Taylor & Francis
Taylor & Francis Group

Neurological Research

A Journal of Progress in Neurosurgery, Neurology and Neurosciences

ISSN: 0161-6412 (Print) 1743-1328 (Online) Journal homepage: https://www.tandfonline.com/loi/yner20

The effect of intravenous ginkgolide on clinical improvement of patients with acute ischemic stroke

Yi Dong, Huiqin Li & Qiang Dong

To cite this article: Yi Dong, Huiqin Li & Qiang Dong (2020): The effect of intravenous ginkgolide on clinical improvement of patients with acute ischemic stroke, Neurological Research, DOI: 10.1080/01616412.2020.1724462

To link to this article: https://doi.org/10.1080/01616412.2020.1724462

NEUROLOGICAL RESEARCH
https://doi.org/10.1080/01616412.2020.1724462

Taylor & Francis
Taylor & Francis Group

ARTICLE

The effect of intravenous ginkgolide on clinical improvement of patients with acute ischemic stroke

Yi Dong[a], Huiqin Li[b] and Qiang Dong[a]

[a]Department of Neurology, Huashan Hospital, Fudan University, Shanghai, China; [b]Depart of Medical Affair, Chengdu Baiyu Pharmaceutical Co., Ltd, Chengdu, China

ABSTRACT

Aims: To compare the efficacy of ginkgolide in the treatment of Chinese patients with ischemic stroke between pre-marketing and post-marketing studies.

Methods: This is a re-analysis of a pre-marketing (phase II/III, multicenter, double-blind, parallel-controlled; February 2005 to September 2005) and post-marketing (phase IV, multicenter, open, single-arm registration; April 2013 to June 2014) studies. The intervention groups received intravenous ginkgolide (10 mL daily, 14 days). Primary outcome was an improvement of National Institute of Health Stroke Scale (NIHSS) and modified Rankin Scale (mRS) scores after 14 days.

Results: In pre- and post-marketing studies, NIHSS and mRS scores all improved, compared to that of baseline ($P < 0.001$) in acute phase. Those factors significantly associated with △NIHSS after 14 days of therapy with ginkgolide were grouping (pre-marketing vs. post-marketing; OR 2.169, 95%CI = 1.462–3.216, $P < 0.001$), male (OR = 1.532, 95%CI = 1.152–2.037, $P = 0.003$), enrollment within 30 days after onset (OR = 1.915, 95%CI = 1.452–2.526, $P < 0.001$) and NIHSS score more than 8 points at baseline (OR = 15.140, 95%CI = 11.436–20.045, $P < 0.001$) after adjustment. Ginkgolide had a greater effect on patients in a relatively acute phase (time of onset to enrollment ≤30 days) and moderate-severe stroke (baseline NIHSS>8 points). Incidences of adverse reactions in the pre-marketing and post-marketing studies were 0.46% and 5.28%, respectively ($P < 0.001$).

Conclusion: Intravenous ginkgolide may improve the outcome of acute ischemic stroke. Differences in effect between pre-marketing and post-marketing studies may be associated with gender, time of onset to enrollment and severity of stroke.

ARTICLE HISTORY
Received 29 January 2019
Accepted 16 November 2019

KEYWORDS
Acute ischemic stroke; intravenous Ginkgolide; modified Rankin score; National Institution of Health Stroke Scale; neurologic function

Introduction

Stroke is a major cause of death in China, also with a large amount of morbidity [1–3]. In the limited time window, the revascularization treatments in acute ischemic stroke are considered to achieve a more favorable outcome [4–6]. The neuroprotection agent is a potential benefit but still less known [7]. Chinese Guidelines stated that neuroprotectants can improve the tolerance of brain cells during ischemia and hypoxia [8].

Ginkgolide is a family of terpenic lactones isolated from the root and leaves of the tree ginkgo biloba. *Ginkgolide* (Baiyu®) is composed of ginkgolide ABCJ and bilobalide. Ginkgolide was shown the contribution on PAF antagonistic effect in both preclinical and clinical studies. On the other hand, bilobalide combined with ginkgolide was found its neuroprotective in acute ischemic stroke [9,10]. In rodent model, the administration of ginkgolide either before or shortly after the middle cerebral artery occlusion was found that it could reduce the cerebral ischemia/reperfusion injury with all aspects of infarct volume, cerebral edema reduction, and improvement of neuron apoptosis and neurologic deficits [11,12,13,14,15,16,17,18,19,20,21,22,23,24,25,26]. Importantly, it has also been reported to improve neurologic function and slow vascular cognitive impairment in patients with acute ischemic stroke [27–30]. However, there are hot debates in the beneficial effect of ginkgolide and its combinations in acute ischemic stroke patients. Only one meta-analysis failed to conclude that ginkgolide family is an effective treatment or not [31].

