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Xueshuantong improves cerebral blood perfusion in elderly patients with lacunar infarction★

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Abstract

A total of 64 patients with acute lacunar infarction were enrolled within 24 hours of onset. The patients received conventional therapy (antiplatelet drugs and hypolipidemic drugs) alone or conventional therapy plus 450 mg *Xueshuantong* once a day. The main ingredient of the *Xueshuantong* lyophilized powder used for injection was *Panax notoginseng* saponins. Assessments were made at admission and at discharge using the National Institutes of Health Stroke Scale, the Activity of Daily Living and the Mini-Mental State Examination. Additionally, the relative cerebral blood flow, relative cerebral blood volume and relative mean transit time in the region of interest were calculated within 24 hours after the onset of lacunar infarction, using dynamic susceptibility contrast magnetic resonance perfusion imaging technology. Patients underwent a follow-up MRI scan after 4 weeks of treatment. There was an improvement in the Activity of Daily Living scores and a greater reduction in the scores on the National Institutes of Health Stroke Scale in the treatment group than in the control group. However, the Mini-Mental State Examination scores showed no significant differences after 4 weeks of treatment. Compared with the control group, the relative cerebral blood flow at discharge had increased and showed a greater improvement in the treatment group. Furthermore, there was a reduction in the relative mean transit time at discharge and the value was lower in the treatment group than in the control group. The experimental findings indicate that *Xueshuantong* treatment improves neurological deficits in elderly patients with lacunar infarction, and the mechanism may be related to increased cerebral perfusion.

Key Words

neural regeneration; traditional Chinese medicine; *Xueshuantong*; cerebral perfusion; lacunar infarction; *Panax notoginseng* saponins; cerebrovascular disease; neuroprotection; grants-supported paper; photographs-containing paper; neuroregeneration

Research Highlights

(1) A prospective randomized double-blind controlled clinical trial was performed to evaluate the therapeutic effect of *Xueshuantong* in elderly patients with lacunar infarction. The results show a potential for clinical application.
(2) After 4 weeks of treatment, *Xueshuantong* improved the clinical symptoms, increased relative cerebral blood flow, and decreased the relative mean transit time in the region of interest in elderly patients with lacunar infarction.
(3) After the risk factors such as gender, age and hypertension were excluded, *Xueshuantong* was shown to significantly reduce the patients' scores on the National Institutes of Health Stroke Scale.

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INTRODUCTION

Lacunar infarction was first reported by Fisher[1] in 1965. It is defined by small cavities that result from the occlusion of an artery, between 2 mm and 20 mm in diameter. It is predominantly localized to the basal ganglia, deep brain white matter or brainstem. When symptomatic, lacunar infarction usually manifests as one of five typical clinical syndromes: pure motor hemiparesis, sensorimotor syndrome, pure sensory syndrome, ataxic hemiparesis, and dysarthria (clumsy-hand syndrome)[2-4]. Occasionally, it causes atypical lacunar syndromes[5], which include dysarthria with central facial paresis, isolated hemiataxia, isolated dysarthria, and hemichorea-hemiballismus. As previously reported[6-8], the risk factors for lacunar infarction include age, gender, hypertension, diabetes mellitus, smoking, previous transient ischemic attack, ischemic heart disease, and carotid atherosclerosis. Of all of these factors, hypertension is thought to be a prerequisite for the development of lacunar infarction[1]; lacunar infarction generally develops in patients with hypertension and/or diabetes mellitus. Lacunar infarction accounts for approximately one quarter of all ischemic strokes in western countries[9]. In China this proportion is as high as 42.3%[10]. Compared with other kinds of stroke, lacunar infarction has favorable short-term outcomes, with almost no short-term mortality, a low risk of recurrent stroke, and a generally excellent recovery. However, recent studies demonstrate that the long-term prognosis is poor. The risk of vascular dementia, stroke recurrence and mortality in the long term is similar to that of non-lacunar stroke[11-14]. Rather than being a relatively benign condition, lacunar infarction can actually be a severely detrimental disease[15].

