ADVANCES IN IBS

Current Developments in the Treatment of Irritable Bowel Syndrome

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Neuromodulation and Neurostimulation for the Treatment of Functional Gastrointestinal Disorders

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G&H What are the general mechanisms of action of electroneuromodulation for functional gastrointestinal disorders?

JC Motility dysfunction is one of the major problems in patients with functional gastrointestinal (GI) disorders. Parasympathetic tone is low in patients with functional GI disorders. By enhancing parasympathetic activity, neuromodulation can improve GI motility.

Abdominal pain is another major problem in patients with functional GI disorders, such as irritable bowel syndrome (IBS), and is attributed to visceral hypersensitivity. Visceral hypersensitivity, in turn, is associated with low-grade inflammation that can be either systemic or localized to the gut. By the enhancement of vagal activity, neuromodulation exerts an anti-inflammatory effect on the gut via a cholinergic anti-inflammatory pathway. The anti-inflammatory effect of neuromodulation leads to improvement in visceral hypersensitivity and mucosal barrier function, resulting in amelioration of abdominal pain.

G&H How has transcutaneous (or noninvasive) neuromodulation for functional GI disorders evolved over time?

JC Transcutaneous neuromodulation for functional GI disorders has been influenced by 2 other modalities, acupuncture and direct-nerve stimulation. Acupuncture is traditionally based on a system of meridians and channels that cannot be proven by Western scientific methods. However, some acupuncture points are very close to nerves that can be used as guides for nerve stimulation. For example, there is a point in the leg below the kneecap known as ST36 that is close to the sciatic, peroneal, and tibial nerves. Stimulation of this point will cause modulation of the sympathetic and parasympathetic systems and thus alter distal gut functions via the anatomic link and upper gut functions via the functional link through the central and vagal nerve systems.

Traditional acupuncture requires needles and particular skills to manipulate the needles. The general concept along with research data led to a novel hybrid of neuromodulation therapy—electroacupuncture. An electrical current is delivered to needles inserted at acupoints. The purpose is to direct the current to activate the autonomic nervous system. One drawback of this modality is that there is no systematic optimization of methodology. Every practitioner has his or her own way of performing this procedure, and it is generally not feasible for a patient to self-administer treatment, which needs to be administered by a practitioner. Transcutaneous neuromodulation mitigates this problem. It is designed to stimulate certain acupuncture points that are in the vicinity of peripheral nerves via surface electrodes instead of needles.

G&H Which nerves have been the main targets of neurostimulation for functional GI disorders?

JC The vagus and sacral nerves have been the targets of research in direct-nerve stimulation, leading to neuromodulation modalities, namely vagal nerve stimulation (VNS) and sacral nerve stimulation. Research on VNS led

to approval from the US Food and Drug Administration (FDA) for its use in the treatment of epilepsy and major depressive disorders. Research on sacral nerve stimulation showed that it has use for treating several disorders of the pelvic organs, such as overactive bladder, urinary retention, and fecal incontinence.

VNS consists of bipolar electrodes, which are wrapped around the left vagus nerve, and an implantable pulse generator, which is positioned below the collarbone. The need for surgical implantation, perioperative risks, and potential side effects limit the applications of VNS for the treatment of diseases of the gut.

Fortunately, advances in nerve stimulation have led to indirect, or transcutaneous, nerve stimulation. Transcutaneous auricular vagal nerve stimulation (taVNS) involves stimulation of the auricular branch of the vagus nerve. The rationale for taVNS of the ear is that the ear is the only site on the surface of the human body where afferent vagus nerve distribution is accessible. Transcutaneous cervical vagal nerve stimulation applies electrical stimulation noninvasively above the cervical vagus nerve via a special hand-held device. Indirect sacral nerve stimulation can be accomplished via transcutaneous or percutaneous tibial nerve stimulation.

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G&H How does electroacupuncture compare with transcutaneous neurostimulation?

JC Transcutaneous neurostimulation has more benefits and versatility than electroacupuncture. The patient can self-administer transcutaneous neurostimulation at home where he or she can self-treat once or twice a day, as prescribed. For IBS, a twice-daily routine is often recommended. For example, a patient who has IBS with constipation (IBS-C) would be instructed to use transcutaneous neurostimulation first in the morning upon rising and again after a large meal.

G&H What have studies shown thus far about the utility of taVNS in patients with IBS-C?

