

● PERSPECTIVE

Prevention and protection against cerebral ischemic injury using acupuncture

Cardiovascular disease is the leading cause of death worldwide. Stroke is the second leading cause of death above the age of 60 years and the leading cause of acquired disability in adults. The main type of stroke is ischemic stroke (80%) and it is subclassified as thrombotic or embolic in nature. A thrombotic stroke or infarction occurs when a clot forms in an artery supplying the brain and accounts for approximately 50% of all strokes, whereas an embolic stroke is the result of a clot formed elsewhere in the body which was subsequently transported through the bloodstream to the brain. The only FDA-approved intervention for ischemic strokes is intravenous administration of tissue plasminogen activator (tPA), which acts by dissolving the blood clot (or recanalization) within 4.5 hours of stroke onset and thereby, improving blood flow to the part of the brain being deprived of blood. Transcranial laser therapy (TLT), administered close to the time of stroke onset, initially showed promising results in ischemic stroke patients but the most recent large scale, multi-center clinical trial NEST-3 was terminated after a futility analysis showed no difference between TLT and sham treatment in the primary endpoint which was disability at 90 days. Critical factors for TLT are the amount of energy that would penetrate the skull and be received by deeper structures in the brain, and the time interval between stroke onset and the initiation of treatment.

Acupuncture has been used for more than 3,000 years as prevention and treatment of various diseases in China and other Asian countries. Clinical trials have shown that acupuncture has a positive effect in stroke, not only for poststroke rehabilitation but also as a preventive strategy which could induce cerebral ischemic tolerance, especially when combined with electrotherapy as electroacupuncture. Identification of patients with a high risk of stroke would allow preventive therapeutic options to be undertaken. This would include those patients who have had a previous history of stroke or experienced a recent transient ischemic attack (TIA).

Changes in cerebral ischemia-reperfusion injury and neuroprotective effect of acupuncture: Many changes take place at the cellular and molecular level when a stroke occurs. The obstruction of a major cerebral vessel (usually the middle cerebral artery), if not resolved within a short period of time, leads to the development of an ischemic core of severely damaged brain tissue that may not be salvageable. The ultimate size of the brain infarct depends on the penumbra, a zone of tissue around the core of the infarct where neuronal electrophysiology is not compromised and blood flow is still maintained above a neuronal disabling level. Decreased blood flow leads to a reduction in phosphocreatinine and adenosine triphosphate (ATP). If the ischemia is prolonged, the energy depletion will be sufficient to lead to severe impairment of cellular function by disruption of ATP-dependent processes.

Inflammation and immune responses play an important role in the outcome of ischemic stroke. Blood-derived leukocytes and resident microglia are the more activated inflammatory cells, accumulating in the brain tissue after cerebral ischemia, leading to inflammatory injury. Microglia, the major source of cytokines and other immune molecules of the central nervous system (CNS), are the first non-neuronal cells that respond to CNS injury, becoming phagocytic when fully activated by neuronal death. Following ischemia, astrocytes are activated in the brain and are capable of secreting inflammatory factors such as cytokines, chemokines and inducible nitric oxide synthase. Activated astrocytes contribute to neuronal survival after ischemic brain injury. They have been shown to maintain ionic homeostasis, scavenge free radicals, provide nutrition and growth factors, promote the formation of new blood vessels, and sustain the regeneration of synapse and nerve cells.

It is considered that acupuncture improves or reverses neuronal impairment in ischemic brain tissue, and regulates energy supply and metabolism in the ischemic area, consistent with a neuroprotective effect.

A Cochrane review (Wong et al., 2013) studied the outcomes reported in four randomized controlled trials (RCTs), including 294 participants, and in which three of the trials investigated electroacupuncture treatment for traumatic brain injury (TBI) and one investigated acupuncture treatment for TBI. It was concluded that the results seem to suggest that acupuncture is efficacious for these indications; however, the low methodological quality of the studies renders the results questionable. In a recent large scale, multicenter RCT in China including 862 patients with limb paralysis 3 to 10 days after ischemic stroke onset, acupuncture treatment of 5 times/week for 3 to 4 weeks to 427 of the patients resulted in fewer deaths or dependent (20.7%) than in the control group (25.8%) at 6 months. The benefit was noted in the subgroup receiving ≥ 10 sessions of acupuncture. Severe adverse events occurred in 7.6% and 8.3% of patients in the two groups, respectively (Zhang et al., 2015).

