Preventive Medicine and Public Health

Doweon Park

The class of Dr. Soneil Guptha on Thursday 8:30 PM

Preventing Strokes in the patients of Transient Ischemic Attack (TIA) caused by High Blood Pressure or Diabetes Mellitus Type 2 with Acupuncture Treatments:

the cross sectional study by Doweon Park

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Abstract

Though stroke is the second leading cause of death in the world, whether acupuncture is effective in preventing stroke for patients with TIA caused by comorbidity of high blood pressure (HBP) or diabetes mellitus type 2 is unknown. This study investigates the effectiveness of acupuncture in decreasing stroke risk among patients with TIA caused by high blood pressure or diabetes mellitus type 2 using the cross sectional study. Three hundred subjects will be initially enrolled into the study and will be randomized into one of three groups, consisting of two cases for acupuncture and one control (each group consists of 100 subjects). Control group will be treated using conventional western treatments and two cases of acupuncture treatments with scalp acupuncture and body acupuncture together will be given on a basis of once a week for initial 3 months protocol (12 treatments total), and reevaluated at 3rd month, 6th month, and 12th month time point. This will be the first study that compares the effects of acupuncture treatments with the comorbidities of high blood pressure or diabetes mellitus type 2 regarding possible reduced risks of strokes in the long term.

Keywords : acupuncture, high blood pressure, diabetes mellitus type 2, transient ischemic attack (TIA), preventing stroke

1. Background

1.1 Description of the condition

Stroke is the second leading cause of death in the world[1]. In the USA, stroke accounted for about one of every 19 deaths in 2010. On average, someone dies of stroke every four minutes[2]. Although age-standardized rates of stroke mortality have decreased worldwide in the past two decades, the absolute numbers of people with first stroke (16.9 million), stroke survivors (33 million), stroke-related deaths (5.9 million), and disability-adjusted life-years (DALYs) lost (102 million) in 2010 were still high and had significantly increased since 1990 (68%, 84%, 26%, and 12% increase, respectively), imposing a great burden on families and communities in low-income and middle-income countries[3] .

1.2 The definition of transient ischemic attack (TIA)

The definition of transient ischemic attack (TIA) has evolved over the past few decades. A TIA is generally considered as one of warning signs of a stroke. Classically, a TIA was defined as a sudden, focal neurological deficit of less than 24 hours in duration. This definition has evolved to incorporate ongoing advances in neuroimaging and acute stroke protocols. For instance, 30%–50% of patients diagnosed to have TIA using the classical 'time-based' criteria were found to have central nervous system (CNS) infarction on diffusion-weighted magnetic resonance imaging (MRI).[4] More recently, the 2009 American Heart Association/American Stroke Association's 'tissue-based' definition of TIA stated that it is "*a transient episode of neurological dysfunction caused by focal brain, spinal cord or retinal ischemia without acute infarction*".[4]

1.3 The diagnosis of Transient Ischemic Attack

The diagnosis of CNS infarction is based both on careful clinical assessment and evidence on advanced neuroimaging[5]. Early neuroimaging is crucial, as it affects decision-making on time-sensitive interventions in acute stroke management. On MRI, a lack of evidence of infarction in patients with symptoms of cerebral ischemia distinguishes a TIA from an acute ischemic stroke. In cases where advanced neuroimaging is not available, CNS infarction is diagnosed when focal neurological deficits persist for 24 hours or more, or until death, whichever is earlier. Proper documentation of evidence for diagnosing TIA or acute stroke is important in view of medicolegal ramifications in insurance claims. TIA and acute ischemic stroke are part of the cerebral ischemia spectrum. TIA represents a milder event in which neurological cell death or infarction has not yet occurred, and thus may be prevented[6].

1.4 Risk factors for TIA

Both TIAs and acute ischemic strokes occur because of cerebral ischemia and are associated with vascular risk factors[13]. Table I summarizes the established modifiable risk factors of TIA and acute ischemic stroke[14].

Table I. established modifiable risk factors of transient ischemic attack and stroke.