JC A study by Shi and colleagues showed that, compared with sham electrical stimulation (the same electrical stimulation as taVNS but delivered to points at the elbow), taVNS significantly increased complete spontaneous bowel movements per week and significantly decreased the visual analog scale pain score and IBS symptom score in patients with IBS-C. Quality-of-life measures as well as rectoanal inhibitory reflex, rectal sensation, and vagal activity improved. Decreases in circulatory proinflammatory cytokines and serotonin levels were detected.

In a preclinical study by Zhang and colleagues, the effects of taVNS on colonic motility were found to be mediated via the vagovagal pathway. The effect of taVNS on rectal sensation is thought to be mediated via the vagal afferent and sacral efferent pathway, as the vagus nerve does not innervate the rectum.

G&H Which neuromodulatory therapies are being used for the treatment of pain associated with functional GI disorders?

JC Clinicians should first remember that, in some patients with IBS-C, pain is perceived as the more problematic symptom. Clinicians should make an effort to learn what symptoms the patient is most troubled by and work on solutions.

Several transcutaneous electrical neural stimulation devices have been cleared by the FDA, but many have limitations in the parameter settings that render them ineffective for patients with functional GI disorders.

A recently published study by researchers at the Medical College of Wisconsin showed that a form of taVNS, percutaneous electrical nerve field stimulation, applied externally to the ear can relieve pain associated with IBS in adolescents. Following treatment, the median composite pain score of treated patients was half that of patients who received sham treatment. Information on its effect on IBS with diarrhea or IBS-C was not examined, however. This taVNS method is approved for the treatment of IBS pain in adolescents and provides a nonpharmacologic method of pain control. A device is needed for adult patients, and the device needs to address both pain and motility related to IBS.

In nerve stimulation research, some investigators are more focused on pathophysiology and others on symptoms. In some instances, researchers are examining

whether devices approved for other disorders have applicability for improving symptoms of IBS. Other research considers the pathophysiology of a disorder and then gradually develops and improves a methodology. Research on transcutaneous neuromodulation, including taVNS and a modality known as transcutaneous electrical acustimulation (TEA), has been ongoing, with the aim of approval for use in the treatment of functional GI disorders. Usage is relatively easy; however, the clinician has to have the proper diagnosis, identify the right spot to stimulate, and calibrate the device for optimum effect.

G&H What is your perspective of TEA?

JC TEA is a step up from electroacupuncture. Electrodes rather than needles are used. Only some select points that are close to the target nerve are used. The practitioner locates the appropriate point, an electrode is placed on it, and a picture of the application is taken and given to the patient so that the patient can apply the treatment at home.

The drawback with this modality is that it is a wearable wired device. This can be inconvenient for some patients. The wiring can be conspicuous, which may deter some patients from using it. Research is ongoing to make the device more like a bandage or an entertainment device instead of a medical device to help avoid the stigma that patients may feel or concerns they may have about admitting to someone that they are wearing a medical device to treat bowel function problems. Research is also ongoing to make this modality easier to use.

G&H What data are available on the utility of TEA for the treatment of IBS?

JC In a single-center clinical study by Hu and colleagues, TEA was reported to significantly improve quality of life in patients with IBS with diarrhea in comparison to patients treated with sham stimulation (no stimulation). A significantly more potent analgesic effect was noted with real stimulation compared with sham stimulation.

Investigation is currently underway on the effects of TEA and different treatment modalities on acute abdominal pain induced by rectal distention in patients with IBS-C. The studies aim to compare the analgesic effect of the optimized method of transcutaneous neuromodulation with medical neuromodulator in patients with IBS-C.

G&H How can clinicians prepare to incorporate these modalities into their practice?

JC Pathophysiologies of IBS and other functional GI disorders are complex and commonly include dysmotility, visceral hypersensitivity, and impaired central processing of sensory inputs. Neuromodulation differs from pharmacologic therapies and is capable of ameliorating these multiple pathophysiologic factors by improving autonomic functions. For example, enhancement of vagal activity by neuromodulation leads to improvement in GI motility. Concurrently, it may also improve visceral pain by inhibiting low-grade inflammation via the cholinergic anti-inflammatory pathway. Furthermore, impaired brain-gut interaction is a hallmark of functional GI disorders, which may be improved with an appropriate method of neuromodulation. Clinically, transcutaneous neuromodulation is attractive, as it is noninvasive, home-based, and self-administrable.

Disclosures

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Suggested Reading

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