Effect of endoscopic pyloric therapies for patients with nausea and vomiting and functional obstructive gastroparesis

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ABSTRACT

Gastroparesis (GP) is associated with loss of interstitial cells of Cajal (ICC) and gastric dysrhythmias such as tachygastria. We hypothesized that a subset of patients with GP, normal 3 cycles per minute (cpm) gastric myoelectrical activity (GMA), and normal upper endoscopy may respond to pyloric therapies.

Aims: To determine the effect of botulinum toxin A (btA) injection or balloon dilation (BD) of the pylorus on symptoms and body weight in patients with GP and 3 cpm GMA.

Methods: Patients were identified who had GP, normal 3 cpm GMA, and normal endoscopy that excluded mechanical obstruction of the pylorus. Electrogastrograms (EGG) with water load tests (WLT) were recorded to determine GMA. Gastric emptying was measured with 4 h scintigraphy. Each patient underwent up to three pyloric treatments with btA or BD.

Results: Thirty-three patients (29 women) with an average age of 42 years were studied. Seventy-nine percent had idiopathic GP and 21% had diabetic GP. The average percent meal retained at 4 h was 42% and each EGG test showed normal 3 cpm GMA. Nausea was the major symptom in 76% of patients. Complete or partial symptom response occurred in 75%, 72%, and 88% of patients after the first, second, or third endoscopic pyloric treatment, respectively. Overall, 78% of the 33 patients reported improvement in symptoms and average weight gain was 1.54 lb from baseline to final treatment (p < 0.04).

Conclusion: Pyloric therapies appear to be effective treatments in symptomatic patients with GP and 3 cpm GMA and controlled trials are warranted.

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1. Introduction

Nausea is a symptom that is difficult to characterize and chronic unexplained nausea leads to numerous diagnostic procedures and empiric, oftentimes unsuccessful, therapies. Triggers for nausea may arise from visceral, vestibular, or chemoreceptor trigger zones which are mediated by numerous neurotransmitters including serotonin, dopamine, histamine and acetylcholine (Singh et al., 2016). Common causes of nausea include medications, toxins, CNS disorders such as migraine, psychiatric disease, labyrinthine disorders, endocrinological and metabolic (Singh et al., 2016). Disorders of the gastrointestinal tract encompassing mechanical and neuromuscular (motility) gastrointestinal disorders are important and common causes of chronic nausea (Anon, 2011).

Chronic nausea and vomiting are common symptoms associated with gastroparesis, a neuromuscular disorder of the stomach. Gastroparesis is defined by delayed gastric emptying in the absence of mechanical obstruction. This disorder often affects diabetic patients and can occur after viral infections and gastric operations. In the majority of patients the cause of gastroparesis is unknown. Gastroparesis is diagnosed by the 4 hour solid phase gastric emptying test when >60% of meal is retained at 2 h or >10% is retained at 4 h (Tougas et al., 2000). The interstitial cells of Cajal (ICC), the pacemaker cells in the stomach, coordinate normal peristaltic gastric contractions. In healthy subjects the normal rhythm of gastric myoelectrical activity (GMA) is 3 cycles per min (cpm) and indicates at least 5 ICCs per high powered field in the corpus/antrum (Lin et al., 2010). If the ICCs are depleted, then bradygastrias, tachygastrias, and conduction abnormalities are found in the majority of patients with gastroparesis (Lin et al., 2010; Grover et al., 2012; O’Grady et al., 2012). An assessment of GMA is obtained by non-invasive electrogastrography. This test records the myoelectrical activity or rhythm of the stomach (Koch & Stern, 2004).

