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REVIEW

Treatment of refractory diabetic gastroparesis: Western medicine and traditional Chinese medicine therapies

Bing Pang, Qiang Zhou, Jun-Ling Li, Lin-Hua Zhao, Xiao-Lin Tong

Bing Pang, Qiang Zhou, Xiao-Lin Tong, Department of Endocrinology, Guang'anmen Hospital, China Academy of Chinese Medical Sciences, Beijing 100053, China
Jun-Ling Li, Beijing University of Traditional Chinese Medicine, Beijing 100029, China
Lin-Hua Zhao, Molecular Biology Laboratory, Guang'anmen Hospital, China Academy of Chinese Medical Sciences, Beijing 100053, China
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Correspondence to: Xiao-Lin Tong, Professor, Department of Endocrinology, Guang'anmen Hospital of China Academy of Chinese Medical Sciences, Room 432, Administration Building, 5 Beixiange Street, Xuanwu District, Beijing 100053, China. xiaolintong66@sina.com
Telephone: +86-10-88001260 Fax: +86-10-63014195
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Abstract

Refractory diabetic gastroparesis (DGP), a disorder that occurs in both type 1 and type 2 diabetics, is associated with severe symptoms, such as nausea and vomiting, and results in an economic burden on the health care system. In this article, the basic characteristics of refractory DGP are reviewed, followed by a discussion of therapeutic modalities, which encompasses the definitions and clinical manifestations, pathogenesis, diagnosis, and therapeutic efficacy evaluation of refractory DGP. The diagnostic standards assumed in this study are those set forth in the published literature due to the absence of recognized diagnosis criteria that have been assessed by an international organization. The therapeutic modalities for refractory DGP are as follows: drug therapy, nutritional support, gastric electrical stimulation, pyloric botulinum toxin injection, endoscopic or surgical therapy, and traditional Chinese treatment. The therapeutic modalities may be used alone or in combination. The use of traditional Chinese treatments is prevalent in China. The effectiveness of these therapies appears to be supported by preliminary evidence and clinical experience, although the mechanisms that underlie these effects will require further research. The purpose of this article is to explore the potential of combined Western and traditional Chinese medicine treatment methods for improved patient outcomes in refractory DGP.

Key words: Refractory diabetic gastroparesis; Nutrition; Gastric electrical stimulation; Botulinum toxin; Traditional Chinese treatment; Surgery

Core tip: In this review, we summarize the latest therapeutic approaches for refractory diabetic gastroparesis (DGP), a condition that may be difficult to treat. For most patients with refractory DGP, invasive and expensive treatment options are frequently applied. They cause mental suffering and are expensive, and not all patients are likely to benefit from these therapies. Therefore, as with many chronic conditions, patients may seek complementary and alternative therapies. In clinical practice, traditional Chinese medicine (TCM) appears efficacious and offers a less invasive treatment option. Moreover, preliminary evidence in the literature has also suggested the efficacy of TCM.

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OUTLINE OF REFRACTORY DIABETIC GASTROPARESIS

Definition and clinical manifestations

First described in 1958, diabetic gastroparesis (DGP) is a well-established complication of diabetes mellitus (DM). As a chronic motility disorder of the stomach that is associated with both type 1 and type 2 DM, DGP is characterized by delayed gastric emptying (GE) of a solid meal with no evidence of mechanical obstruction. The most common disabling symptoms of DGP include nausea, vomiting, postprandial fullness, early satiety, and bloating[1-3]. In some patients with DGP, symptoms such as severe, persistent nausea and vomiting may be very difficult to treat, which together define refractory DGP. This condition is often unresponsive to medical therapy, and because patients are unable to maintain nutrition *via* the oral route, frequent emergency department visits and/or hospitalization may be necessary[2,4,5]. The overall prevalence of refractory DGP has not been determined; however, severe symptoms necessitating multiple hospitalizations are estimated to occur in 2% to 5% of patients with gastroparesis (GP)[6].

Refractory DGP contributes to a range of morbidity issues, including weight loss, malnutrition due to inadequate caloric and fluid intake, electrolyte disturbances and dehydration, poor glycemic control, recurrent episodes of diabetic ketoacidosis, and increased healthcare utilization[1,5-7]. These effects on health may also decrease work performance and disrupt normal life, which may themselves be disabling consequences. Notably, refractory DGP is increasingly recognized for its significant economic burden on the health care system[8-10].

Pathogenesis

The pathogenesis of DGP has been related to autonomic neuropathy of the vagal innervation of the stomach in up to 40% of cases[11,12]. Many of the metabolic and hormonal disturbances caused by DM may also lead to impaired gastric tonicity and antral contractions[13].

Diagnosis

To date, there has been no accepted definition for the diagnosis of refractory DGP; most diagnostic parameters are drawn from the published literature and are based on reported clinical experiences. The key diagnostic criteria are as follows: (1) documented diagnosis of DGP for more than one year; (2) refractoriness or intolerance to antiemetics and prokinetics after more than 6 mo on a full regimen of standard medical therapy; (3) more than 7 emetic episodes per week or chronic daily nausea; and (4) delayed GE (> 60% retention at 2 h and/or > 10% at 4 h on the basis of a standardized scintigraphic method for GE of a solid meal)[14-16]. Based on published literature, spleen-kidney yang deficiency syndrome is thought to be common for refractory DGP in traditional Chinese medicine[17-20].

Efficacy evaluation

The efficacy of treatment for refractory DGP demands closer evaluation, as the subjective symptoms reported by patients, rather than sole reliance on results of GE tests, play an important role in the evaluation of treatment efficacy. The efficacy evaluation associated with an objective indicator may not be ideal, as some reports have indicated a poor correlation between improvement in GP symptoms and GE test results[21,22]. Additionally, frequent vomiting and generalized weakness may also interfere with the performance of this complicated objective test, as it is very difficult to complete GE studies in patients with severe nausea and vomiting. The subjective symptoms are the only measures that directly reflect the patient's experience of symptom severity, functioning, and well-being[23].

Quantification of the severity and characteristics of GP symptoms has been facilitated by the introduction of validated questionnaires. The Gastroparesis Cardinal Symptom Index (GCSI) has been the most widely used validated questionnaire and best reflects the subjective symptoms reported by patients, with a high correlation between these symptoms and GE. The GCSI is an assessment of symptom severity over a two-week period that incorporates nine symptoms assessed by three subscales (postprandial fullness/early satiety, nausea/vomiting, and bloating) and represents a subset of the more comprehensive Patient Assessment of Gastrointestinal Symptoms[24-26]. Furthermore, weekly vomiting frequency and severity, the SF-36 Health Status Survey questionnaire, nutritional status, and weight of patients are also commonly measured parameters for study enrollment and efficacy evaluation in research trials.

TREATMENT OVERVIEW

Management

Strategies for the treatment of refractory DGP in clinical practice are based on controlling symptoms (particularly nausea and vomiting), improving delayed GE, and providing dietary and hydration measures to stabilize weight and support nutrition[2]. First among the general principles that apply to refractory DGP treatment is the establishment of an accurate diagnosis of GP. Second, the metabolic status should be evaluated and glycemic control should be optimized, as hyperglycemia has been demonstrated to delay GE and to weaken the effects of prokinetic drugs on GE. In patients with DM, glycemic control includes dietary measures, which generally include restricted meal volumes, increased meal frequency, small-particle foods, and supplementary nutrition. The avoidance of excess fat and dietary fiber is necessary, as these dietary elements may aggravate delayed GE. With respect to drug therapy, standard drugs should be administered before patients are categorized as drug-refractory. For patients with medically refractory gastroparesis, gastric electrical stimulation (GES) is a minimally invasive surgical method that should be considered for severe symptoms, especially nausea and vomiting. Pyloric botulinum toxin

(BTX) injection has also been used recently for refractory DGP, as reported in several small case studies. More aggressive treatments include hospitalization for the intensive management of high glucose levels with insulin administration, intravenous hydration, and intravenous administration of antiemetic and prokinetic agents[1,2,26-28]. Enteral or parenteral nutritional support and/or surgical intervention may also be necessary. Gastrectomy is performed as a last option and under conditions of strict patient selection. The different therapeutic modalities may be used alone or in combination, according to the needs of the individual patients. The use of traditional Chinese medicine (TCM) in the treatment of refractory nausea and vomiting is extensive. Preliminary evidence that has indicated the effectiveness of TCM appears to support the efficacy of TCM utilized in clinical practice. Additional research on the mechanism(s) of action of TCM, involving large-scale, randomized controlled trials, is warranted to strengthen the evidence base for future studies. The purpose of this article is to present the optimal, combined benefits of Western medicine and traditional Chinese treatments for refractory DGP for improved patient outcomes.

