Absence of the Interstitial Cells of Cajal in Patients With Gastroparesis and Correlation With Clinical Findings

Jameson Forster, M.D., Ivan Damjanov, M.D., Zhiyue Lin, M.S., Irene Sarosiek, M.D., Paul Wetzel, M.D., Richard W. McCallum, M.D.

The interstitial cells of Cajal (ICCs) are fundamental in the generation of gastric slow waves. The role of these cells in gastroparesis has not been established. We studied 14 gastroparetic patients (9 diabetic, 4 idiopathic, and 1 postsurgical) for whom standard medical therapy had failed and who had been treated with a gastric electrical stimulator for at least 3 months. All patients had a full-thickness antral gastric wall biopsy at the time of surgery. The biopsy samples were stained with c-kit and scored for the presence of ICCs. Baseline electrogastrogram recordings were obtained for 30 minutes in the fasting state and for 2 hours after a test meal. The patients assessed their total symptom score at baseline and at 3 months. Five patients had almost no ICCs and were compared with nine patients with 20% to normal cell numbers. Both groups did respond symptomatically to gastric electrical stimulation. However, patients with depleted ICCs had significantly more tachygastria and had significantly greater total symptom scores at baseline and after 3 months of gastric electrical stimulation. ICCs are absent in some patients (up to a third) with diabetic or idiopathic gastroparesis, and the absence of these cells is associated with abnormalities of gastric slow waves, worse symptoms, and less improvement with gastric electrical stimulation. (J GASTROINTEST SURG 2005;9:102–108) © 2005 The Society for Surgery of the Alimentary Tract

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The condition of gastroparesis predominately affects patients with longstanding diabetes but may occur after surgery or without a known etiology (idiopathically). Patients suffer from a variety of symptoms, including nausea, vomiting, epigastric pain, premature satiety, abdominal fullness, bloating, epigastric pain, and weight loss. The major diagnostic abnormality is gastric dysmotility, which is commonly measured scintigraphically. The presence of more than 10% of a standard meal remaining at 4 hours has been suggested to be the gold standard diagnostic test. Treatment has long focused on improving gastric motility with prokinetic medications, including metoclopramide, domperidone, and erythromycin, and on treating nausea with antiemetics. If standard medical therapy fails, surgical options include placement of a feeding gastrostomy or jejunostomy or performing a vagotomy and pyloroplasty, partial gastrectomy, or a total gastrectomy. Electrical pacing of the stomach to promote contractions has been introduced, but the treatment requires an external stimulator and transabdominal electrodes. This technique additionally converts the abnormal gastric rhythm of...
tachygastria to a normal rhythm. Recently, an implantable device (Enterra Therapy, Medtronic, Minneapolis, MN), initially termed, incorrectly, a gastric pacemaker, has become available from Medtronic for treatment of gastroparesis. Our initial published report demonstrated a marked reduction in both nausea and vomiting and a mild effect on gastric emptying in 25 patients suffering from longstanding gastroparesis. This device does not promote contractions or normalize tachygastrical rhythms\(^\text{17}\) and should be called a gastric electrical stimulator (GES).

Networks of the interstitial cells of Cajal (ICCs) pace gastrointestinal phasic motor activity necessary for the orderly propulsion of digested food, by producing slow waves. The ICCs were discovered by Dr. Cajal in 1893 and thought originally to be fibroblasts.\(^\text{8–10}\) These slow waves are initiated by inward currents in the ICCs, which depolarize in the muscularis propria smooth muscle. The depolarizations activate ion channels, which initiate contractions ensuring coordinated motor responses to neural reflexes. In the stomach, the networks of ICCs in the myenteric plexus pace these slow waves. These cells occur throughout the gastrointestinal tract and are in close proximity to enteric nerves. They stain for CD117, and on electron microscopy have dense granules.\(^\text{10,11}\) Their loss has been implicated in the gastroparesis of diabetes based on a strain of mice that spontaneously become both diabetic and gastroparetic.\(^\text{7}\) This device does not promote contractions or normalize tachygastrical rhythms\(^\text{17}\) and should be called a gastric electrical stimulator (GES).

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We hypothesized that the ICCs may play a role in gastroparetic patients. We obtained full-thickness biopsies of the antrum of the stomach during the surgery to place the GES and specially stained these biopsy samples for the presence of ICC. The presence of ICCs was correlated with both gastric electrical recordings and the patient’s self-assessed total symptom score (TSS). We learned that those patients with absent or deficient ICC populations had dysrhythmic gastric myoelectric activity and more severe symptoms of gastroparesis.

**MATERIALS AND METHODS**

**Subjects**

The gastric wall biopsy samples of 14 patients with refractory gastroparesis (9 diabetic, 4 idiopathic, and 1 postsurgical) undergoing laparotomy for GES placement were analyzed. The research protocol was approved by the Human Subjects Committee at the University of Kansas Medical Center, and written consent forms were obtained from all subjects.

**Surgical Procedure**

The GES system used consisted of three components: the implanted pulse generator, two leads, and the stimulator programmer (Medtronic). During the abdominal surgery, one pair of unipolar electrodes was placed into the muscularis propria of the stomach 9.5 and 10.5 cm proximal to the pylorus on the greater curvature. The electrodes were secured to the serosa of the stomach using 5-0 silk sutures. The other ends of the electrodes were connected to the pulse generator, which was placed in a subcutaneous pocket above the abdominal wall fascia to the right of the umbilicus.\(^\text{7}\) The GES was initiated within 48 hours of surgery. The stimulus parameters used in this study were low energy and high frequency parameters: pulse width, 330 µsec; pulse (current) amplitude, 5 mA; and frequency, 14 Hz, cycle ON time of 0.1 second and cycle OFF time of 5.0 seconds. During the implantation surgery, gastric wall biopsy samples were taken from the antrum and preserved in formalin. These biopsies were taken by cutting out 1 cm\(^2\) of gastric wall and leaving the mucosa intact. The defect was closed with interrupted 3-0 silk sutures.

**Immunohistochemistry**

Immunohistochemical staining was performed using the Dako Autostainer (Dako, Carpenteria, CA). Monoclonal antibodies purchased from Dako were used according to the standard protocol. To this end, the paraffin-embedded tissue was deparaffinized in xylene and alcohol, rehydrated, and placed into 10 mmol/L citrated buffer, pH 6, antigen retrieval solution. The tissue covered with buffer was placed into the microwave for 10 minutes, followed by blockage of endogenous peroxidase in 0.3% hydrogen peroxide for 30 minutes. The primary antibodies to CD117, neurofilaments, and S-100 were applied for 30 minutes, washed, and incubated with the secondary horseradish peroxidase–labeled antibodies and streptavidin peroxidase. For color development, diaminobenzidine hydrogen peroxide was used creating a brown reaction. Ethyl green was used for counterstaining.

All slides were examined microscopically and scored by a pathologist (I.D.) blinded to the clinical status of the patient for the presence of ICCs. The findings were expressed as follows: normal number of ICCs, equivalent to normal controls; reduced number of ICCs equivalent to 20–40% of the control: almost complete loss of ICCs, to the point that not more than 5 cells were seen per 10 high-power fields (<10% of the control). The slides stained with antibodies to neurofilaments and S-100 were used for general orientation and to ascertain that nerve cells...