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SYSTEMATIC REVIEW

Medium- and long-term efficacy of ligustrazine plus conventional medication on ischemic stroke: a systematic review and meta-analysis

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Abstract

OBJECTIVE: To evaluate the medium- to long-term efficacy of ligustrazine plus conventional medicine treating ischemic stroke.

METHODS: Randomized controlled trials (RCTs) testing ligustrazine in the treatment of acute ischemic stroke were retrieved from Cochrane Library, PubMed, Excerpta Medica Database, Chinese Medical Journal Database, Chinese Biomedical Database, China National Knowledge Infrastructure Database, and Chinese Clinical Trial Register, and then identified by the inclusive and exclusive criteria. The quality of trials was assessed with the Cochrane Handbook 5.1, a risk of bias assessment tool. RevMan 5.1 was used for meta-analysis.

RESULTS: Three RCTs involving 643 patients were included. Compared to conventional medicine treatment alone, ligustrazine plus conventional medicine treatment showed significant difference in reduction of stroke recurrence either at the end of 1-year follow-up [*RR*=0.42, 95% *CI* (0.18, 0.94), *P*< 0.05] or 3-years observation [*RR*=0.48, 95% *CI* (0.27, 0.83), *P*<0.05]. The ligustrazine group also showed higher survival rate [*RR*=1.67, 95% *CI* (1.02, 0.2.71), *P*<0.05] and significantly better effective rate [*RR*= 1.28, 95% *CI* (1.10, 1.50), *P*<0.05] than that of the control group at the end of 1 year visit. Only one trial conducted safety assessment and no adverse events were reported. The methodological quality of all the trials included was generally poor.

CONCLUSION: The findings provided evidence that the combination of ligustrazine and conventional medication was medium- and long-term beneficial to the patients suffering ischemic stroke. But more RCTs of high quality are needed to further prove the efficacy and safety of using ligustrazine for ischemic stroke.

Key words: Tetramethylpyrazine; Stroke; Time; Secondary prevention; Review; Meta-analysis

INTRODUCTION

Ischemia, the most common type of stroke,[1] is the major cause of death, disability and long-period hospitalization in China.[2] The economic burden will be continuously rising in the coming 20 years for treating it in

developing countries due to aging population and changes of life style.[3] Except anti-platelet therapy, Chinese patent medicine (CPM) has been used for the prevention and treatment of ischemic stroke in China.[4] However, the efficacy of the CPM was controversial in clinical studies. Therefore, application of evidence-based methodology to evaluate these trials is important for confirmation of CPM efficacy.

Ligustrazine (Tetramethylpyrazine, short form as TMP),[5] a bioactive ingredient extracted from a widely-used Chinese herb, Chuanxiong (*Rhizoma Chuanxiong*), was proved to have beneficial effect on cerebrovascular diseases in pharmacological experiments. It targets at platelet-aggregation inhibition,[6] vessel-dilation enhancement,[7] cerebral blood flow increase[8] and neurological protection.[9] CPM made of TMP has been clinically used in patients with ischemic stroke for over 10 years.[10]

Our previous evidence-based study indicated that TMP injection used in acute phase of ischemic stroke was safe and beneficial in hemodynamics while showed no better improvement in current neurological deficit.[11] In order to provide more evidence for the combination of TMP and conventional medication in the treatment of ischemic stroke, we analyzed randomized controlled trials (RCTs) of ischemic stroke treated with TMP plus conventional medication, which carried out follow-up for more than 3 months.

MATERIALS AND METHODS

Eligibility

Eligible studies were defined as RCTs with either known methodology or not. Patients meeting the diagnosis criteria of ischemic stroke with confirmation of computed tomography (CT) or magnetic resonance imaging (MRI) scanning of any sex and age were included. The primary outcomes included death or survival and recurrence while the secondary measurement was clinical efficacy. It was calculated according to the improvement neurological deficit and daily life. All outcomes were measured at least at the end of 3-month follow-up.

Search strategy and study selection

Studies including all language were electronically searched in PubMed (1966-2012), the Cochrane Library (issue 12, 2012), Excerpta Medica Database (EMbase) (1980-2012), Chinese Clinical Trial Register (ChiCRT, 2005-2012), Chinese Biomedical Database (CBM, 1979-2012), China National Knowledge Infrastructure Database (CNKI, 1979-2012), and Chinese Medical Journal Database (CMJD, 1989).