Drug therapy

The standard drug therapy for DGP, essentially unchanged over the past decade, mainly relies on the use of prokinetic agents, such as erythromycin, metoclopramide, and domperidone, which are the cornerstones of refractory DGP therapy. Tegaserod, cisapride, bethanechol, and other drugs are also commonly used; however, the use of cisapride is markedly restricted or may be discontinued due to side effects[5]. Prokinetic agents have been demonstrated as the mainstay of treatment in patients with DGP, although the benefits may be short-lived and some diabetic patients may respond poorly[1,2,26,27]. A meta-analysis involving 514 patients from 36 clinical trials revealed that erythromycin was the most potent stimulant of GE[29], while a double-blind multicenter trial reported metoclopramide and domperidone as being equally effective in reducing symptoms of nausea and vomiting in patients with DGP[30]. The antiemetic medications used included phenothiazine, a serotonin 5-HT3 receptor antagonist, an antihistamine, and low-dose tricyclic antidepressants. The D2 receptor antagonists metoclopramide and domperidone also have some anti-emetic effects and are usually administered to patients with nausea and/or vomiting. Although the use of antiemetic agents may delay stomach emptying, some patients who experience insufficient relief from prokinetic drug therapy or who develop unacceptable toxicity to prokinetics may respond positively to antiemetics. In patients with refractory DGP, prokinetic agents and antiemetic medications are often used in combination to reduce symptoms. Patients with DM should also be counseled regarding the need to achieve tighter glycemic control. More aggressive glucose monitoring that allows for the frequent dosing of short-acting insulin preparations to prevent post-prandial hyperglycemia is likely to be effective, as the prevention of hyperglycemic spikes and widely fluctuating glycemia may be more important than the maintenance of a given steady-state blood glucose level[31]. In summary, the monitoring of 2-h postprandial blood glucose levels may be useful, as the potential advantages of optimal glucose control are increased antral contractility, correction of gastric dysrhythmias, and accelerated GE[32,33].

Recently, a proof-of-concept study[34] demonstrated that a ghrelin receptor agonist (TZP-101) significantly improved GE and may be well tolerated in DM patients with moderate-to-severe chronic GP. Wo *et al*[35] conducted a multicenter, randomized, double-blind, placebo-controlled study of TZP-101 in DGP patients with severe nausea/vomiting. They reported a reduction in the GCSI Nausea/Vomiting subscale score of 3.82 ± 0.76 (P = 0.011) at the end of treatment compared with baseline in the 80 μg/kg group, a result that reached statistical significance. The investigators demonstrated that TZP-101 was able to reduce the frequency and severity of nausea and vomiting, as well as the overall symptoms, to a substantial and significant degree in a subset of the most refractory DGP patients.

Nausea and vomiting are often the most debilitating symptoms for patients with refractory DGP. Aprepitant, a neurokinin-1 receptor antagonist, has been approved in the US for nausea and vomiting associated with surgery and cancer chemotherapy. Chong *et al*[36] reported a case of refractory nausea in a patient with DGP who was successfully treated with aprepitant. This treatment was continued for 4 mo, and the patient showed a rapid and significant response to the agent, with improvements in both nausea and vomiting, despite an absence of significant effects of aprepitant on accelerated GE. The 5-HT2 receptor antagonist mirtazapine[37] has also been shown to be effective in a single report involving refractory DGP. The severe recurrent nausea and vomiting that persisted for over 7 mo in this case improved dramatically within a few days of once-daily mirtazapine administration. However, controlled studies may be warranted to further evaluate the benefit of these medications in improving symptoms in patients with DGP.

Other symptoms, such as early satiety, have been related to the functional dyspepsia caused by defects in fundic accommodation. The use of nitrates, buspirone, sumatriptan, and selective serotonin reuptake inhibitors may relax fundic muscles in this condition, but no relevant studies have indicated their efficacy in the management of early satiety in patients with GP[5]. The pathogenesis of abdominal pain, which can be disabling in patients with GP, is postulated to be due to sensory rather than motor dysfunction[38]. Thus, treatments that aim to reduce sensory afferent dysfunction may be more effective. However, agents commonly used in clinical practice, including tricyclic antidepressants, gabapentin, paroxetine, and opiates, have been generally unsatisfactory in treating this pain. In a case report[39], a 50-year-old woman who had suffered from type 1 DM for 20 years was described

as having chronic abdominal pain and malnutrition due to severe DGP and was successfully treated with a celiac plexus block (CPB). This patient was able to successfully avoid any narcotic use, with successful analgesia achieved and maintained for 10 wk following CPB.

Nutritional support

Nutritional support is often overlooked in patients with DGP, and few randomized controlled trials have evaluated the effects of nutritional intervention on outcomes[33]. For patients with refractory DGP who are unable to meet caloric and fluid needs *via* oral dietary modifications, enteral alimentation or total parenteral nutrition (TPN) should be considered.

Enteral alimentation is the preferred route for nutritional and hydration supplementation in patients with recurrent vomiting and unpredictable oral intake. Clinically common intubations for enteral alimentation are as follows: nasogastric tube, nasoduodenal/nasojejunal tube, gastrostomy tubes, PEG-J or Jet-PEG, jejunostomy, and dual gastrostomy and jejunostomy. The criteria for initiation of enteral nutrition supplementation include unintentional loss of more than 5%-10% of the usual body weight during a period of 3-6 mo and/or repeated hospitalizations for refractory symptoms[40]. Enteral feedings may maintain nutrition, relieve symptoms, improve glycemic control, and reduce emergency department visits or hospitalizations in patients with normal small bowel function[1]; however, a relatively high incidence of both major and minor complications, including infection, tube migration, and dislodgement[41,42], have been reported.

Jejunostomy tube (J-tube) placement is the most common route for enteral alimentation and is a relatively inexpensive, safe, and physiological option for refractory DGP[28]. The feeding J-tube that bypasses the paralyzed stomach is usually placed by laparotomy or laparoscopy[43]. J-tubes enable jejunal nutrient and medication delivery and avoid gastric penetration that may interfere with proper electrode placement for gastric electrical stimulation. A disadvantage of the J-tube is the inability to vent the stomach, and the most common complications are tube obstruction and skin infection[28,40]. Enteral feedings can be initiated 24 h after J-tube placement. They are initiated with diluted infusions and are gradually advanced to iso-osmolar preparations at relatively low infusion rates (*e.g.*, 20 mL/h) that are then increased to the target infusion rate that supports nutrition and hydration, typically at least 60 mL/h over 12-15 h/d[28,40]. With regard to the important "rule of J-tube feeding," oral caloric intake should not occur when the J-tube is running, because calories within the small bowel will inhibit gastric emptying and induce further nausea and/or vomiting[28].

Fontana *et al*[43] investigated the long-term results and complications of J-tube placement. A retrospective analysis was performed on 26 patients with a mean follow-up of 47 mo (1-130 mo). The results indicated that 83% of the patients demonstrated improved overall health status, which was the only indicator that reached statistical significance. Symptoms of nausea/vomiting, hospitalization rate, and nutritional status were also slightly improved. There were 23 major and 42 minor complications identified in this study, as well as one death that was directly caused by the J-tube placement, although a large proportion of the morbidity and mortality rates was clearly attributed to the malignant nature of DM and other chronic illness-related factors. Jacober *et al*[44] reported the benefits of J-tube feeding in 4 diabetic patients with refractory GP. They demonstrated that the J-tube may be effective in providing nutrition, fluids, and medications in cases of either normal or abnormal small intestinal motor function. Technological improvements may influence the placement of J-tubes and their efficacy[28,43]. Ginsberg *et al*[45] used an endoscopically placed clip that assisted with tube placement and may have possibly prevented later accidental dislodgement. In summary, in cases of patients who fail medical therapy, the placement of a J-tube may present an available option with acceptable morbidity and mortality rates. Prospective, randomized controlled trials of J-tube use are required to provide more specific evidence for the efficacy of this therapy.

