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Research Progress of Acupuncture in the Treatment of Post-Stroke Depression

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Abstract: ***Post-stroke depression (PSD) is a prevalent complication in stroke survivors, characterized by persistent mood disorders that hinder rehabilitation and reduce quality of life. This study examines recent scholarly endeavors focusing on acupuncture (AC) as a feasible therapeutic approach for PSD. By analyzing contemporary literature, it elucidates the Traditional Chinese Medicine (TCM) perspective on PSD and evaluates AC's effectiveness. AC stands out as a promising modality of treatment owing to its potency and negligible side effects, with mechanisms including neurotransmitter modulation, neurotrophic factor regulation, neuronal apoptosis inhibition, inflammatory response modulation, and so on. This review offers valuable insights into PSD from a TCM perspective and highlights AC's potential as a therapeutic intervention, contributing to knowledge advancement and informing clinical practice in PSD management.***

Keywords: Post-stroke depression, Acupuncture, Traditional Chinese medicine, Research progress**.**

1. Introduction

Stroke, a prominent global disability factor, significantly diminishes healthy life span through sequelae like paralysis, dysphasia, dysphagia, epilepsy, and cognitive decline [1]. Post-stroke depression (PSD), affecting 30-33% of stroke survivors [2], is a critical emotional consequence characterized by hopelessness, apathy, communication avoidance, and sleep disorders, impeding daily activities and rehabilitation. PSD not only enhances recurrence risks but also compromises functional recovery and quality of life, tripling to quadrupling mortality in affected individuals [3]. Despite stroke being the precipitating factor, PSD's underlying mechanisms remain obscure, diagnosed through clinical symptoms and scales, hindered by communication difficulties and cognitive impairments in many patients. Current pharmacological interventions are limited, ineffective in approximately 40% to 60% of cases, and associated with cardiovascular risks, thereby reducing patient compliance [4]. Acupuncture (AC), as a common therapeutic method of Traditional Chinese Medicine (TCM), has demonstrated favorable efficacy in treating depression, accompanied by no adverse effects, and has gradually emerged as a promising approach in the management of PSD. This paper presents a comprehensive review of the recent advancements in research pertaining to AC as a treatment modality for PSD, intending to offer valuable insights and guidance for clinical practitioners caring for PSD patients.

2. Understanding of PSD from the Perspective of TCM

2.1 Based on the Theory of Qi, phlegm, and Stasis

Qi, the essential life force, circulates bodily fluids for nourishment and metabolism. Qi deficiency leads to slow fluid metabolism and phlegm formation. Disruptions in vital energy dynamics cause fluid stagnation and phlegm accumulation, obstructing fluid passage and inducing blood stasis or extravasation. The interplay between yang (qi) and yin (blood) is crucial, qi insufficiency promotes blood stasis, while phlegm blocks meridians, inducing blood stagnation and further qi disruption. This cycle depletes qi, blood, and fluids, forming a closed loop of disease [5]. Stroke, due to severe qi imbalance, disrupts blood circulation, impacting the brain and causing emotional disturbances. Post-stroke, phlegm accumulation exacerbates liver dysfunction and depression, while blood stasis obstructs vessels, perpetuating a cycle of depletion and stagnation. Tan Yan postulates that post-stroke pathology is predominantly stasis-based, with other factors transforming into stasis, damaging the brain and heart, and contributing to post-stroke depression [6]. Qi, phlegm, and stasis are intricately linked to the onset and progression of post-stroke depression, influencing each other in a mutual and dynamic manner. Across different stages of post-stroke depression, their prominence varies, leading to a shifting etiology and pathogenesis [7]. This interconnectedness fosters a vicious cycle, prolonging the disease state. Therefore, therapeutic strategies focus on enhancing Qi, resolving phlegm and stasis, and nourishing blood. Such an approach aims to disrupt the reciprocal cycle of Qi, phlegm, and stasis, providing innovative perspectives for clinical management of PSD [8].

2.2 Based on the Theory of Liver

PSD falls under the category of "depressive disorders" in TCM, with a pivotal pathogenesis of liver dysfunction, impairing Qi circulation and causing stagnation [9]. The liver, responsible for ascending Qi and storing blood, is vital for maintaining vessel patency and regulating emotional states. Following the Five-Element theory, liver dysfunction impacts the heart, leading to mental disturbances [10]. Disrupted liver function hinders Qi-blood and body fluid circulation, resulting in blood stagnation and phlegm formation, which obstruct meridians and exacerbate PSD symptoms [11]. Thus, clinical treatment of PSD must address pathological factors caused by liver dysfunction [12].