We identified and selected the studies through the following procedure. Initially RCTs testing TMP were included and then abstracts were screened to exclude non-ischemic stroke studies and duplicate publications. Then the full text of remaining articles were carefully read and studies mismatching the diagnostic and outcome eligibility were eliminated. All articles were maintained and classified in MedRef database (version 3.0, King Yee, Beijing, China).

Data management

The extracted data were entered into the Excel library, covering publication information, methodological design, participants, intervention, control, death, survival, recurrence and efficacy.

Methodological assessment

The methodological assessment was conducted using risk of bias assessment tool according to the principle of Cochrane Handbook for Systemic Reviews of Interventions 5.1.[12] Six aspects were evaluated, including randomization sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting and other bias source.

The study identification, data extraction and methodological assessment were conducted by two reviewers separately. Once the dispute occurred, a third person would be invited for verification.

Statistical analysis

Review Manager (RevMan) (version 5.1.Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011) was used to conduct the Meta-analysis. Because the outcomes were all presented in dichotomous data, they were reported by relative risk (*RR*) with 95% confidence interval (*CI*). Heterogeneity between trials was tested by *Chi*-square test. For the study with good homogeneity ($P>0.1$, $I^2<40\%$), fixed model was used for Meta-analysis. If there was heterogeneity, subgroups analysis was conducted or the random model was used with results carefully explained. Funnel plot analysis was carried out to detect the publication bias if more than 10 RCTs were finally included.

RESULTS

Search results

A total of 3 RCTs[13-15] were finally included into the review. All studies were published in Chinese. The flow diagram of search and identification results is shown in Figure 1.

Study characteristics

A total of 643 patients aged 31 to 82 years old[13-15] were included into the review. All trials applied modern diagnostic criteria[16,17] of ischemic stroke and CT or MRI scanning for confirmation. All experiment groups received conventional medicine treatment (anti-platelet therapy included) as well as TMP injection, daily dosages of which varied from 80-240 mg. Each study had different treatment timing after stroke onset; one start-

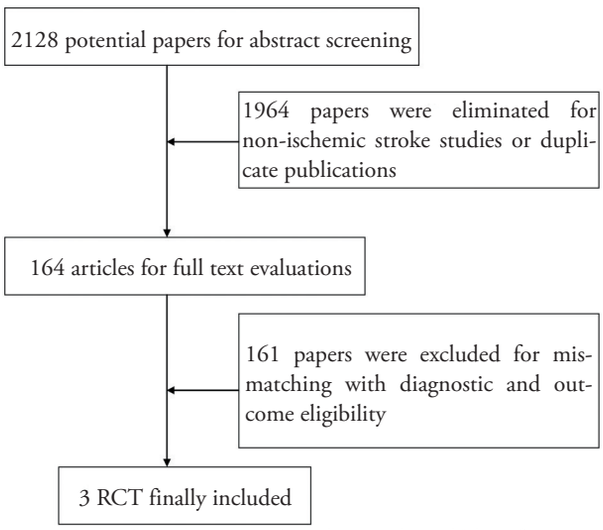

Figure 1 The flow diagram of study search and identification
RCT: randomized controlled trials

ed within 14 days,[13] one within 100 days[14] and the rest within 6 months.[15] The total duration of TMP therapy were also different; one trial had a 10-days continuous treatment at 2-months interval for 3 years,[15] one had a 1-week interval treatment for 1 months[13] and the remaining one had a constant treatment for 1 year.[14] Two trials conducted 1-year follow-up[13,14] while another one visited the participants for 3 years.[15] One trial assessed the 1-year and 3-years recurrence as well as 3-years survival;[15] one[14] reported the effectiveness based on the neurological deficit improvement and daily life ability grading recommend at the Chinese National Cerebrovascular Diseased Conference in 1995;[18] the rest showed the 1-year recurrence of ischemic stroke.[13] None of the trials reported the mortality or fatality. Only one of the studies conducted safety evaluation and no adverse events were found.[13] Details are shown in Table 1.

Methodological quality and risks of bias

The methodological quality of all the trials included was generally poor. No trial described the method of randomization and allocation concealment. None of the trials used blinding. All trials simply reported the baseline information and only one conducted the comparability analysis.[15] No drop-out or lost to follow-up were mentioned and none applied intention-to-treat analysis. The risks of bias were shown in Figure 2.