In animal stroke models, acupuncture therapy was reported to cause improvements in cerebral blood flow, angiogenesis, infarct size, inflammation, apoptosis, oxidative stress, number of neuronal cells and neural progenitor cells. Also to effect alterations in levels of growth factors *e.g.*, glial cell line derived neurotrophic factor (GDNF), brain derived neurotrophic factor (BDNF), vascular endothelial growth factor (VEGF), tumor necrosis factor- α (TNF- α), maintain structural integrity of astrocytes and stimulate specific signal pathways (Li et al., 2013).

Neuroprotective effect of acupuncture pretreatment for preventing stroke: A TIA, or mini-stroke, is a warning of an impending stroke. It may appear hours, days, weeks or months before a full stroke, but is more common within days or a few weeks. Also an individual who has previously had a stroke is susceptible to having another stroke in the near future. Only a very small number of studies have been performed to assess the clinical efficacy of acupuncture pretreatment for the prevention of stroke. In a recent study 35 cases of TIA received acupuncture therapy at these points of the Governor Vessel (flows along the midline of the back up to the head) GV3, GV4, GV9, GV12, GV14, GV15, GV16, GV20 and also EX-B2 (lateral to midline of back, 1st thoracic vertebra to 5th lumbar vertebra) (Figure 1), 6 times/week with an interval of one day between two weeks, and 21 days of treatment constituting a session. The comparison group was 35 cases treated with western medicine, whereby aspirin 100 mg/day was taken orally each night, and 21 days of medication being one session. There were 3 days at the interval between two sessions in each group and a total of 2 sessions was required. Transcranial Doppler was performed before treatment and in the two sessions of treatment to measure mean flow velocity of middle cerebral artery, vertebral artery, basilar artery and pulsatility index. The acupuncture treatment based on promoting the circulation of the Governor Vessel achieved superior efficacy on TIA and less adverse reaction compared to aspirin medication (Yu et al., 2013).

Patients with TBI (*e.g.*, car accidents, falls) are at increased risk of stroke. A recent study compared 7,409 newly diagnosed TBI survivors aged 20 years or older in Taiwan who had used at least two courses (one course including six consecutive treatments) of acupuncture with 29,636 patients with no acupuncture. The selection of acupuncture point was made by Traditional Chinese Medicine (TCM) physicians who conducted clinical assessment in accordance with TCM principles such as GV26 (Tseng et al., 2013). TBI patients with acupuncture treatment had a lower incidence of stroke (4.9 per 1,000 person-years) compared to those without acupuncture treatment (7.5 per 1,000 person-years) (Shih et al., 2014). Stroke-related medications such as anticoagulants, antiplatelet agents, and lipid-lowering agents were identified as potential confounding factors in the association between acupuncture treatment and stroke. Also, the study was limited by a lack of information regarding lifestyles, biochemical profiles, TBI severity, and acupuncture points used in the treatments (Shih et al., 2014).

Biomarkers for TIA and ischemic stroke: The diagnosis of a TIA based on symptoms and signs only is notoriously difficult and biomarkers of brain ischemia might improve the recognition, and target management and prognosis of TIA patients. Elevated levels of brain natriuretic peptide (BNP) have been associated with an increased risk of incident stroke (Komori et al., 2008). More recently, serum levels of platelet basic protein (PBP) and ceruloplasmin were significantly different between patients with TIA ($n = 20$) or minor stroke ($n = 15$) compared to patients with migraine or seizure ($n = 12$). In a second cohort of

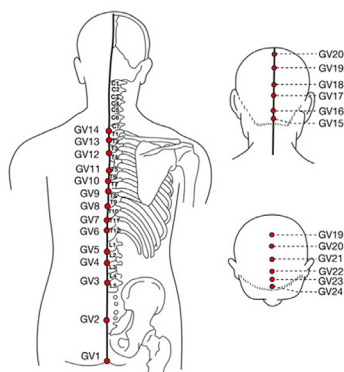


Figure 1 Acupuncture points of Governing Vessel.
The Governing Vessel was previously named Du Meridian, so GV10 acupuncture point for example is the same as DU10 acupuncture point.

patients, PBP serum concentrations were significantly increased in the ischemic samples (TIA, $n = 22$ and minor stroke, $n = 20$) compared to the controls ($n = 12$), while ceruloplasmin tended towards increased concentrations in the ischemic groups. Hence, PBP is identified as a potential serum biomarker for TIA, and a larger sample size may find that ceruloplasmin is an additional candidate biomarker (George et al., 2015).