2.3 Based on the Theory of Spleen and Stomach

The pathogenesis of PSD in TCM involves not only liver dysfunction but also spleen and stomach malfunctions, collectively contributing to the onset and progression of PSD. The spleen and stomach, responsible for receiving, digesting, and absorbing nutrients, are the sources of Qi and blood, which are the material basis for mental activities. Qi and blood deficiency directly affects mental state. The spleen stores Ying, which houses "yi" (consciousness, thinking, and memory). Spleen deficiency disrupts these mental functions [13]. All six emotions (joy, anger, worry, sadness, fear, and shock) originate from "thinking," which regulates emotional changes. Excessive thinking can cause Qi stagnation, damaging spleen and stomach functions. The spleen governs ascending clear Qi, while the stomach descends turbid Qi, ensuring smooth Qi circulation [14].

2.4 Based on the Theory of "Yang Governs Yin"

Based on the Yellow Emperor's Internal Classic and Treatise on Febrile Diseases' focus on yang qi [15], the Fuyang School identifies post-stroke yang qi dysfunction as the primary pathogenesis of PSD, guided by the "Yang Governs Yin" theory. They propose the "sanjiao regular sequence therapy," emphasizing "clearing yang" and "warming yang" principles. Treatment involves unblocking the middle and upper jiao first, followed by warming the lower jiao, to restore yin-yang harmony. This ensures the five viscera function smoothly, aiding PSD recovery. Clinical practice has shown remarkable efficacy, presenting a fresh perspective on PSD syndrome differentiation and treatment [16].

3. Efficacy of AC in the treatment of PSD

For centuries, AC has been recognized as an effective intervention for depressive disorders. Recently, its efficacy in treating PSD has garnered increasing clinical acknowledgment, attracting extensive global research attention. Numerous observational and clinical trials have established AC's efficacy in treating PSD [17]. Zhang Jingsha et al. evaluated AC for post-stroke depression PSD. Their findings showed AC's efficacy was comparable to Flupentixol and Melitracen, with earlier therapeutic onset. Thus, AC emerged as an efficacious, rapid-acting alternative for PSD treatment [18]. A randomized controlled trial (RCT) of 76 PSD patients compared routine stroke treatment with AC therapy. After 4 weeks of weekly AC at specific acupoints and a 90-day follow-up, both groups showed improvements in depression and daily functioning. Notably, the AC group had significantly higher neurotransmitter levels and beneficial gut microbiota changes. These findings justify AC's clinical use in alleviating PSD symptoms [19]. A scoping review of RCTs evaluating AC for PSD systematically searched six databases, yielding 231 RCTs involving diverse AC techniques. Descriptive statistics revealed that, while adverse events were reported in 13% of studies, many studies demonstrated high effectiveness rates, thereby underscoring the prevalence and efficacy of AC for PSD [20].

4. Efficacy of Acupuncture-Related Therapies

Electroacupuncture (EA) is a variant of AC that involves the application of electrical signals to acupuncture points. While AC utilizes needles for manual stimulation, EA employs electrical currents for a more standardized and potentially stronger stimulation.A study compared EA and escitalopram (ESC) in PSD patients. Baseline characteristics were similar. Both treatments improved depression and function, with EA showing superior short-term outcomes. Both reduced inflammations, with comparable safety and efficacy, suggesting EA as a viable alternative for mild-to-moderate PSD [21]. Wa Cai et al. assessed EA vs. sham EA in 65 PSD patients over 4 weeks. EA significantly improved scores on multiple scales by week 2, and these improvements were sustained till week 8, indicating efficacy and safety in alleviating PSD symptoms [22]. A network meta-analysis, leveraging ranking probability, indicated scalp acupuncture combined with conventional acupuncture as the most efficacious treatment for PSD, followed by auricular and eye acupuncture [23]. Additional meta-analysis of 62 studies found AC, alone or with TCM/repetitive transcranial magnetic stimulation (rTMS), surpassed western medicine (WM) in alleviating PSD [24]. Hu Xiaoli's study found AC, rTMS, and their combination reduced PSD symptoms and Hamilton depression scale (HAMD) scores, with the combination most effective [25]. In an RCT, acupuncture-Tuina outperformed WM in PSD, with higher efficacy, increased neurotransmitters, reduced HAMD/National Institute of Health stroke scale (NIHSS) scores, and improved electroencephalogram ratios, suggesting neurotransmitter modulation and brain wave benefits [26]. A 12-week study found psychological Intervention (PI)+EA therapy for PSD had an efficacy rate higher than PI alone. PI+EA significantly reduced HAMD-17 and Sleep Scores at 8 weeks, with no adverse events, suggesting its superiority and safety over PI monotherapy [27]. Another RCT of 100 PSD patients showed that AC and emotional intervention, when added to conventional therapy, significantly improved efficacy, leading to better clinical outcomes and improved daily functioning [28]. A study by Junyan Zhang demonstrated that the use of AC combined with music therapy reduced depression in PSD patients [29]. Kun Zhang's meta-analysis of 13 RCTs shows that acupuncture plus antidepressants significantly improves PSD outcomes, reducing both HAMD and NIHSS scores, and increasing the effective rate and Barthel index [30]. Xue Wang's meta-analysis of 24 RCTs found AC combined with WM improved PSD, outperforming WM alone in efficacy [31]. Additional study showed AC combined with antidepressants significantly enhanced self-rating depression scale (SDS) scores, demonstrating superiority in managing PSD [32].

