Editorial

Sustained effects of acupuncture in treatment of chronic constipation

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Chronic functional constipation especially among older people is a common gastrointestinal (GI) disease worldwide (1,2). The conventional medical management of chronic constipation includes laxatives. However, about 50% of patients are unsatisfied with their typical treatment (3).

Concomitantly, complementary medicine increasingly is used in addition to conventional treatment in Western countries. Among a number of complementary treatment modalities, manual acupuncture (MA) and electroacupuncture (EA) have been used to treat various disorders such as elevated blood pressure, pain, intestinal discomfort and among others (4). Acupuncture has been used in China for thousands of years to treat a variety of GI problems including chronic functional constipation (5), but the scientific evidence for the effectiveness of acupuncture and the underlying mechanisms remains insufficient that restrains the use of acupuncture in functional constipation in Western countries. To date, the largest acupuncture clinical trial published on constipation is the Acupuncture for Chronic Severe Functional Constipation: A Randomized, Controlled Trial (6). In this multicenter trial, investigators have shown that standardized MA and EA at ST25, SP14 and ST37 significantly increase complete spontaneous bowel movements (CSBM) from a mean of 0.4 to 2.6 per week during the 8-week treatment and a 12-week follow-up in 536 patients. In sham acupuncture group, mean CSBM/week is modified from 0.4 to 1.3 in 539 patients. Acupuncture treatment induces minimal side effects. The authors conclude that acupuncture treatment could provide an alternative and safe medical treatment for the management of chronic severe functional constipation.

Inherent issues, important considerations in the interpretation of the results in this trial include a suitable control therapy and assessor blinding. The report also does not describe about responsiveness or rate of effectiveness of the effects of acupuncture treatment on functional constipation. In general, an ideal control regimen should be inert, identical to the factor being investigated in appearance and sensation, and without nonspecific physiological effects. This trial's sham control properly used identical number of acupuncture needles, but the needles were inserted at different locations. Although double-blinded trials are preferred, this trial includes single-blinding i.e., patients and evaluators but not acupuncturists. Despite these two major limitations, this largest randomized and controlled trial has provided evidence that shows effectiveness of acupuncture for chronic constipation. A smaller trial of 67 participants with similar treatment protocol but at lower frequency of acupuncture stimulation reported similar outcome (7). Another trial by Wu *et al.* also supports these findings (8). In aggregate, these trials demonstrate an important aspect of acupuncture in the treatment of chronic functional constipation i.e., acupuncture exerts a long lasting anti-constipation in addition to the relief of constipation during the treatment. This hallmark of prolonged action of acupuncture is superior to the conventional therapy of laxatives that provides only transient temporary relief.

Although the precise mechanisms underlying anti-functional constipation effect of EA remain unclear, several studies suggest that acupuncture enhances gastrointestinal

motility by evoking somato-autonomic reflex and activating spinal-supraspinal pathways (9) that contribute to the effectiveness of acupuncture for functional constipation. In this respect, previous studies have demonstrated that the main pathophysiology associated with functional constipation is insufficient colonic motility (1). The regulation of colonic motility is influenced by the central and the autonomic nervous system (10). While sympathetic nervous system predominantly inhibits gastrointestinal muscle activity, the parasympathetic system regulates propulsive colonic motility (10). Increased sympathetic activity delay gastric emptying and likely induces decreased colon motility (11,12). The parasympathetic efferent exerts both excitatory and inhibitory actions on colon motility. Increase in colon activity seems to involve a cholinergic pathway while decrease of motility occurs through non-adrenergic and non-cholinergic mechanism (13). The vago-vagal gastro-colonic reflexes through activation of afferent and efferent pathways of the vagus nerve are induced by responses to stimuli in the gut (intrinsic stimuli) and involve the dorsal vagal complex (DVC) in the brainstem. Moreover, sympathetic and parasympathetic related central regions including DVC [area postrema (AP), nucleus tractus solitaries (NTS), dorsal motor nucleus of the vagus (DMV)], ventrolateral medulla, raphe nuclei, Barrington's nucleus, periaqueductal gray, paraventricular nucleus (PVN), and among others mediate gastrointestinal function (10).