Recurrence

The recurrence at the end of 1 year follow-up was reported in 2 trials.[13,15] The recurrence events in control groups were significantly higher than that of experimental groups [*RR*=0.42, 95% *CI* (0.18, 0.94), *P*< 0.05] (Figure 3). The recurrence at the end of 3 years follow-up was reported in only 1 trial.[15] The recurrence events in control groups were significantly higher than that of experimental groups [*RR*=0.48, 95% *CI* (0.27, 0.83), *P*<0.05] (Figure 4).

Death or survival

Death was not reported in any trials included. One trial reported the survival at the end of 3 year follow-up.[15] The survival rate in experimental groups were also significantly higher than that of the control groups [*RR*= 1.67, 95%*CI* (1.02, 2.71), *P*<0.05] (Figure 5).

Efficacy

The efficacy at the end of 1 year follow-up was analyzed and compared in only 1 trial.[14] The experimental group showed significantly better effective rate than that in control group [*RR*=1.28, 95% *CI* (1.10, 1.50), *P*<0.05] (Figure 6).

DISCUSSION

The time course of recovery from ischemic stroke should be considered when selecting the timing of assessment. Spontaneous recovery of neurological function does not plateau until 3 to 6 months after stroke, especially the severe ones.[19] Six months, at lease 3 months after stroke might be the appropriate time to measure the efficacy.[20] So it's better to measure long-term outcomes in order to evaluate the definite effect of the intervention. Considering the pathophysiology of stroke impairment and healing, we included the trials which assessed the outcomes in at least 3 months in this review and found TPM plus conventional medicine was a beneficial therapy. This result showed that additional use of TMP for a longer period strength-

Table 1 Summary of studies included in the review

Study	Number (E/C)	Gender (E/C)		Age (years) (E/C)	Intervention (E/C)	Follow-up (years)	Outcome		
		Male	Female				Death/ Survival	Recurrence	Effectiveness
Zhang XJ 2005[15]	42/30	27/22	8/15	45-82 Mean 67/ 49-84 Mean 71	TMP plus CMT/CMT	3	Known	Known	Unknown
Liu HL 2002[14]	258/261	134/139	124/122	40-79 Mean 61/ 39-80 Mean 62	TMP plus CMT/CMT	1	Unknown	Unknown	Known
Yang L 2000[13]	32/20	28	24	31-81 Mean59/ 40-80 Mean 60	TMP plus CMT/CMT	1	Unknown	Known	Unknown

Notes: E: experimental group; C: control group; TMP: ligustrazine; CMT: conventional medicine treatment. The studies are labeled as the first author with the publishing year.

