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Complementary Traditional Chinese Medicine Therapy for Traumatic Brain Injury

Ching-Chih Chen, Yu-Chiang Hung and Wen-Long Hu

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Abstract

The number of cases of traumatic brain injury (TBI) is increasing daily, predominantly because of the increasing rate of motor vehicle accidents. TBI has become one of the major causes of mortality and morbidity worldwide among individuals of all ages. TBI-inducing accidents usually occur very suddenly, leading to a heavy burden for both families and society at large. Beside conventional treatments such as surgery, medication, and rehabilitation, traditional Chinese medicine (TCM) is a promising complementary therapy that is practiced worldwide. This chapter will investigate the advances in TCM therapy for TBI.

Keywords: traumatic brain injury, traditional Chinese medicine, herbal medicine, acupuncture, Tai Chi Chuan

1. Introduction

1.1. Definition

Traumatic brain injury (TBI) is defined as an impairment of brain function that is caused by an external force [1].

1.2. Epidemiology

TBI has becoming a major health and socioeconomic problem all over the world [1]. It affects people of all ages including those living in both low-income countries and high-income countries [2]. TBI contributes largely to worldwide mortality and morbidity. According to the Centers for Disease Control and Prevention of the United States, in 2013, there were a

recorded 2.8 million TBI-related emergency department visits, hospitalizations, and deaths in the United States alone; there were nearly 50,000 TBI-induced deaths and 282,000 TBI-related hospitalizations [3]. The World Health Organization (WHO) has predicted that, by 2020, TBI will be one of the main health problems and the principle cause of disability [4]. Blunt head injury caused by motor vehicle crashes is most common in young adults and children, whereas falling is the most common cause of TBI in older individuals. The incidence of TBI is twice as much for men than for women [5]. Although the average mortality rate appears to be decreasing, a review published in 2015 has indicated that there are, nonetheless, still no signs of a decreasing incidence of TBI in Europe [2].

1.3. Impact

The high incidence of TBI-associated disability and death incurs many costs and social challenges [5]. In the United States, the cost of TBI has been estimated to be greater than USD 75 billion per year, and the cost for one patient in their whole lifetime is estimated at USD 396,000 [6]. Indeed, even after emergency treatment and hospitalization, deficits persist, even in cases of mild TBI. These include both physical and neurobehavioral impairments, which result in activity limitations, a lack of social participation, and communication difficulties [7], and potentially years of rehabilitation are required after acute treatment. Therefore, it is crucial to raise concern for the recruitment of healthcare resources for TBI treatment and rehabilitation and even to consider potential alternative treatments for survivors of TBI.

2. Etiology

In the United States, the top three major etiologies of TBI are falls, motor vehicle accidents, and being struck by an object. Each of these has been reported to account for 47, 15, and 14%, respectively, of all TBI-related emergency department visits, hospitalizations, and deaths [8]. Moreover, blast-induced TBI accounted for 67–88% of all the TBIs among the casualties in warfare [9]. Falls were reportedly more common in the youngest and oldest age groups. Motor vehicle accidents have the highest fatality rate, followed by intentional self-harm [3]. Other etiologies include assault, “unknown,” bicycle and other transport accidents, and suicide attempts [10].

3. Classification

TBI is classified into mild, moderate, and severe on the basis of Glasgow Coma Scale (GCS) score, which ranks functional ability from 1 to 15. Mild TBI (GCS 14–15) accounts for 80% of TBI [5]. Although it is termed “mild,” the sequelae may be long lasting. Moderate TBI (GCS 9–13) accounts for 10% of TBI [5]. The mortality rate of TBI without other physical injuries is less than 20%. Among patients with moderate TBI, 40% demonstrated abnormal computed tomography (CT) findings, and 8% required neurosurgery [5]. Severe TBI (GCS 3–8) has a mortality rate approaching 40%, and less than 10% of patients are reported to experience a good recovery [5].

TBI can be categorized into primary and secondary brain injury based on whether the damage is directly or indirectly caused by the trauma.

4. Pathophysiology

4.1. Primary brain injuries

Primary brain injuries are those caused by direct mechanical forces to the brain, which contribute to deformation of brain tissue and disruption of normal brain function. When encountering a force against the head, the soft brain hits the intracranial surface of the skull, resulting in brain damage at the area of contact and at the area opposite to the point of contact. The location and severity of such an impact directly influence the patient's outcome. Penetration to the brain can tear axons and damage neuron conduction, and vascular damage could lead to blood and leukocyte migration into the normally immune-privileged brain [11]. Primary brain injuries include contusions, intracranial hematomas, diffuse axonal injuries, direct cellular damage, loss of electrochemical function, and blood-brain-barrier (BBB) dysfunction.