In a subtype of patients with gastroparesis, normal or high amplitude 3 cpm GMA is present rather than gastric dysrhythmias. These discordant findings were reported in patients with gastroparesis due to pyloric stenosis (Brazana et al., 1998). We identified a group of patients with gastroparesis and normal 3 cpm GMA who had normal pyloric appearance at endoscopy. These findings suggested neuromuscular dysfunction of the pylorus, similar in concept to pyloric stenosis, as the cause of the gastroparesis in these patients with 3 cpm GMA. Thus, these patients underwent endoscopic therapies for pyloric dysfunction: balloon dilation (BD) and injection of butulinum toxin A (bTA). Injection of bTA into the pylorus improved symptoms associated with GP (Gupta et al., 2002; Lacy et al., 2002, 2004; Miller et al., 2002; Bromer et al., 2005), but randomized controlled trials failed to show bTA treatment improved symptoms more than placebo (Arts et al., 2006, 2007; Friedenberg et al., 2008). In these trials, however, the presence of normal 3 cpm GMA was not used to select GP patients for pyloric therapy. The aim of our study was to determine the effect of bTA or BD on symptoms and weight in patients with GP and normal 3 cpm GMA.

2. Materials and methods

2.1. Patients

The study was approved by the Wake Forest Baptist Medical Center institutional review board. A computerized endoscopy database was used to identify patients who underwent upper endoscopy and injection of bTA or BD of the pylorus between January 1, 2004 and December 31, 2014. The charts were reviewed to identify patients who had pyloric interventions that were preceded by a gastric emptying study and electrogastrography with water load test (WLT). Medical records were reviewed to identify chief symptoms of GP, weight measurements, and the symptomatic response to bTA or BD treatments. The indication for treatment in all patients was lack of improvement in symptoms on conventional medical therapy. Medications for GP symptoms that were tried by the patients included promethazine, prochlorperazine, metoclopramide, erythromycin, ondansetron, domperidone, and dronabinol.

2.1.1. Inclusion criteria

Inclusion criteria for study enrollment were documented symptoms of GP, delayed 4-hour, solid-phase gastric emptying study, normal or increased amplitude 3 cpm gastric myoelectrical pattern in response to the WLT, normal endoscopy and abdominal imaging that excluded mechanical obstruction of the pylorus, and one or more pyloric treatment interventions (BD and/or bTA).

2.1.2. Exclusion criteria

Patients with prior pyloric intervention at another institution, patients who did not have at least one pyloric interventions at our institution, patients with another planned intervention (such as placement of a gastric electrical stimulator) for the treatment of GP within four weeks after bTA or BD, and patients who started a new medication for the treatment of GP within four weeks of planned bTA or BD were excluded.

2.1.3. Solid-phase gastric emptying test (GET)

GET was performed in the nuclear medicine department at Wake Forest Baptist Medical Center using a standard protocol (Tougas et al., 2000; Guo et al., 2001). After an overnight fast, the patient consumed a test meal that consisted of EggBeaters sandwich and 300 mL of water. The scrambled eggs (EggBeaters) were labeled with 0.5 mCi technetium Tc 99m sulfur colloid. Scintigraphic images were obtained at 0, 30, 60, 120, 180, and 240 min after meal ingestion. Patients were instructed to stop prokinetic or narcotic medications 5 days prior to the study. A region of interest was drawn around the stomach for all images acquired. The percentage of meal retained at 2 and 4 h after meal ingestion was calculated. Normal solid-phase gastric emptying with this meal is < 60% retention at 2 h and < 10% at 4 h for technetium Tc 99m labeled solids and abnormality of either value at 2 or 4 h is considered delayed gastric emptying (Tougas et al., 2000; Guo et al., 2001).

2.1.4. Electrogastrogram with water load test

Three silver-silver chloride electrodes were placed on the skin in the epigastrium using the standard positions (Koch & Stern, 2004). The electrodes were connected to the recording device (3 CPM Company, Towson, MD). Electrogastrogram (EGG) signals reflect ongoing gastric myoelectrical activity and were recorded before and after the WLT (Koch & Stern, 2004; Koch et al., 2000). The EGG recording was analyzed by custom software that provides a frequency analysis (running spectral analysis) of the gastric electrical rhythm before and after the WLT. Normal gastric myoelectrical activity is approximately 3 cpm (2.5–3.75 cpm); gastric dysrhythmias are tachygastria (3.75–10 cpm) or bradygastria (< 2.5 cpm) (Koch & Stern, 2004; Koch et al., 2000). EGGs were recorded for 15 min before and for 30 min after the WLT (Koch & Stern, 2004). The volume of water ingested by healthy subjects is 550 mL ± 150 mL (Koch & Stern, 2004).