Parameter	Prevalence* (%)[9]	Odds ratio of cerebral ischaemia[11]
Modifiable risk factor		
Hypertension	23.5	2.64
Diabetes mellitus	11.3	1.36
Hyperlipidaemia	17.4	–
Obesity	10.8†	1.65‡
Smoking	14.3	2.09
Atrial fibrillation	–	–
Unhealthy diet	–	1.35
Psychosocial stress	–	1.30
High alcohol intake	–	1.51
Protective factor		
Regular physical activity	–	0.69

*Prevalence among adults aged 18–69 yr (2010). †Body mass index ≥ 30 kg/m^2.
‡Elevated waist-to-hip ratio.

And the 2010 INTERSTROKE study found that five modifiable risk factors (hypertension, current smoking, abdominal obesity, unhealthy diet and physical inactivity) accounted for more than 80% of strokes[15].

1.5 Description of the intervention

Acupuncture is one of the main modalities of treatment in traditional Chinese medicine and can be traced back more than 3000 years in China[7]. Possible mechanisms of the effects of acupuncture on neurological conditions include stimulation of neuronal cell proliferation[8], facilitation of neural plasticity[9], reduction of the post-ischemic inflammatory reaction[10], and prevention of neuronal apoptosis[11]. One report found that acupuncture intervention based on promoting the circulation of the Governor Vessel and regulating mentality achieves the superior efficacy on TIA and less adverse reactions as compared with aspirin[12].

However, whether acupuncture is effective in preventing stroke for patients with TIA caused by comorbidity of high blood pressure (HBP) or diabetes mellitus type 2 is unknown. This study investigates the effectiveness of acupuncture in decreasing stroke risk among patients with TIA caused by high blood pressure or diabetes mellitus type 2 using the cross sectional study.

2. Methods

2.1 Standard of care treatment

Standard of care treatment include high-intensity physical activity, blood pressure control, statin therapy, and antiplatelet agents. Significant relative risk reduction of stroke may be achieved with high-intensity physical activity (64%)[16], blood pressure control (30%–40%)[17,18], statin therapy (16%–33%)[19,20], and antiplatelet agents (18%–37%)[21,22].

2.2 Study design

This study is a cross sectional study consisting of three cohorts. The control cohort group will receive only standard of care treatment based on each participant's medical conditions related to TIA and the other two treatment cohort groups with the comorbidity of high blood pressure or type 2 diabetes mellitus will receive standard of care treatment based on each participant's medical conditions and acupuncture. Diabetes will be defined by a fasting blood glucose of ≥ 126 mg/dL on ≥ 2 occasions or treatment with hypoglycemic medications, and hypertension by blood pressure ≥140/90 mmHg on ≥2 occasions or if patient was being treated with anti-hypertensive drugs[23].

Volunteers will be informed about the investigation verbally and using written information. Subjects will have time to decide whether to take part in the study, and discuss any questions they have about the investigation. Each participant will give informed written consent to be enrolled in the investigation. Three hundred subjects will be initially enrolled into the study and will be randomized into one of three groups, consisting of two cases for acupuncture and one control (each group consists of 100 subjects). Each patient will have a number between 1 and 3, and each number will be assigned to one of our study groups. Neither participants nor the researchers know which group will receive acupuncture intervention and which group will undergo standard intervention. Only the acupuncturist will be informed of group allocations to use the appropriate intervention for each participant.

Acupuncture treatment will be given on a basis of once a week for initial 3 months protocol (12 treatments total), and reevaluated at 3rd month, 6th month, and 12th month. Scalp needles and body acupuncture needles will be used as a main acupuncture treatment protocol (specific

acupuncture treatment details outlined in ‘Manipulations’ section). Patients in the control group will only receive conventional care, which will be the same as the acupuncture group. However, no acupuncture treatments will be given during the whole study period to the control group.

3. Subjects

3.1 Samples

300 patients between 35–80 years of age with TIA within the past 1 year will be included. The treatment group of 200 patients with onset of stroke between two to twelve months will be included with conventional treatment and acupuncture treatment. The control group of 100 patients with onset of stroke between two to twelve months will be included with only conventional treatment.

