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Shocking the GI tract: Electrical stimulation from top to bottom

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Abstract

Electrical stimulation of the gastrointestinal tract has been touted as a possible therapy for intestinal motor dysfunction since 1963 when Bilgutay, et al., reported the use of transluminal electrical stimulation to induce peristalsis. In the late 1960???s and 1970???s the myoelectrical activity of the gastrointestinal tract was elucidated along with its relationship to gut contractility. Out of this initial research several clinical applications of gastrointestinal electrical stimulation have arisen. These include gastric electrical stimulation (GES) for treatment of gastroparesis, sacral nerve stimulation (SNS) for treatment of fecal incontinence and constipation and electrical stimulation of the lower esophageal sphincter (LES) for treatment of severe gastroesophageal reflux disease (GERD). GES is a low energy, high frequency system that stimulates the nerves that innervate the gastric antral muscle. GES improves nausea and vomiting, decreases medical costs, decreases hospital days and improves quality of life in patients with gastroparesis refractory to dietary and pharmacological interventions. SNS is a low energy, high frequency system that directly stimulates the third sacral nerve root. SNS significantly improves severe fecal incontinence and constipation compared with optimal medical therapy. Electrical stimulation of the LES for treatment of GERD is the newest electrical stimulation therapy. Studies published in the last two years demonstrate sustained improvement in GERD outcome and GERD-HRQL, elimination of the need for daily GERD medications and sustained normalization of esophageal acid exposure compared to standard medical therapy for severe GERD. Electrical stimulation of the gastrointestinal tract continues to have great potential for many GI disorders.

Gastric electrical stimulation (GES) is primarily used in patients who have gastric motility disorders characterized by delayed gastric emptying without signs of mechanical obstruction. GES therapy with the Medtronic Enterra system (Medtronic Inc., Minneapolis, MN) has been reported to reduce the clinical symptoms of gastric motility disorders like gastroparesis which is characterized by nausea, vomiting, early satiety, bloating, anorexia, and abdominal pain.The stomach triggers patterns of electromechanical activity through long-lasting waves of depolarization that begin in the corpus and slowly move down to the duodenum, which is termed the slow wave. Gastric slow waves are myogenic in nature and persist even after blocking the nervous activity by isolating the stomach. ICC are electrically paired with smooth muscle cells so that depolarization is linked between ICC and muscle. If the depolarization is large enough to activate the smooth muscle L-type Ca2+ channels, then a contraction occurs. This suggests that ICC has an important role in peristalsis of the stomach and the pathogenesis of gastroparesis. Wang et al. observed a marked reduction in the density of the intramuscular ICC and ICC located at submucosal border of the circular muscle layer at the antrum of rats with induced diabetes mellitus and decreased gastric emptying.The exact mechanism of action of GES and its effect on the interstitial cells of Cajal (ICC) is relatively unknown, but previous studies hypothesized that GES acts via several mechanisms: early and durable gastric prokinetic effect, early anti-inflammatory effect, and early anti-arrhythmic effect. Animal models in diabetic rats showed an increase of c-kit+ cells (molecular marker for ICC) within intramuscular and myenteric layers of antrum after long-pulse GES implant. Mast cells are localized in the gastrointestinal tract and play a key role in the inflammatory process. Their activation could lead to the release of pro-inflammatory mediators without degranulation. A number of studies have documented an increased number of mast cells in the gastrointestinal mucosa in patients with several gastrointestinal diseases, particularly in functional gastrointestinal disorders.

We hypothesized that permanent GES might have an effect on ICC cells and that actions of GES may correlate to the number of mast cells seen on full thickness biopsies (FTBx) of the stomach after stimulation.The effect of GES on ICC cells and mast cells is not well defined. We found, in this group of 20 patients, that GES was associated with increased ICC counts in about one-half of the patients. A recent study has reported that GES has improved the regeneration of ICCs in diabetic rats, which enhanced delayed gastric emptying [7], but to our knowledge, this is the first study that reports increasing ICC levels after GES placement in patients.Increased levels of ICC, in our study, could be related to less inflammation, indirectly measured by mast cells levels, and partially attributed to GES. Prior studies reported improvement of serologic markers for inflammation with long-term electrical stimulation on

The GI tract of animals and humans. A previous study in mice showed delayed gastric emptying was associated with increased production of proinflammatory and reduced production of anti-inflammatory factors by macrophages, leading to loss of ICC.Worsened levels of ICC were related with a significant increase of mast cell count (p=0.007). Also, there was an increase in the number of mast cells during repeated biopsy in both groups, but only was statistically significant in the group with worsened ICC (p=0.004). This data suggest that GES does not control all the inflammation within the population studied. The effect of GES in alternative pathways of inflammation seen in gastroparesis that does not involve mast cells should be studied.

It is crucial to understand the effect of GES on ICC, not only because of their important role in the pathogenesis of gastroparesis, but also because ICC count could predict improvement of gastroparesis symptoms in patients with neurostimulation. Omer et al. observed that patients with normal to moderate depletion of ICC showed better improvement in vomiting and bloating after GES therapy compared with patients who have severe depletion.

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