2.1.5. Endoscopy with bTA or BD treatment

Patients underwent upper endoscopy (Pentax Medical Company, Montvale, NJ) after an overnight fast. Midazolam and fentanyl and occasionally, diazepam were administered for sedation. Breath CO₂ and cardiopulmonary monitoring were carried out on all patients. Routine inspection of the esophagus, the stomach, and the proximal duodenum was performed.

2.1.5.1. bTA injection

A 23-gauge needle (Variject; Microvasive Endoscopy, Boston Scientific Corp, Natick, MA) was introduced through the biopsy channel. bTA (25 units) (Botulinum Allergan) was injected into each of the four quadrants of the pylorus for a total of 100 units.
2.1.5.2. Balloon dilation of the pylorus. In some patients, a Through The Scope (TTS) balloon (Cook Medical, Winston-Salem, NC) 20 mm in diameter and 5 cm in length was introduced through the biopsy channel and passed into the pyloric channel under direct vision. The balloon was inflated to 20 mm diameter with 50 cm³ of water for 2 min. The balloon was then deflated and removed.

2.1.6. Assessment of symptoms and response

Symptoms were assessed via chart review before and after pyloric intervention with btA, or BD. At the visit before the endoscopic pyloric therapy, the symptom that was most bothersome was identified and designated as the patient’s “major” symptom. In addition, other reported symptoms were classified as “minor” symptoms. The 9 major symptoms that were reviewed in the charts were adapted from the Gastroparesis Cardinal Symptom Index (GCSI) questionnaire and included nausea, regurgitation, vomiting, fullness, early satiety, postprandial fullness, loss of appetite, bloating, and swollen abdomen (Revicki et al., 2003). Each pyloric intervention was followed by a GI clinic visit within 1 to 3 months.

A positive response to treatment was defined as partial or complete resolution of the major symptom for at least 4 weeks as determined at the first follow up visit. Complete improvement was assessed by a percentage of symptom improvement that was obtained subjectively. One hundred percent improvement was considered complete improvement, >50% improvement was considered partial improvement and anything <50% was considered no improvement or a negative response. Patients who had partial or no improvement of their major symptom after the first intervention were then treated with the alternate intervention if the patient chose to undergo further intervention. For example, if a patient did not improve with btA, then BD was performed during the next endoscopy. Patients who failed to improve after 2 consecutive interventions were considered non-responders. In those patients who responded to the first treatment (or the alternate intervention), the duration of response was determined by counting the number of weeks from the date of the initial pyloric intervention until the date when symptoms recurred. The end of the response period was also determined by the date when patients requested increased doses of their medications, required new medications to control symptoms of GP, or complained of worsening GP symptoms. In some cases additional endoscopic pyloric interventions were performed.

3. Results

3.1. Patient characteristics

Thirty-three patients met the study inclusion criteria. There were 29 women and 4 men with a median age of 42 years (range 18–66 years) (Table 1). The causes of GP were diabetes in seven patients (21%) and idiopathic in 26 patients (79%). The dominant symptom reported by the patients were nausea (n = 26), vomiting (n = 5), epigastric fullness and early satiety (n = 2). The average percent retention of the solid-phase test meal was 70% (normal < 60%) and 42% (normal < 10%) at 2 and 4 h, respectively. In each patient the EGG recordings with water load test showed normal or high amplitude, 3 cpm GMA, and consistent 3 cpm peaks in the spectral analysis (Fig. 1). Fifteen of 33 patients ingested normal volumes of water. The average volume ingested was 432 mL.

3.2. Botulinum toxin A and balloon dilation

Fig. 2 summarizes the treatment effect of endoscopic pyloric therapy with btA or BD. For their first pyloric therapy, 25 of the 33 patients had pyloric injection with btA and 8 patients had BD. The selection of the first treatment modality was at the discretion of the treating physician (KK). Patients with no symptom relief three months after the first therapy (for example, balloon dilation) underwent a second pyloric therapy with the alternate therapy (for example, btA). Three patients who initially responded to btA were switched to BD due to cost considerations. These three patients responded positively to the BD.