The pathophysiology of lacunar infarction is as yet incompletely understood[16]; it is usually regarded as an alteration of cerebral blood flow in the distribution area of penetrating arteries. Hemodynamic factors, embolic occlusion, thrombotic arteriopathies, inflammation, endothelial dysfunction, and other factors have been proposed as possible mechanisms. Recent observations suggest that endothelial dysfunction might be an important mechanism for lacunar infarction, and there is growing evidence that endothelial dysfunction is involved in the pathogenesis of lacunar infarction[17-19]. The endothelium has many physiological functions, such as the maintenance of adequate vessel tone and hemostasis, and the expression of adhesion molecules. Recent studies suggest that dysfunction of the cerebral microvascular endothelium may be the primary step in the process of lacunar infarction, leading to increasing permeability of the blood-brain barrier in microvessels[20]. This increased permeability causes blood products to reach the perivascular space and induces neuronal damage[21-22]. Kim *et al* [23] enrolled 45 patients with lacunar infarction and 44 age- and sex-matched patients who did not have lacunar infarction as the control group. They evaluated endothelial function using nitrogen-mediated dilatation and flow-mediated dilatation of the brachial artery. Compared with the control group, flow-mediated dilatation was lower in the lacunar infarction group; nitrogen-mediated dilatation was similar in the two groups. Results showed that endothelial function was impaired in the lacunar infarction group, and endothelial dysfunction might play an important role in the pathogenesis of lacunar infarction. Knottnerus *et al* [24] determined antigen levels of total and free full-length tissue factor pathway inhibitor in 149 lacunar infarction patients and 42 controls. Free full-length tissue factor pathway inhibitor was determined in 15 controls and a random subset of 17 lacunar infarction patients. Compared with the controls, levels of free full-length tissue factor pathway inhibitor were higher in lacunar infarction patients. The authors demonstrated that tissue factor pathway inhibitor, as a marker of endothelial activation, may play a substantial role in the pathogenesis of lacunar infarction. Altered hemodynamics is another important mechanism of lacunar infarction. Some studies[25-26] have asked whether there were brain perfusion deficits associated with lacunar infarction and progressive lacunar infarction. Poppe *et al* [25] studied the occurrence of MRI perfusion-weighted imaging abnormalities in 22 patients with lacunar infarction or transient ischemic attack. Fifteen patients (68.2%) had abnormalities in MRI perfusion-weighted imaging, such as decreased cerebral blood flow, decreased cerebral blood volume, or delayed mean transit time. Four patients (18.2%) experienced early clinical deterioration (National Institutes of Health Stroke Scale worsening of ≥ 3 points within 72 hours of event); all of these had brain perfusion abnormalities. No patients with normal MRI perfusion-weighted imaging showed deterioration. Yamada *et al* [26] studied CT-measured cerebral blood flow, cerebral blood volume, and mean transit time as predictors of progression in 26 patients with lacunar infarction admitted within 24 hours after onset. Thirteen patients worsened, whereas the other 13 patients did not; the patients who worsened exhibited lower cerebral blood flow and higher mean transit time.

Elderly people, who have several aging-related changes in the brain and more cardiovascular risk factors, showed an increased vulnerability to lacunar infarction. Elderly patients often have poorer outcomes than younger individuals; however, they receive less effective treatment[27]. Statins and antiplatelet agents have proved to be beneficial in lacunar infarction, but the use of these therapies in the elderly is limited[27]. More effective and safer drugs should thus be investigated for the treatment of lacunar infarction. If new drugs aim to correct endothelium dysfunction, improve local perfusion, and inhibit inflammation, effective therapies may be found. *Xueshuantong*, which is extracted from the important traditional Chinese medicinal herb *Panax notoginseng*, is reported to have extensive anti-inflammatory action and to correct endothelium dysfunction in cell-based and animal studies[28-29]. In the clinic, *Xueshuantong* is frequently reported as a beneficial agent to treat acute ischemic stroke[30]. However, the use of *Xueshuantong* for the treatment of lacunar infarction subtypes in elderly patients is rarely reported, and its effects on cerebral perfusion are unconfirmed. We hypothesized that *Xueshuantong* could improve local brain perfusion through its anti-inflammatory effects and by correcting endothelium dysfunction. This study focused on the efficacy of *Xueshuantong* for lacunar infarction in elderly patients and examined its effects on cerebral perfusion, to increase treatment options for elderly patients with acute lacunar infarction.