5. Mechanism of AC in the Treatment of PSD

The pathogenesis of PSD may be multifactorial, involving a combination of ischemia-induced neurobiological dysfunctions against a backdrop of psychosocial distress [33]. Nonpharmacological treatments encompass psychological interventions, noninvasive brain stimulation therapy, exercise, and AC [34]. Among them, the mechanisms underlying AC for PSD constitute a key research frontier [35].

5.1 Effect on Neurotransmitters

Serotonin (5-Hydroxytryptamine, 5-HT), noradrenaline (norepinephrine, NE), and dopamine (DA) are key monoaminergic neurotransmitters mainly in the brainstem, projecting to regions regulating emotions and cognition. Stroke impacting these areas reduces 5-HT and NE synthesis, contributing to PSD onset [36]. Disturbances in the 5-HT system constitute a crucial factor in emotional dysregulation, with stress-induced perturbations in the 5-HT system disrupting circadian rhythms and enhancing vulnerability to depression [37]. Research has indicated that insufficient NE in stroke patients can contribute to the onset of PSD, thereby suggesting that enhancing monoamine neurotransmitter levels may alleviate depressive behaviors. Qin Yanqiang et al. found that combined scalp and abdominal AC at specific points elevates 5-HT, DA, NE levels, effectively treating PSD [38]. A study by Sun Peiyang et al. demonstrated that AC can enhance the levels of monoamine neurotransmitters in the hippocampus, repair hippocampal neuronal damage, and alleviate depressive-like behaviors in PSD model rats [39].

Glutamate (Glu) and gamma-aminobutyric acid (GABA) are crucial amino acid neurotransmitters, with N-methyl-D-aspartate receptor (NMDAR) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) being vital excitatory Glu receptors in the central nervous system (CNS). Depression has been implicated in associations with alterations in concentrations of Glu and GABA, as well as hyperactivation of their respective receptors. AC may alleviate depressive symptoms by balancing excitatory and inhibitory neurotransmitters [40]. Yan Jianing's study shows EA reduces Glu, AMPAR and NMDAR levels in rats with PSD, hinting at a molecular mechanism for its therapeutic benefits [41].

5.2 Effect on Related Signaling Pathways

Brain-derived neurotrophic factor (BDNF), a ubiquitous neurotrophin in the brain, crucially maintains hippocampal structure and function, and modulates neurosynaptic plasticity [42]. Neurotrophic tyrosine kinase receptor type B (TrkB) serves as the receptor for BDNF signaling, while cAMP-response element binding protein (CREB) acts as a crucial upstream regulator in the BDNF signaling pathway. Lower serum BDNF levels in PSD patients indicate its dysregulation as a critical factor in PSD onset [43]. Meng Dexuan's research revealed a significant reduction in the activity of the CREB/BDNF/TrkB signaling pathway in PSD model rats, accompanied by alterations in synaptic plasticity [44]. Another research indicates that EA at Siguan acupoints alleviates depressive symptoms by enhancing BDNF/TrkB expression in the hippocampus [45]. Sun Peiyang's study demonstrated AC may enhance neuronal survival, development, and function via the CREB/BDNF/TrkB pathway in PSD rats, ameliorating depressive-like behaviors [46]. Li Shaoyuan observed significant reductions in extracellular regulated protein kinases (ERK), CREB protein, and gene expression in the model group, which increased post-ear concha EA, improving depressive behavior in rats [47]. Zhang Yingjie showed EA upregulates BDNF/ERK/CREB, enhancing neuroprotection, motor function, and alleviating PSD symptoms [48].

