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Review Article

NEW PROGRESS IN THE TREATMENT OF GASTROPARESIS

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ABSTRACT

Gastroparesis (Gp) is a gastric dysmotility syndrome characterized by delayed gastric emptying after removing organic obstruction of the gastric outflow tract. The clinical symptoms are nausea, vomiting, early satiety, abdominal pain, and upper abdominal fullness sense. The causes of gastroparesis are various, and its common causes are idiopathic, diabetes, and abdominal surgery. At present, it is widely believed that the etiology of gastroparesis is related to damage of interstitial cells of Cajal and macrophage-mediated immune infiltration. The treatment of gastroparesis is mainly aimed at enhancing gastric motility, accelerating gastric emptying, and alleviating symptoms of patients, and drugs with a fast curative effect and few adverse effects are lacking. Gastric electrical stimulation (GES) and gastric peroral endoscopic myotomy (G-POEM) have achieved favorable clinical results, providing new directions for the treatment of refractory gastroparesis. In this review, we discussed the new treatment programs of gastroparesis by Western medicine and traditional Chinese medicine and the current status of treatment of refractory gastroparesis with gastric electrical stimulation and gastric peroral endoscopic myotomy. we also explored new treatment methods for Gp, such as stem cell transplantation technology and immunotherapy.

Key words: Gastroparesis; etiology; diagnosis; gastric motility drugs; traditional Chinese medicine treatment; gastric electrical stimulation; gastric peroral endoscopic myotomy.

INTRODUCTION

Gastroparesis（Gp） is a gastric dysmotility syndrome characterized by delayed gastric emptying after removing organic obstruction of the gastric outflow tract. The clinical symptoms are nausea, vomiting, early satiety, abdominal pain, and upper abdominal fullness sense [1-3]. Experiments by William Hirsch and others showed that the number of emergency department visits and related costs for the initial diagnosis of Gp (with or without secondary diabetes) increased significantly from 2006 to 2013. The number of emergency visits for Gp increased from 15,459 times in 200,6 to 36 820 times in 2013, an increase of 138%; the total cost related to admission increased from $ 286 million to $ 592 million, an increase of 107%[3]. Another epidemiological survey showed that women are more likely to suffer from Gp than men. In 2007, the age-adjusted prevalence of definite Gp per 100,000 people was 9.6 for men and 37.8 for women[1]. A community survey by Enrique showed that 1.8% of community subjects had delayed gastric emptying, but only 0.02% of the subjects were diagnosed, indicating that many patients with Gp may remain undiagnosed[4]. This shows that Gp increases the burden of social medical resources and has posed a serious threat to our physical and mental health.

In recent years, with the research on gastric physiology, animal models and tissue biopsy of patients with Gp, we have gained a new understanding of the etiology and pathogenesis of Gp, and we have also made great breakthroughs in treatment. However, there is still a lack of fast, effective, and safe drugs for the treatment of Gp, and some patients with refractory Gp have not improved their symptoms after treatment with drugs and surgery. Therefore, we must make further investigations on the treatment of Gp[5].

In this review, firstly, we reviewed the various causes of Gp and related experimental studies for the diagnosis of Gp. Secondly, we discussed the treatment programs related to Gp with Western medicine and traditional Chinese medicine and the new progress of surgical treatment for refractory Gp in recent years. Finally, we explored new treatment methods for Gp, such as stem cell transplantation technology and immunotherapy.

Etiology of Gastroparesis

The causes of Gp are various (Table 1), the most common ones are idiopathic gastroparesis (IGP), diabetic gastroparesis (DGP), and postoperative gastroparesis (PGS). According to the epidemiological study of Jung HK et al. in Olmsted County, Minnesota, from 1996 to 2006, among the 83 diagnosed patients with Gp, IGP accounted for 49.4%, DGP accounted for 25.3%, drug causes (psychotropic drugs) accounted for 22.9%, connective tissue disease accounted for 10.8%, PSG accounted for 7.2%, and malignant tumors (familial adenomatous polyposis and Myeloproliferative leukemia) accounted for 2.4%[3]. In recent years, we have a more profound understanding of the pathogenesis of Gp, from unknown causes to gastrointestinal nerve damage, gastrointestinal smooth muscle lesions, damaged interstitial cells of Cajal (ICC), and immune infiltration. This provides a direction for us to study the treatment of gastroparesis. Next, we will describe the pathogenesis of Gp from different causes.

IGP is a common but poorly understood disease. Among patients with Gp, the proportion of IGP is the largest. In a clinical study of 243 patients with IGP, 88% of the patients were female, 46% were overweight, 50% had acute symptoms, 19% have reported pre-infection symptoms, and 36% had severe anxiety. It indicates that the occurrence of IGP may be related to gender, weight, infection, and mental state[6].