4.2. Secondary brain injuries

Secondary brain injuries are caused by a cascade of secondary events after primary injuries of the brain. One common example is secondary neurotoxic cascade, which leads to progressive brain damage and eventually results in poor outcomes. The process of secondary neurotoxic cascade involves a massive release of neurotransmitters into synaptic clefts; this ultimately induces mitochondrial damage and leads to cell death and necrosis [12, 13]. The inflammatory response can also cause secondary damage in TBI, especially around the locations of contusions and hemorrhages. Neurotransmitter release and inflammatory responses can last days after TBI, leading to BBB dysfunction and immune-mediated activation of cell death and apoptosis.

5. Conventional treatment and rehabilitation

5.1. Conventional treatment

Emergent treatment for TBI, including surgery and intensive care, is crucial because cerebral edema can lead to several pathologies associated with primary and secondary injuries [14]. Initially, prehospital care is primarily aimed at preventing hypoxia and hypotension, which can lead to secondary brain injury; hence, fluid resuscitation with crystalloids and colloids and oxygen supplementation are implemented. Osmotherapy with rapid infusion of mannitol, which creates an osmolality gradient to maintain fluid in vessels, therefore, improves focal cerebral blood flow. Decompressive craniectomy has also been practiced on TBI patients to lower intracranial pressure and treat brain edema for decades [1].

5.2. Rehabilitation treatment

Further rehabilitation strategies include hyperbaric oxygen therapy, noninvasive brain stimulation, and limb or organ function reconstruction [4]. Hyperbaric oxygen therapy has been shown to inhibit apoptosis, suppress inflammation, protect the integrity of the BBB, and promote angiogenesis and neurogenesis [15, 16]. Several studies have revealed that noninvasive brain stimulation, including transcranial magnetic stimulation and transcranial direct current stimulation, can reduce TBI-associated depression, tinnitus, neglect, memory deficits, and attention disorders [4]. Another study demonstrated that electrical stimulation enhanced energy and glucose metabolism in patients who could not voluntarily exercise [17].

5.3. Outcomes and prognosis

Experience has shown that about 85% of recovery occurs within 6 months after head injury [1]. The most frequently used scale for outcome prediction is the GCS scale; however, further detailed functional and neuropsychological assessment is required during rehabilitation to fully assess outcomes. Early and intensive rehabilitation is recommended in order to obtain the best possible functional outcome and social reintegration [1].

6. Traditional Chinese medicine in the treatment of TBI

Traditional Chinese medicine (TCM), which has been practiced in China for thousands of years, has attracted increasing attention in recent years. There is sufficient evidence supporting the clinical benefits of TCM in the treatment of TBI, including Chinese herbal medicine compounds, acupuncture, and electroacupuncture [18–20]. This chapter will thus discuss the complementary treatment of TBI with TCM.

6.1. Chinese herbal medicine for TBI

Chinese herbal medicine treatment comes in different forms, including decoctions, pills, and powders. Numerous studies have suggested that Chinese medicine has multiple neuroprotective effects, including improvement of brain edema, anti-inflammatory responses, and anti-oxidative effects. Reviews of several studies have concluded that TCM plays an important role in the prevention and treatment of neural diseases and is potentially effective in neural regeneration and CNS functional recovery [21, 22].

6.1.1. Single Chinese herb for TBI

Ginseng, the root of *Panax ginseng* C.A. Meyer (Araliaceae), has been widely used for treating qi depletion patterns. Generally, qi represents the energy flow in the meridian that maintains the proper function of the organs, and therefore, qi depletion represents a decrease of function

of the organs. The biologically active substance in Ginseng is ginsenoside, which has been reported to have neuroprotective effects, regulate nerve-regulating factors, and improve the proliferation of neural stem cells. This suggests that ginsenoside might improve the recovery of neurological functions, such as memory and learning [23, 24]. Rhein (the active part of *Rheum rhabarbarum*) also has the potential to be utilized as a neuroprotective drug in TBI because of its anti-oxidative effects and its ability to cross the BBB and it increases permeability the BBB [25, 26] (Table 1).

