

## FEATURE ARTICLE

### Acupuncture Analgesia in Migraine

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Migraine is the most common headache diagnosis. Intermittent debilitating attacks are characterized by autonomic, gastrointestinal, and neurologic symptoms<sup>(1)</sup>. Migraine is a chronic, often inherited condition involving brain hypersensitivity and a lowered threshold for trigeminal-vascular activation. The pathogenesis of migraine is very complicated, and has not yet been fully understood. There are several hypotheses, such as vascular theory, neurogenic theory, the trigeminal nerve vascular theory, genetic theory and so on<sup>(2)</sup>.

There is no curative treatment for migraine, although there does exist various options for pharmacological treatment. Drug treatment with  $\beta$ -adrenoceptor blockers, calcium antagonists, or other agents has been shown to reduce the frequency of migraine attacks; however, the success of treatment is usually modest<sup>(1)</sup>. Acupuncture has been increasingly used as adjunctive treatment in primary headache syndromes and there is growing evidences from clinical trials that it might be beneficial in the treatment of migraine, with an effect size comparable to pharmacologic treatment<sup>(3)</sup>. Despite its popularity, there's still some controversy as to the difference between the specific and the nonspecific effects of acupuncture<sup>(4)</sup>.

#### Acupuncture Analgesia in Migraine in Clinical Practice

Migraine falls into the category of "Lateral head wind" in Chinese medicine (CM). Migraine is caused by Shaoyang (少阴) meridian. Besides those on head, acupoints of Hand and Foot Shaoyang meridians should be selected. Based on CM meridian theory, acupoints commonly used for migraine in clinic include Qiuxu (GB-40), Taiyang (EX-HN5), Sanyinjiao (SP-6), Xuanzhong (GB-39), Taixi (KI-3), Fengchi (GB-20), Taichong (LR-3), Hegu (LI-4), Waiguan (SJ-5), etc.

In 1998, the National Institutes of Health (NIH)

stated that acupuncture could be a useful adjunct treatment or an acceptable alternative treatment in several disturbances, including headache<sup>(5)</sup>. In the recent years, a growing number of systematic reviews indicate the potential value of acupuncture for the prevention and treatment of migraine. A multi-center clinical observation showed that 6-month treatment of electroacupuncture (EA) at the acupoint Qiuxu (GB-40) was effective for migraine, compared with the Tianshu (ST-25) treatment<sup>(3)</sup>. The three-center randomized controlled study showed that EA at Taiyang (EX-HN5) could reduce attack frequency of migraine of liver (肝)-yang hyperactivity type, with better efficiency and less side effect than that of the routine Western medication<sup>(6)</sup>. Moreover, verum acupuncture over 6 weeks demonstrated at least similar effect on migraine prophylaxis by  $\beta$ -blocker on a daily basis for 6 months.

However, in recent years, several randomized controlled trials conducted in the Western countries argued that acupuncture showed no more effect than sham acupuncture or minimal acupuncture in reducing migraine headaches, although it was more effective than no treatment<sup>(4,7)</sup>.

The disparity of the study outcomes might attribute to the different treatment strategies (acupuncture points, type of stimulation, frequency, etc.), different controls (minimal acupuncture, placebo acupuncture, transcutaneous electrical nerve stimulation and waiting list), and different evaluation methods and so on. Therefore, strictly designed, large-scale randomized controlled trials need to be further conducted to provide more convinced evidences for treating migraine with acupuncture. Fortunately, large-

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scale multi-center randomized controlled trials are now undergoing<sup>(8)</sup>.

In addition, acupuncture is still an adjunctive or complementary therapy with moderate analgesic effect, and the integration of acupuncture and analgesics is often used in the treatment of migraine. It is demonstrated that the group treated with acupuncture plus Rizatriptan (a selective agonist of the 5-HT 1B/1D receptors) provided a steady improvement in comparison to the use of only Rizatriptan<sup>(9)</sup>. Moreover, combined treatments of acupuncture and massage, moxibustion, Chinese herbal medicine, acupoint injection are also used for the treatment of migraine.

### **Acupuncture Analgesia in Migraine in Experimental Model**

Investigation of the aetiology and the treatment of migraine is complicated by the debilitating, intermittent nature of attacks, and the lack of widely accepted experimental models. Numerous agents have been used in attempts to develop such a model, including acetazolamide, histamine, iodinated contrast media, m-chloro-phenylpiperazine, red wine, reserpine, visual stimulation and nitroglycerin (GTN)<sup>(10)</sup>. Of these agents, studies using GTN have been the most widely published.