RESULTS

Quantitative analysis of participants

Between October 2009 and April 2011, we enrolled 64 elderly patients who had been admitted to the First Affiliated Hospital, School of Medicine, Zhejiang University, within 24 hours of onset of first-time acute lacunar infarction. Of these, 33 patients were included in the control group and underwent conventional therapy only (antiplatelet drugs and hypolipidemic drugs). The other 31 patients composed the treatment group, and received both conventional therapy and *Xueshuantong*. All patients were involved in the final analysis.

Inclusive criteria and random allocation

Seventy-eight consecutive patients with lacunar infarction were collected, and of those, 67 met the inclusion criteria and were enrolled. Patients were randomized into two groups (treatment group and control group), using a computer-generated list, to receive *Xueshuantong* or not. Of the 67 enrolled patients, three patients were excluded by the investigator: two in the treatment group and one in the control group. Finally, 64 patients were included in the result analysis, including 31 in the treatment group and 33 in the control group (Figure 1).

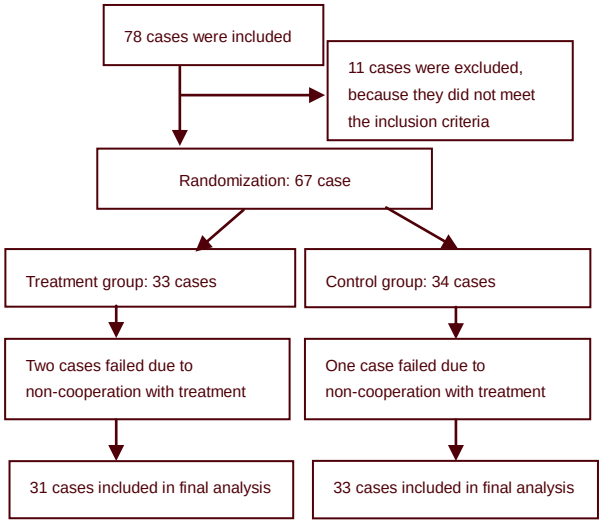

Figure 1 Flow chart of participant enrollment.

Baseline information of lacunar infarction patients

Table 1 shows the clinical characteristics of the patients in the two groups. There were no significant differences in terms of baseline clinical characteristics (sex and age) or risk factors (diabetes mellitus, hypertension, atrial fibrillation, hyperlipidemia and smoking) between the treatment group and control group at the onset of lacunar infarction ($P > 0.05$).

Table 1 Patient's demographics at onset of lacunar infarction

Variable	Treatment group (n = 31)	Control group (n = 33)	t/X^2	P
Age (mean±SD, year)	80.1±5.6	79.3±7.3	0.507	0.614
Sex (male/female, n)	23/8	25/8	0.021	0.885
Diabetes mellitus [n(%)]	10 (32)	11 (33)	0.008	0.927
Hypertension [n(%)]	25 (81)	24 (73)	0.558	0.455
Atrial fibrillation [n(%)]	7 (23)	8 (24)	0.025	0.875
Hyperlipidemia [n(%)]	17 (55)	16 (48)	0.258	0.611
Smoker [n(%)]	6 (19)	8 (24)	0.223	0.636

There was no significant difference in clinical characteristics or risk factors between the control group and the treatment group. The chi-square test was used to compare proportions, and the independent-samples t-test was used to compare continuous variables.

Effect of *Xueshuantong* on the cerebral perfusion parameters of lacunar infarction patients

Dynamic susceptibility contrast magnetic resonance perfusion imaging showed that, after 4 weeks of treatment, both groups showed an increase in relative

cerebral blood flow and a decrease in relative mean transit time. Compared with the control group, the relative cerebral blood flow at discharge were significantly increased and showed a greater improvement in the treatment group ($P < 0.01$ or $P < 0.05$), while the relative mean transit time at discharge and the reduction in mean transit time also showed significant differences between *Xueshuantong* treated and untreated patients ($P < 0.05$). However, there was no significant difference in the relative cerebral blood volume of the two groups at discharge (Figures 2 and 3).

Effect of *Xueshuantong* on the clinical outcomes of lacunar infarction patients

After 4 weeks of treatment, both groups showed a reduction in National Institutes of Health Stroke Scale scores and an improved score for Activity of Daily Living. However, there was no significant difference between the two groups in the Mini-Mental State Examination scores at discharge. Compared with the control group, the improvements in the above parameters were more apparent in lacunar infarction patients after *Xueshuantong* treatment (Figure 4).