Of the 33 patients that underwent their first pyloric therapy, 25 (75%) of patients reported complete or partial improvement of their symptoms and six of these patients required no further intervention. Weight increased an average of 2.6 lb in responders. Of the 25 patients that had a second EGD and pyloric therapy, 18 (72%) reported complete or partial symptomatic improvement; only 4 patients in this group were non-responders after two treatments, and 3 patients in this group that had a positive response after first treatment did not respond after second treatment. The median symptom-free interval after the second intervention in the responders was 4 months. Weight increased an average of 1 lb in responders. Two patients developed epigastric pain for several hours after BD of the pylorus. For these two patients btA was used for their subsequent procedure. There were no other acute or delayed adverse events after upper endoscopy or the injection of btA in any patient receiving these treatments.

As shown in Fig. 2, thirteen of 17 patients (88%) reported complete or partial symptomatic improvement after their third pyloric therapy. The other four patients reported no improvement in symptoms. Of these four nonresponders, only one patient reported no improvement in symptoms after any of the three pyloric therapies and another patient reported improvement after the first two EGDs and no improvement after the third treatment.

Overall, 78% of the thirty-three patients who underwent pyloric treatments reported complete or partial improvement in their chief symptom. Weight increased significantly after the second and third endoscopic therapies with average gain of 1 and 4 lb, respectively. The
average weight gain for all the patients from baseline to final treatment averaged 1.54 lb ($p = 0.001$) with a range from $-12$ to $+29$ lb.

4. Discussion

The normal gastric pacemaker rhythm is 3 cpm. The 3 cpm rhythm is produced by normal numbers of gastric ICCs and the normal balance of parasympathetic and sympathetic nervous system activity (Lin et al., 2010; Grover et al., 2012; O’Grady et al., 2012; Koch, 2011). The normal 3 cpm GMA controls the frequency and velocity of gastric peristaltic contractions that are needed for normal gastric emptying. In contrast, tachygastria, bradygastrias, and conduction defects occur in patients with GP (4–6, 20). In these patients ICCs are depleted ($<5$ ICCs/hpf) in the gastric corpus and antrum (Lin et al., 2010; Grover et al., 2012; O’Grady et al., 2012). Thus, our patients with gastroparesis and normal or high-amplitude 3 cpm GMA are a distinct subtype of GP—obstructive GP. High-amplitude 3 cpm GMA and gastroparesis was previously reported in patients with fixed stenoses at the pylorus (Brzana et al., 1998). Our carefully selected patients with GP and 3 cpm GMA had normal appearing pyloric sphincters at endoscopy and after pyloric treatments with btA or BD, 78% reported improvement in symptoms and average weight increased significantly.

Dyschalasia, a term used by Fisher et al., is the premature closure of the pylorus during antral peristalsis, a dyssynchrohy of antral and pyloric coordination that results in delayed gastric emptying (Fisher, 1985). Previous unblinded studies of endoscopically directed pyloric treatments for GP with btA (Gupta & Rao, 2002; Lacy et al., 2002, 2004; Miller et al., 2002; Bromer et al., 2005) reported symptom improvement ranging from 43% to 77% of patients. However, double-blind trials of btA showed improvement in only 38% to 50% of GP patients, a response no better than placebo (Arts et al., 2006, 2007; Friedenberg et al., 2008). In these studies, none of the patients were selected on the basis of GP in combination with normal or high-amplitude 3 cpm GMA. Our results suggest selection of GP subtype with obstructive pathophysiology will respond better to pyloric therapies. Double-blind, placebo-controlled trials of pyloric therapies in this subtype of GP are needed.

