Upper Limb Ischemic Postconditioning as Adjunct Therapy in Acute Stroke Patients: A Randomized Pilot

Yuejuan Li, MD, Keke Liang, MD, Long Zhang, MD, Yamei Hu, MD, Yunli Ge, and Jianhua Zhao, PhD

Objective: This study aims to observe the clinical effect of upper limb ischemic postconditioning (LIPostC) as an adjunct to treatment with acute stroke patients, possibly due to increased cerebral perfusion. *Methods:* We perform a randomized blinded placebo controlled trial in nonthrombolysis patients with acute ischemic stroke, within 72 hours of ictus, divided into the LIPostC group and control group. The LIPostC group is induced by 4 cycles of intermittent repeated limb ischemia: alternating 5 minutes inflation (20 mm Hg above systolic blood pressure) and 5 minutes deflation performed manually using a standard upper arm blood pressure cuff in the nonparetic arm. The control group receives a sham procedure (cuff inflation to 30 mm Hg). Patients underwent the intervention from the time of enrollment to Day 14. Comparison of National Institutes of Health Stroke Scale (NIHSS) score, cerebral infarction volume, relative Perfusion weighted imaging (PWI) parameters (regional relative cerebral blood flow, regional relative mean transit time; preintervention [day 0], day 14, day 90), modified Rankin Scale (mRS; the preintervention score [day 0], the curative ratio at day 90 [we define 0-1 score as close to recovery or full recovery]). *Results:* Sixty eligible patients with acute stroke (29 LIPostC and 31 control) are recruited age 65 years (SD 12.22), blood pressure 156/74 mm Hg (SD 14/10), and NIHSS score 5.98 (SD 3.35), mRS score 2.25 (SD .79). Only 1 in the LIPostC group is intolerant the first cycle to give up. All patients tolerate the sham procedure. Two patients experience recurrent stroke versus none in the LIPostC group. Day 90, compared with the control group, there is a significant decrease the NIHSS score, regional relative mean transit time ($P < .05$) and increase the curative ratio of mRS, regional relative cerebral blood flow($P < .05$) in the LIPostC group, which infarct volume decreased by 31.3% ($P < .05$). *Conclusions:* LIPostC after acute stroke is well tolerated and appears safe and feasible. LIPostC may improve neurological outcome, and protective mechanisms may be increased cerebral blood flow to improve cerebral perfusion. A larger trial is warranted.

Key Words: Limb ischemic postconditioning—cerebral blood flow—stroke—National Institutes of Health Stroke Scale—modified rankin scale

Stroke is a leading cause of death and disability worldwide.[1] Intravenous administration of alteplase (rtPA) within 4.5 hours of symptom onset is currently the only approved drug treatment of acute ischemic stroke.[2] Most patients do not fit in this time window especially in developing countries, such as China. Meanwhile, various forms of neuroprotection have proven effective in animal models of acute ischemia, but their translations into successful therapies in human stroke have so far been unsuccessful.[3] So it is still an urgent task for neurologists worldwide to figure out a new way to improve the outcomes of ischemic stroke patients. Applying transient limb ischemic after a stroke can induce neuroprotection.[4] The protective effect seemingly involves the activation of multiple

From the Departments of Neurology, Zhengzhou University People's Hospital, Zhengzhou, China.

Received May 13, 2018; revision received July 14, 2018; accepted July 22, 2018.

Financial Support: Henan Provincial International Science and Technology Cooperation Project the project number: 152102410083.

Address correspondence to Jianhua Zhao MD, PhD, Departments of Neurology, Zhengzhou University People's Hospital, Zhengzhou, 7th Street Weiwu Road, Zhengzhou, MA 450003, China. E-mail: sjnk2011@163.com

1052-3057/$ - see front matter

https://doi.org/10.1016/j.jstrokecerebrovasdis.2018.07.039

endogenous defense mechanisms. These include an up-regulation of nitric oxide levels, improve cerebral blood flow in the ischemic penumbrab,[5] and regulate heat-shock protein. Limb ischemic postconditioning (LIPostC) is an attractive prospect because it bears minimal cost and will be simple to administer. It may decrease stroke risk in patients with intracranial arterial stenosis and applying LIPostC in prehospital stroke patients is feasible.[6] In the current study, we aim to demonstrate tolerability and feasibility of LIPostC in patients presenting to hospital with acute stroke while simultaneously investigating potential mechanisms of action.

