THE ROLE OF ACUPUNCTURE AND STEM CELL THERAPY IN ENHANCING STROKE RECOVERY

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Abstract

Stroke is an acute neurological disorder caused by disrupted blood flow to the brain, depriving cells of oxygen. From 1990 to 2019, it was the world's second-leading cause of death and the third-leading cause of combined death and disability. Acupuncture plays a role in stem cell treatment by activating the body's natural recovery processes through physical stimulation, aiding the recovery and rehabilitation of stroke patients. Several studies have explored combining stem cell therapy with acupuncture, yielding promising results in improving patient outcomes. This review assesses the effectiveness of combining acupuncture with stem cell therapy for stroke recovery. Analysis of seven randomized controlled trials shows that both stem cell transplantation and acupuncture contribute to the rehabilitation of stroke patients. When applied together, this combined therapy improves the survival, retention, and functional differentiation of implanted stem cells, creating a synergistic effect that amplifies the benefits of each treatment and compensates for their individual limitations. Key acupuncture points for this combination therapy include GV20, GV14, LI11, ST36, and GV26, with treatment durations ranging from 10 to 22 days.

Keywords

Stem cell, stroke, acupuncture, electroacupuncture

Introduction

Stroke is defined as a focal neurological deficit resulting from changes in the blood supply to brain tissue. Stroke can be further classified into ischemic and hemorrhagic types. Successive studies have shown that between 1990 and 2019, stroke had become the second leading cause of death and the third leading cause of disability worldwide. Furthermore, according to WHO, stroke can be defined as rapidly developing regional (or global) clinical manifestations of disturbance of cerebral function lasting more than a day, with no apparent cause other than vascular.[1,2]

In the case of ischemic stroke, the underlying pathological processes are due to insufficiency of blood and oxygen supply caused by narrowing of blood vessels (thrombosis) or blockage of blood vessels (embolism). Therefore, cell structures become damaged, resulting in necrosis, which is proceeded by bursts in membrane alterations, excessive levels of an excitatory neurotransmitter (glutamate), oxidative stress, and infiltration of leukocytes. This eventually provokes an inflammatory response, causing cellular dysfunction and worsening the condition further by exerting cytotoxic effects along with a breakdown of the blood barrier which exposes neural tissue to free radicals and inflammatory cells. Both the necrosis stage and later associated apoptosis contribute towards total cell death at different time frames. Hypertension is one of the main risk factors and triggers for stroke.[3,4]

Risk factors, including high blood pressure (hypertension), diabetes, blood vessel abnormalities, and bad lifestyle choices, might contribute to stroke. Thromboembolism frequently results from heart-related embolisms or atherosclerosis. In order to differentiate between ischemic and hemorrhagic stroke, which require distinct therapies, prompt diagnosis is crucial. The primary objectives of treatment are to restore blood flow, reduce inflammatory damage, and prevent further oxidative stress-related damage.[5]

Stem cells are cells that can differentiate into specialized cell types and replicate indefinitely, ranging between totipotent, pluripotent, multipotent, oligopotent, and unipotent. Mesenchymal stem cells (MSCs) are a particular type of stem cell that can be harvested from the bone marrow, adipose tissue, or umbilical cord blood and possess the ability to move to damaged sites, differentiate, and release bioactive factors. MSCs are known to have immunosuppressive activities, enhance angiogenesis, and prevent apoptosis, hence assisting with tissue regeneration. MSCs have been proven to be effective in the management of several conditions such as stroke, brain injury, degenerating diseases, and even some immune disorders, which makes them a safe and desirable regenerative therapy applicable in the clinical setting.[6]

For therapeutic purposes, acupuncture therapy involves inserting needles into specific points on the body. Modern mechanisms include neurotransmitter release and nervous system stimulation to improve pain sensation and increase bodily functions. Acupuncture points, which include nerve endings and sensory receptors, maintain a crucial role in modulation and regeneration through the Primo Vascular System (PVS).