Electroacupuncture parameters for treating TIA and cerebral ischemic injury: In a study using the rat model of cerebral ischemia (middle cerebral artery occlusion, MCAO), electroacupuncture (EA) 5 Hz/20 Hz at 1 mA for 30 minutes at DU20 and DU26 greatly reduced the infarct volume, improved neurological deficit, and decreased the death rate. Similar results were obtained with EA at left LI11 and PC6. In contrast, EA at right LI11 and PC6 did not lead to any significant change in the infarct volume, neurological deficit, and the death rate. EA at left GB34 and SP6 also had an inconspicuous effect on the ischemic injury EA at DU20 and DU26 or at left LI11 and PC6 immediately induced a significant increase in cerebral blood flow, while EA at right LI11 and PC6 or at GB34 and SP6 did not increase cerebral blood flow. These findings show that EA protection against cerebral ischemia is acupoint specific (Zhou et al., 2013a). In addition, there are optimal EA frequencies for maintaining the structural integrity of ischemic brain tissue. Using a rat model of MCAO, EA 15 and 30 Hz at bilateral LI11 and ST36 decreased neurological deficit, increased glial fibrillary acidic protein expression, and alleviated ultrastructural damage of astrocytes at the edge of the infarct compared with no treatment or EA 100 Hz (Xiao et al., 2013). Furthermore, EA-induced neuroprotection against cerebral ischemia/reperfusion injury depends on an optimal EA-duration. In rats exposed to right MCAO for 60 minutes followed by 24-hour reperfusion, EA 5 Hz/20 Hz at 1 mA was applied to DU26 and DU20 acupoints for 5, 15, 30, and 45 minutes. It was shown that 30 minutes of EA, starting at 5 minutes after the onset of MCAO (EA during MCAO) or 5 minutes after reperfusion (EA after MCAO) significantly reduced infarct volume, improved neurological deficit, and decreased the death rate. Also in the group of EA during MCAO, the protective effect was proportional to the increase in the period of stimulation, with increased protection in response to EA from 5 to 30 minutes of stimulation. EA for 45 minutes did not cause a decrease in infarct volume or neurological deficits and instead showed an increase in death rate in this group (Zhou et al., 2013b).

Future perspectives: The studies in rats and mice have demonstrated a preventive and protective effect of EA against cerebral ischemic injury. In order to define and characterize both the short and long-term effects of EA treatment in patients with stroke or TIA, it seems imperative to develop large, well-designed RCTs. Moreover, the results highlighted here, to date, suggest that EA, combined with current therapies such as thrombolytic agents, antiplatelet medications, anticoagulants and statins, may provide additive treatment benefits that are still largely unexplored. Despite the use of antiplatelet agents, usually aspirin, in patients who have had an ischemic stroke, there is still a substantial rate of recurrence of 8%, and no difference was found between aspirin and the anticoagulant warfarin in the prevention of recurrent ischemic stroke, death or rate of major hemorrhage (Mohr et al., 2001). Scalp acupuncture in patients with acute ischemic stroke appears to be able

to improve neurological deficit scores and clinical effective rate when compared with western conventional medicines (Wang et al., 2012). Eye acupuncture combined with western medicine caused a significant improvement in neurological function deficit score compared to western medicine by regulating endothelin and calcitonin with increased blood flow in the cerebral infarct (Bai et al., 2015). Statins given within 4 weeks of stroke onset improve stroke outcomes at 90 days compared with patients not given statins (Stead et al., 2009), and may when given in combination with acupuncture result in more favorable outcomes. The pleiotropic effects of statins are probably more important at least in the first 3 to 7 days after stroke and include dose-dependent elevation of endothelial nitric oxide synthase, enhanced endogenous tPA, exertion of an anti-thrombotic effect, improved collateral blood flow, and decreased inflammatory mediators. Some recent studies have used DU26, PC6 and SP6 as the main points to treat acute cerebral infarction, while usually points on the head and limbs (e.g., DU20, GB20, TE5) and scalp points are combined. Acupuncture combined with conventional medicines is safe and more effective than medication alone in the treatment of acute cerebral ischemic injury.