6.1.2. Traditional Chinese herbal formulae for TBI

TCM formulae are potentially neuroprotective and beneficial in cases of brain edema through a reduction of brain water content, improvement of the permeability of the BBB, and reduction of tumor necrosis factor-alpha (TNF- α)/nitric oxide (NO) levels after TBI [27]. One study has demonstrated that the Sheng-Nao-Kang decoction, which contains 15 different traditional Chinese medicines, has a protective effect against ischemia and reperfusion injuries [28]. The Shen-Nao-Kang decoction was developed to activate blood circulation, dissipate blood stasis, and dredge meridians and collaterals [28]. The Xuefu-Zhuyu (XFZY) decoction is also documented to have multiple benefits for TBI, including improving neurological recovery after TBI, reducing TBI-induced elevation of arachidonic acid (a precursor of prostaglandins and leukotrienes) levels in the brain, restraining the TBI-induced increase of pro-inflammatory factors in the brain, and inhibiting the inflammatory pathways mediated by Akt/mammalian target of rapamycin (mTOR)/p70S6 kinase [29]. NeuroAid is a TCM compound that contains 14 different herb components and has been found to have neuroprotective and neurorestorative actions in animal models and, hence, leads to improved cognitive function following TBI [30, 31] (Table 2).

Study	N	Design	Herb extracts	Conclusion
Hu et al. [23]	48	(1) Animal model (2) RCT	GTS	GTS alleviates secondary brain injury and improves neurological function through regulation of the expression of nerve growth related factors
Ji et al. [24]	24	(1) Animal model (2) RCT	GTS	GTS has a neuroprotective effect after TBI
Xu et al. [25]	36	(1) Animal model (2) RCT	Rhein	Rhubarb (and its component rhein) has anti-oxidative properties and decreases the overproduction of free radicals after oxidative stress in TBI
Tang et al. [26]	6:6:6	(1) Animal model (2) RCT	Rhein	Rhubarb could ameliorate cerebral edema; rhein may inhibit the transcription and translation of the aquaporin-4 gene

GTS, ginseng total saponins; TBI, traumatic brain injury; RCT, randomized controlled trial

Table 1. Studies on the effects of single herbal medicines on brain injury.

6.2. Acupuncture and electroacupuncture for TBI

6.2.1. The benefit of treating patients with TBI through acupuncture and electroacupuncture

In TCM theory, acupuncture regulates the function of qi, blood, and organs through the stimulation of acupoints and eliminates pathogenic factors [32]. Acupuncture plays an important role in treating TBI, and its popularity as a supplementary treatment continues to increase. In the first year after TBI, patients in one study that received acupuncture treatment experienced a decreased risk of hospitalization and lower use of emergency medical care compared to patients who did not receive acupuncture treatment [33]. In an animal study, early, low-frequency electroacupuncture treatment after TBI was shown to be beneficial, decreasing TNF- α expression in activated microglia and astrocytes and reducing neural apoptosis and, therefore, improving functional outcome after TBI [34]. Neural stem cell proliferation and differentiation could also be affected by acupuncture, by upregulating gene expression, shortening the time for recovery, and regulating astrocyte proliferation and differentiation [35, 36]. Despite these aspects of neural recovery, some sequelae after TBI have also been shown to be benefited by acupuncture. Insomnia after TBI is a common complaint; one study has found that acupuncture has beneficial effect on the perception of sleep or sleep quality as well as benefiting cognition in 24 adult patients with TBI [37]. In patients with spastic muscle hyperactivity and chronic disorders of consciousness following TBI, evidence has shown that acupuncture can immediately reduce the excitability of spinal motor neurons [38]. However, another study has shown that acupuncture could increase the excitability of the corticospinal system; this suggests that acupuncture might accelerate the recovery of motor function in patients with disorders of consciousness following TBI [20]. Moreover, a cohort study has demonstrated that patients with TBI who received acupuncture had a lower risk of new-onset stroke than those who did not receive acupuncture [39] (**Table 3**).

Study	N	Design	TCM compound	Conclusion
Yang et al. [27]	25	(1) Systematic review (2) Animal model		TCM compound recipes may improve brain edema via increasing BBB permeability and decreasing TNF- α /NO expression after TBI
Chen et al. [28]	36	(1) RCT (2) Animal model	Sheng-Nao-Kang	Sheng-Nao-Kang demonstrates a protective effect against cerebral ischemia/reperfusion injury
Xing et al. [29]	64	(1) RCT (2) Animal model	XFZY decoction	XFZY decoction reduces mNSS, AA, TNF- α , and IL-1 β levels and downregulates AKT/mTOR/p70S6K proteins in the brain; XFZY decoction may reduce TBI-associated inflammation
Quitard et al. [30]	6:6:6	(1) RCT (2) Animal model	NeuroAid (MLC901)	MLC901 has neuroprotective and neurorestorative effects in TBI animal models

TNF- α , tumor necrosis factor α ; NO, nitric oxide; TBI, traumatic brain injury; RCT, randomized controlled trial; mNSS, modified neurologic severity score; AA, arachidonic acid; mTOR, mechanistic target of rapamycin; XFZY, Xuefu-Zhuyu

Table 2. Studies on the effects of traditional Chinese medicine compounds in the treatment of brain injury.