The experiment on the effect of acupuncture in the migraine animal models is relatively limited. It is demonstrated that EA at acupoint Neiguan (PC-6) reduced the plasma CGRP level in rats injected with subcutaneous GTN, indicating that EA at Neiguan could regulate vascular extension, improve the nerve inflammation, thus relieving migraine symptoms<sup>(11)</sup>.

### **Possible Effects of Acupuncture on Migraine**

The mechanism of acupuncture analgesia has not yet been fully understood. However, during the past decades remarkable progress has been made in exploring mechanisms of EA analgesia. A large number of literature has revealed that the essence of acupuncture analgesia is mainly the activation of the endogenous antinociceptive system to modulate pain transmission and pain response, resulting in the diminution of pain perception and aversive reactions<sup>(12)</sup>. The neural process involves the integration of different neurotransmitters and modulator systems at various levels of the central nervous system.

Due to the complexity of the pathogenesis, the mechanism of acupuncture analgesia in migraine is probably more complicated. However, there are still some investigations revealing the underlying mechanisms, and there are also some points that could be taken into consideration.

#### **1. Autonomic Effect of Acupuncture in Migraine**

A dysregulation of the autonomic nervous system is discussed as a pathogenetic factor in migraine. The clinical effects of acupuncture on migraine might be mediated by a modulation of the autonomic nervous system. With a reduction of the low-frequency power of heart-rate variability related to the clinical effect, investigation showed that verum acupuncture treatment might have a beneficial influence on the autonomic nervous system in migraineurs<sup>(13)</sup>. The study indicated that the mechanism of acupuncture action might be due to a reduction of sympathetic nerve activity. In addition, neurophysiologic data from animals showed that on the spinal level, acupuncture exerted an effect on autonomic outflow to the viscera by somatovisceral reflexes. Dilatation of cerebral vascular vessels and improvement of autoregulation in the brain by acupuncture stimulation may also explain the effectiveness of acupuncture in treatment of migraine<sup>(14)</sup>.

#### **2. Possible Involvement of 5-HT in Acupuncture Analgesia in Migraine**

Migraine patients usually have a systemic disturbance of 5-HT metabolism, associated with low 5-HT plasma levels between attacks and increased levels and release of platelet 5-HT during attacks<sup>(15)</sup>. Pizotifen and Methysergide, the 5-HT receptor antagonists, are often used to prevent the migraine attack.

#### **3. Possible Involvement of Nitric Oxide (NO) in Acupuncture Analgesia in Migraine**

The potent vasodilator and messenger molecule NO is believed to play a key role in migraine pathogenesis<sup>(16)</sup>. NO donors such as GTN can cause greater dilation of the middle cerebral artery and were more likely to develop migraine-like headaches. Infusion of GTN leads to a migraine attack in migraineurs with a latency of 4 to 6 h.

In addition, compared with the migraine rat model group, the levels of NO in acupuncture therapy group and acupuncture prevention group were

significantly reduced<sup>(17)</sup>. The above studies indicated that the regulation of NO and NOS may be another pathway of acupuncture analgesia in migraine, though the role of NO in the peripheral and central system is very complex.

#### 4. Possible Involvement of Neuropeptides in Acupuncture Analgesia in Migraine

Migraine attack begins with a central activation of the fibers of the trigeminal ganglion (trigeminovascular system). Activation of the fibers results in the release of vasoactive peptides at the perivascular ends of the fibers. Among these peptides are calcitonin gene-related peptide (CGRP), a potent dilatator at arterioles, and substance P (SP), which also dilates the venous wall and induces plasma protein extravasation<sup>(2)</sup>. It is demonstrated that EA at acupoint Neiguan (PC-6) reduced the plasma CGRP level which is up-regulated by subcutaneous GTN injection in rats<sup>(13)</sup>. Inhibition of the neuropeptides release might be another mechanism underlying acupuncture analgesia for migraine.

Due to the special phenotypes of migraine, the clinical effects of acupuncture treatment would be further confirmed using evidence based medicine methods. Especially, the acupuncture treatment combined with different drugs, even Chinese medicine would exert better effects in most patients. On the other hand, the mechanism of acupuncture analgesia in migraine should be further investigated, no matter what the effects on the peripheral and central nervous system are. We are sure that the progress of the acupuncture research might bring more benefits to the patients with migraine.

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