Acupuncture can improve tissue microenvironment, enhance microcirculation, and increase growth factors.[7,8]

Ischemic stroke can be treated using joint acupuncture and stem cell therapy as they execute a complementing mechanism in the process of treatment. The focus of acupuncture therapy is to alter the brain's environment, increase blood circulation in the brain, and protect the blood-brain barrier, while stem cells contribute to recovery through the differentiation of neural stem cells into neurons in the peri-ischemic striatum and through paracrine mechanisms by producing neurotrophic factors and immunoregulatory effects.[7,9] Such therapy offers compensatory effects by elevating stem cell survival and migration, through immunomodulation via inhibition of pro-inflammatory cytokines and upregulation of neurotrophins, and also by the presence of synergistic effects that boost stem cell maturation and engender neurogenesis. This coupled therapy works optimally in stroke patients by enhancing the microenvironment and reducing oxidative stress.[10]

Complementary use of modern therapies including stem cell transplantation and acupuncture also show synergistic effects in stroke recovery. This narrative review intends to search for and summarize previously published articles focusing on the role of acupuncture therapy and stem cell therapy in stroke recovery.[10]

Materials and Methods

A literature search was conducted using the PubMed and Google Scholar databases. Study limitations included publications from the last 10 years, randomized controlled trial design, written in English, and full-text availability. Keywords used include: stem cell, stroke, acupuncture, and electroacupuncture. However, it should be noted that the research is still limited to animal models, particularly rats.

Results

Table 1. Summary of Stem Cell and Acupuncture Research in Stroke Patients

AUTHOR	STUDY	INTERVENTION	CONTROL	DURATION	OUTCOME
Ahn et al (2019)[11].	RCT	MCAO+MSC+EA MCAO+TrkB (T)-MSC+EA	Sham EA Group MCAO Group MCAO+MSC Grup MCAO+TrkB (T)-MSC	10 or 20 days	The combination of EA therapy with TrkB-MSC has increased the expression of BDNF and NT4, by promoting the differentiation of TrkB-MSC, and improving motor function. Making it a potentially effective therapy for ischemic stroke.
Kim et al (2018)[12].	RCT	Combined mBMSC and EA	MCAO treated with vehicle	12 days	Co-treatment with MSC and EA could enhance neurotrophic factor expression by regulating neurogenesis in the brain, resulting in better therapeutic

					effects compared with single treatment.
Zhang et al (2020)[9].	RCT	Group 1: Exosomal miRNA regulation by EA therapy. Group 2: Analyzing the function of miRNA in the effects of EA therapy through the combination of MCAO, EA, and miR-146b inhibitor.	Sham group MCAO group MCAO + inhibitor injection group MCAO group with miR-146b inhibitor	21 days	EA has enhanced endogenous neural stem cell differentiation via exosomal miR-146b and also improved neurological deficits caused by ischemic stroke.
Kim et al (2014)[13].	RCT	MCAO and EA group	Sham group	10 days	EA therapy improves post-stroke functional recovery by increasing NSC proliferation and differentiation through BDNF and VEGF signaling pathways.
Zhao et al (2015)[14].	RCT	EA group Acupuncture points GV20 (Baihui), GV26 (Shuigou)	Sham group	21 days	EA therapy significantly oved post-stroke neurological ion recovery, where a significant ase in the number of BrdU/GFAP /NeuN cells was observed in the rea.
Deng et (2021)[15].	RCT	MSCs+EA	Sham group MSC transplantation group EA group	14 days	EA enhances the differentiation of transplanted MSCs into neuron-like cells, increases the expression of BDNF and NGF, improves neurological function, which may contribute to the improvement of brain tissue structure and reduction of further injury.
Deng etal (2022)[16]	RCT	EA+iPSC-Evs	Sham group Sham Acu group MCAO group iPSC-EVs group EA group	72 hours (3 days)	EA therapy combined with iPSC-EVs improved neurological deficits and reduced infarct volume by inhibiting neuronal apoptosis, and the underlying mechanisms involved suppression of Th1 and Th17 responses and enhancement of Treg responses.