Our study is aimed to perform a retrospective analysis with pooled data from phase II to IV clinical trials, in order to compare the consistency of the results between the pre-marketing and post-marketing clinical studies.

Methods

Study design and participants

This was a retrospective re-analysis of data from phase II, III and IV clinical trials investigating the efficacy of intravenous *Ginkgolide* (Baiyu®, an agent composited with 51% ginkgolide ABCJ and 48% bilobalide, Chengdu hundred pharmaceutical Co. Ltd) in patients

CONTACT Qiang Dong dong_qiang@fudan.edu.cn No.12 Urimuqi Middle Road, Jin An District, Shanghai 200040, China
Supplemental data for this article can be accessed here.

with acute ischemic stroke. Detailed information of each study were demonstrated in Supplemental Table 1. The inclusion, exclusion and withdrawal criteria were essentially consistent between the various clinical trials. The individual trials were conducted in accordance with the principles of the Declaration of Helsinki and approved by the ethics committee of the participating institutions. All study participants provided informed written consent for inclusion in the original studies.

All the data for patients treated with intravenous ginkgolide (10 ml) daily in the phase II, III and IV trials were re-analyzed in the present study (any missing data were replaced by mean values). Data from the phase II and III trials were considered together as the pre-marketing study, and data from the phase IV trial were considered as the post-marketing study. In phase II, III, IV trials, patients were enrolled during 7 days to6 months after acute onset. The intravenous *Ginkgolide* (Baiyu®) would be continuously performed for 14 days. All details of the intervention were also listed in Supplemental Table 1.

Primary endpoint

The primary endpoint was the improvement in neurologic function, as assessed from the National Institutes of Health Stroke Scale (NIHSS) score and modified Rankin scale (mRS) score, in patients with ischemic stroke after 14 days of treatment with intravenous ginkgolide. Effectiveness was defined as a reduction in NIHSS score (△NIHSS) of >4 points (i.e. $NIHSS_{enrolment}$ – $NIHSS_{day14}$ >4 points) or NIHSS score less than 4 [32]. Setting of the primary endpoint event was consistent between the phase II, III and IV clinical trials.

Safety evaluation

Any adverse events during the test period were recorded and their relationships with the study drug were determined as either definitely related, highly possibly related, possibly related, possibly unrelated and definitely unrelated; the former three relationships were judged to be an adverse response to the study drug. In addition, the incidence of adverse events at day 14 of treatment was calculated.

Statistical analysis

Statistical analyses were conducted using SPSS 21.0 software (IBM Corp., Armonk, NY, USA). Measurement data were subjected to tests of normality. Data with a normal distribution are expressed as the mean ± standard deviation (SD), and those with a non-normal distribution are expressed as median (range or interquartile range [IQR]). Count data are expressed as *n* (%). Baseline consistency analysis was conducted using the non-parametric Mann–Whitney U-test. Factors associated with the clinical effectiveness of ginkgolide were investigated using binary logistic regression analysis, in which △NIHSS was considered as the dependent variable (binary data), and age, gender, time of onset to enrollment, systolic and diastolic blood pressure and baseline NIHSS score were considered as independent variables (other variables were screened out by univariate analysis using the chi-squared test or Student's *t*-test). Odds ratios (ORs) and 95% confidence intervals (95%CIs) were calculated in the logistic regression analysis. Excluded/missing data were replaced by average values. $P < 0.05$ was taken to indicate a significant difference.

Results

Baseline data for the participants in the pre-marketing and post-marketing studies

The demographic and clinical characteristics of the participants in the pre-marketing and post-marketing studies at enrolment are presented in Table 1. There were no significant differences between the pre-marketing and

Table 1. Baseline clinical characteristics of the participants in the pre-marketing and post-marketing studies.

	Pre-marketing study (phases II and III) (*N* = 437)	Post-marketing study (phase IV) (*N* = 3652)	*P* value
Male, *n* (%)	225 (51.5)	2260 (61.9)	<0.001
Age (years), median (interquartile)	62 (55–68)	62 (56–70)	0.045
Body mass index (kg/m^2), median (interquartile)	24.2 (22.9–25.95)	24.3 (22.6–26.0)	0.841
Time from onset to enrollment (days), median (interquartile)	37 (20–75)	29 (10–60)	<0.001
Blood pressure (mmHg), median (interquartile)			
Systolic blood pressure	130 (130–140)	130 (125–140)	0.871
Diastolic blood pressure	80 (75–85)	80 (76–88)	0.236
Baseline NIHSS score, median (interquartile)	9 (7–11)	4 (2–6)	<0.001
Baseline mRS score, median (interquartile)	3 (2–3)	2 (1–3)	<0.001
Comorbid diseases, *n* (%)			<0.001
Hypertension only	77 (17.62)	1364 (37.35)	
Diabetes mellitus only	19 (4.35)	231 (6.33)	
Hyperlipidemia only	1 (0.23)	129 (3.53)	
Hyperuricemia only	0	7 (0.19)	
Two of the above comorbidities	5 (1.14)	580 (15.88)	
Three of the above comorbidities	0	94 (2.57)	
None	314 (71.85)	1247 (34.15)	

