Effect of Yiqihuoxue Formula for the treatment of ischemic stroke
A retrospective study
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Abstract
This retrospective study assessed the feasible effect of Yiqihuoxue Formula (YQHXF) for the treatment of patients with ischemic stroke (IS).

A total of 66 patients with IS were included in this retrospective study. All patients received routine treatment, and were divided into two groups: a treatment group (n = 33) and a control group (n = 33). In addition to the routine treatment, all patients in the treatment group also underwent YQHXF treatment. All patients in both groups were treated for a total of 8 weeks. The outcomes were assessed by National Institute of Health Stroke Scale (NIHSS), modified Rankin scale (mRS), Barthel index scale (BIS), stroke-specific quality of life (SS-QOL) scale, and adverse events. All outcomes were measured before and after the treatment.

After treatment, patients in the treatment group showed better improvements in NIHSS scale (P = 0.01), mRS (P < 0.01), BIS (P = 0.04), and SS-QOL scale (P = 0.04), than patients in the control group. No treatment-associated adverse events were recorded in this study.

The results of this study indicated that YQHXF may benefit for patients with IS.

Abbreviations: BIS = Barthel index scale, IS = ischemic stroke, mRS = modified Rankin scale, NIHSS = National Institute of Health Stroke Scale, SS-QOL = stroke-specific quality of life, YQHXF = Yiqihuoxue Formula.

Keywords: effect, ischemic stroke, safety, yiqihuoxue formula

1. Introduction
Stroke is a very common neurological disease, and is also the leading cause of disability and mortality worldwide.\textsuperscript{[1–5]} It is defined as the interruption of blood flow in a brain-supplying artery after having narrow or occlusion in blood vessels.\textsuperscript{[5,6]} It is characterized by irreversible cell damage in the ischemic core, which causes motor and sensory deficits on the attacked body side.\textsuperscript{[5]} It has been reported that ischemic stroke (IS) is the most common type stroke, and it accounts for about 85% of all stroke cases.\textsuperscript{[7,8]} Up to date, its 5-year fatality rate is about 50%, and 40% of stroke survivors are disabled.\textsuperscript{[5]} Thus, there is a strong demand for its treatment.

It is reported that alternative herbal medicine, such as Yiqihuoxue Formula (YQHXF) can preserve tissue in areas where perfusion is reduced.\textsuperscript{[9–13]} It also helps restoring blood flow to avoid infarction, which can minimize the effects of ischemia.\textsuperscript{[14–19]} However, insufficient data is available to support the evidence of YQHXF for the treatment of patients with IS. Thus, this retrospective study investigated the feasible effects of YQHXF for patients with IS.

2. Patients and methods
2.1. Ethical consideration
This retrospective study was approved by the ethics medical committee of The Second Affiliated Hospital of Xi’an Medical University. We collected all patient records at The Second Affiliated Hospital of Xi’an Medical University. In addition, all patients had provided the written informed consent.

2.2. Study design
This retrospective study included a total of 66 eligible patients with IS, who were admitted at the The Second Affiliated Hospital of Xi’an Medical University from January 2016 to December 2017. We divided those patients into a treatment group (n = 33),
and a control group (n = 33). All patients were assigned to the treatment group and the control group according to the different treatments they received. All of them in both groups administered routine treatment. Additionally, patients in the treatment group also received YQHXF for a total of 8 weeks. All outcomes were measured before and after treatment. The data analyst was blind to the treatment schedule in this study.

2.3. Patients

Patients were included if they met the following criteria:

1. diagnosed as IS according to the Chinese Cerebrovascular Disease Prevention and Treatment Guideline[20];
2. age between 18 and 75 years;
3. time of insult from 5 weeks to 6 months after initial stroke onset;
4. presence of IS-induced neurological deficits, with National Institute of Health Stroke Scale (NIHSS) between 5 and 20; and
5. provided written informed consent.

We excluded patients if they were pregnant or lactation, intracerebral hemorrhage, difficulty to understand or to collaborate during the treatment, intracardiac thrombus, sepsis, cancers, severe heart, liver or kidney diseases, and cancer. In addition, we also excluded patients if they did not provide written informed consent and incomplete patient information. Furthermore, we also excluded patients if they undertook YQHXF 1 month prior to the study treatment.

2.4. Treatment schedule

All eligible stroke survivors in both groups administered routine treatment based on the Chinese Cerebrovascular Disease Prevention and Treatment Guideline.[20] In addition, patients in the treatment group received YQHXF (Astragalus 60g, Angelica tail 15g, Chuanxiong Rhizome 12g, Red Peony Root 12g, Geosaurus 20g, Peach Kernel 6g, Safflower 6g, Salvia Miltiorrhiza 12g, Heliotrope 12g, Cinnamomum Cassia Presl 6g), once daily at every morning and evening before meals. All treatments they received. All patients in both groups administered YQHXF for a total of 8 weeks. All outcomes were detected before and after treatment.