Methods

Trail Design

The design of this study is a single-center, open-label, outcome observer single-blinded, randomized study is described elsewhere, placebo-controlled trial.

The study is being conducted in China. The study protocol was approved by Institutional Review Board.

The study is registered with Clinical Trial.gov, number ChiCTR-IOR-15006549.

Participants

We plan to recruit adult (age range 18-75 years old) patients of either gender who has ischemic stroke with the following inclusion and exclusion criteria, and take place between June 2015 and June 2017 at Zhengzhou University People's Hospital, Zhengzhou, China.

Trail Protocol

Adult patients with an ischemic stroke in the past 24-72 hours causing arm or leg weakness are eligible.

Individuals who meet any of the following criteria will be excluded from the study: (1) mRS score > 3; (2) thrombolysis for index event, significant comorbidity; (3) previous diseases of the brain: intracranial aneurisms or arteriovenous malformations, brain surgery or hemorrhagic stroke; (4) stroke within the last 3 months; (5) heart diseases: infectious endocarditis or suspicion of septic emboli, pericarditis, ventricular thrombosis, aneurisms of the heart wall, or major heart failure; (6) serious diseases: cancer, AIDS, dementia, significant abuse, renal failure, liver diseases such as liver failure, cirrhosis, portal hypertension, and active hepatitis; (7) pregnancy; (8) clinical examination: unconsciousness (NIHSS > 25); (9) imaging: contraindications for MRI scans. Cerebral neoplasm or abscess; known hypersensitivity to Gadovist or any of its ingredients; acute or chronic severe renal impairment (Glomerular filtration rate (GFR) < 30 mL/min/1•73 m^2); acute renal insufficiency of any severity due to the hepato-renal syndrome or in the perioperative liver transplantation period. Caution with using Gadovist to patients with severe cardiovascular disease, and only to be used after a risk-benefit assessment. Caution with using Gadovist in patients with low threshold for seizures; (10) lab data: blood glucose < 2.8 mmol/L or >22 mmol/L.[7]

Intervention and Control Treatments

The randomization is made via telephone by a staff nurse or an on-call physician not involved in the study. The randomization is performed by drawing from a large number of sealed opaque envelopes containing treatment instructions for the ambulance staff. The treatment allocation code is stored in a way such that they remained inaccessible to staff participating in the clinical follow-up or subsequent data analysis. On-call physicians examining patients on arrival at the department of neurology were not blinded to treatment instructions. These physicians did not participate in data analysis or follow-up clinical ratings. The readers of MRI scans are blinded to treatment allocation. The patients are randomly divided into the LIPostC group and the control group.

All patients in the control and LIPostC groups will receive foundational treatment, including blood vessel expansion, free radical elimination in the acute stage, blood pressure and blood glucose stabilization, and antiplatelet (aspirin, 100-300 mg/d) and lipid-lowering (atorvastatin, 20 mg/d) drugs, throughout the day 90 study period. All treatments will strictly follow guideline recommendations and will be adjusted according to each patient's situation.

LIPostC is performed on the stroke unit in 24-72 hours after ischemic stroke on set. Intervention: 4 cycles of intermittent limb ischemia; alternating 5 minutes inflation (20 mm Hg above systolic blood pressure) and 5 minutes deflation performed manually using a standard upper arm blood pressure cuff in the nonparetic arm. Patient position is not specified. The control group received a sham procedure (cuff inflation to 30 mm Hg).

Patients underwent a limb postconditioning session every 24 hours from the time of enrollment to day 14 (or discharge if before day 14). After completion of each preconditioning session, subjects are asked (if possible) to rate pain on a visual analog pain scale (VAS), which range from 0 (no pain) to 10 (the worst imaginable pain).[8] Safety end points are risks of expected treatment-related local or systemic adverse events, including the number of patients having pain with arms assessed by VAS, redness or swelling of arms, skin petechiae on arms, palpitation, and dizziness. After each session, the extremity is examined for tissue breakdown or signs of neurovascular injury.

Procedures (Fig 1)

Preintervention, patients are evaluated by a short neurological examination, and NIHSS scoring, ECG, blood tests, MRI, and cerebral infarction volume are performed. When a history of stroke is confirmed and MRI shows acute infarct, patients are recorded. The patient's signed consent to participate in the MRI follow-up study is obtained. Follow-up MRI to measure cerebral infarction volume and NIHSS are performed after day 14 and day