mRS, modified Rankin scale; NIHSS, National Institutes of Health Stroke Scale.

post-marketing groups in body mass index, systolic blood pressure and diastolic blood pressure, but there were significant differences between groups in gender, age, time of onset to enrollment, severity of stroke at baseline, mRS score and comorbidities ($P < 0.05$).

Effect of ginkgolide injection on the neurologic function of patients with acute ischemic stroke

As shown in Table 2, the NIHSS and mRS scores of patients treated for 14 days with intravenous ginkgolide were significantly decreased, as compared with the baseline values at enrolment, in both the pre-marketing and post-marketing studies ($P < 0.001$). As shown in Figure 1, the proportion of patients with a mRS score ≤2 points was higher after 14 days of treatment with ginkgolide than that at baseline in the phase II study (66.3% vs. 38.8%), phase III study (60.0% vs. 34.5%) and phase IV study (81.7% vs. 69.4%). Compared with the baseline values, the proportion of participants in the pre-marketing study with an mRS score of 3 points was decreased by about 20% after 14 days of treatment with ginkgolide (Figure 1).

Analysis of the consistency between the pre-marketing and post-marketing studies in the effectiveness of intravenous ginkgolide

To analyze the consistency between the pre-marketing and post-marketing studies with regard to the effectiveness of intravenous ginkgolide on neurologic function in patients with stroke, univariate analysis (using the chi-squared test) was first performed to determine the associations of risk factors (grouping, gender, age, time of onset to enrollment, body mass index, systolic blood pressure, diastolic blood pressure and baseline NIHSS score) with △NIHSS. The univariate analysis returned significant associations of △NIHSS with male and more severe stroke (baseline NIHSS>8 points) ($P < 0.05$) but non-significant associations of △NIHSS with grouping, age, time of onset to enrollment, body mass index, systolic blood pressure and diastolic blood pressure. Significant factors in the univariate analysis (gender and baseline NIHSS) were included in the logistic regression analysis. In addition, based on clinical experience that disease duration at enrolment could influence the effects of PAF pathway, the time of onset to enrollment was also entered into the logistic regression analysis. Furthermore, since the aim of this study was to explore whether the study type (pre-marketing or post-marketing) influenced the observed effects of ginkgolide therapy, grouping was also included as an independent variable in the logistic regression analysis.

As shown in Table 3, those factors significantly associated with △NIHSS after 14 days of therapy with ginkgolide were grouping (pre-marketing vs. post-marketing; OR 2.169, 95%CI = 1.462–3.216, $P < 0.001$), male (OR = 1.532, 95%CI = 1.152–2.037, $P = 0.003$), enrollment within 30 days after onset (OR = 1.915, 95%CI = 1.452–2.526, $P < 0.001$) and NIHSS score more than 8 points at baseline (OR = 15.140, 95%CI = 11.436–20.045, $P < 0.001$) after adjustment.

Table 2. Effects of intravenous ginkgolide on NIHSS and mRS scores in participants in the pre-marketing and post-marketing studies.

	Baseline	After ginkgolide therapy for 14 days	*P* value (Mann–Whitney U test)
National Institutes of Health Stroke Scale score			
Pre-marketing study (phase II and phase III)	9 (7–11)	7 (5–9)	<0.001
Post-marketing study (phase IV)	4 (2–6)	2 (1–4)	<0.001
Modified Rankin scale score			
Pre-marketing study (phase II and phase III)	3 (2–3)	2 (2–3)	<0.001
Post-marketing study (phase IV)	2 (1–3)	1 (1–2)	<0.001

Data shown as median (interquartile).