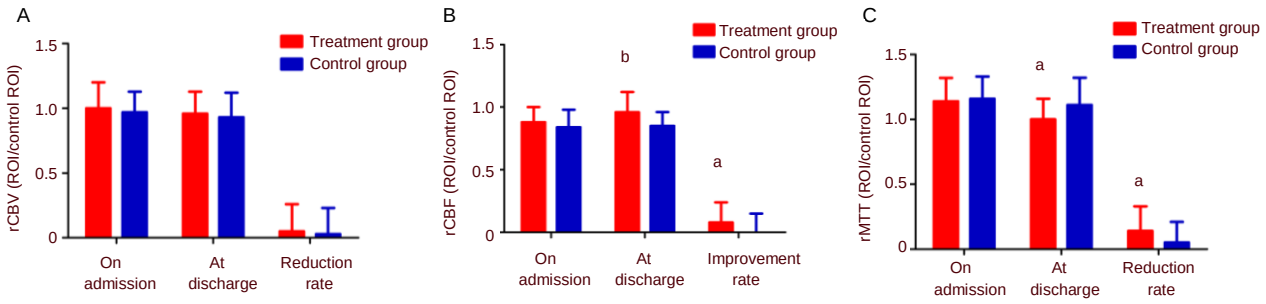

Figure 2 Alterations in the cerebral perfusion of lacunar infarction patients treated with *Xueshuantong* or conventional therapy only.

(A) Average rCBV results. Reduction rate = rCBV on admission – rCBV at discharge.

(B) Average rCBF results. Improvement rate = rCBF at discharge – rCBF on admission.

(C) Average rMTT results. Reduction rate = rMTT on admission – rMTT at discharge

All values are expressed as mean ± SD; there are 31 patients in the treatment group and 33 patients in the control group. [a]$P < 0.05$, [b]$P < 0.01$, *vs*. control group using independent-samples *t*-test.

rCBV: Relative cerebral blood volume; rCBF: relative cerebral blood flow; rMTT: relative mean transit time; ROI: region of interest.

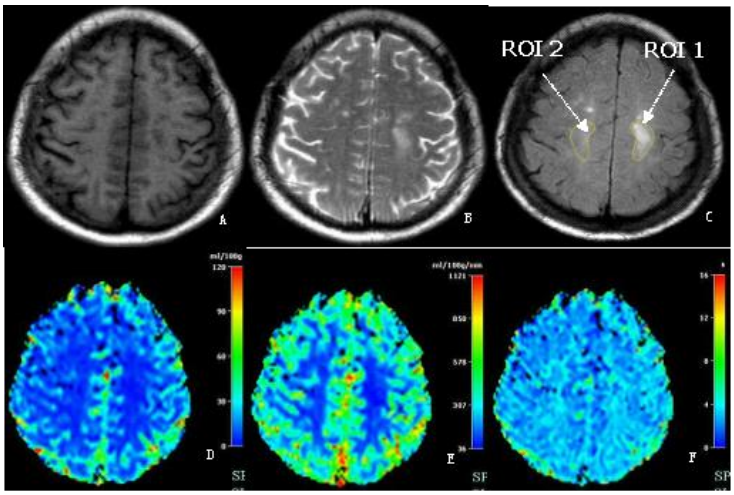

Figure 3 MRI and perfusion-weighted imaging scans from a 78-year-old man with dysarthria and right extremity weakness.

Baseline MRI, acquired 16 hours after symptom onset, revealed a lesion in the left centrum ovale. Baseline T1-weighted images (A), T2-weighted images (B), fluid-attenuated inversion recovery (C), cerebral blood volume (D), cerebral blood flow (E), mean transit time (F). On the fluid-attenuated inversion recovery map on MRI scans, a region of interest (ROI) was manually drawn based on the largest high signal intensity areas (ROI 1). Another control region of interest (ROI 2) was manually drawn based on the mirroring position to ROI 1 in the contralateral hemisphere.