In patients with severe vomiting and fullness, the placement of a gastrostomy tube (G-tube) for intermittent decompression and the venting of secretions may help to provide some symptom relief, but it is a poor choice for feeding due to delayed GE. The G-tube can be placed endoscopically, surgically, or by fluoroscopy guidance. Hejazi *et al*[28] indicated that G-tube decompression is advocated in cases of intestinal pseudo-obstruction rather than in the usual setting of gastroparesis given that the infusion of liquid meals into the stomach *via* a G-tube is unsafe due to the likelihood of symptom exacerbation and the risk of pulmonary aspiration caused by delayed GE. Data from Revicki *et al*[46] revealed that 6 of 8 patients were able to return to work or school with a venting gastrostomy. Kim *et al*[47] performed a non-randomized study of 8 patients, the results of which included relief of nausea and some gastric decompression in the treatment of refractory idiopathic GP.

Clinical data on other types of tubes have been limited until now. The nasogastric tube is usually inserted for acute management by gastric decompression. Short-term nasojejunal feeding is often used to help determine whether a patient may tolerate chronic small bowel feedings *via* permanent enteral access[1,2,28,40].

Enteral alimentation is more acceptable than TPN in most patients. TPN introduces the risk of catheter-related infections, which is an important concern in diabetic patients; moreover, TPN is more expensive than enteral alimentation. However, in cases of severe malnutrition in which an adequate nutritional and hydration state cannot be maintained; in patients with small-bowel dysmotility, including chronic intestinal pseudo-obstruction, who are unable to tolerate J-tube feedings; and when surgery is planned, patients may benefit from the short-term use of TPN. TPN may maintain short-term normalization of GE and provide supplemental caloric support combined

with tight blood glucose control. In general, each liter of TPN requires the addition of 30-40 units of regular insulin, depending on the patient's previous insulin requirements and the TPN contents (1 unit of regular insulin per 5 g of carbohydrate or 15 g of protein)[2].

GES

GES is a rapidly evolving treatment for patients with refractory symptoms related to DGP[48]. GES involves the surgical implantation of unipolar electrodes into the muscular layer of the gastric antrum, as well as a pulse generator in the abdominal wall to deliver low-energy, 0.1-s pulse trains at a high frequency of 12 cycles/min of electrical energy, which is higher than the normal slow-wave gastric activity of 3 cycles/min[49-51]. The early use of GES was reported by Lin *et al*[52] and McCallum *et al*[53] in 1998. The findings from two randomized trials that demonstrated good results prompted the US Food and Drug Administration to approve the usage of high-frequency, low-energy GES (Enterra Therapy System, Medtronic, Minneapolis, United States) with a Humanitarian Device Exemption in March 2000. The mechanism of action of GES is postulated to be the modulation of function of the autonomic nervous system and enteric nervous system, which affects the secretion of gastrointestinal hormones, reduces gastric sensitivity to distention, changes antral motor function, and enhances fundic relaxation[48]. A direct central nervous system effect is also involved, whereby energy stimulates a central nausea and vomiting center in the brain[49]. Recent studies have demonstrated that GES is an effective and safe treatment for patients with refractory DGP[16,51,54-57].

Lin *et al*[57] reported a GES study involving the largest sample size and the longest follow-up period to date. In this retrospective assessment, 221 patients (142 with DGP) were treated with Enterra (Medtronic); 188 patients underwent follow-up visits, and data were collected for up to 10 years (mean, 56 mo; range 12-131 mo). This therapy was reported to reduce the need for hospitalizations, limit the need for prokinetic and antiemetic medications, improve nutritional status, and decrease total symptom scores (TSSs). Two-hour gastric retention decreased from a median of 70% at baseline to 66%, and 4-h retention decreased from 37% to 30% at the time of last follow-up. The limited data showed a decrease in mean HbA1c levels. In this long-term study, the complications and overall safety of GES therapy were well documented; specifically, 24 patients (11%) underwent device removal, mainly due to infection, lack of efficacy, and small-bowel obstruction. This report also discussed the relationship between symptom improvement and stimulation energy, concluding that energy parameters and increasing voltage do not explain the likelihood of symptom reduction.

McCallum *et al*[55] also investigated outcomes in 55 patients who kept the device on or off over one year in a prospective, placebo-controlled study. The median reduction in weekly vomiting frequency (WVF) during the initial 6 wk was 57% ($P < 0.001$) compared with the baseline values. The WVF and TSS (frequency and severity) were not significantly different between patients who kept the device turned on or off during the crossover period. At 12 mo, the WVF decreased significantly compared with baseline, with a median reduction of 67.8% ($P < 0.001$), while the frequency and severity of the TSS were also reduced from baseline to 12 mo ($P < 0.001$). Patients also had significant improvements in GE, quality of life, and number of hospitalization days. The stimulation during the initial 6 wk significantly decreased DGP symptoms prior to the double-blind, randomized phase. An explanation for this finding may be the possibility of sustained memory or carryover effects from the 6 "active" weeks, which emphasizes the neuroplasticity of the mechanisms controlling nausea and vomiting by the central nervous system. Stimulation was administered for 1.5 mo before the randomized controlled trial (RCT) (6 mo) in the study by McCallum *et al*[54], and the results from the RCT period may have been affected by the previous stimulation.

McKenna *et al*[49] reported short-term results in 19 patients who had the device activated for a mean of 38 wk. Within 6 wk, the WVF had significantly decreased in 75% of patients with DGP, the TSS improved after 6 wk of stimulation and remained improved throughout the 12-mo follow-up, and nuclear medicine GE studies normalized in 80% of patients with DGP. However, there was no significant difference in health and quality of life as measured by the SF-36, most likely as a result of the relatively small sample size. This study concluded that GE correlated poorly with actual symptomatic outcomes, while Hou indicated that GES not only significantly improved symptoms but also improved 2- and 4-h GE in GP patients[56]. Therefore, further studies are needed to resolve these results.

The Worldwide Anti-Vomiting Electrical Stimulation Study[16] was a randomized, controlled, double-blind trial. During the 2 × 1-mo crossover phase, the device was alternately turned on and off, followed by a non-controlled observational phase. Included in the study were 33 patients, 17 of whom were diabetics, and most were followed for 12 mo. Patients in this study experienced a significant decrease in vomiting frequency and symptom scores, and they reported feeling significantly better when the devices were turned on than when they were turned off. The mean quality of life scores were nonequivalent at baseline. However, these changes did not reach statistical significance during the RCT phase, perhaps due to the relatively brief stimulation time, which lasted for only 2 mo.

In conclusion, the majority of studies on GES have demonstrated that GES therapy is effective in decreasing nausea and vomiting scores, promoting GE[54-56], reducing gastroparesis-related hospitalizations[54,57], improving health-related quality of life[57], and controlling hemoglobin A1C levels in diabetics[54-56,57]. Kastenmeier *et al*[58] found GES to be beneficial for eliminating reliance on supplemental nutrition, with 60% of patients able to eliminate all supplemental nutrition within a mean of 5

mo post procedure. A meta-analysis showed similar feeding success postoperatively, with the majority (78%) of patients no longer requiring enteral or parenteral nutrition.

GES treatment is expensive and invasive, and not all patients are likely to benefit from this therapy[59]. According to the literature, three parameters were found to have an impact on its clinical efficacy: the etiology of GP, main symptoms, and use of narcotics. Patients with DGP did better than patients with idiopathic GP, while patients in whom nausea and vomiting were the main symptoms exhibited a more favorable response than patients in whom abdominal pain was the main symptom. Additionally, patients who were not taking narcotics had better outcomes than those who were using narcotics at the study onset[51]. Furthermore, there was a tendency for non-responders to be female and to have suffered GP symptoms for a longer period of time prior to initiating therapy[59].