Study	N	Design	Test group	Control group	Acupoints	Conclusion
Tang et al. [34]	6:6:6	RCT animal study	EA	(1) Control (2) Sham	DU20, DU26, LI4, and KI1	EA ameliorates TBI neuroinflammation in the acute stage by attenuating TNF- α expression
Zhang et al. [35]	36:36:16:16	RCT animal model	Acupuncture	(1) Model (2) Normal (3) Sham	DU20, DU26, DU16, DU15, and LI4	Acupuncture promotes <i>notch1</i> , <i>hes1</i> , and <i>hes5</i> expression in brain tissue, which are important for stem cell proliferation
Jiang et al. [36]	32:36:36	RCT animal model	Acupuncture	(1) Normal (2) TBI	DU20, DU26, DU16, DU15, and LI4	Acupuncture induces endogenous neural stem cell proliferation and differentiation
Zollman et al. [37]	12:12	Pilot RCT	Acupuncture	WCM	KI3, HR3, BL60, LR3, LI4, PC7, DU20, ear point Tranquilizer, and Shen Men	Acupuncture is beneficial for treatment of insomnia and improving cognitive function after TBI
Matsumoto-Miyazaki et al. [20]	12	Crossover study	Acupuncture first	Control first	DU26, Ex-HN3, LI4, and ST36	Acupuncture could improve corticospinal tract excitability and, therefore, improve spastic muscle hypertonia in patients with TBI
Matsu moto-Miyazaki et al. [36]	11	Crossover study	Acupuncture first	Control first	DU26, Ex-HN3, LI4, and ST36	Acupuncture could reduce the excitability of spinal motor neurons and improve spastic muscle hypertonia in patients with TBI
Shih et al. [37]	29,636	Cohort study	Acupuncture treatment	Non-acupuncture treatment		Compared to patients with TBI not receiving acupuncture, those with acupuncture have a lower risk of new-onset stroke

EA, electroacupuncture; TBI, traumatic brain injury; RCT, randomized controlled trial; TNF- α , tumor necrosis factor- α ; WCM, Western conventional medicine

Table 3. Studies on the effects of acupuncture and electroacupuncture in the treatment of brain injury.

6.2.2. Zusanli (ST36)

Zusanli (ST36) is an acupoint on the stomach meridian that is rich in blood and qi. Stimulation of this point has several effects in TCM theory, including supplementing the qi and blood, fortification of the spleen, and harmonizing the stomach. Several neuroprotective effects of ST36 have been noted in recent studies, including enhancing neural plasticity, suppressing neuron apoptosis, increasing cerebral blood flow, and improving microcirculation [40]. One study found that acupuncture performed at certain acupoints, including Baihui (DU20), Renzhong (DU26), Hegu (LI4), and Zusanli (ST36), improved neurological recovery after TBI through the brain-derived neurotrophic factor (BDNF)/tropomyosin receptor kinase B (TrkB) pathway; not only was this effect immediate, but it persisted for 168 hours after acupuncture [32]. Electroacupuncture at ST36 might also encourage neurological recovery through upregulation of angiopoietin-1 and angiopoietin-2 [40]. Moreover, electroacupuncture at ST36 could enhance endothelial cell proliferation and, consequently, upregulate the level of hypoxia-inducible factor-1 α (HIF-1 α) protein, which accelerates angiogenesis [41] (**Table 4**).

6.2.3. Baihui (DU20)

DU20, also named GV20, when the ears are folded, DU20 is located at the midpoint of the connecting line between the auricular apices [42]. According to TCM theory, DU20 belongs

Study	N	Design	Test group	Control group	Acupoints	Conclusion
Zhou et al. [40]	30:30:30	RCT animal model	Stroke-EA group	(1) Sham (2) Stroke-no acupuncture	ST36	EA in ICH rats remarkably increases Angiopoietin-1 and -2 levels
Li et al. [32]	20:20:20:20	RCT animal model	(1) TBI + Acupuncture group (2) TBI + Acupuncture + K252 α group	(1) TBI (2) TBI-placebo-acupuncture group	DU20, DU26, LI4, ST36	Acupuncture aids neurological recovery through activation of the BDNF/TrkB pathway
Luo et al. [41].	24:24:24:24	RCT animal model	(1) ICH + Acupuncture	(1) Sham (2) ICH group (3) ICH non-acupoint acupuncture	ST36	EA at ST36 increases the number of cerebral endothelial cells and increases the expression of HIF-1 and may, therefore, accelerate ICH-induced angiogenesis