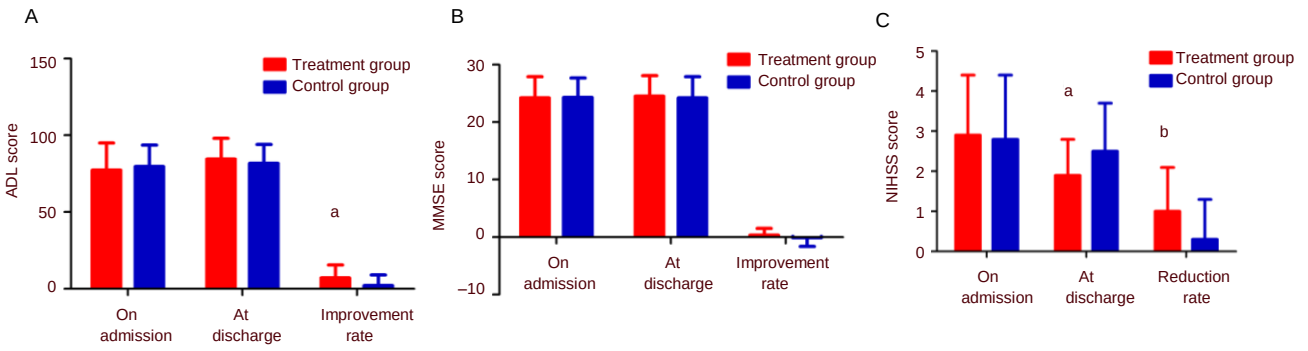

Figure 4 Alterations in clinical outcomes of lacunar infarction patients treated with *Xueshuantong* or conventional therapy only.

(A) Average ADL scores. Improvement rate = ADL scores at discharge – ADL scores on admission. Higher ADL scores were associated with a favorable outcome.

(B) Average MMSE scores. Improvement rate = MMSE scores at discharge – MMSE scores on admission. Higher MMSE scores were associated with a favorable outcome.

(C) Average NIHSS scores. Reduction rate = NIHSS scores on admission – NIHSS scores at discharge. Lower NIHSS scores were associated with a favorable outcome.

All values are expressed as mean ± SD; there are 31 patients in the treatment group and 33 patients in the control group. $^{a}P < 0.05$, $^{b}P < 0.01$ *vs*. control group using independent-samples *t*-test.

NIHSS: National Institutes of Health Stroke Scale; ADL: Activity of Daily Living; MMSE: Mini-Mental State Examination.

Influencing factors for the reduction in National Institutes of Health Stroke Scale scores

A multiple regression model was used to adjust the correlation between the reduction in National Institutes of Health Stroke Scale score and sex, age, diabetes mellitus, atrial fibrillation, hypertension, smoking, hyperlipidemia, National Institutes of Health Stroke Scale scores on admission, and *Xueshuantong* use. The final model included only one variable that remained significant after its application. In the final model, only the use of *Xueshuantong* (standardized partial coefficient = 0.327; $P = 0.008$) was significantly associated with the reduction in National Institutes of Health Stroke Scale scores.

DISCUSSION

Ischemic stroke is a common cause of death throughout the world, occurring mostly in elderly people (aged ≥ 65 years). It is reported that, after the age of 55 years, the stroke rate doubles for each successive decade[31]. About 80% of ischemic strokes occur in individuals aged 65 years or over[32-33]. Lacunar infarction, a subtype of ischemic stroke, accounts for one quarter of these. Compared with younger patients, elderly patients with lacunar infarction recover more slowly, and have more severe stroke deficits at presentation and poorer outcomes (in terms of mortality rate and disability). Despite this, elderly patients usually receive less effective treatment. For example, recombinant tissue plasminogen activator, which remains the only approved therapy for acute lacunar infarction, is not normally used in older people. One contributing factor to this is that elderly patients have been excluded from or underrepresented in studies of the use of recombinant tissue plasminogen activator. Therefore, it is particularly important to establish safe and effective treatments for elderly lacunar infarction patients, to reduce the incidence of lacunar infarction and improve outcomes.

Xueshuantong has shown extensive effects in cerebrovascular diseases, including ischemic stroke. Previous studies have shown multiple beneficial effects of *Xueshuantong* on the cerebrovascular system, such as preventing neurotoxicity[34], inhibiting vascular smooth muscle cell proliferation[35], inhibiting inflammation-induced monocyte adhesion and endothelial adhesion molecule expression[36], attenuating atherogenesis through anti-inflammatory actions and regulation of the blood lipid profile[37].