5.3 Effect on Hypothalamic-Pituitary-Adrenal (HPA) Axis

HPA axis dysregulation, induced by stroke-elevated cytokines, triggers glucocorticoid release, increasing cortisol and risk of PSD [49]. A study indicates stroke patients experience HPA axis stress activation, causing depression. Stroke lesions may disrupt HPA axis inhibitors, prolonging activation. Excessive glucocorticoids during acute stroke impair feedback, enhancing HPA axis hyperfunction [50]. Neuroinflammation-induced cytokines activate HPA axis, causing PSD. As a result, modulating HPA axis hormones is crucial for PSD treatment. Administration of AC can inhibit hyperactivation of the HPA axis, thereby ameliorating depressive symptoms [51].

5.4 Modulate Proinflammatory Cytokine Expression

Stroke-induced blood brain barrier disruption permits immune cell infiltration, inducing CNS inflammation [52]. Inflammatory cytokines, including tumor necrosis factor-α (TNF-α) and interleukin (IL), promote PSD post-stroke by upregulating indoleamine-2,3-dioxygenase (IDO), reducing tryptophan to kynurenine, and decreasing 5-HT in the frontal cortex and basal ganglia [53]. TNF-α, an inflammatory cytokine, orchestrates necrosis/apoptosis via intracellular signaling [54]. Cerebral ischemia activates microglia, enhancing cytokine secretion, causing neurodegeneration and PSD. AC may alleviate this via anti-inflammatory pathways. Liu Lili et al. stimulated acupuncture points in rats and subsequently observed reductions in the serum levels of TNF-α, IL-1β, and IL-1βR, as well as decreased IL-1βR protein expression in the hippocampus. These findings indicate that the AC treatment exerted antidepressant effects. Furthermore, the study suggests that these effects implicate one of the potential mechanisms through which AC may be efficacious in the treatment of PSD [55].

5.5 Regulate Intestinal Microbiome

Intestinal microbiome engages in a multifaceted, two-way communication with the neurological system through the gut-brain connection [56]. Intestinal dysfunction and dysbiosis resulting from stroke can contribute to the pathogenesis of PSD through various mechanisms including immune, endocrine, and nervous system pathways [57]. Research indicates that AC improves the depression in PSD patients through regulating the intestinal microbiome and suppressing inflammatory processes [58].

5.6 Others

Mitochondria serve as the primary source of cellular energy and function as signaling organelles that regulate numerous cellular processes, playing a crucial role in maintaining cellular function and survival [59]. Research has shown that EA at Baihui can enhance CB1R expression, augment mitochondrial function, and consequently regulate depressive-like behaviors [60]. An imbalance in oxidant-antioxidant status results in oxidative stress, potentially contributing to neuronal cell death and the

development of depressive symptoms following stroke [61]. Cai Wa et al. found AC increased Superoxide dismutase (SOD), glutathione (GSH), reduced Malondialdehyde (MDA), easing oxidative stress and PSD symptoms [62]. PSD patients exhibit a marked reduction in Nerve Growth Factor (NGF) concentration in their serum [63]. Wang Bo's study demonstrated that Xingshen Qibi acupuncture elevates NGF levels in PSD patients' serum [64]. Research indicates that the Yuanluo Tiaoshen Acupuncture also has an extremely similar effect [65].

6. Summarizing and Looking Forward

AC has demonstrated remarkable potential in treating PSD. As research progresses, the emphasis shifts towards refining AC's application and unraveling its complex mechanisms. Consequently, future endeavors in this field should prioritize conducting comprehensive and multi-disciplinary studies, leveraging technologies such as metabolomics, proteomics, and genomics. These advancements will facilitate the exploration of potential pathways, including the brain-gut axis and mitochondrial dysfunction, which may underlie AC's therapeutic effects on PSD. Furthermore, there is an urgent need for large-scale, standardized clinical trials to validate AC's efficacy and establish objective evaluation criteria. These trials should transcend subjective scales by incorporating neuroimaging and other objective measures. Personalized treatment plans, which integrate AC with other therapeutic modalities, could significantly enhance patient outcomes, tailored to individual patient profiles and responses. However, despite promising results, the lack of standardization in AC protocols, including acupuncture points, techniques, and stimulation parameters, poses significant challenges. Addressing these issues through rigorous research and establishing evidence-based guidelines will be pivotal for the widespread adoption and optimization of AC in PSD management. Continuous exploration and refinement of AC's therapeutic potential offer promising prospects for improving the lives of PSD patients, fostering neurological recovery, and alleviating the societal burden of this condition.

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Author Profile

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