Xu XZ,2020; Zhang CJ, et al.,2021)[17]. There was no statistical heterogeneity among the studies (P= 0.38, I2=0%), so a fixed-effects model was used. The results of the meta-analysis showed that the BI scores of the treatment group were higher than those of the control group (MD=11.48, 95% CI: 9.71, 13.24, P<0.00001) .

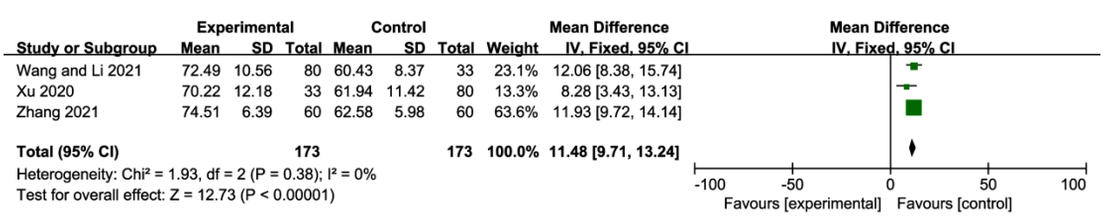

Figure 8. The BI scores of the treatment group were higher than those of the control group.

4.5 Publication bias

The funnel plots for treatment efficiency showed that there was no significant publication bias in the study. However, there may be some heterogeneity.

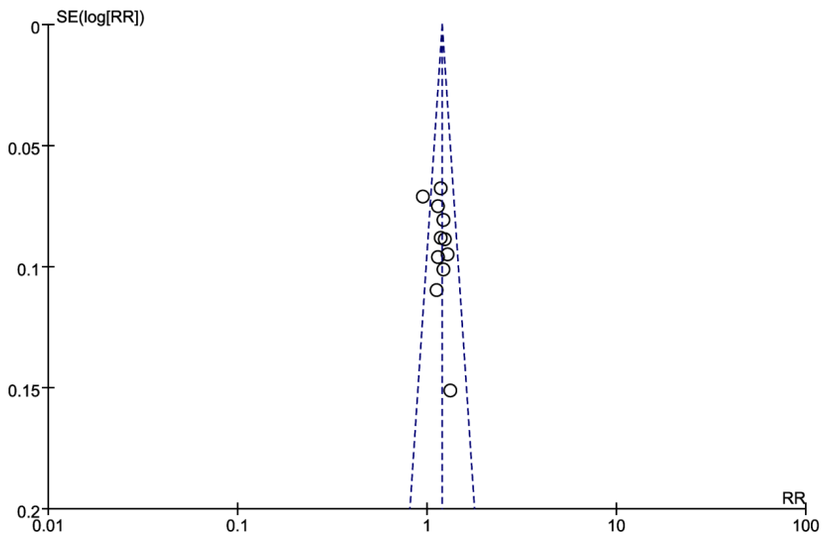

Figure 9. Funnel plot of comparison of treatment efficiency between the treatment group and the control group.

5. Discussion and Conclusion

This study included 977 patients from 11 studies and analyzed five outcomes, including neurological function scores, clinical efficacy, biomarker levels, quality of life evaluations and safety evaluations.

The study included a meta-analysis of outcomes reported ≥3 times, including NIHSS scores, treatment efficiency, complication rates, IL-6 levels, TNF-α levels, and BI scores. The meta-analysis results showed that, compared to the control group, the treatment group had better improvement in neurological deficits, increased treatment efficiency, reduced complication rates, lowered levels of some inflammatory factors, and improved activities of daily living. Other outcomes were evaluated using descriptive analyses, suggesting the treatment group may have had superior improvements in coma degree, cognitive levels, prognosis, physical health, reduced TCM syndrome scores, lowered hs-CRP, IL-1β, IL-8, MMP-9, MDA, Hcy, ET, NE, epinephrine, and DA levels, and increased SOD and NO levels.