Patients with diabetic or idiopathic GP and gastric dysrhythmias such as tachygastria represent a different GP subtype due in part to ICC depletion and/or enteric nerve dysfunction in the corpus and antrum (Lin et al., 2010; Grover et al., 2012; O’Grady et al., 2012). Recent studies with serosal electrode recordings and histological evaluation of full-thickness gastric biopsies showed that normal 3 cpm gastric slow wave activity is present when there are $>5$ ICCs/hpf in the gastric corpus or antrum (Lin et al., 2010; Grover et al., 2012; O’Grady et al., 2012; Cheng et al., 2013). On the other hand, patients with idiopathic and diabetic GP with $<5$ ICCs/hpf have a spectrum of gastric dysrhythmias and conduction defects (Lin et al., 2010; Grover et al., 2012; O’Grady et al., 2012; Cheng et al., 2013). The normal 3 cpm GMA in our patients indicates a normal complement of ICC cells in the corpus-antrum. Thus, we hypothesized that the likely pathophysiological mechanism underlying GP in our patients with normal 3 cpm GMA was pyloric dysfunction, e.g. pylorospasm or dyschalasia. In a recent study using sleeve manometry and EndoFLIP device, compliance abnormalities of the pylorus were found in 42% of patients with GP (Snape et al., 2016), further indicating the potential role of the pylorus in delaying gastric emptying. Pyloroplasty improved gastric emptying in GP patients (Hibbard et al.,...
First Therapeutic EGD
N=33
Symptom Improvement N=25
+Weight Δ 2.6lb
P=0.09

25 BtA
8 BD

N=21 N=4

+ - + -

Second Therapeutic EGD
N=25
Symptom Improvement N=18
+Weight Δ 1.00lb
P=0.04

17 BtA
8 BD

N=14 N=3

+ - + -

Third Therapeutic EGD
N=17
Symptom Improvement N=13
+Weight Δ 4.06lb
P=0.004

10 BtA
7 BD

N=8 N=2

+ - + -

2011) and highlights the importance of pyloric neuromuscular dysfunction in some patients with GP. Histological studies of ICCs, enteric neurons, and smooth muscle of the pylorus and measurement of pyloric compliance and pressure may be helpful in examining the full spectrum of pyloric neuromuscular dysfunction in patients with GP and normal 3 cpm GMA (Lin et al., 2010).

It is important to exclude mechanical obstruction of the pylorus and duodenum with endoscopic examination of the pylorus and distal duodenum in all patients with GP especially those with 3 cpm GMA, since GP may be due to neuromuscular dysfunction or mechanical stenosis (Cengia & Koch, in press). The presence of normal 3 cpm GMA and GP, suggests normal numbers of ICCs are present and that neuromuscular dysfunction of the pylorus is the likely underlying mechanism of the GP if mechanical obstruction is excluded. Our experience also suggests at least two pyloric treatments with btA or BD may be required in these patients with neuromuscular dysfunction of the pylorus to reduce symptoms and improve weight gain.

Medical therapies for the symptoms associated with GP are scant. Pro-motility agents like metoclopramide may improve symptoms (Reynolds & Putnam, 1992; Erbas et al., 1993; Snape et al., 1982; Perkel et al., 1980), but it is not appropriate in gastric outlet obstruction and significant side effects limit long-term use. Erythromycin loses effectiveness with time, and domperidone is only available through an FDA special program (Reynolds & Putnam, 1992; Erbas et al., 1993; Snape et al., 1982; Perkel et al., 1980), and neither drug would help symptoms due to obstructive gastroparesis. Gastric electrical stimulation fails to help symptoms in 40 to 50% of patients (McCallum et al., 2010). A portion of these patients may actually have a functional obstructive subtype of GP as described here, and gastric electrical stimulation would not be expected to provide benefit in these patients. Our results emphasize the importance of identifying the functional obstructive GP subtype because rational treatment approaches for pyloric dysfunction then can be considered.

In summary, a subset of patients with GP and normal 3 cpm GMA represents a functional obstructive phenotype of GP. The obstructive form of GP may be due to fixed pyloric stenosis or pylorospasm/dyschalsia. In our patients with GP, 3 cpm GMA, and normal pyloric appearance at endoscopy, pyloric therapies with btA and BD improved symptoms and weight. Two or more treatments may be needed for symptom improvement and weight gain. Further investigation of functional obstructive GP will stimulate improved and more rational treatment approaches for patients with nausea and vomiting due to this subtype of GP.

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References