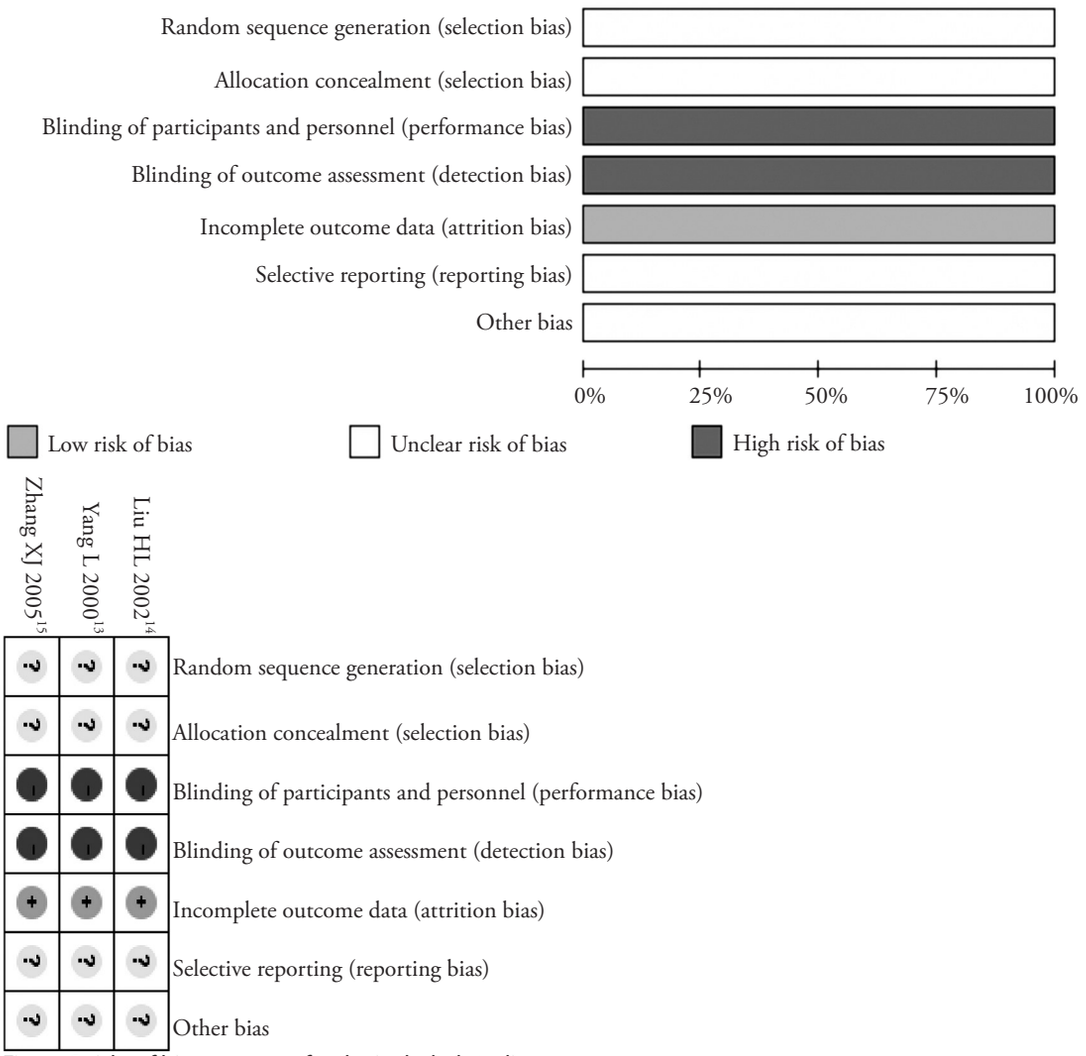

Figure 2 risks of bias summary for the included studies

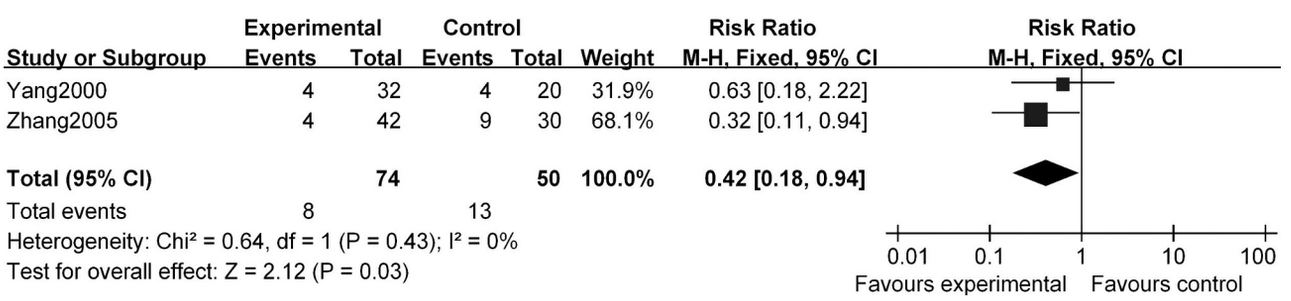

Figure 3 Comparision of 1-year recurrence rate between ligustrazine + CMT and CMT
CMT: conventional medicine treatment.

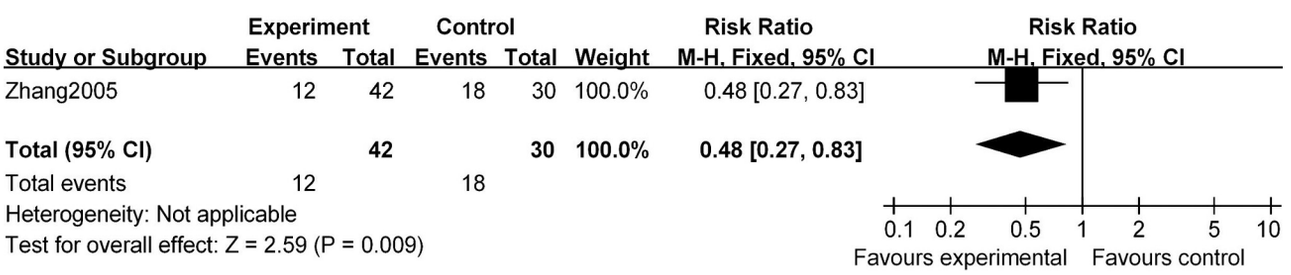

Figure 4 Comparision of 3-year recurrence rate between ligustrazine + CMT and CMT
CMT: conventional medicine treatment.

ened survivability, reduced recurrence, and improved efficacy in terms of neurological function and daily life ability.