In recent years, studies have highlighted pathophysiological mechanisms and potential therapeutic targets for ICH, bringing new perspectives to its treatment. Secondary brain injury after ICH is linked to inflammation, oxidative stress (OS), neurocytotoxicity, and coagulation cascade reactions, with mechanisms so complex and not fully elucidated, making clinical translation challenging. This highlights the promise of multitargeted neuroprotective therapy (An et al., 2017; Shao et al., 2019)[18]. Immune and inflammatory responses are crucial in ICH brain injury and repair, where blood components enter the brain parenchyma, activating microglia, astrocytes, and mast cells, releasing proinflammatory and anti-inflammatory factors, and free radicals, leading to neurological damage (Ren et al., 2020)[19]. OS results from reactive oxygen species (ROS) accumulation, originating from activated phagocytes and non-phagocytes (microglia, astrocytes, etc.), mitochondrial dysfunction, and erythrocyte lysis products, causing DNA damage, inducing phagocytosis, autophagy, apoptosis, various cell damage types, and mediating inflammation (Duan et al., 2016; Yao et al., 2021; Zhang et al., 2022)[20]. Studies show that ICH's pathophysiological mechanisms are complex, with potential therapeutic targets interacting. Thus, multitargeted or multimodal therapeutic measures for ICH warrant further investigation.

TMGTY is composed of Gastrodia elata (Tianma), Uncaria Rhynchophylla (Gouteng), Concha Haliotidis (Shijueming), Gardenia Jasminoides (Zhizi), Scutellaria Baicalensis (Huangqi), Achyranthes Bidentata (Chuanniuxi), Eucommia Ulmoides (Duzhong), Leonurus Japonicus (Yimucao), Taxillus Sutchuenensis (Sangjisheng), Caulis Polygoni Multiflori (Shouwuteng), and Zhufushen. Recently, TMGTY herbal formulas or monomers have been studied for ICH intervention. Gastrodin from Gastrodia elata inhibits OS and apoptosis after ICH (Liu et al., 2020). Isorhynchophylline from Uncaria Rhynchophylla exerts antioxidative effects by upregulating miR-122-5p to inhibit ferroptosis (Zhao et al., 2021). Baicalin from Scutellaria Baicalensis reduces brain edema, improves neurological function, inhibits NF-κB, MAPKs, ROS/NLRP3 pathways, inhibits ferroptosis, and protects the blood-brain barrier, exerting anti-inflammatory and antioxidative effects (Zhou et al., 2014; Chen et al., 2016; Duan et al., 2021; Chen et al., 2022). Aucubin from Eucommia Ulmoides reduces IL-1β, NF-κB, and TNF-α in ICH mouse models, exerting antineuroinflammatory effects (Yang et al., 2022). Leonurine from Leonurus Japonicus reduces cerebral edema after ICH, improves neurological function, inhibits inflammation, and protects

blood-brain barrier integrity (Lin et al., 2016).

Although TMGTY has a long history and definite clinical efficacy in the treatment of ICH, there is still a lack of research on the relationship between the pharmacological basis of TMGTY and potential targets for ICH treatment, especially the synergistic and quantitative-effect relationships among the herbs, which are questionable. Therefore, the pharmacological basis and mechanism of action of TMGTY need to be further investigated.

The following limitations should be noted: 1) The included studies were conducted and published in Chinese, possibly introducing bias; 2) The number of outcomes and sample sizes in the individual studies were small, and some outcomes lacked standardization, leading to potential bias and subjectivity; 3) Some studies had inappropriate or unclear randomization methods and did not mention allocation concealment or blinding, affecting reliability; 4) Most studies did not perform TCM syndrome differentiation, and there were differences in basic treatments, potentially affecting results; 5) The studies lacked reports on adverse drug reactions, introducing possible bias in safety evaluation.

Compared with conventional treatment alone, combined TMGTY and conventional treatment for ICH could better improve clinical efficacy, neurological function and quality of life, reduce complication rates, and influence the injury and prognosis of ICH by affecting biomarkers. Due to the limitations of the study, the quality of the included trials was not high, and the selection of outcomes was not closely integrated with the study of the pathophysiological mechanism of ICH. Therefore, more clinical RCTs with higher quality, standardized designs, large samples and multiple centers are needed in the future to validate and support this conclusion.

Acknowledgments

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