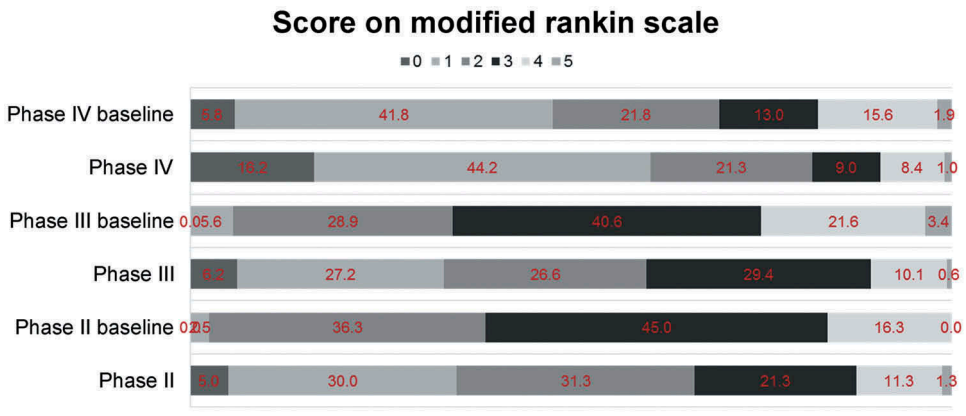

Figure 1. Modified Rankin scale scores for the study participants. Shown for each clinical trial (phase II, III and IV) are the proportions of participants with each modified Rankin scale score at baseline and after 14 days of treatment with daily ginkgolide injections.

Table 3. Multivariable logistic regression analysis of the factors associated with clinical improvement (ΔNIHSS>4) after 14 days of therapy with ginkgolide injections.

	P value	Odds ratio (95%CI)
Grouping (post-marketing studies as reference)	<0.001	2.169 (1.462, 3.216)
Sex (female as reference)	0.003	1.532 (1.152, 2.037)
Time of onset to enrollment (Time of onset to enrollment>30 days as reference)	<0.001	1.915 (1.452, 2.526)
NIHSS score at baseline (NIHSS score ≤8 points as reference)	<0.001	15.140 (11.436, 20.045)

95%CI, 95% confidence interval; NIHSS, National Institutes of Health Stroke Scale. Multivariable logistic regression was adjusted by onset age, sex, baseline NIHSS, time of onset to enrollment and grouping.

Subgroup analyses of data from the pre-marketing and post-marketing studies

The clinical data from the pre-marketing (phase II and III) and post-marketing (phase IV) studies were subjected to subgroup analyses to further investigate the factors affecting the clinical effectiveness of ginkgolide (Table 4). The effect of ginkgolide therapy on △NIHSS was influenced by time of onset to enrollment at enrollment (i.e. greater improvement for a time of onset to enrollment ≤30 days vs. >30 days) in both the pre-marketing study (OR = 2.686, 95%CI = 1.295–5.571, $P = 0.008$) and post-marketing study (OR = 1.655, 95% CI = 1.219–2.248, $P = 0.01$). The effectiveness of ginkgolide therapy was also influenced by baseline NIHSS score (i.e. greater improvement for a baseline NIHSS score >8 points vs. ≤8 points) in both the pre-marketing study (OR = 1.449, 95%CI = 1.161–2.507, $P = 0.032$) and post-marketing study (OR = 1.053, 95%CI = 1.040–1.074, $P < 0.001$). In addition, the effect of ginkgolide on △NIHSS was significantly better in male patients than in female patients in the phase IV study (OR = 1.508, 95%CI = 1.102–2.063, $P = 0.01$).

Safety analysis

Among the 437 participants in the pre-marketing (phase II and III) study, two (0.46%) experienced adverse reactions, which mainly manifested as facial flushing, dizziness, headache, nausea, vomiting and epigastric distension. No severe adverse events occurred among participants in the pre-marketing study.

Among the 3652 participants in the post-marketing (phase IV) study, there were a total of 301 drug-related adverse events in 189 patients, an incidence of 5.18%. Severe adverse events occurred in 8 cases (0.22%). In addition to the adverse reactions observed in the pre-marketing group, the post-marketing group also experienced the following adverse events: erythrasma, pruritus, tiredness, chest tightness, palpitation, erythema, maculopapular rash, abnormal liver function, fever and arthralgia. These adverse reactions were mainly mild or moderate and were alleviated after discontinuation of the drug. The frequency, number of cases and incidence of adverse reactions in the post-marketing group are shown in Supplemental Table 2. Interestingly, there is no symptomatic hemorrhagic stroke among 4089 cases.

Discussion

This study found that treatment with ginkgolide for 14 days resulted in reductions in the NIHSS and mRS scores in both the pre-marketing and post-marketing studies. Furthermore, grouping (pre-marketing vs. post-marketing) was a factor influencing the improvement in NIHSS scores after therapy, and the difference in therapeutic effect between the pre-marketing and post-marketing studies might also be associated with gender, time of onset to enrollment time from onset to enrolled and severity of stroke. In addition, subgroup

Table 4. Subgroup analyses of clinical improvement (ΔNIHSS > 4) from the pre-marketing and post-marketing studies.