Pyloric BTX injection

BTX has been previously used for the treatment of spasm of the gastrointestinal sphincters. More recently, pyloric BTX injection has been evaluated for use in patients who are refractory to standard management in several small case studies, open-label trials, and RCTs, although BTX does not have an FDA-labeled indication for this use. BTX injection therapy achieved the goal of improving GE by decreasing the release of excitatory transmitter substances and promoting muscle relaxation[24,60].

A few uncontrolled, open-label studies (< 30 cases) have indicated that the injection of 80-200 units of BTX during endoscopy in a circumferential manner at four to five sites into the pylorus was effective in improving GE and decreasing symptoms in patients with DGP[61-64]. Symptoms decreased by an average of 45% (range, 29%-58%), while GE improved by a mean of 42% (range, 33%-50%), with a decreased symptom duration lasting 1-4 mo after injection[40]. In a report by Coleski *et al*[65] on 179 patients (81 patients with DGP), the duration of the response ranged from 1-4 mo, and 51.4% of the patients experienced a symptomatic response to BTX. The study concluded that responses to pyloric BTX depended on dose and were maintained with repeated injections. Another study[66] showed that higher doses of BTX (150-200 units) were more likely to yield reductions in nausea and vomiting compared with a dose of 100 units and that a longer evaluation time also appeared to correlate with an improved response.

However, a study by Coleski *et al*[65] indicated that the response rate (35%) in patients with vomiting as a major symptom of GP was significantly lower than that in patients without vomiting (57%). BTX injection may decrease the severity of subjective symptoms, but these symptoms may not include nausea and vomiting, which may even recur and worsen.

Additionally, this therapy has not been demonstrated to be effective in RCTs[67,68]. In a randomized, double-blind, placebo-controlled trial[68], 32 patients were randomized to BTX A or placebo for a 1-mo follow-up period. The results indicated that symptom improvement was achieved in 37.5% and 56.3% of the individuals in the botulinum and control groups, respectively. Although improvement in GE was observed in the botulinum group, it was not superior to that in the placebo group. The BTX group demonstrated improvement in GE; however, this improvement was not significantly different compared with that in the placebo group. Some limitations existed, *e.g.*, the insufficient sample size and the short follow-up period. In the future, this therapy will require more in-depth testing and verification. To date, no serious adverse events have been attributable to BTX. The major limiting factors are related to insurance coverage and the inconvenience of undergoing endoscopy[2].

Surgical therapy

Surgical therapy is increasingly employed in the treatment of patients with refractory DGP. Surgical therapy is a reasonable option to consider in patients who suffer from medically refractory nausea and vomiting, fail to achieve benefits from medical therapy, and present with weight loss or aspiration, as well as in patients who experience difficulty in taking oral medications. Unfortunately, this therapy has historically been plagued by high morbidity rates without consistent symptom response rates[68]. Thus, in cases of judicious patient selection with careful assessments of the risk for malnutrition caused by surgery and following surgery, as well as the risk of renal failure, among other concerns, surgery may be performed. Traditional surgical options include sub-total gastrectomy or esophagojejunostomy, surgical drainage procedures (pyloroplasty or pyloromyotomy), gastric stimulator implantation, gastrostomy/jejunostomy tube insertion and total parenteral nutrition, pancreatic transplantation in diabetics. Generally, sub-total gastrectomy and completion gastrectomy comprise an effective therapy which can reduce symptoms, enhance delayed GE, and improve quality of life[49,69-71].

Saridena *et al*[69] reported on the outcomes in 9 patients with refractory GP (6 of whom were diabetic patients with a fully intact stomach) who underwent total gastrectomy with a mean follow-up of 3.5 years (range, 1-5 years), with six patients available for follow-up. In all patients, refractory nausea and vomiting were reduced by an average of 55%, and the frequency of hospitalization was significantly decreased. Their nutritional status was stabilized with the insertion of J-tubes, and there was a considerable improvement in the quality of life after total gastrectomy.

Watkins *et al*[72] examined the long-term outcomes in patients with intractable vomiting due to DGP. Symptomatic relief in patients with a preoperative grade of Visick Ⅲ-Ⅳ was evaluated objectively and reached 43% in 6 of 7 patients almost immediately after surgery. However, these results were accompanied by risks of subsequent renal failure and poor life expectancy.

Very limited data from uncontrolled studies have shown a small improvement of symptoms with pylo-

roplasty or pyloromyotomy[73]. Surgical pyloroplasty resulted in some benefit in 30% of patients with GP[74]. Hibbard *et al*[75] reported excellent outcomes in patients who underwent minimally invasive pyloroplasty for refractory GP and proposed that a completely endoscopic pyloroplasty may be an even less invasive treatment option with advance of technology. A retrospective analysis reviewed the collective data of 28 patients, 26 of whom had undergone laparoscopic pyloroplasty and 2 of whom had undergone endoscopic pyloroplasty. The pre- and post-operative symptom severity scores (SSS), GES, and medication use were evaluated. The use of prokinetic agents was significantly reduced from 89% to 14%. The mean GES T-1/2 was decreased from 320 to 112 min (P = 0.001) and normalized in 71% of patients. Significant improvements in the SSS were observed at 1 mo and persisted for 3 mo. Symptoms were reported as improved at the 1-mo follow-up in 83% of patients.

Sarosiek *et al*[76] initiated a controlled study in which GES was replaced with surgical pyloroplasty (PP) to improve GE and symptom control in patients with DM and other conditions. Forty-nine patients (17 diabetic, 9 idiopathic, and 23 post-vagotomy) underwent GES implantation, and 26 (53%) additionally received PP, with a mean follow-up of 7 mo. The TSS, 4-h GE, adverse events, and hospitalizations were observed at baseline and at the last follow-up. The results indicated that the TSS of patients in both the GES plus PP and GES groups significantly improved compared with their baseline scores; however, the TSS was not significantly different between the two groups. GE was improved by 64% at 4 h (P < 0.001) in patients with GES and PP, compared with 7% after GES therapy alone. No adverse events accompanied the addition of PP to GES. The authors concluded that in drug-refractory GP, the addition of PP to GES substantially accelerated GE, as well as that PP added to GES may sustain improved long-term symptom control, particularly in the post-vagotomy setting.

TCM

TCM and acupuncture are common modalities in complementary and alternative therapies, both of which have a long history of use in the treatment of refractory nausea and vomiting and also help to alleviate abdominal distension[2,5,40]. Some clinical guidelines and reviews have recommended acupuncture as a treatment method for DGP[2,5,40]. Many patients with incurable diseases, such as refractory DGP, particularly in China, are advised to visit a traditional Chinese physician[2].

Professor Tong conducted a study[77] based on a nearly six-year clinical practice. The method of retrospective analysis was applied to collect data on 47 patients with recurrent vomiting who were followed for three months. Xiaoban Xiatang combined with Suye Huanglian Tang was administered most frequently in this study. The severity of overall symptoms, particularly nausea/vomiting, and the postprandial fullness/early satiety and bloating subscale of the GCSI were evaluated before and after treatment. The results indicated that symptom relief after treatment was significantly improved compared with baseline (P < 0.05) and that the efficacy increased with time. Fasting blood glucose levels and HbAlc also improved with treatment.

Generally, Xiaoban Xiatang combined with Suye Huanglian Tang contributes to improving symptoms of severe nausea and vomiting rapidly[78-80]. Xiaoban Xiatang is composed of Rhizoma Pinelliae (Ban Xia) and ginger (Sheng Jiang). Ginger is a traditional Chinese antiemetic agent that exhibits weak 5-HT3 receptor antagonist properties and gastric slow-wave anti-dysrhythmic effects in humans[81,82]. This prescription may effectively alleviate nausea and vomiting *via* inhibition of NK1 receptor activity, antagonized motilin activity, and release of intestinal serotonin (5H-T)[79,80,83,84]. Suye Huanglian Tang is composed of Rhizoma Coptidis (Huang Lian) and Perilla Leaf (Su Ye), which has been used to treat intractable vomiting, mainly based on clinical experience[85-87] and without current pharmacological confirmation. Abdominal distention is also an important symptom in DGP. The traditional Chinese formula Zhizhu Tang is commonly used to treat postprandial fullness/early satiety and bloating by improving gastrointestinal motility. Zhizhu Tang is composed of Atractylodes macrocephala and Citrus aurantium. Liu *et al*[88] reported that Tangweian Jianji, which is mainly composed of Zhizhu Tang, may reduce symptoms of diabetic gastrointestinal disorder *via* a pathway that involves changes in the morphometric and biomechanical remodeling of the esophageal and intestinal wall.