Acupuncture and EA stimulate sites on the body (acupoints) for 15 to 30 min activating, in part, somatic sensory nerves and neural pathways involving regions in the brain. For instance, stimulation of somatosensory nerves with acupuncture on constipation activates neurons in the Barrington's nucleus and DMV to modify parasympathetic outflow and increase distal colonic motility (9). The commonly used acupoints ST36 and ST37 activating similar neural pathway (14) influence colonic motility in dogs (15), mouse (16) and rats (17,18). The experimental findings show that acupuncture increases parasympathetic activity mediated by a cholinergic pathway to restore reduced colonic contraction and delayed transit time (15). Gao *et al.* have shown with intravenous blockade of muscarinic (M3) cholinergic receptors that acupuncture treatment improves distal colonic motility likely through M3 receptors (17). Acupuncture stimulation at ST25 appears to activate neurons in the medio-caudal NTS and rostroventral lateral medulla to influence sympathetic outflow and increase motility of the distal colon (9). However, it is not clear if EA at ST36 enhances the colonic motility by EA at ST25. Together, stimulation of somatic sensory nerves by EA appears to modify the function of central neuronal pathways and regions leading to its anti-constipation. The mechanism and central processing of the action of EA applied simultaneously at both specific acupoints ST36 and ST25 deserve further studies to fine tune the stimulating parameters.

Extrinsic stimuli such as stress and anxiety induce dysregulation of colonic movement contributing to functional constipation (10). For instance, during stress corticotropin-releasing factor (CRF) containing neurons in the hypothalamic region PVN project to and release CRF in medullary regions AP, NTS and DMV inducing functional bowel disease (19,20). Both chronic and acute stresses increase the level of CRF in the Barrington's nucleus in the brain. This brain region critically is involved in regulation of colonic motility and associated with decreased colonic activity in functional constipation (10). Altogether, stress influences activity in the Barrington's nucleus, and the parasympathetic or vagal descending pathway that, in turn, affects vagal tone in the gastrointestinal tract and hence colonic motility. Acupuncture can activate neurons in the Barrington's nucleus and DMV to modify parasympathetic outflow leading to increase in distal colonic motility and hence EA likely can treat stress induced functional constipation (9).

The mechanisms underlying the prolonged anti-constipation effect of acupuncture (6) is unclear. Previously, we have observed a prolonged action of acupuncture on arterial blood pressure regulation in animals and men (21,22). To understand the mechanisms associated with the EA-prolonged actions on blood pressure regulation, we have conducted a series of neurophysiological studies. In this respect, the experimental studies on reflex (pressor) and sustained (hypertension) elevated blood pressure as well as decreased hemodynamics (depressor and bradycardia) demonstrated extensive central processing of the actions of EA at P5-P6 and ST36-ST37 involving number of cardiovascular nuclei spanning from the hypothalamus to the brainstem, neuronal projections and circuitry, and a list of neuromodulators and transmitters activating specific receptor subtypes (14,23-29). These neural mechanisms participate in the prolonged EA-inhibition of sympathoexcitation and parasympathoexcitation (30,31). Acupuncture applied once for 30 min or repeatedly increases mRNA expression and synthesis of opioids important in the actions of EA lasting for days (21,32). Furthermore, EA P5-6 aims to normalize the altered neuronal activity during

elevated and decreased blood pressure. Altered neuronal activity in response to sympathetic or parasympathetic evoked activity becomes normalized following prolonged stimulation of the somatosensory nerves by EA on blood pressure regulation (33,34). The cellular firing activity and cardiovascular responses are altered for at least 50 to 60 min following EA suggesting that action of acupuncture during central processing includes neural plasticity. Thus the underlying mechanisms of EA on cardiovascular regulation contributing to the long lasting acupuncture effects appear to rebalance the autonomic system through central processing by complex neural pathways and unique synaptic transmission and to influence the availability of EA-related neurochemicals. Since mounting evidence demonstrates that EA at P5-P6 decreases hyperactive sympathetic neuronal activity, acupuncture may modify colon motility and functional constipation in response to sympathetic-induced delayed gastric emptying. Considering that acupuncture on constipation also activates many brain regions and pathways (mentioned above), these central neuronal mechanisms may also contribute to the prolonged anti-constipation effect of acupuncture. The assumptions warrant investigations.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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