Subgroup	Pre-marketing study (phase II and III)	OR (95%CI)	*P* value	Post-marketing study (phase IV)	OR (95%CI)	*P* value
Gender		1.340 (0.668, 2.688)	0.410		1.508 (1.102, 2.063)	0.010
Female	15 (7.08)			70 (5.03)		
Male	23 (10.22)			172 (7.61)		
Age		2.537 (1.597, 6.385)	0.840		1.101 (0.821, 1.477)	0.519
≥65 years	17 (9.24)			104 (7.15)		
<65 years	21 (8.30)			138 (6.28)		
Baseline NIHSS		1.449 (1.161, 2.507)	0.032		1.053 (1.040, 1.074)	<0.001
≤8	11 (5.07)			83 (2.62)		
>8	27 (12.27)			159 (32.92)		
Baseline SBP		1.790 (1.217, 5.635)	0.330		2.545 (1.878, 3.991)	0.733
≤150 mmHg	33 (8.01)			200 (6.30)		
>150 mmHg	5 (20.0)			42 (8.82)		
Onset to enrollment		2.686 (1.295, 5.571)	0.008		1.655 (1.219, 2.248)	0.001
>30 days	12 (5.04)			79 (4.42)		
≤30 days	26 (13.07)			163 (8.74)		

95%CI, 95% confidence interval; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; SBP, systolic blood pressure.

analysis showed that the effect of ginkgolide was greater in the patients' onset less than the time of onset to enrollment 30 days and baseline NIHSS more than 8 points. Importantly, safety analysis demonstrated that the incidences of adverse reactions in the pre-marketing and post-marketing studies were low (0.46% and 5.28%), with very few serious adverse events (0% and 0.22%). Taken together, our findings indicated that intravenous ginkgolide may be safe and effective for the treatment of acute ischemic stroke in patients in China.

It should be noted that the pre-marketing clinical study had stringent inclusion and exclusion criteria, with the exclusion of patients with hyperuricemia and restrictions of baseline NIHSS and age. Therefore, the rate of comorbidities was relatively low in pre-marketing studies. By comparison, the post-marketing phase IV study had less restricted inclusion criteria and thus more closely reflected the clinical situation in the real world. These differences in inclusion and exclusion criteria between the pre-marketing and post-marketing studies likely accounted for the observed differences in age, time of onset to enrollment, NIHSS score, mRS score and comorbidities.

The pathogenesis of cerebral infarction [33] is complex and associated with platelet adhesion, vascular endothelial injury, platelet aggregation, lipid metabolism disorders, atherosclerosis and a hypercoagulable state, as well as vascular stenosis and occlusion. Acute cerebral infarction leads to cerebral hypoxia-induced anoxia, which results in disorders of cell metabolism, neurotoxicity, oxidative stress and a cascade of cellular changes. Studies have revealed that, following cerebral infarction, the neurons in the ischemic penumbra lose their function but retain an intact structure. The function of these neurons may be restored to varying degrees if the blood supply is recovered in time, thereby reducing delayed neuronal damage [34].

Ginkgolide (Baiyu®) is consisted with two major components, includes ginkgoid and bilobalide. Early in-vitro studies found that ginkgolide injection could inhibit platelet aggregation and that the antagonism of platelet-activating factor (PAF)-induced platelet aggregation was superior to that of aspirin and clopidogrel [35,36]. Clinically, ginkgolide has been reported the potential efficacy in the treatment of atherosclerotic cerebral infarction, recanalization of occluded basilar arteries and treatment of acute ischemic stroke when given in combination with alteplase (within the thrombolysis time window) [37,38]. Bilobalide has been reported as neuroprotection, maintains the integrity of vascular endothelial cells, promotes angiogenesis and inhibits microglia [39], and numerous studies have demonstrated that bilobalide can attenuate infarct volume, cerebral edema, neuronal damage and neurologic deficits [40,41]. Clinically, a combination of bilobalide with mecobalamin might be associated with a better outcome in the treatment of diabetic peripheral neuropathy than mecobalamin alone [42].

In this study, re-analyses of the clinical data from pre-marketing and post-marketing studies revealed that the NIHSS score was significantly decreased after 14 days of treatment with ginkgolide injection, compared with that at enrolment. These data indicated that ginkgolide could improve neurologic function in patients with ischemic stroke. These findings are consistent with previous studies in patients with acute ischemic stroke [27–30].