Professor Tong proposed the thought of a "combination of symptom, syndrome and disease" as a treatment guide for refractory DGP[20]. In patients with recurrent nausea and vomiting that cause great distress, the main aim of treatment is to relieve symptoms. Because the main symptoms are viewed as the key factors in syndrome differentiation, the principal prescription should be related to the main symptoms[20,84]. Xiaoban Xiatang combined with Suye Huanglian Tang is commonly employed, and the decoction must be taken in small doses at short intervals. When nausea and vomiting were mostly alleviated, Professor Tong performed "syndrome differentiation". Based on its pathogenesis, "spleen-kidney yang deficiency syndrome" is believed to be common in refractory DGP, and the therapeutic method invokes warm yang to dissipate cold and an increase in qi to fortify the spleen. The Fuzi Lizhong Decoction is established as a fundamental prescription that may improve immune system function[18-20,78,89]. The characteristics of "diseases" and the glycemic level also need to be considered.

Among the existing complementary and alternative therapies, acupuncture is the most-studied method for the treatment of nausea and vomiting of diverse etiologies. The antiemetic effects of acupoint PC6 stimulation have been well established based on a systematic review[90]. The mechanism of action may be associated with effects on autonomic nerve function related to gastric

motility and changes in gastric hormone levels[91,92]. Kim *et al*[93] presented a case report of a patient with refractory DGP who suffered from frequent nausea, vomiting, and lack of appetite. The patient was treated with 16 sessions of acupuncture for 8 wk as an adjunct to conventional drug treatment, which remained the same during the treatment course. After the treatment period, the GCSI score was reduced from 2.4 to 0.6 and the GE time, as measured by solid meal gastric scintigraphy, showed a significant reduction from 135 to 93 min. At a 4-mo follow-up visit after treatment, the patient reported complete reduction of subjective symptoms. According to a single-blinded, randomized pilot study[92], acupuncture therapy may also reduce postprandial fullness as well as early satiety and bloating subscale scores at the end of treatment, as measured by the GCSI. Because most TCM treatments for severe gastroparesis in China are reported as case reports[94,95], prospective RCTs are warranted to obtain a higher level of evidence.

In conclusion, TCM methods are often applied for the treatment of nausea and vomiting and to help alleviate abdominal distension. TCM methods, which are non-invasive and inexpensive, appear to be effective and promising based on clinical practice and some preliminary evidence. With regard to Western therapy, the process of diagnosis and treatment is standardized, and the effectiveness of Western methods has been demonstrated in large-scale clinical trials. The purpose of this review is to propose a combination of Western and TCM methods and to explore the respective advantages of these therapies.

CONCLUSION

The treatment of refractory DGP includes drug therapy, nutritional support, GES, pyloric BTX injection, endoscopic or surgical therapy, and complementary and alternative therapies in selected patients. The different therapeutic modalities may be applied alone or in combination according to the needs of the individual patient. In the past 10 years, experience with GES has represented a major advance in this field, offering new hope for patients with severe symptoms and for those who are refractory to standard medical therapy[28]. While economically acceptable, effective and safe treatment modalities are limited, TCM and acupuncture therapies appear to be promising based on clinical practice and preliminary evidence, despite a low level of evidence. Surgical therapy with feeding tubes and/or gastric resection surgery is reserved for patients who do not respond to gastric stimulation therapy to augment nutrition and aid in medication delivery. The goals of therapy include the relief of symptoms, normalization of nutrition and hydration status, optimization of glycemic control in diabetic patients, and improvement in GE, when appropriate. Future therapies will be guided by our increased understanding of the pathophysiology of DGP, as well as by studies of non-invasive approaches that may be widely employed to treat refractory DGP.

REFERENCES

1 **Parkman HP**, Hasler WL, Fisher RS. American Gastroenterological Association medical position statement: diagnosis and treatment of gastroparesis. *Gastroenterology* 2004; **127**: 1589-1591 [PMID: 15521025 DOI: 10.1053/j.gastro.2004.09.054]

2 **Abell TL**, Bernstein RK, Cutts T, Farrugia G, Forster J, Hasler WL, McCallum RW, Olden KW, Parkman HP, Parrish CR, Pasricha PJ, Prather CM, Soffer EE, Twillman R, Vinik AI. Treatment of gastroparesis: a multidisciplinary clinical review. *Neurogastroenterol Motil* 2006; **18**: 263-283 [PMID: 16553582 DOI: 10.1111/j.1365-2982.2006.00760.x]

3 **Horowitz M**, Harding PE, Maddox AF, Wishart JM, Akkermans LM, Chatterton BE, Shearman DJ. Gastric and oesophageal emptying in patients with type 2 (non-insulin-dependent) diabetes mellitus. *Diabetologia* 1989; **32**: 151-159 [PMID: 2753246 DOI: 10.1111/j.1440-1746.1986.tb00104.x]

4 **Camilleri M**. Clinical practice. Diabetic gastroparesis. *N Engl J Med* 2007; **356**: 820-829 [PMID: 17314341 DOI: 10.1056/NEJMcp062614]

5 **Waseem S**, Moshiree B, Draganov PV. Gastroparesis: current diagnostic challenges and management considerations. *World J Gastroenterol* 2009; **15**: 25-37 [PMID: 19115465 DOI: 10.3748/wjg.15.25]

6 **Syed AA**, Rattansingh A, Furtado SD. Current perspectives on the management of gastroparesis. *J Postgrad Med* 2005; **51**: 54-60 [PMID: 15793344]

7 **Abell TL**, Malinowski S, Minocha A. Nutrition aspects of gastroparesis and therapies for drug-refractory patients. *Nutr Clin Pract* 2006; **21**: 23-33 [PMID: 16439767 DOI: 10.1177/011542650602100123]

8 **Hyett B**, Martinez FJ, Gill BM, Mehra S, Lembo A, Kelly CP, Leffler DA. Delayed radionucleotide gastric emptying studies predict morbidity in diabetics with symptoms of gastroparesis. *Gastroenterology* 2009; **137**: 445-452 [PMID: 19410575 DOI: 10.1053/j.gastro.2009.04.055]

9 **Reddymasu SC**, Sarosiek I, McCallum RW. Severe gastroparesis: medical therapy or gastric electrical stimulation. *Clin Gastroenterol Hepatol* 2010; **8**: 117-124 [PMID: 19765675 DOI: 10.1016/j.cgh.2009.09.010]

10 **Ma J**, Rayner CK, Jones KL, Horowitz M. Diabetic gastroparesis: diagnosis and management. *Drugs* 2009; **69**: 971-986 [PMID: 19496627]

11 **Vinik AI**, Ziegler D. Diabetic cardiovascular autonomic neuropathy. *Circulation* 2007; **115**: 387-397 [PMID: 17242296 DOI: 10.1161/CIRCULATIONAHA.106.634949]

12 **Timratana P**, El-Hayek K, Shimizu H, Kroh M, Chand B. Laparoscopic gastric electrical stimulation for medically refractory diabetic and idiopathic gastroparesis. *J Gastrointest Surg* 2013; **17**: 461-470 [PMID: 23288718 DOI: 10.1007/s11605-012-2128-7]

13 **Parkman HP**, Camilleri M, Farrugia G, McCallum RW, Bharucha AE, Mayer EA, Tack JF, Spiller R, Horowitz M, Vinik AI, Galligan JJ, Pasricha PJ, Kuo B, Szarka LA, Marciani L, Jones K, Parrish CR, Sandroni P, Abell T, Ordog T, Hasler W, Koch KL, Sanders K, Norton NJ, Hamilton F. Gastroparesis and functional dyspepsia: excerpts from the AGA/ANMS meeting. *Neurogastroenterol Motil* 2010; **22**: 113-133 [PMID: 20003077 DOI: 10.1111/j.1365-2982.2009.01434.x]