This study aimed to examine the role of *Xueshuantong* in

cerebral perfusion, which plays an important part in the pathogenesis of lacunar infarction[38], in elderly patients. In this study, we found that *Xueshuantong* improved the outcomes of elderly patients with acute lacunar infarction. Patients treated with *Xueshuantong* exhibited a significant reduction in National Institutes of Health Stroke Scale scores and a significant improvement in Activity of Daily Living scores compared with those not treated with *Xueshuantong*. These findings show that *Xueshuantong* has significant beneficial effects for elderly patients with lacunar infarction and may improve neurological deficits. Another important functional outcome is cognitive impairment in lacunar infarction patients, which has received growing attention in the past decade. A previous study[2] showed that cognitive functions are not normally affected in lacunar infarction patients during the acute phase. However, the development of dementia and cognitive impairment is a matter of concern in the long term. Nevertheless, our study showed that Mini-Mental State Examination scores were low for both groups. In the treatment group, the mean scores of the Mini-Mental State Examination were as follows: on admission, 24.2 ± 3.7; at discharge, 24.5 ± 3.6. In the control group, the mean scores of the Mini-Mental State Examination were as follows: on admission, 24.3 ± 3.4; at discharge, 24.2 ± 3.7. Upon further analysis of our study, a possible reason for the low scores at admission (as well as at discharge) is the fact that patients in this study were elderly (mean age 79.7 years) and may have been poorly educated.

The severe reduction of blood supply seen in acute lacunar infarction is one of the leading causes of death and one of the major causes of neurological disability. To date, several imaging techniques[39-40] have been used to evaluate ischemia and hypoperfusion, including perfusion-weighted MRI. Perfusion-weighted imaging has become increasingly popular as it can provide more information and lead to more accurate and effective therapeutic interventions. In this study, perfusion-weighted MRI was measured using dynamic susceptibility contrast magnetic resonance perfusion imaging. This method uses the susceptibility effect of a paramagnetic contrast agent, which is injected as a bolus and compartmentalized in the intravascular space. After its first pass through the neuronal vasculature, this agent induces a temporary signal change. By capturing the first pass using a T2-weighted imaging sequence, we obtained a signal-time curve, which could be used to calculate several parameters describing cerebral perfusion. The most common parameters include mean transit time, cerebral blood volume, and cerebral blood flow. In this study, the relative mean transit time was more than 1 and the relative cerebral blood flow was less than 1 in both groups on admission. The findings showed that the cerebral blood flow decrease and the mean transit time increase were more prominent in the region of interest. Based on these findings, which are similar to those of previous studies[25, 41-42], we suggest that hypoperfusion may be an early feature in lacunar infarction.

Previous studies[25-26, 43] have revealed that cerebral perfusion is associated with early clinical deterioration. Yamada *et al* [26] found that progressive lacunar infarction could be predicted by hypoperfusion. Additionally, Poppe *et al* [25] suggested that patients identified as having normal perfusion-weighted imaging were at a lower risk of early clinical deterioration. In our study, the follow-up MRI revealed a significant improvement in cerebral hypoperfusion in the treatment group. *Xueshuantong* may improve the cerebral hypoperfusion of elderly patients with acute lacunar infarction. Furthermore, we found a coinciding improvement in neurological deficits (assessed using the National Institutes of Health Stroke Scale and Activity of Daily Living scores). From these results, we can infer that *Xueshuantong* has the capacity to improve the outcomes of elderly patients with acute lacunar infarction, and that the improvements in cerebral hypoperfusion may be the underlying mechanism.

There are, however, some limitations to our study. First, our sample size was limited to 64 patients. This small sample size was partly a result of strict inclusion criteria, which were based on radiological lacunar criteria of small-vessel disease, not clinical lacunar semiology. However, by excluding patients aged < 65 years old, and only including patients with first-time acute lacunar infarction who were admitted to our hospital within 24 hours after onset of lacunar infarction, we were able to limit a number of potential confounding variables. Second, although this study is the first to assess the potential benefits of *Xueshuantong* using perfusion-weighted MRI, and the findings suggest that the use of *Xueshuantong* is associated with a favorable clinical course in the early stages of lacunar infarction, long-term outcome and prognosis were not observed.