The severity of acute ischemic stroke is determined by the reduction of cerebral blood flow (CBF) and the reperfusion timing.[21] Once the artery is occluded, CBF is sharply decreasing and the neuron dies in very short time, mostly in a few hours and several days.[22] Penum-

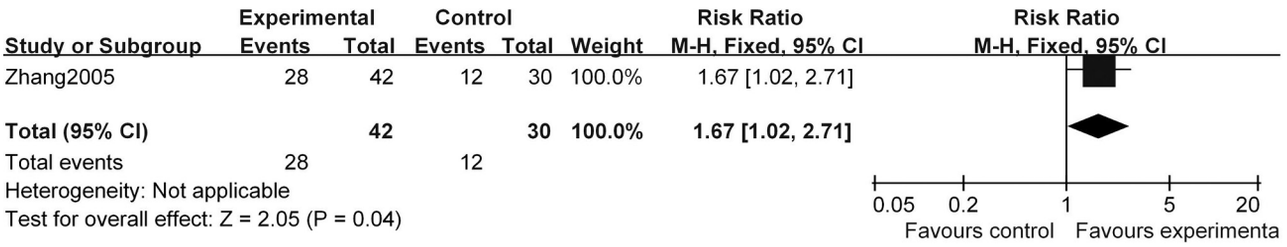

Figure 5 Comparision of 3-year survival rate between ligustrazine + CMT and CMT
CMT: conventional medicine treatment.

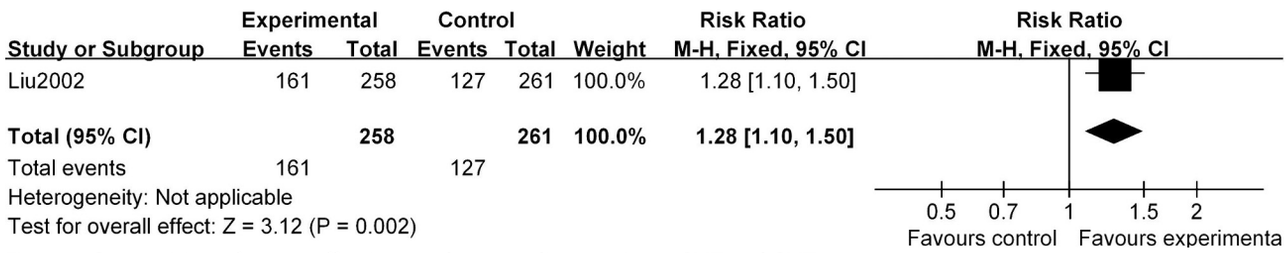

Figure 6 Comparision of 1-year effective rate between ligustrazine + CMT and CMT
CMT: conventional medicine treatment.

bra was marginal area between the ischemic center and normal brain tissue, normally recovering in 4.5 h, which was called time window.[23] Thrombolysis is the only recommend therapy to reducing neurological deficit and disability in the time window.[24] However, it hasn't been widely used in developing countries, because timely treatment seldom occurs with lack of comprehensive post-thrombolysis monitoring and rescue professionals.[25] Therefore, the prevention of stroke recurrence is important in China, especially in remote and undeveloped areas. In our study, the combined use of TMP and conventional medication was proved to reduce the recurrence of ischemic stroke either at the end of 1 or 3 years follow-up compared to conventional therapy alone, which provides clinical evidence for medical professionals.

The goal for ischemic stroke management is to reduce the death and disability, which should be used as the main outcome to evaluate any intervention.[26] However, it was found that very few RCTs applied primary endpoint (death or dependency) to assess the effect of TMP for ischemic stroke in this study and only 1 trial reported the survival rate at the end of 1-year follow up. Besides, the poor quality of the eligible literatures was another problem. First, blinding was not introduced in all trials included, the baseline was varied and few studies conducted safety evaluation. Second, all trials were not reported in accordance with the CONSORT statement.[27] Third, registration was not conducted to present full transparency for the performance and reporting of the trials.[28]

CONCLUSION

The findings in the study show that TMP combined with conventional treatment was beneficial to the patients with ischemic stroke in a medium- and long-term way. Yet more RCTs with better methodology and rigorous practice are needed to further corroborate the findings.

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