14 **Tougas G**, Eaker EY, Abell TL, Abrahamsson H, Boivin M, Chen J, Hocking MP, Quigley EM, Koch KL, Tokayer AZ, Stanghellini V, Chen Y, Huizinga JD, Rydén J, Bourgeois I, McCallum RW. Assessment of gastric emptying using a low fat meal: establishment of international control values. *Am J Gastroenterol* 2000; **95**: 1456-1462 [PMID: 10894578 DOI: 10.1111/j.1572-0241.2000.02076.x]

15 **Lin Z**, Sarosiek I, Forster J, Ross RA, Chen JD, McCallum RW. Two-channel gastric pacing in patients with diabetic gastroparesis. *Neurogastroenterol Motil* 2011; **23**: 912-e396

[PMID: 21806741 DOI: 10.1111/j.1365-2982.2011.01754.x]
16 **Abell T**, McCallum R, Hocking M, Koch K, Abrahamsson H, Leblanc I, Lindberg G, Konturek J, Nowak T, Quigley EM, Tougas G, Starkebaum W. Gastric electrical stimulation for medically refractory gastroparesis. *Gastroenterology* 2003; **125**: 421-428 [PMID: 12891544 DOI: 10.1016/S0016-5085(03)00878-3]
17 **China Association of Traditional Chinese Medicine**. Guideline for TCM Diabetes Prevention and Treatment. Beijing: Traditional Chinese Medicine Press of China, 2007: 39
18 **Tong XL**. Tang Luo Za Bing Lun. Beijing: Science Press, 2010: 150
19 **Liu WK**, Dong L, Su H. Experiential examples of syndrome differentiation and treatment on diabetic gastrointestinal dysfunction by Professor Tong Xiao-Lin. *Sichuan Zhongyi* 2010; **28**: 4-6
20 **Pang B**, Zhou Q, Li JL, Tong XL. Clinical Experience from Tong Xiao-Lin in treating diabetic gastroparesis. *Zhonghua Zhongyiyao Zazhi* 2014; In press
21 **Talley NJ**. Diabetic gastropathy and prokinetics. *Am J Gastroenterol* 2003; **98**: 264-271 [PMID: 12591039 DOI: 10.1111/j.1572-0241.2003.07268.x]
22 **Jones KL**, Russo A, Stevens JE, Wishart JM, Berry MK, Horowitz M. Predictors of delayed gastric emptying in diabetes. *Diabetes Care* 2001; **24**: 1264-1269 [PMID: 11423513 DOI: 10.2337/diacare.24.7.1264]
23 **Sarnelli G**, Caenepeel P, Geypens B, Janssens J, Tack J. Symptoms associated with impaired gastric emptying of solids and liquids in functional dyspepsia. *Am J Gastroenterol* 2003; **98**: 783-788 [PMID: 12738456 DOI: 10.1111/j.1572-0241.2003.07389.x]
24 **Revicki DA**, Rentz AM, Dubois D, Kahrilas P, Stanghellini V, Talley NJ, Tack J. Gastroparesis Cardinal Symptom Index (GCSI): development and validation of a patient reported assessment of severity of gastroparesis symptoms. *Qual Life Res* 2004; **13**: 833-844 [PMID: 15129893 DOI: 10.1023/B:QURE.0000021689.86296.e4]
25 **Revicki DA**, Camilleri M, Kuo B, Norton NJ, Murray L, Palsgrove A, Parkman HP. Development and content validity of a gastroparesis cardinal symptom index daily diary. *Aliment Pharmacol Ther* 2009; **30**: 670-680 [PMID: 19558608 DOI: 10.1111/j.1365-2036.2009.04078.x]
26 **Hasler WL**. Gastroparesis: symptoms, evaluation, and treatment. *Gastroenterol Clin North Am* 2007; **36**: 619-647, ix [PMID: 17950441 DOI: 10.1016/j.gtc.2007.07.004]
27 **Abrahamsson H**. Treatment options for patients with severe gastroparesis. *Gut* 2007; **56**: 877-883 [PMID: 17519490 DOI: 10.1136/gut.2005.078121]
28 **Hejazi RA**, McCallum RW. Treatment of refractory gastroparesis: gastric and jejunal tubes, botox, gastric electrical stimulation, and surgery. *Gastrointest Endosc Clin N Am* 2009; **19**: 73-82, vi [PMID: 19232282 DOI: 10.1016/j.giec.2008.12.010]
29 **Sturm A**, Holtmann G, Goebell H, Gerken G. Prokinetics in patients with gastroparesis: a systematic analysis. *Digestion* 1999; **60**: 422-427 [PMID: 10473966 DOI: 10.1159/000007687]
30 **Patterson D**, Abell T, Rothstein R, Koch K, Barnett J. A double-blind multicenter comparison of domperidone and metoclopramide in the treatment of diabetic patients with symptoms of gastroparesis. *Am J Gastroenterol* 1999; **94**: 1230-1234 [PMID: 10235199]
31 **Gentilcore D**, O'Donovan D, Jones KL, Horowitz M. Nutrition therapy for diabetic gastroparesis. *Curr Diab Rep* 2003; **3**: 418-426 [PMID: 12975033 DOI: 10.1007/s11892-003-0087-9]
32 **Lehmann R**, Honegger RA, Feinle C, Fried M, Spinas GA, Schwizer W. Glucose control is not improved by accelerating gastric emptying in patients with type 1 diabetes mellitus and gastroparesis. a pilot study with cisapride as a model drug. *Exp Clin Endocrinol Diabetes* 2003; **111**: 255-261 [PMID: 12951630 DOI: 10.1055/s-2003-41283]
33 **Kashyap P**, Farrugia G. Diabetic gastroparesis: what we have learned and had to unlearn in the past 5 years. *Gut* 2010; **59**: 1716-1726 [PMID: 20871131 DOI: 10.1136/gut.2009.199703]
34 **Ejskjaer N**, Vestergaard ET, Hellström PM, Gormsen LC, Madsbad S, Madsen JL, Jensen TA, Pezzullo JC, Christiansen JS, Shaughnessy L, Kosutic G. Ghrelin receptor agonist (TZP-101) accelerates gastric emptying in adults with diabetes and symptomatic gastroparesis. *Aliment Pharmacol Ther* 2009; **29**: 1179-1187 [PMID: 19298585 DOI: 10.1111/j.1365-2036.2009.03986.x]
35 **Wo JM**, Ejskjaer N, Hellström PM, Malik RA, Pezzullo JC, Shaughnessy L, Charlton P, Kosutic G, McCallum RW. Randomised clinical trial: ghrelin agonist TZP-101 relieves gastroparesis associated with severe nausea and vomiting--randomised clinical study subset data. *Aliment Pharmacol Ther* 2011; **33**: 679-688 [PMID: 21214610 DOI: 10.1111/j.1365-2036.2010.04567.x]
36 **Chong K**, Dhatariya K. A case of severe, refractory diabetic gastroparesis managed by prolonged use of aprepitant. *Nat Rev Endocrinol* 2009; **5**: 285-288 [PMID: 19444262 DOI: 10.1038/nrendo.2009.50]
37 **Kim SW**, Shin IS, Kim JM, Kang HC, Mun JU, Yang SJ, Yoon JS. Mirtazapine for severe gastroparesis unresponsive to conventional prokinetic treatment. *Psychosomatics* 2006; **47**: 440-442 [PMID: 16959934 DOI: 10.1176/appi.psy.47.5.440]
38 **Farmer AD**, Kadirkamanathan SS, Aziz Q. Diabetic gastroparesis: pathophysiology, evaluation and management. *Br J Hosp Med* (Lond) 2012; **73**: 451-456 [PMID: 22875523]
39 **Wu DJ**, Dib C, Hoelzer B, McMahon M, Mueller P. Coeliac plexus block in the management of chronic abdominal pain due to severe diabetic gastroparesis. *BMJ Case Rep* 2009; **2009**: [PMID: 22121392 DOI: 10.1136/bcr.06.2009.1986]
40 **Camilleri M**, Parkman HP, Shafi MA, Abell TL, Gerson L. Clinical guideline: management of gastroparesis. *Am J Gastroenterol* 2013; **108**: 18-37; quiz 38 [PMID: 23147521 DOI: 10.1038/ajg.2012.373]
41 **Cogen R**, Weinryb J, Pomerantz C, Fenstemacher P. Complications of jejunostomy tube feeding in nursing facility patients. *Am J Gastroenterol* 1991; **86**: 1610-1613 [PMID: 1951238]
42 **Karamanolis G**, Tack J. Nutrition and motility disorders. *Best Pract Res Clin Gastroenterol* 2006; **20**: 485-505 [PMID: 16782525 DOI: 10.1016/j.bpg.2006.01.005]
43 **Fontana RJ**, Barnett JL. Jejunostomy tube placement in refractory diabetic gastroparesis: a retrospective review. *Am J Gastroenterol* 1996; **91**: 2174-2178 [PMID: 8855743]
44 **Jacober SJ**, Narayan A, Strodel WE, Vinik AI. Jejunostomy feeding in the management of gastroparesis diabeticorum. *Diabetes Care* 1986; **9**: 217-219 [PMID: 3084186]
45 **Ginsberg GG**, Lipman TO, Fleischer DE. Endoscopic clip-assisted placement of enteral feeding tubes. *Gastrointest Endosc* 1994; **40**: 220-222 [PMID: 8013825 DOI: 10.1016/S0016-5107(94)70170-9]
46 **Revicki DA**, Rentz AM, Dubois D, Kahrilas P, Stanghellini V, Talley NJ, Tack J. Development and validation of a patient-assessed gastroparesis symptom severity measure: the Gastroparesis Cardinal Symptom Index. *Aliment Pharmacol Ther* 2003; **18**: 141-150 [PMID: 12848636 DOI: 10.1046/j.0269-2813.2003.01612.x]
47 **Kim CH**, Nelson DK. Venting percutaneous gastrostomy in the treatment of refractory idiopathic gastroparesis. *Gastrointest Endosc* 1998; **47**: 67-70 [PMID: 9468426 DOI: 10.1016/S0016-5107(98)70301-3]
48 **Guerci B**, Bourgeois C, Bresler L, Scherrer ML, Böhme P. Gastric electrical stimulation for the treatment of diabetic gastroparesis. *Diabetes Metab* 2012; **38**: 393-402 [PMID: 22742875 DOI: 10.1016/j.diabet.2012.05.001]
49 **McKenna D**, Beverstein G, Reichelderfer M, Gaumnitz E, Gould J. Gastric electrical stimulation is an effective and safe treatment for medically refractory gastroparesis. *Surgery* 2008; **144**: 566-572; discussion 572-574 [PMID: 18847640 DOI: 10.1016/j.surg.2008.06.024]