EA, electroacupuncture; ICH, intracranial hemorrhage; TBI, traumatic brain injury; BDNF, brain-derived neurotrophic factor; TrkB, tropomyosin receptor kinase B; HIF-1, hypoxia-induced factor-1; RCT, randomized controlled trial

Table 4. Studies on the effects of acupuncture at ST36 for the treatment of brain injury.

to the governor vessel, which governs the yang qi all over the body. The function of DU20 is to wake the brain and open the orifices, lift the spirit, tonify yang, strengthen the ascending function of the spleen, dredge qi and the blood, and lift up yang qi [43]. Therefore, researchers have targeted a combination of DU20 and ST36 for the treatment of cerebral injury; results revealed that rats with cerebral ischemia reperfusion injuries had better neurological scores and reduced volumes of brain infarction than those who did not receive postoperative treatment [44]. Another study found that acupuncture and electroacupuncture at DU20 and ST36 could decrease the infiltration of inflammatory cells and pro-inflammatory enzymes [45]. More importantly, acupuncture and electroacupuncture significantly attenuate the expression of aquaporins in the ischemic brain, including aquaporin 4 and aquaporin 9, indicating that protective mechanisms are partially dependent on the reduction of inflammation-related brain edema [46]. One study of electroacupuncture at DU20 demonstrated improvements in the microenvironment via neural regeneration and neuroprotection in newborn rats with TBI [47] (Table 5).

6.3. Tai Chi Chuan for TBI

Tai Chi Chuan (also known as “Tai Chi”), as a traditional Chinese aerobic exercise, has been popular in both the Western and Eastern worlds for years. Tai Chi Chuan was used as a novel supplementation to a comprehensive rehabilitation program [48]. Many studies have demonstrated the physiological and psychological benefits of Tai Chi Chuan in chronic conditions, including benefits in cardiovascular function, musculoskeletal condition, and reduction of anxiety [49]. In one randomized pilot study, patients with TBI were allocated to either a Tai Chi group (n = 20) that received supervised Tai Chi instruction for 8 weeks (1 h per week) or

Study	N	Design	Test group	Control group	Acupoints	Conclusion
Chen et al. [44]	24:24:24	RCT animal model	Acupuncture group	(1) Sham-operated group (2) Model group	DU20, ST36	Acupuncture at DU20 and ST 36 in rats could upregulate miRNA 124 and reduce the expression of laminin and integrin β 1
Xu et al. [45]	48:48:48:8	RCT animal model	Acupuncture group	(1) Sham operated (2) Model (3) Normal	DU20, ST36	Acupuncture at DU20 and ST36 could reduce or delay the expression of HSP70 and TNF- α , which are related to neuroprotection
Chen et al. [47]	6:6:6:6	RCT animal model	20-min fetal distress + DU20 group	(1) Blank control group (2) 20-min fetal distress group (3) 20-min fetal distress-non-acupoint group	DU20	EA regulates NeuroD expression by affecting the brain’s microenvironment

RCT, randomized controlled trial; miRNA, micro ribonucleic acid; HSP-70, heat-shock protein 70; TNF- α , tumor necrosis factor- α ; EA, electroacupuncture

Table 5. Studies on the effect of acupuncture at DU20 on brain injury.

a control group (n = 20) that performed a non-exercise leisure activity for the same amount of time. The results revealed that the Tai Chi group had a better mood and higher self-esteem scores [50]. Another study investigated the effects of a 6-week Tai Chi practice in patients with TBI and revealed increased happiness and energy, with significant improvements in sadness, confusion, anger, tension, and fear compared to a control group [51]. However, there was no significant difference in fatigue between the intervention group and control group. Although our knowledge of the mechanisms underlying such effects of Tai Chi Chuan is still lacking, evidence suggests that smooth exercise can improve mood and self-esteem and might, therefore, help patients with TBI become more involved in social activities.

7. Conclusions

The use of TCM as a complementary treatment for TBI is becoming increasingly popular. Although more evidence on the effects and mechanisms of TCM therapy is certainly required, previous results are encouraging. Chinese herbal medicine, acupuncture, and Tai Chi Chuan were found to have beneficial effects in patients with TBI. The possible mechanisms and effects of TCM for the treatment of TBI have been shown and proven to be effective based on animal studies mostly. Nevertheless, we are optimistic regarding the results of further TCM studies and look forward to more evidence confirming the TCM theory, as this would be beneficial for all patients.

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