



Combined approaches for the relief of spinal cord injury-induced neuropathic pain



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ABSTRACT

The adequate treatment of spinal cord injury (SCI)-induced neuropathic pain still remains an unresolved problem. The current medications predominantly used in the SCI-induced neuropathic pain therapy are morphine, anticonvulsants, antidepressants, and antiepileptics, which suggests that psychiatric aspects might be important factors in the treatment of neuropathic pain.

It is well documented that the modulation of the sensory events is not a unique way for achieving pain relief. In addition, pain patients still express dissatisfaction and complain of unwanted effects of the medications, suggesting that alternative approaches for the treatment of neuropathic pain are essential. In psychiatry, pain relief represents relaxation and a feeling of comfort and satisfaction, which suggests that cognitive and emotional motivations are important factors in the treatment of neuropathic pain. The comorbidity of chronic pain and psychiatric disorders, which is well recognized, suggests that the effective therapeutic relief for neuropathic pain induced by SCI can be achieved in conjunction with the management of the sensory and psychiatric aspects of patient.

In this review, we address the feasibility of a combined acupuncture and pharmacotherapy treatment for the relief of neuropathic pain behavior following SCI.

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1. Introduction

Traumatic spinal cord injury (SCI) causes multiple dysfunctions in the sensory systems, such as neuronal hyperexcitability in the central nervous system (CNS) including the spinal cord, brain stem, thalamus, and cortex, which consequently result in neuropathic pain.^{1–6} In patients with SCIs, abnormalities in the sensory functions persist throughout the patients' lives and adversely influence the quality of life, often resulting in suicides.^{7,8} Previous studies have shown that SCIs cause consistent neuronal hypersensitivity and increased withdrawal response to external stimuli, such as allodynia (non-painful stimuli are perceived as painful) and hyperalgesia (painful stimuli are perceived as extremely painful); these are interpreted as neuropathic pain-like behaviors due to the alteration of the neurochemical and neuroanatomical distribution following SCI.^{9–11}

The candidate substances for the treatment of the SCI-induced neuropathic pain are well documented; experimental rodent-SCI model studies have revealed the cellular mechanisms involved in the various SCI conditions. The medications predominantly used currently for neuropathic pain therapy are morphine, anticonvulsants, antidepressants, and antiepileptics, such as GABApentin, pregabalin, lamotrigine, and amitriptyline; the pain relief achieved through these medications suggests that the psychiatric aspects of a patient are important factors in neuropathic pain treatment.^{12–17} A majority of the pain patients, however, report dissatisfaction and adverse outcomes such as fever, nausea, dizziness, rashes, weakness, drowsiness, and other psychiatric disorders.^{18–20} Taken together, these facts suggest that the effective treatment of SCI-induced neuropathic pain can be achieved in conjunction with the management of the sensory and psychiatric aspects of the patients, and that it is essential to develop non-pharmacological therapeutic approaches such as alternative medicine, to facilitate the therapeutic effect of the pharmacological approaches for neuropathic pain treatment.

In this review, we address the attenuation of the SCI-induced neuropathic pain through the management of the sensory and psychiatric behaviors involving acupuncture and pharmacological treatment to increase the efficacy of neuropathic pain treatment.

2. Acupuncture on for SCI-induced pain therapy

2.1. Acupuncture therapy

In oriental medicine, acupuncture is the most well-known therapeutic approach for the management of several pathological conditions including both sensory abnormalities and psychiatric disorders such as pain and anxiety/depression, respectively.^{21–23} The critical aspect of acupuncture therapy is the stimulation of the acupuncture needle inserted at a specific acupoint, which is a suitable spot for acupuncture on the body, rather than the needle insertion itself. Adequate acupuncture stimulation at the specific acupoint through vibration, twirling, or electrical impulses triggers the biological responses that cause the prevention, alleviation, or attenuation of the pathophysiological conditions such as pain, depression, and anxiety through the activation of the primary afferent fibers including the myelinated A β - and A δ -fibers and the unmyelinated C-fibers that contribute to the enhanced neuronal excitability and neuropathic pain.^{24–27} Acupuncture therapy for pain control has been widely used in oriental medicine for hundreds of years without an understanding of the underlying mechanism for the attenuation of pain. The conventional mechanism for the acupuncture-induced analgesia is the activation of the inhibitory descending pathways that trigger the inhibition of the ascending pain pathways.²⁸ For