3.2 Inclusion criteria

Patients between 35–80 years of age with TIA within past 1 year will be included. Patients with onset of TIA between two to seven days beforehand, the NIHSS(National Institutes of Health Stroke Scale) score between 5 and 14, and displaying clear consciousness and stable vital signs will be only included if it is their first incidence of stroke. We will exclude severe stroke (the NIHSS score between 15 and 24) after the trial commencement, because the severe stroke patients need more frequently skilled care, which may be beyond our treatment program.

3.3 Exclusion criteria

Excluded from the study will be patients who suffered from serious heart, liver, and kidney-related diseases, or blood coagulation dysfunction, and patients unable to complete the MMSE (Mini–Mental State Examination) test or bedside swallowing assessment (BSA). Congenital

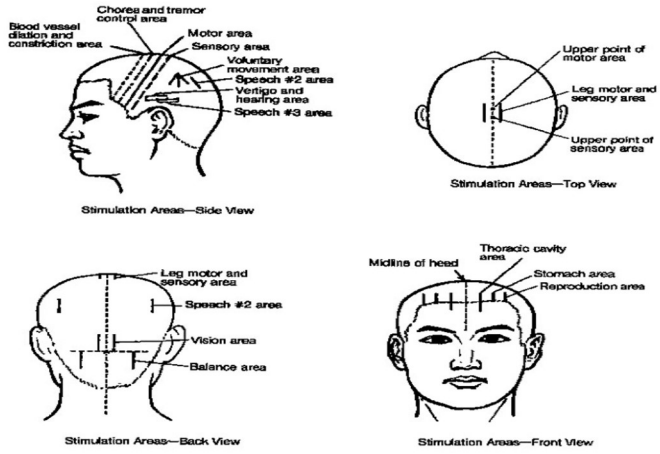
disabilities will be also excluded. Patients who suffered POCI (Posterior Circulation Infarcts) in OCSP (Oxford shire Community Stroke Project) classification, or received thrombolytic therapy or who participated in other clinical trials within previous three months, and women who were pregnant or breast-feeding will be also excluded from this study.

3.4 Intervention

Traditional Chinese style acupuncture will be used in accordance with the Advanced Textbook of traditional Chinese Medicine and Pharmacology, and the textbook of Acupuncture and Moxibustion Administration Methods[24].

The acupuncture will be performed by three acupuncture doctors who have a master and doctoral degree with more than five years of clinical experiences, and will have been trained previously to perform the same protocols. For scalp acupuncture, two to three needles will be penetrated through the top midline, the motor region (MS-6), and the sensory region (MS-7) of the lesion side[25].

Fig 1 Zone Chart



In each session, the points for the affected side of the body in the time of TIA related episode, acupuncture will be as follows: LI15

(Jianyu), LI11 (Quchi), LI10 (Shousanli), TE5 (Waiguan), and LI4 (Hegu) for upper extremities; ST34 (Liangqiu), ST36 (Zusanli), GB34 (Yanglingquan), SP6 (Sanyinjiao), ST40 (Fenglong), ST41 (Jiexi), and LR3 (Taichong) for lower limbs. The points for the experience of dysphagia will be added as follow : GB20 (Fengchi), EX-HN14 (Yiming), BL10 (Tianzhu), GV16 (Fengfu), Gongxue (1 cun below GB20), and CV23 (Lianquan).For the experience of cognitive impairment, GV20 (Baihui), GV24 (Shenting), GB13 (Benshen), EX-HN-1 (Sishencong) will be added. Chinese-made Huan-Qui needles will be inserted 1-1.5 cun deep into the tissue, seeking a pain response.

3.5 Manipulations

Manipulations of scalp acupuncture: the needles will be swiftly inserted into the subcutaneous tissue of the scalp in a horizontal direction. When acupuncture needles (the stainless steel needle, 0.25 mm × 40 mm in size) reach the subgaleal layer and the practitioner feels the weak insertion resistance, needles will be further inserted to the depth of 30 mm ~ 40 mm by twirling method. Patients will be placed in a sitting position during the needle insertion, but they will be lying down on the bed after insertion.