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References

- Bai ZH, Zhang ZX, Li CR, Wang M, Kim MJ, Guo H, Wang CY, Xiao TW, Chi Y, Ren L, Gu ZY, Xu R (2015) Eye acupuncture for stroke: a systematic review and meta-analysis. *Evid Based Complement Alternat Med* 2015:871327.
- George PM, Mlynash M, Adams CM, Kuo CJ, Albers GW, Olivot JM (2015) Novel TIA biomarkers identified by mass spectrometry-based proteomics. *Int J Stroke* 10:1204-1211.
- Komori T, Eguchi K, Tomizawa H, Ishikawa J, Hoshida S, Shimada K, Kario K (2008) Factors associated with incident ischemic stroke in hospitalized heart failure patients: a pilot study. *Hypertens Res* 31:289-294.
- Li X, Wang Q (2013) Acupuncture therapy for stroke patients. *Int Rev Neurobiol* 111:159-179.
- Mohr JP, Thompson JL, Lazar RM, Levin B, Sacco RL, Furie KL, Kistler JP, Albers GW, Pettigrew LC, Adams HP, Jackson CM, Pullicino P (2001) A comparison of warfarin and aspirin for the prevention of recurrent ischemic stroke. *N Engl J Med* 345:1444-1451.
- Shih CC, Hsu YT, Wang HH, Chen TL, Tsai CC, Lane HL, Yeh CC, Sung FC, Chiu WT, Cheng YG, Liao CC (2014) Decreased risk of stroke in patients with traumatic brain injury receiving acupuncture treatment: a population-based retrospective cohort study. *PLoS One* 9:e89208.
- Stead LG, Vaidyanathan L, Kumar G, Bellolio MF, Brown RD, Suravaram S, Enduri S, Gilmore RM, Decker WW (2009) Statins in ischemic stroke: just low-density lipoprotein lowering or more. *J Stroke Cerebrovasc Dis* 18:124-127.
- Tseng YJ, Hung YC, Hu WL (2013) Acupuncture helps regain postoperative consciousness in patients with traumatic brain injury: a case study. *J Altern Complement Med* 19:474-477.
- Wang Y, Shen J, Wang XM, Fu DL, Chen CY, Lu LY, Lu L, Xie CL, Fang JQ, Zheng GQ (2012) Scalp acupuncture for acute ischemic stroke: a meta-analysis of randomized controlled trials. *Evid Based Complement Alternat Med* 2012:480950.
- Wong V, Cheuk DK, Lee S, Chu V (2013) Acupuncture for acute management and rehabilitation of traumatic brain injury. *Cochrane Data Base Sys Rev* 3:CD007700.
- Xiao Y, Wu X, Deng X, Huang L, Zhou Y, Yang X (2013) Optimal electroacupuncture frequency for maintaining astrocyte structural integrity in cerebral ischemia. *Neural Regen Res* 8:1122-1131.
- Yu NT, Han W, Zhang L, Zhu LL, Wang QW, Zhang GQ, Liu BY (2013) Precautionary study on acupuncture pretreatment for stroke at early stage. *Zhongguo Zhen Jiu* 33:980-984.
- Zhang S, Wu B, Liu M, Li N, Zeng X, Liu H, Yang Q, Han Z, Rao P, Wang D (2015) Acupuncture efficacy on ischemic stroke recovery multicenter randomized controlled trial in China. *Stroke* 46:1301-1306.
- Zhou F, Guo J, Cheng J, Wu G, Sun J, Xia Y (2013a) Electroacupuncture and brain protection against cerebral ischemia: specific effects of acupoints. *Evid Based Complement Alternat Med* 2013:804397.
- Zhou F, Guo J, Cheng J, Wu G, Xia Y (2013b) Effect of electroacupuncture on rat ischemic brain injury: importance of stimulation duration. *Evid Based Complement Alternat Med* 2013:878521.