example, electroacupuncture results in the increase of 5-HT levels, which, in turn, results in the inhibition of the ascending pain signals.²⁹ In addition, studies in the peripheral neuropathic pain animal models have demonstrated acupuncture-induced neuropathic pain control in the animals; acupuncture modulated the re-distribution of the pain-mediating substances such as the opioids, proinflammatory cytokines, neurotrophins, neurotransmitters, and neuropeptides,³⁰ or the pain-mediating signaling molecules including ephrin-B/EphB and MAPK-ROS,^{31,32} in both the peripheral and central nervous systems, following spinal nerve ligation and spinal cord injury, respectively. Electroacupuncture was revealed to be effective for the treatment of pain and psychiatric conditions. The literature was shown to ameliorate mechanical allodynia by down-regulating the IFN- γ and P2XR expression in the spinal cord^{33,34}; it also facilitated the antidepressive and anxiolytic effects of the neuropathic pain conditions.^{35,36} Taken together, these data suggest that acupuncture is useful in the attenuation of neuropathic pain and psychiatric disorders. However, the systematic study of the efficacy of the combined sensory and psychiatric treatments not yet been fully investigated.

2.2. Acupuncture and clinical effectiveness

A review of the literature reveals that the acupuncture treatment at specific acupoints induces neuroprotection and the attenuation of neuropathic pain. A previous study has reported that acupuncture at specific acupoints such as DU26 (Shui Gou, located on the face) and DU16 (Feng Fu, located on the back of the neck) induced anti-oxidative and anti-inflammatory effects through the downregulation of interleukin-1 β (IL-1 β), interleukin-6 (IL-6), and tumor necrosis factor- α (TNF- α). These inflammatory substances have been well characterized as strong candidates for the induction of neuropathic pain and neurodiseases following SCI; this fact, taken together with the findings of the previous study, strongly suggest the role of acupuncture in the induction of neuroprotection and pain attenuation following SCI.³⁷ In addition, acupuncture at the GV26 (Shui Gou, located at the junction of the upper and middle third of the philtrum) and GB34 (Yang Ling Quan, located anterior and inferior to the head of the fibula) acupoints produced analgesic effect by inhibiting the JNK activation through the attenuation of the astrocytic activation and the astrocyte-induced inflammatory substances such as the chemokine monocyte chemoattractant protein-1 (MCP-1) and the macrophage inflammatory protein-1 β and 3 α .³⁸ These data suggest that the acupuncture-induced attenuation of neuropathic pain following SCI is probably mediated by a neuronal-glia mechanism. A recent systematic review suggested the efficacy of acupuncture in neurological recovery following SCI. Randomized control trials with bias-adjusted meta-analysis revealed that acupuncture promoted neurological recovery (recovery rates, RRs), motor function (weight mean differences, WMD), and function recovery (standardized mean differences, SMD) following SCI.³⁹ Taken together, the findings of these studies suggest that acupuncture treatment would be a good therapeutic approach to promote the recovery of the SCI-induced abnormal pathophysiology.

The current approaches for the treatment of the SCI-induced neuropathic pain are predominantly pharmacological in nature; however, patients undergoing pharmacological treatment often complain of pain, dissatisfaction with the pain relief, and adverse outcomes, highlighting the need for safer and more comfortable therapeutic approaches. In clinical reports, acupuncture treatment was shown produce about 40% satisfaction in pain relief for up to 3 months in SCI patients.^{40,41} However, the report also described that the severe pain patients did not experience pain relief by acupuncture. Acupuncture with magnetizing was more effective for SCI-induced pain therapy than pharmacological treatment or other therapies, and the pain relief experienced with acupuncture

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