2.5. Outcome measurements

Outcomes were measured by NIHSS scale,[21] modified Rankin scale (mRS),[22,23] Barthel index scale (BIS),[24] stroke-specific quality of life (SS-QOL) scale, and adverse events. NIHSS scale is used to objectively quantify neurological impairment in patients with stroke survivors, and it consists of 11 items, each of which scores from 0 to 4, with a total of 42.[21] The score of 0 means normal function, while that of 42 indicates worst function.[22] mRS is commonly utilized for detecting degree of disability or dependence in daily activities of stroke survivors.[22,23] Its scale varies from 0 (perfect health) to 6 (death).[22,23] BIS is an ordinal scale and is widely utilized to assess the performance in activities of daily living.[24] It yields a score of 0 to 100, with higher score suggesting less independent.[24] SS-QOL scale is a patient-centered outcome measurement, and is designed to specifically evaluate health-related quality of life for stroke survivors.[25] It has 49 items encompassing 12 fields. Each item is graded on a 5-point scale, with higher score noting better quality of life.[25] All outcomes were detected before and after treatment.

2.6. Statistical analysis

This study employs SAS package (Version 7.0; SAS Institute Inc, Cary, NC) to analyze baseline and outcome data. All discontinuous data were analyzed using Mann–Whitney U test or t test, while all categorical data were analyzed using Pearson’s chi-square test or Fisher’s exact test. We defined a 2-side value of \( P < .05 \) as having statistical significance.

Although several associated studies report the combined therapy involved YQHXF for the treatment of IS, there is still insufficient evidence to specifically support the effects of YQHXF for patients with IS. Considering no study directly closes to the effects of YQHXF for IS, the minimum number of patients necessary to evaluate its effects with sample size of 33 patients in each group, and an expected dropout rate of 10%,[26]

3. Results

We summarized general characteristics of patients in both groups in Table 1. No statistical differences regarding all characteristics were detected between two groups in this study (Table 1).

After treatment, all outcomes in the treatment group showed better outcome measurements in NIHSS scale (\( P = .01 \), Table 2), mRS (\( P < .01 \), Table 3), BIS (\( P = .04 \), Table 4), and SS-QOL scale (\( P = .04 \), Table 5), than those in the control group. No adverse event was reported in patients of both groups in this study.

| Table 1 |
|---|
| Comparison of general characteristics between two groups. |

| Characteristics | Treatment group (n = 33) | Control group (n = 33) | \( P \) |
|---|---|---|---|
| Age (year) | 63.2 (9.4) | 64.5 (10.1) | .59 |
| Gender | | | |
| Male | 20 (60.6) | 17 (51.5) | .46 |
| Female | 13 (39.4) | 16 (48.5) | .46 |
| Race (Chinese Han) | 33 (100.0) | 33 (100.0) | – |
| Educational background | | | |
| Primary school and below | 8 (24.2) | 6 (18.2) | .55 |
| Secondary school | 12 (36.4) | 14 (42.4) | .61 |
| High school | 7 (21.2) | 8 (24.2) | .77 |
| College or university | 6 (18.2) | 5 (15.2) | .74 |
| BMI (kg/m²) | 24.1 (2.5) | 23.3 (2.8) | .22 |
| Duration of post-stroke (month) | 3.2 (1.0) | 2.9 (1.3) | .29 |
| Co-morbidities | | | |
| Cardiovascular diseases | 11 (33.3) | 8 (24.2) | .42 |
| Respiratory diseases | 5 (15.2) | 7 (21.2) | .52 |
| Osteoarthritis diseases | 3 (9.1) | 6 (18.2) | .20 |
| Other | 6 (18.2) | 4 (12.1) | .49 |
| NIHSS | 11.1 (1.9) | 11.4 (1.7) | .50 |
| mRS | 3.3 (0.9) | 3.4 (1.1) | .69 |
| BIS | 61.3 (17.2) | 59.8 (16.4) | .72 |
| SS-QOL | 96.7 (23.1) | 99.5 (26.0) | .64 |

Data are present as mean ± standard deviation or number (%). BIS = Barthel index scale; BMI = body mass index; mRS = modified Rankin scale; NIHSS = National Institute of Health Stroke Scale; SS-QOL = stroke-specific quality of life.
This study suffers from several limitations. First, it has an intrinsic limitation because it is a retrospective study. Second, this study only appraised the effects of YQHXF for IS after 2 months treatment and no further follow-up assessment was reported in the original case records. Third, lacking of randomization and blinding to patients and researchers may increase the selection risk. Finally, the sample size of this study is still small. Thus, further similar study should enlarge its sample size to warrant the findings of this study.

5. Conclusion

The results of this study showed that YQHXF may be efficacious for patients with IS.

Author contributions

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References

[1] GBD 2016 Stroke CollaboratorsGlobal, regional, and national burden of stroke, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet 2019;18:439–58.

[2] Wu S, Wu B, Liu M, et al. Stroke in China: advances and challenges in epidemiology, prevention, and management. Lancet Neurol 2019;18:394–405.