50 **US Food and Drug Administration**. H990014-Enterra Therapy System (formerly named Gastric Electrical Stimulation (GES) system). Cited 22 Sep 2010. Available from: URL: http://www.fda.gov/cdrh/ode/H990014sum.html

51 **Maranki JL**, Lytes V, Meilahn JE, Harbison S, Friedenberg FK, Fisher RS, Parkman HP. Predictive factors for clinical improvement with Enterra gastric electric stimulation treatment for refractory gastroparesis. *Dig Dis Sci* 2008; **53**: 2072-2078 [PMID: 18080765 DOI: 10.1007/s10620-007-0124-7]

52 **Lin Z**, Hou Q, Sarosiek I, Forster J, McCallum RW. Association between changes in symptoms and gastric emptying in gastroparetic patients treated with gastric electrical stimulation. *Neurogastroenterol Motil* 2008; **20**: 464-470 [PMID: 18086205 DOI: 10.1111/j.1365-2982.2007.01054.x]

53 **McCallum RW**, Dusing R, McMillin C. Fluoro-deoxyglucose (FDG) positron emission tomography (PET) in gastroparetic patients before and during gastric electrical stimulation (GES). *Gastroenterol* 2005; **128**: A622 abstract

54 **McCallum RW**, Lin Z, Forster J, Roeser K, Hou Q, Sarosiek I. Gastric electrical stimulation improves outcomes of patients with gastroparesis for up to 10 years. *Clin Gastroenterol Hepatol* 2011; **9**: 314-319.e1 [PMID: 21185396 DOI: 10.1016/j.cgh.2010.12.013]

55 **McCallum RW**, Dusing RW, Sarosiek I, Cocjin J, Forster J, Lin Z. Mechanisms of symptomatic improvement after gastric electrical stimulation in gastroparetic patients. *Neurogastroenterol Motil* 2010; **22**: 161-167, e50-51 [PMID: 19719511 DOI: 10.1111/j.1365-2982.2009.01389.x]

56 **Zhang J**, Chen JD. Systematic review: applications and future of gastric electrical stimulation. *Aliment Pharmacol Ther* 2006; **24**: 991-1002 [PMID: 16984493 DOI: 10.1111/j.1365-2036.2006.03087.x]

57 **Lin Z**, McElhinney C, Sarosiek I, Forster J, McCallum R. Chronic gastric electrical stimulation for gastroparesis reduces the use of prokinetic and/or antiemetic medications and the need for hospitalizations. *Dig Dis Sci* 2005; **50**: 1328-1334 [PMID: 16047482 DOI: 10.1007/s10620-005-2782-7]

58 **Kastenmeier AS**, Makris KI, Dunst CM, Swanstrom LL. Gastric Electrical Stimulation: Surgical Complications and Impact on Supplemental Nutrition (Poster). Chicago, IL: DDW Annual Meeting, 2011

59 **Musunuru S**, Beverstein G, Gould J. Preoperative predictors of significant symptomatic response after 1 year of gastric electrical stimulation for gastroparesis. *World J Surg* 2010; **34**: 1853-1858 [PMID: 20411386 DOI: 10.1007/s00268-010-0586-1]

60 **Abrahamsson H**. Severe gastroparesis: new treatment alternatives. *Best Pract Res Clin Gastroenterol* 2007; **21**: 645-655 [PMID: 17643906]

61 **Lacy BE**, Zayat EN, Crowell MD, Schuster MM. Botulinum toxin for the treatment of gastroparesis: a preliminary report. *Am J Gastroenterol* 2002; **97**: 1548-1552 [PMID: 12094882 DOI: 10.1111/j.1572-0241.2002.05741.x]

62 **Lacy BE**, Schettler-Duncan VA, Crowell MD. The treatment of diabetic gastroparesis with botulinum toxin. *Am J Gastroenterol* 2000; **95**: 2455-2456 [DOI: 10.1111/j.1572-0241.2000.02514.x]

63 **Bromer MQ**, Friedenberg F, Miller LS, Fisher RS, Swartz K, Parkman HP. Endoscopic pyloric injection of botulinum toxin A for the treatment of refractory gastroparesis. *Gastrointest Endosc* 2005; **61**: 833-839 [PMID: 15933684 DOI: 10.1016/S0016-5107(05)00328-7]

64 **Arts J**, van Gool S, Caenepeel P, Verbeke K, Janssens J, Tack J. Influence of intrapyloric botulinum toxin injection on gastric emptying and meal-related symptoms in gastroparesis patients. *Aliment Pharmacol Ther* 2006; **24**: 661-667 [PMID: 16907899 DOI: 10.1111/j.1365-2036.2006.03019.x]

65 **Coleski R**, Anderson MA, Hasler WL. Factors associated with symptom response to pyloric injection of botulinum toxin in a large series of gastroparesis patients. *Dig Dis Sci* 2009; **54**: 2634-2642 [PMID: 19184429 DOI: 10.1007/s10620-008-0660-9]

66 **Coleski R**, Hasler W. Clinical and gastric functional predictors of symptom response to pyloric injection of botulinum toxin in patients with gastroparesis. *Neurogastroenterol Motil* 2005; **17**: 628A