In summary, the present study demonstrates that *Xueshuantong* can improve the outcomes of elderly patients with acute lacunar infarction. The mechanism of this beneficial effect is suggested to be that

Xueshuantong increases cerebral perfusion in acute lacunar infarction patients, thereby improving cerebral blood flow and reducing mean transit time during treatment. These results suggest that *Xueshuantong* has potentials as a therapeutic agent for acute lacunar infarction in the elderly. In future studies, a greater number of randomized controlled trials are needed to draw a reliable conclusion regarding the consideration of *Xueshuantong* as a useful agent in the treatment of acute lacunar infarction in the elderly.

SUBJECTS AND METHODS

Design

A prospective, randomized, double-blind controlled trial.

Time and setting

The study was completed at the Ward of Geriatrics, the First Affiliated Hospital, School of Medicine, Zhejiang University, China between October 2009 and April 2011.

Subjects

This study comprised 64 elderly patients with first-time acute lacunar infarction, who were admitted to the Geriatric Ward in our hospital within 24 hours of onset of lacunar infarction. Before performing MRI and magnetic resonance angiography, 12-lead electrocardiograms, chest CT, carotid echography, and laboratory examinations were performed in all patients. All patients were diagnosed with acute lacunar infarction, confirmed by MRI (Philips Achieva 3.0 T; Philips Medical Systems Nederland B.V., Amsterdam, Netherlands) and magnetic resonance angiography on admission.

Patients were included in the study if they presented with a conventional clinical lacunar syndrome (pure motor hemiparesis, sensorimotor syndrome, pure sensory syndrome, ataxic hemiparesis, and dysarthria/clumsy-hand syndrome) and MRI findings of a subcortical, basal ganglia or brainstem lesion with a diameter of < 2 cm. The exclusion criteria were: age < 65 years; patients with an obvious tendency to bleed; patients who were allergic to *Xueshuantong* or the magnetic resonance contrast agent; patients with severe liver failure, heart failure, renal failure or malignancy; and patients who had suffered from cardioembolic or atherothrombotic infarction, or an unknown case of ischemic stroke.

Of the 64 patients, 48 were male and 16 were female; their mean age was 79.7 ± 6.5 years. Twenty-one (33%) had diabetes mellitus; 49 (77%) had hypertension; 15 (23%) had atrial fibrillation; 33 (52%) had hyperlipidemia; 14 (22%) were smokers.
This study received the patients' written consent and was in accordance with the *Declaration of Helsinki*.

Methods

Double-blind method

Sixty-four patients were randomly divided into two groups for this blind, randomized control study. In this trial, no study-related interventions were made. All patients remained blinded to the study group assignment throughout this trial; although the doctors who took care of patients knew whether the patients were taking *Xueshuantong* or not, they were unaware of the protocol, objective, and end-points of the study. The data gatherers and outcome assessors were co-investigators who did not care for any patient in the clinic. Once the patients were enrolled in our trial, two co-investigators recorded basic demographic data and treatment of all new admissions and continued to follow them independently from the doctors who were caring for them in the ward. All patients were followed for 4 weeks. At day 28, ward doctors were asked to administer a follow-up MRI scan to the patients.

Treatment method

Xueshuantong (license No. 090801) was provided by Wu-Zhou Biopharmaceutical (Guangxi Zhuang Autonomous Region, China), state medical permit No. Z20025652. The main ingredient of the lyophilized powder used for injection was *Panax notoginseng* saponins. It was administered together with conventional therapy consisting of simvastatin (0090405; Hangzhou Merck Sharp & Dohme Pharmaceutical Co., Ltd., Hangzhou, Zhejiang Province, China, 20 mg per tablet) and aspirin (116704; Bayer Healthcare Co., Ltd., Leverkusen, Germany, 0.1 g per tablet). For the treatment group patients, 450 mg of *Xueshuantong* [30], diluted in 250 mL of saline, was drip-infused intravenously over a period of 60 minutes and repeated every day for 28 days. A total of 31 patients received both *Xueshuantong* and conventional therapy (treatment group), and the other 33 patients received conventional therapy only (control group).