** Randomized controlled trial (RCT), Electroacupuncture (EA), middle cerebral artery occlusion (MCAO), neural stem cell (NSC), Brain-derived neurotrophic factor (BDNF), vascular endothelial growth factor (VEGF), Bromodeoxyuridine (BrdU), glial fibril lary acidic protein (GFAP), neuronal marker (NeuN), Dentate gyrus (DG), mesenchymal stem cells (MSC), nerve growth factor (NGF), induced pluripotent stem cells-Extracellular Vesicles (iPSC-Evs), T helper (Th1) and Th17.

Discussion

Acupuncture and stem cell therapy are used together to treat ischemic stroke in a complementary manner. Acupuncture and stem cell therapy are used together to treat ischemic stroke in a complementary manner. Stem cells aid recovery through

differentiation through differentiation and paracrine actions; acupuncture helps regulate the brain microenvironment, by increasing cerebral blood flow, and maintaining the integrity of the blood-brain barrier. This combination therapy provides compensatory effects: By regulating cytokines such as SDF-1 and VEGF, acupuncture also enhances the capacity of stem cells to survive, and migrate to the lesion site; immunomodulatory effects: where the combination therapy increases the production of neurotrophic factors such as BDNF, helping brain tissue repair while suppressing pro-inflammatory cytokines such as TNF-γ and IL-1β; synergistic effects: Compared with monotherapy, this combination enhances endogenous neurogenesis, stimulates the growth and differentiation of stem cells into neurons and astrocytes, and significantly improves.[10,12]

Research by Kim et al showed that combining mesenchymal bone marrow stem cell (mBMSC) therapy with electroacupuncture (EA) provided a synergistic effect that significantly accelerated motor function recovery after ischemic stroke in mice. This combined approach effectively reduced striatal atrophy, increased neural progenitor cell proliferation in the SVZ and striatum, and increased the production of neurotrophic factors such as BDNF and NT4, especially in the damaged brain area. In addition, this therapy increased the expression of phosphorylated CREB protein. These results highlight that the combination of mBMSC and EA is more effective in enhancing neurogenesis and recovery than using either treatment alone.[11]

Ahn et al explored the use of electroacupuncture (EA) combined with TrkB-transfected mesenchymal stem cells (TrkB-MSCs) for ischemic stroke treatment. Their findings indicated that this combined approach significantly enhanced motor function compared to either treatment alone. By day 30 after MCAO, the group receiving TrkB-MSCs with EA exhibited the highest retention of implanted MSCs and regulated neurotrophic factor expression by activating TrkB receptors and CREB transcription. By day 60, EA further encouraged the differentiation of TrkB-MSCs into mature, neuron-like cells. This effect was reversed when TrkB antagonists were introduced, highlighting the importance of BDNF and NT4 in the recovery process. The study demonstrated that combining TrkB-MSCs with EA effectively supports motor recovery and promotes stem cell differentiation in ischemic stroke.[12]

Zhang et al demonstrated that EA promotes the differentiation of endogenous neural stem cells into neurons by upregulating exosomal microRNA, specifically miR-146b, to repair neurological injury following ischemic stroke. In the mouse model of ischemic stroke, EA enhanced the levels of exosome biomarkers such as TSG101 and CD81 in the peri-ischemic striatum and induced the expression of miR-146b, which is crucial for the NeuroD1-mediated neurogenesis. Inhibition of miR-146b was shown to abrogate this effect both in vivo and in vitro. EA also improved neurological deficits through this mechanism, showing its potential as a robust non-pharmacological treatment for ischemic stroke.[9]

Kim et al in their study showed that EA stimulation at GV20 (Baihui) and GV14 (Dazhui) points significantly improved functional recovery after ischemic stroke. EA promoted the proliferation and differentiation of neural stem cells (NSCs) in the

subventricular zone (SVZ) and hippocampus in the ipsilateral hemisphere, although the number of surviving and differentiated NSCs was limited. This treatment also increased the mRNA and protein expression levels of neurotrophic factors, such as the protein levels of neurotrophic factor (BDNF) and vascular endothelial growth factor (VEGF), which play important roles in neurogenesis and angiogenesis, respectively. BDNF and VEGF signaling pathways were activated, including phosphorylation of phosphatidylinositol-3-kinase, to promote the formation of new neuroblasts. These findings demonstrate the ability of EA to enhance post-stroke NSC-mediated functions through stimulation of neurogenesis and related signaling molecules.[13]