67 **Arts J**, Holvoet L, Caenepeel P, Bisschops R, Sifrim D, Verbeke K, Janssens J, Tack J. Clinical trial: a randomized-controlled crossover study of intrapyloric injection of botulinum toxin in gastroparesis. *Aliment Pharmacol Ther* 2007; **26**: 1251-1258 [PMID: 17944739]

68 **Friedenberg FK**, Palit A, Parkman HP, Hanlon A, Nelson DB. Botulinum toxin A for the treatment of delayed gastric emptying. *Am J Gastroenterol* 2008; **103**: 416-423 [PMID: 18070232 DOI: 10.1111/j.1572-0241.2007.01676.x]

69 **Saridena PR**, Saridena RA, Sarosiek I. Is total gastrectomy a good option for refractory gastroparesis? One site experience. *Am J Gastroenterol* 2008; **103**: A147

70 **Forstner-Barthell AW**, Murr MM, Nitecki S, Camilleri M, Prather CM, Kelly KA, Sarr MG. Near-total completion gastrectomy for severe postvagotomy gastric stasis: analysis of early and long-term results in 62 patients. *J Gastrointest Surg* 1999; **3**: 15-21, discussion 21-23 [PMID: 10457319 DOI: 10.1016/S1091-255X(99)80003-1]

71 **Jones MP**, Maganti K. A systematic review of surgical therapy for gastroparesis. *Am J Gastroenterol* 2003; **98**: 2122-2129 [PMID: 14572555 DOI: 10.1111/j.1572-0241.2003.07721.x]

72 **Watkins PJ**, Buxton-Thomas MS, Howard ER. Long-term outcome after gastrectomy for intractable diabetic gastroparesis. *Diabet Med* 2003; **20**: 58-63 [PMID: 12519321]

73 **Sodhi SS**, Guo JP, Maurer AH, O'Brien G, Srinivasan R, Parkman HP. Gastroparesis after combined heart and lung transplantation. *J Clin Gastroenterol* 2002; **34**: 34-39 [PMID: 11743243 DOI: 10.1097/00004836-200201000-00007]

74 **Nguyen LB**, Parker S, Snape WJ. Is pyloroplasty a surgical option in the treatment of refractory gastroparesis? *Gastroenterology* 2007; **132**: M1151.4Abstract

75 **Hibbard ML**, Dunst CM, Swanström LL. Laparoscopic and endoscopic pyloroplasty for gastroparesis results in sustained symptom improvement. *J Gastrointest Surg* 2011; **15**: 1513-1519 [PMID: 21720926 DOI: 10.1007/s11605-011-1607-6]

76 **Sarosiek I**, Forster J, Lin Z, Cherry S, Sarosiek J, McCallum R. The addition of pyloroplasty as a new surgical approach to enhance effectiveness of gastric electrical stimulation therapy in patients with gastroparesis. *Neurogastroenterol Motil* 2013; **25**: 134-e80 [PMID: 23113904 DOI: 10.1111/nmo.12032]

77 **Li JL**, Li M, Pang B, Zhou Q, Zhao XY, Liu HX, Tian JX, Tong XL. "Combination of symptoms, syndrome and disease": Treatment of refractory diabetic gastroparesis. *World J Gastroenterol*; In press

78 **Qian Q**, Chen W, Yue W, Yang Z, Liu Z, Qian W. Antiemetic effect of Xiao-Ban-Xia-Tang, a Chinese medicinal herb recipe, on cisplatin-induced acute and delayed emesis in minks. *J Ethnopharmacol* 2010; **128**: 590-593 [PMID: 20097280 DOI: 10.1016/j.jep.2010.01.027]

79 **Xu XY**, Lian JW. The impact of Xiao-Banxia-Tang on motilin in mice. *Guoyi Luntan* 2002; **17**: 45-46

80 **Nie K**, Ma SQ. The therapeutic effect of Xiao-Banxia-Tang on chemotherapy allotriophagia in mice. *Zhongyao Yaoli Yu Linchuang* 2007; **23**: 32-33

81 **Gupta YK**, Sharma M. Reversal of pyrogallol-induced delay in gastric emptying in rats by ginger (Zingiber officinale). *Methods Find Exp Clin Pharmacol* 2001; **23**: 501-503 [PMID: 11876024 DOI: 10.1358/mf.2001.23.9.662137]

82 **Gonlachanvit S**, Chen YH, Hasler WL, Sun WM, Owyang C. Ginger reduces hyperglycemia-evoked gastric dysrhythmias in healthy humans: possible role of endogenous prostaglandins. *J Pharmacol Exp Ther* 2003; **307**: 1098-1103 [PMID: 14534370 DOI: 10.1124/jpet.103.053421]

83 **Yuan MZ**. Clinical Experience from Tong Xiao-Lin in treating diabetic vomiting with Pinellia. *Shandong Zhongyi Zazhi*

2012; **31**: 762-763
84 **Li JL**, Zhou Q, Pang B, Li M, Tian JX, Tong XL. The experience of treatment on diabetes combined with vomiting by Professor Tong Xiao-Lin. *Liaoning Zhongyi Zazhi* 2013; **40**: 1-3
85 **Li H**. 34 cases of syndrome differentiation and treatment variation on intractable hyperemesis gravidarum. *Shaanxi Zhongyi* 2011; **32**: 1454-1455
86 Zhang JF. Su Ye Huang Lian Tang treated on severe gastrointestinal side effects caused by interferon. *Shaanxi Zhongyi Xueyuan Xuebao* 2007; **30**: 33
87 **Deng WJ**. Modified Su Ye Huang Lian Tang in treating 15 patients with chronic renal failure. *MudanjiangYixueyuan Xuebao* 1998; **19**: 84-85
88 **Liu GF**, Zhao JB, Zhen Z, Sha H, Chen PM, Li M, Zhang JC, Yuan MZ, Gao W, Gregersen H, Tong XL. Effect of tangweian jianji on upper gastrointestinal remodeling in streptozotocin-induced diabetic rats. *World J Gastroenterol* 2012; **18**: 4875-4884 [PMID: 23002359 DOI: 10.3748/wjg.v18.i35.4875]
89 **Zhou LB**, Li BZ, Zhang JQ, Tong XL. Case examples of treatment with Fuzi Lizhong Decoction applied by Professor Tong Xiao-Lin. Collection of papers in the 12th National Diabetic Conference on TCM: 311-314
90 **Ezzo J**, Streitberger K, Schneider A. Cochrane systematic reviews examine P6 acupuncture-point stimulation for nausea and vomiting. *J Altern Complement Med* 2006; **12**: 489-495 [PMID: 16813514 DOI: 10.1089/acm.2006.12.489]
91 **Ouyang H**, Yin J, Wang Z, Pasricha PJ, Chen JD. Electroacupuncture accelerates gastric emptying in association with changes in vagal activity. *Am J Physiol Gastrointest Liver Physiol* 2002; **282**: G390-G396 [PMID: 11804862 DOI: 10.1152/ajpgi.00272.2001]
92 **Wang CP**, Kao CH, Chen WK, Lo WY, Hsieh CL. A single-blinded, randomized pilot study evaluating effects of electroacupuncture in diabetic patients with symptoms suggestive of gastroparesis. *J Altern Complement Med* 2008; **14**: 833-839 [PMID: 18721079 DOI: 10.1089/acm.2008.0107]
93 **Kim KH**, Kim TH, Choi JY, Kim JI, Lee MS, Choi SM. Acupuncture for symptomatic relief of gastroparesis in a diabetic haemodialysis patient. *Acupunct Med* 2010; **28**: 101-103 [PMID: 20466737 DOI: 10.1136/aim.2009.002204]
94 **Yu Y**, Yang Y. One case: combination of traditional Chinese and Western medicine in treatment of severe diabetic gastroparesis. *Zhongguo Zhongyiyao Xiandai Yuancheng Jiaoyu* 2011; **9**: 84
95 **Ma YJ**. Clinical observation on severe diabetic gastroparesis. *Zhongguo Shiyong Yiyao* 2011; **6**: 114-115

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