The present study was not designed to elucidate the mechanisms underlying this beneficial effect of ginkgolide. Previous studies have identified a variety of mechanisms that might contribute to the neuroprotective effects of ginkgoid components, with increasing cerebral blood flow [17,20], inhibition of inflammation with reductions in the levels of nuclear factor kappa-B, tumor necrosis factor-alpha, interleukin-beta-1, interleukin-6 and other inflammatory mediators [15,24,40,43,44], down-regulation of JNK1/2 and p38 MAPK signaling pathways [40], decreased production of reactive oxygen species and anti-oxidative actions [15,17,21,40], attenuation of mitochondrial dysfunction [13,41], suppression of neurotransmitter release and excitotoxicity [31,39,41], up-regulation of brain-derived neurotrophic factor [12], modulation of metabolic pathways [45], alteration of the phenotype of microglia/macrophages [14], protection of blood-brain barrier integrity [19,24,43], enhanced astrocyte viability/activity and secretion of erythropoietin [46] and activation of pathways involving heme oxygenase-1 [16,23,26]. Of note, there is no symptomatic hemorrhagic stroke over 4000 cases in our study. We would like to hypothesis the ginkgolide as a safe PAF antagonism which might reduce the risk of hemorrhagic event. In recent years, studies have found that risk factors for the occurrence of stroke include previous stroke, age, hypertension, hyperlipidemia, body mass index, smoking and alcohol [47]. In this study, the beneficial effect of ginkgolide was found to be associated with gender, severity of stroke at enrollment and time of onset to enrollment, while the benefits were unlikely to be diminished by age or other comorbidities. Furthermore, all these results were consistent between the phase II–III and phase IV trials. Further studies are needed to confirm and extend these interesting findings.

This retrospective study has several limitations. Firstly, this is a retrospective study of previous studies. Therefore, we only had limited data due to the previous study protocols. The protocols and study year were varied which caused the stroke population of pre-marketing studies and post-marketing study varying in our study. This may cause the limitation to

extend our findings to whole stroke population. Secondly, we have reported the outcome as NIHSS improvement after short-term treatment. Although it would be more meaningful there was an improvement in mRS which indicated the function outcome, the trend in NIHSS scores was consistent with that of mRS which was more sensitive. Finally, the present study was not designed to elucidate the mechanisms underlying this beneficial effect of ginkgolide. Although there were several hypotheses in PAF antagonism and neuroprotective effect, further randomized-controlled studies on mechanism are needed to prove the effectiveness.

In summary, intravenous ginkgolide in the first 30 days after stroke were effective at improving the neurologic function of patients with acute ischemic stroke. The beneficial effect of ginkgolide was greater in males, in patients with a baseline NIHSS score >8 points (i.e. more severe neurologic deficit). In addition, the phase II/III/IV clinical studies demonstrated that the therapy was well tolerated, with a low incidence of adverse events and a very low incidence of serious adverse events. Future studies could be focused on additional antiplatelet agent, such like ginkoglide to prevent a recurrent stroke.

Acknowledgments

Dr Yi Dong and Dr Qiang Dong designed the study. Huiqin Li provided the original data of all the trials. Dr Yi Dong performed the data analysis and draft the manuscript. All authors approved the final version of manuscript.

Disclosure statement

No potential conflict of interest was reported by the authors.

Notes on contributors

Yi Dong is an attending of Neurology Department, Huashan Hospital.

Huiqin Li is an agent of Medical Affair Department, Baiyu Lcd.

Qiang Dong is the chief of Neurology Department, Huashan Hospital.

ORCID

Yi Dong http://orcid.org/0000-0001-6630-112X

References

[1] Feigin VL, Forouzanfar MH, Krishnamurthi R, et al. Global and regional burden of stroke during 1990-2010: findings from the Global Burden of Disease Study 2010. Lancet. 2014;383:245–254.

[2] Wang Y, Cui L, Ji X, et al. The China National Stroke Registry for patients with acute cerebrovascular events: design, rationale, and baseline patient characteristics. Int J Stroke. 2011;6:355–361.

[3] Liu L, Wang D, Wong KS, et al. Stroke and stroke care in China: huge burden, significant workload, and a national priority. Stroke. 2011;42:3651–3654.

[4] Khatri P, Abruzzo T, Yeatts SD, et al. Good clinical outcome after ischemic stroke with successful revascularization is time-dependent. Neurology. 2009;73:1066–1072.

[5] Rha JH, Saver JL. The impact of recanalization on ischemic stroke outcome: a meta-analysis. Stroke. 2007;38:967–973.