[3] Sprick JD, Mallet RT, Przyklenk K, et al. Ischaemic and hypoxic conditioning: potential for protection of vital organs. Exp Physiol 2019;104:278–94.

[4] Wang W, Jiang B, Sun H, et al. Prevalence, incidence, and mortality of stroke in China: results from a Nationwide Population-Based Survey of 480 678 adults. Circulation 2017;137:739–71.

[5] Hankey GJ. Stroke. Lancet 2017;389:641–54.

[6] Campbell BC, Christensen S, Tress BM, et al. Failure of collateral blood flow is associated with infarct growth in ischemic stroke. J Cereb Blood Flow Metab 2013;33:1168–72.

[7] Musuoka TD, Wilton SB, Traboulsi M, et al. Diagnosis and management of acute ischemic stroke: speed is critical. CMAJ 2015;187:887–93.

[8] Ramiro L, Simats A, Garcia-Berrocoso T, et al. Inflammatory molecules might become both biomarkers and therapeutic targets for stroke management. Ther Adv Neurol Disord 2018;11:1756286618789340.

[9] Zhang LM, Du MR, Yang J, et al. Clinical observation of Yu Huo Xue Recipe combined with western medicine routine treatment of acute ischemic stroke. Hebei Tradit Chin Med 2020;42:281–6.

[10] Wan HY, Bie XD, Yao Z, et al. Treating ischemic stroke patients of deficiency of qi and yin syndrome and static blood obstructing collaterals syndrome by Yangyin Yu Huo Xue Recipe: a clinical study of therapeutic effect. Chin J Integr Med 2015;35:281–6.

[11] Wu MM, Hu JP, Wang J. Advances in experimental research on prevention and treatment of cerebral ischemia with Yu Huo Xue method. J Anhui Univ Tradit Chin Med 2014;33:86–9.
[12] Qi X, You JM, Wang ZP, et al. Effect of Yiqi Huoxue Recipe on angiogenesis on clinical efficacy of cerebral infarction of Qi deficiency and blood stasis type. J Hunan Univ Tradit Chin Med 2013;33:60–4.

[13] Wang ZR, Zhao YL, Qu YZ, et al. Effect of Yiqi Huoxue Fang on nerve cell apoptosis and related gene expression after cerebral ischemia/reperfusion. First Aid Integr Chin West Med Mag 2006;6:333–7.

[14] Hu JP, Wang J, Li J. The effect of Yiqi Huoxue Fang on nerve cell apoptosis and HSP70 protein expression after cerebral ischemia-reperfusion injury. Chin J Exp Pharmacol 2005;2;72–3.

[15] Bie XD, Wan HT, Chen YQ. Protective effect of active substances of Yangyin Yiqi Huoxue Fang on cerebral ischemic injury. Chin J Basic Med Tradit Chin Med 2002;11:33–5.

[16] Hu GH, Hu Z, Sheng W, et al. Study on the effect of Yiqi Huoxue Fang on angiogenesis and HGF of ischemic myocardium in rats. Chin J Emerg Tradit Chin Med 2013;22:1478–9.

[17] Huang TQ, Yi CT, Chu YW, et al. Interventional effect of Yiqi Huoxue Fang on rat model of focal cerebral ischemia-reperfusion injury. Chin J Emerg Tradit Chin Med 2013;22:1549–50.

[18] Lv L, Hu JP, Wang J, et al. Effects of Yiqi Huoxue Fang and Bushen Shengsui Fang on Notch3 and Frizzled2 mRNA and protein expression in rats with cerebral ischemia-reperfusion. Chin J Pathophysiol 2013;29:1171–4.

[19] Li K, Zhang P, Zhou J. Experimental study on the effect of Yiqi Huoxue Bushen Recipe on the expression of c-Fos and c-Jun after cerebral ischemic injury in rats. World J Integr Tradit Chin West Med 2015;10:27–9.

[20] Rao ML. Guidelines for the Prevention and Treatment of Cerebrovascular Diseases in China. Beijing: People’s Medical Publishing House; 2007. 46–55.

[21] Hage V. The NIH stroke scale: a window into neurological status. Nursing Spectrum 2011;24:44–9.

[22] Wilson JL, Hareendran A, Grant M, et al. Improving the assessment of outcomes in stroke: use of a structured interview to assign grades on the modified rankin scale. Stroke 2002;33:2243–6.

[23] Saver JL, Filip B, Hamilton S, et al. Improving the reliability of stroke disability grading in clinical trials and clinical practice: the Rankin Focused Assessment (RFA). Stroke 2010;41:992–5.

[24] Mahoney FI, Barthel D. Functional evaluation: the Barthel Index. Maryland State Med J 1965;1:46–61.

[25] Williams LS, Weinberger M, Harris LE, et al. Development of a stroke-specific quality of life scale. Stroke 1999;30:1362–9.

[26] Johanson GA, Brooks GP. Initial scale development: sample size for pilot studies. Educ Psychol Meas 2010;70:394–400.