Manipulations of body acupuncture: the needle will be inserted into the points to a depth of between 30 mm and 40 mm according to different regions in a supine position. Manual stimulation will be applied to the body acupoints until the patients experience the needling sensation (called Deqi in Chinese acupuncture)[12]. For nape-acupuncture on dysphagia: after the scalp acupuncture needle insertion, patients with dysphagia receive nape-acupuncture in a sitting position during the needle insertion, then lie supine with a pillow padded under the occiput to avoid the needles touching the bed. The retention of body acupuncture and nape-acupuncture

will be thirty minutes. The order of acupuncture treatment was as follows: For insertion: scalp acupuncture-nape-acupuncture (for dysphagia)-body acupuncture. For withdrawing needles: the body acupuncture-nape-acupuncture-the scalp acupuncture. Needles will be removed quickly, within 1–2 min, and social interaction during the acupuncture session will be minimal.

4. Statistical Analysis

4.1 Data and Statistics

NIHSS, mainly developed for using in acute stroke trials, strongly predicts the likelihood of a patient's recovery after stroke at early stage [26]. This measure will be used as a primary outcome in this trial, and a good result of NIHSS may implicate a good functional recovery in a long-term process. The SPSS software (Statistical Package for Social Sciences, IBM, Chicago, Illinois, USA) will be used for statistical analysis with descriptive statistics (mean, median, interquartile range, and standard deviation) being determined for each variable. In all cases, $P \leq 0.05$ is considered to be significant. The sample size will be calculated based on a former study conducted in this field. The required sample size was estimated to be 100 patients in each study group at a power of 80% and a confidence interval of 95%. Approximately 100 patients will be initially recruited to each group to allow for drop out and possibly do analysis in subgroups (male, female). As acupuncture is still not very popular and common in USA, we believe that a larger safety margin will be needed to allow for possible drop outs in the course of this rather long-term study[27].

4.2 Outcome measures

Participants will receive assessments at week 0 (baseline), week 12(after treatment) ,week 24(1st follow-up), and week 52 (2nd follow-up). The NIHSS index for neurologic deficit evaluation will be used as the primary outcome measurements. Secondary outcome measures include prospectively using functional outcome scales and HRQOL (Health-related Quality of Life) scores. The functional outcome scales include the mRS (modified Rankin Scale) and the BI (Barthel Index). The mRS is a disability scale ranging from no symptoms (0) to dead (6), and BI is an ordinal measure of activities of daily living performance with scores ranging from complete bedridden dependence (0) to full independence (100)[28]. We will use previously published definitions of favorable outcome (BI of 95 or 100 and mRS score 0 or 1) at the 3-month, 6-month, and 12-month time point[29].

5. Significance

Acupuncture can exert its effect on blood pressure by several different mechanisms. In human study, acupuncture has been shown to regulate blood pressure by changes in aldosterone, renin, angiotensin II and endothelin- 1, and by regulating neurotransmitters including GABA, serotonin, and endocannabinoids. The long lasting effects of the acupuncture can be attributed to GABA and opioids in rVLM, neural circuitry between the ventrolateral and arcuate periaqueductal grey matter, and by prolonging the increase in preproenkephalin mRNA levels and encephalin levels in the rVLM and arcuate. The role of renin, norepinephrine and aldosterone have been shown to have a role in long-lasting inhibitory effects of acupuncture on sympathetic activity in hypertensive patients who have undergone electroacupuncture treatment[31,31].

Also numerous experimental studies have demonstrated that acupuncture can correct various metabolic disorders such as hyperglycemia, overweight, hyperphagia, hyperlipidemia,

inflammation, altered activity of the sympathetic nervous system and insulin signal defect, all of which contribute to the development of insulin resistance. In addition, acupuncture has the potential to improve insulin sensitivity. The evidence has revealed the mechanisms responsible for the beneficial effects of acupuncture, though further investigations are warranted[32].

To the best of our knowledge this will be the first study that compares the effects of acupuncture treatments with the comorbidities of high blood pressure or diabetes mellitus type 2 regarding possible reduced risks of strokes in the long term.

Some caveats of this study merit comments. First, this study does not include differentiating pattern diagnosis based on TCM principles which is commonly employed for the effective treatment. Second, we might have to ignore comorbidities and underlying diseases, because many risk factors can possible coexist and could have been complicated by other medical diseases. Third, there is no differentiating in sampling in terms of demographic factors such as age, sex, ethnicity, etc. And fourth, there is a possible blinding bias to patients and study facilitators.

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