[6] Wardlaw JM, Murray V, Berge E, et al. Thrombolysis for acute ischaemic stroke. Cochrane Database Syst Rev. 2014;7:Cd000213.

[7] Kaihua W, Longjian H, Guangshan Z, Xinhua Z. Advances in research on acute ischemic stroke. J Guangxi Univ Chin Med. 2016;19:72–76.

[8] Chinese Society of Neurology. Guidelines for diagnosis and treatment of acute ischemic stroke in China (2014). Chin J Neurol. 2015;48:246–257.

[9] Nash KM, Shah ZA. Current perspectives on the beneficial role of Ginkgo biloba in neurological and cerebrovascular disorders. Integr Med Insights. 2015;10:1–9.

[10] Nabavi SM, Habtemariam S, Daglia M, et al. Neuroprotective effects of ginkgolide B against ischemic stroke: a review of current literature. Curr Top Med Chem. 2015;15:2222–2232.

[11] Cao L, Lan X, Wang L, et al. The neuroprotective effects of ginkgolide on acute cerebral ischemia/reperfusion injury in rats. Chin J Clin Pharmacol Ther. 2015;20:721–726.

[12] Wei H, Sun T, Tian Y, et al. Ginkgolide B modulates BDNF expression in acute ischemic stroke. J Korean Neurosurg Soc. 2017;60:391–396.

[13] Zhou X, Wang HY, Wu B, et al. Ginkgolide K attenuates neuronal injury after ischemic stroke by inhibiting mitochondrial fission and GSK-3beta-dependent increases in mitochondrial membrane permeability. Oncotarget. 2017;8:44682–44693.

[14] Shu ZM, Shu XD, Li HQ, et al. Ginkgolide B protects against ischemic stroke via modulating microglia polarization in mice. CNS Neurosci Ther. 2016;22:729–739.

[15] Wei J, Fang W, Sha L, et al. XQ-1H suppresses neutrophils infiltration and oxidative stress induced by cerebral ischemia injury both in vivo and in vitro. Neurochem Res. 2013 Oct 12;38:2542–2549. [Epub ahead of print].

[16] Nada SE, Shah ZA. Preconditioning with Ginkgo biloba (EGb 761(R)) provides neuroprotection through HO1 and CRMP2. Neurobiol Dis. 2012;46:180–189.

[17] Huang M, Qian Y, Guan T, et al. Different neuroprotective responses of Ginkgolide B and bilobalide, the two Ginkgo components, in ischemic rats with hyperglycemia. Eur J Pharmacol. 2012;677:71–76.

[18] Yang Q, Fang W, Lv P, et al. Therapeutic neuroprotective effects of XQ-1H in a rat model of permanent focal cerebral ischemia. Pharmacology. 2012;89:1–6.

[19] Lv P, Fang W, Geng X, et al. Therapeutic neuroprotective effects of ginkgolide B on cortex and basal ganglia in a rat model of transient focal ischemia. Eur J Pharm Sci. 2011;44:235–240.

[20] Sun J, Li Y, Fang W, et al. Therapeutic time window for treatment of focal cerebral ischemia reperfusion