MRI scan

Prior to perfusion, lacunar infarction was confirmed by MRI on admission for all patients. Specifically, T2-weighted, diffusion-weighted and fluid-attenuated inversion recovery MRI were used to identify lacunar infarction, and magnetic resonance angiography was used to evaluate the occlusive changes in the cerebral

arteries. Once lacunar infarction was confirmed by MRI and magnetic resonance angiography, perfusion-weighted imaging was performed immediately after a bolus of intravenous gadolinium-diethylenetriamine pentaacetic acid (Bayer Schering Pharma AG, Berlin, Germany), using fast field echo-echo planar imaging (repetition time 2 000 ms; echo time 40 ms; flip angle 75°; matrix 128 × 128; number of signal averages 1; field of vision 24 cm × 24 cm; section thickness 5 mm; intersection gap 1 mm; scan time 82 seconds). For perfusion-weighted imaging, 0.1 mmol/kg gadolinium-diethylenetriamine pentaacetic acid was delivered at a rate of 4 mL/s using a MR-compatible power injector (Medrad, Inc., Warrendale, PA, USA). The perfusion-weighted imaging data was transferred to a workstation for data processing. Cerebral blood volume, mean transit time and cerebral blood flow maps were generated by the processing software (release 1.2; Philips Medical Systems Nederland B.V.). A signal-time curve was obtained by capturing the first pass of gadolinium-diethylenetriamine pentaacetic acid in a T2-weighted imaging sequence. From this curve, values for cerebral blood volume and mean transit time were generated; cerebral blood flow was obtained using the formula: cerebral blood flow = cerebral blood volume/ mean transit time. The regions of interests were defined as the largest high signal intensity areas on the T2 fluid-attenuated inversion recovery images obtained at admission. The mirroring positions to the regions of interests in the contralateral hemisphere were used as control regions of interests. Both the regions of interests and the control regions of interests (in the contralateral regions) were determined manually (Figure 3). Measurements of cerebral blood volume, cerebral blood flow and mean transit time were obtained from these two regions of interests. Dynamic susceptibility contrast magnetic resonance perfusion imaging is unable to provide absolute values for cerebral blood volume; hence, relative cerebral blood volume was calculated as the ratio of regions of interests to control regions of interests, which represented the cerebral blood volume of the regions of interests. Similarly, the cerebral blood flow and mean transit time in the regions of interests were expressed as relative cerebral blood flow and relative mean transit time.

Evaluation of clinical outcomes

To evaluate the clinical outcomes of all elderly lacunar infarction patients, the National Institutes of Health Stroke Scale score, Activity of Daily Living score and Mini-Mental State Examination score were completed by patients, both on admission to the ward and at discharge. The National Institutes of Health Stroke Scale score and the Activity of Daily Living score were used to evaluate neurological deficits[44], and cognitive impairment was evaluated by Mini-Mental State Examination[2]. Low scores for Activity of Daily Living or high scores for National Institutes of Health Stroke Scale were associated with neurological deficits, and low scores for Mini-Mental State Examination were associated with cognitive impairment. The reduction in the National Institutes of Health Stroke Scale scores indicated an improvement in clinical outcome, and the improvement in Activity of Daily Living score or in the Mini-Mental State Examination score also indicated an improvement in outcomes.

Statistical analysis

We compared patients who received *Xueshuantong* in our study (treatment group) with those who did not (control group). Baseline characteristics and outcome variables (cerebral perfusion and clinical outcomes) were compared between the treatment group and control group. All continuous variables were expressed as mean ± SD, the chi-square test was used to compare proportions, and the independent-samples *t*-test was used to compare continuous variables. Multiple regression analysis was used for multivariate analysis, in which we examined the correlation between the reduction of the National Institutes of Health Stroke Scale scores and all variables that were related to this outcome. Reported models include the variables that remained significantly related to the outcome. SPSS 16.0 software (SPSS, Chicago, IL, USA) was used for all analyses. A P value of < 0.05 was considered statistically significant; all reported probability values were two-sided.

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Author contributions: Qifeng Gui designed the study and wrote the paper. Shihong Ying processed perfusion-weighted imaging data. All authors performed the study and approved the final version of the paper.

Conflicts of interest: None declared.

Ethical approval: This study received ethical approval by the First Affiliated Hospital, School of Medicine, Zhejiang University, China.

Author statements: The manuscript is original, has not been submitted to or is not under consideration by another publication, has not been previously published in any language or any form, including electronic, and contains no disclosure of confidential information or authorship/patent application/funding source disputations.

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