The study by Zhao et al showed that EA could significantly improve the recovery of neurological function in rats with ischemic stroke caused by MCAO. EA promoted the proliferation and differentiation of NSCs in the hippocampal DG, as evidenced by the increased number of BrdU+/GFAP+ and BrdU+/NeuN+ cells. The current study also demonstrated that EA increased the expression of Notch1 and Hes1, which are involved in the mechanism of NSC proliferation and differentiation, further supporting the potential of EA as a therapy for neurological recovery after stroke.[14]

Li Deng et al elaborated that the combination of EA with MSC transplantation therapy can achieve a synergistic effect in improving neurological function recovery after ICH in a rat model. The combination of MSC + EA enhanced the differentiation of MSCs into neuron-like cells and the expression of neurotrophic factors such as BDNF and NGF. Better neurological recovery was demonstrated by mNSS scores, gait analysis, and reduced brain injury. The results of this study also exhibited that the combination therapy increased brain glucose uptake, mitochondrial number, anti-inflammatory Arg-1 cells, and reduced apoptosis and pro-inflammatory iNOS cell expression. At the molecular level, the expression of mitochondria-related proteins (COX4, OGDH, PDH-E1β) and antiapoptotic proteins (Bcl-2) increased, while proapoptotic proteins (Bax) decreased. This study confirmed that EA enhances the efficacy of MSC therapy by modulating inflammation, energy metabolism, and brain tissue protection.[15]

Peying Deng et al. showed that the combination of electroacupuncture (EA) and induced pluripotent stem cell-derived extracellular vesicles (iPSC-EV) had a synergistic neuroprotective effect on a mouse model of ischemic stroke. This combined therapy effectively improved neurological deficits, improved motor function, reduced infarct volume, and suppressed neuronal apoptosis. Furthermore, the combination of EA and iPSC-EV reduced the inflammatory response by reducing the activity of T helper cells (Th1 and Th17) and increasing the activity of T regulatory cells (Treg). This therapy also modulates the IL-33/ST2 axis, which plays a role in inhibiting the activation of microglia and astrocytes, thereby reducing tissue damage. These findings suggest that the combination of EA and iPSC-EV has the potential to provide an innovative and effective therapeutic approach for ischemic stroke and other tissue injuries.[16]

Combining acupuncture with stem cell therapy is considered a promising approach for the treatment of stroke, especially ischemic stroke. Acupuncture works by influencing

the brain microenvironment, increasing cerebral blood flow, and restoring the integrity of the blood-brain barrier. Acupuncture points that are often used in research include GV20 (Baihui), GV14 (Dazhui), LI11 (Hegu), ST36 (Zusanli), and GV26 (Renzhong) (Figure 1). Stimulation of these points can directly affect the nervous system, increase blood circulation in the microarea, and stimulate the release of neurotransmitters and growth factors.

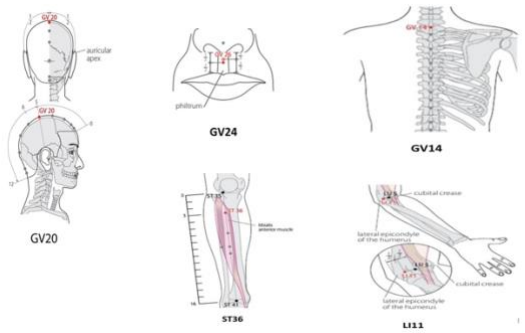

Figure 1. The most commonly acupuncture points[17]

Conclusions

The combination therapy of produces a synergistic effect, accelerating neurogenesis and angiogenesis, and facilitating the regeneration of damaged nerve tissue. Thus, acupuncture does not only act as a complement to stem cell therapy, but also plays an important role in modulating and optimizing its efficacy during stroke treatment. The combination of acupuncture with stem cell therapy offers great benefits in treating ischemic stroke and has been shown to have better results synergistically than alone.

Competing Interests

The authors declare no conflicts of interest with any individuals or organizations in any form.

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