injury with XQ-1h in rats. Eur J Pharmacol. 2016;666:105–110.
[21] Ma S, Yin H, Chen L, et al. Neuroprotective effect of ginkgolide K against acute ischemic stroke on middle cerebral ischemia occlusion in rats. J Nat Med. 2012;66:25–31.
[22] Yang ZZ, Li J, Li SX, et al. Effect of ginkgolide B on striatal extracellular amino acids in middle cerebral artery occluded rats. J Ethnopharmacol. 2011;136:117–122.
[23] Shah ZA, Nada SE, Dore S. Heme oxygenase 1, beneficial role in permanent ischemic stroke and in Gingko biloba (EGb 761) neuroprotection. Neuroscience. 2011;180:248–255.
[24] Liu YG, Li FJ, Wang J, et al. Effects of Ginkgolide B on inflammation induced by cerebral ischemia-reperfusion in rats. Zhong Yao Cai. 2010;33:578–580.
[25] Fang W, Deng Y, Li Y, et al. Blood brain barrier permeability and therapeutic time window of Ginkgolide B in ischemia-reperfusion injury. Eur J Pharm Sci. 2010;39:8–14.
[26] Saleem S, Zhuang H, Biswal S, et al. Ginkgo biloba extract neuroprotective action is dependent on heme oxygenase 1 in ischemic reperfusion brain injury. Stroke. 2008;39:3389–3396.
[27] Zhu PH, Deng TX. Effect of ginkgo leaves on functional prognosis in patients with acute ischemic stroke. Contemp Med. 2015;21:142–143.
[28] Li SS, Fang Q, Zhang XJ, et al. The effect of ginkgo ketone dispersible tablets on neurological and cognitive functions in patients with acute and convalescent ischemic stroke: a multicenter, randomized, open, controlled clinical study. The 17th National Symposium on Neurology in Jiangsu Province; Oct 31; Nantong, Jiangsu: Jiangsu Medical Association; 2014. p. 288.
[29] Oskouei DS, Rikhtegar R, Hashemilar M, et al. The effect of Ginkgo biloba on functional outcome of patients with acute ischemic stroke: a double-blind, placebo-controlled, randomized clinical trial. J Stroke Cerebrovasc Dis. 2013;22:e557–563.
[30] Demarin V, Basic Kes V, Trkanjec Z, et al. Efficacy and safety of Ginkgo biloba standardized extract in the treatment of vascular cognitive impairment: a randomized, double-blind, placebo-controlled clinical trial. Neuropsychiatr Dis Treat. 2017;13:483–490.
[31] Zeng X, Liu M, Yang Y, et al. Ginkgo biloba for acute ischaemic stroke. Cochrane Database Syst Rev. 2005;4:Cd003691.
[32] Hoffman JR, Schriger DL. A graphic reanalysis of the NINDS Trial. Ann Emerg Med. 2009;54:329–336.
[33] Qiu B, Xiao Z. Clinical observation on treatment of acute cerebral infarction with ginkgo lactone diterpene Portuguese amine injection. Chin J Integr Med Cardio/Cerebrovascular Dis. 2015;13:1033–1035.
[34] Li HL, Yin XX. Clinical observation on treatment of acute ischemic stroke with ginkgo lactone diterpene Portuguese amine injection. Mod Hosp. 2017;17:239–244.
[35] Xu L, Huang Y. The effects of Bai Yu ginkgolide injection on platelet aggregation in rabbits. J Emergency Traditional Chin Med. 2014;23:638–643.
[36] Xu L, Zhang TJ. The effects of Baiyu ginkgolide injection combined with aspirin, clopidogrel on platelet aggregation and ultra structure changes. J Zunyi Med Univ. 2015;38:25–27.
[37] Zhang H, Qin X, Zhao D, et al. One case receiving recanalization of occluded basilar artery with ginkgolide injection. Chin J Pract Nerv Dis. 2016;19:128–142.
[38] Li C, Dai YJ, Guo W, et al. Clinical study on Ginkgo biloba lactone injection combined with rt-PA intravenous thrombolysis in treatment of acute ischemic stroke. Drug Eval Res. 2017;40:764–768.
[39] Lang D, Kiewert C, Mdzinarishvili A, et al. Neuroprotective effects of bilobalide are accompanied by a reduction of ischemia-induced glutamate release in vivo. Brain Res. 2011;1425:155–163.
[40] Jiang M, Li J, Peng Q, et al. Neuroprotective effects of bilobalide on cerebral ischemia and reperfusion injury are associated with inhibition of pro-inflammatory mediator production and down-regulation of JNK1/2 and p38 MAPK activation. J Neuroinflammation. 2014;11:167.
[41] Schwarzkopf TM, Hagl S, Eckert GP, et al. Neuroprotection by bilobalide in ischemia: improvement of mitochondrial function. Pharmazie. 2013;68:584–589.
[42] Li JW. The efficacy of ginkgolide with methylcobalamin in treating diabetic peripheral neuropathy. Shenzhen J Integr Traditional Chin West Med. 2015;25:57–58.
[43] Fang W, Sha L, Kodithuwakku ND, et al. Attenuated blood-brain barrier dysfunction by XQ-1H following ischemic stroke in hyperlipidemic rats. Mol Neurobiol. 2015;52:162–175.
[44] Wang X, Qin ZH, Shi H, et al. Protective effect of Ginkgolids (A+B) is associated with inhibition of NIK/IKK/IkappaB/NF-kappaB signaling pathway in a rat model of permanent focal cerebral ischemia. Brain Res. 2008;1234:8–15.
[45] Geng JL, Aa JY, Feng SQ, et al. Exploring the neuroprotective effects of ginkgolides injection in a rodent model of cerebral ischemia-reperfusion injury by GC-MS based metabolomic profiling. J Pharm Biomed Anal. 2017;142:190–200.
[46] Wu X, Zhou C, Du F, et al. Ginkgolide B preconditioning on astrocytes promotes neuronal survival in ischemic injury via up-regulating erythropoietin secretion. Neurochem Int. 2013;62:157–164.
[47] Sun M, Jiang YN. Clinical analysis of high-risk factors of stroke and exploration of preventive measures. National Med Front China. 2010;5:63.