DGP is a common complication of diabetic patients. According to reports in the literature, more than 50% of diabetic patients are accompanied by Gp, and it is the most common type 2 diabetic patients[7]. At present, it is mainly believed that the pathogenesis of DGP is related to factors such as autonomic neuropathy, gastrointestinal hormone disorders, gastric tissue cell disease, and blood glucose levels[8]. A Mayo Clinic study showed that most of the patients with Gp can observe ICC cell reduction, macrophage infiltration, autonomic neuropathy, and smooth muscle fibrosis, but macrophage infiltration and ICC reduction are most common[9]. We also found macrophage infiltration in the gastric tissue of diabetic gastroparesis mice. An imbalance in the proportion of M1 type and M2 type macrophages was detected, the gene expression of M1 type macrophages (pro-inflammatory macrophages) increased, and the expression of M2 type macrophages (anti-inflammatory macrophages) decreased. The reduction of M2 macrophages may be related to the reduction of HO-1 upregulation, which may be a new direction for the treatment of Gp[10].

PGS usually occurs after abdominal surgery. Upper abdominal surgery is the most common, such as cryoablation of pancreatic cancer (50%-70%), pancreaticoduodenectomy (5.1%), and gastrectomy (0.4-5.0%)[11]. It is currently believed that vagus nerve injury is an important cause of postoperative gastroparesis. The damage of the vagus nerve leads to weakened gastric motility, which affects gastric emptying. Neuro-chemical factors, inflammatory reactions, opioid anesthetics, hypotension and vasoconstriction drugs, electrolyte imbalances, radiofrequency ablation, and other factors are also considered to have important reasons for the occurrence of postoperative gastroparesis[12-15]. Some scholars believe that the retrograde slow-wave propagation across the anastomotic scar is also a cause of postsurgical gastric dysfunction, but how to produce aberrant anastomotic conduction needs further research and confirmation[16].

Common causes	Idiopathic, diabetes, and post-abdominal surgery
Other causes	Connective tissue disease, mesenteric ischemic disease, malignant tumors (familial adenomatous polyposis and Myeloproliferative leukemia), nervous system diseases (including Parkinson's disease), eating disorders, metabolic/endocrine diseases, drugs (e.g. anticholinergics, calcium channel antagonists, and opioids)

Table 1: Causes of gastroparesis

Diagnosis of Gastroparesis:

Diagnosis of Gp: Firstly, combine the patient's clinical symptoms, such as nausea, vomiting, early feeling of fullness, abdominal pain, abdominal distension, and other discomforts. Secondly, exclude gastrointestinal mechanical obstruction by gastroscope or barium meal. Finally, a qualitative examination of

delayed gastric emptying is performed. There are three tests to objectively demonstrate delayed gastric emptying: scintigraphy, wireless motility capsule, and breath testing. The scintillation scan is the gold standard for diagnosing delayed gastric emptying. For solid-phase testing, most centers use 99mTc sulfur colloid-labeled egg sandwiches as the test meal, and standard imaging is performed at 0, 1, 2, and 4 hours. At present, the gastric emptying scintillation scan is an internationally recognized gold standard for the diagnosis of gastric emptying disorders. It can be diagnosed as gastric emptying disorders if the retention is greater than 10% in 4 hours. Before doing the gastric emptying barrier test, we must stop all drugs that affect gastrointestinal motility 48-72 hours ago, and control blood sugar below 275 mg/dl[17]. wireless motility capsule and breath testing have been used for clinical diagnosis of Gp. Compared with the radionuclide scintillation scan, the advantages are shorter time, lower cost, and safer, but the accuracy is lower than the radionuclide scintillation scan. The clinical trials further proved[18, 19].

Recently Bonta et al. proposed a new standard, suggesting that 2h gastric retention >65% for emptying delay, <40% for normal emptying, before measuring the 4h gastric retention rate between the two. To this end, a multi-center cohort study was carried out. Compared with the gold standard, the accuracy reached 95.8%. Using the Bonta standard shortened the study time of most patients. An effective compromise has been reached between reducing resource use, improving patient convenience, and maintaining accuracy[20].

DISCUSSION AND RESULT

The current treatment of Gp is mainly to enhance the peristalsis of the stomach, accelerate gastric emptying, and relieve the symptoms of patients. Gp treatment is divided into general treatment and targeted treatment. The general treatment is mainly to adjust the diet, correct electrolyte disorders, supplement nutrition, and control blood sugar. Psychological intervention is also a very important treatment method for patients with Gp[17, 21]. Targeted treatment includes drug therapy and surgical treatment. Drug therapy is the preferred treatment for patients with gastroparesis. Currently, the most commonly used drugs for the treatment of Gp are gastric motility drugs and antiemetic drugs. However, for patients with refractory gastroparesis who have a diet adjustment of more than 6 months and a maximum tolerated gastric motility drug response, a suitable surgical plan can be selected, such as gastric electrical stimulation, most or total gastric resection, and Endoscopic surgery for pylorus.

Drug therapy:

Targeted treatment includes drug therapy and surgical treatment. Drug Commonly used gastric motility drugs include dopamine receptor antagonists[22-28], motilin receptor antagonists[29-32], 5-HT4 receptor antagonists[33-36], and ghrelin receptor agonists[37-41], etc (Table 2). Metoclopramide is a dopamine D2 receptor antagonist. It is the only drug approved by the US FDA for the treatment of Gp. It is the first choice for the clinical treatment of Gp. It is also a 5-HT3 receptor antagonist and 5-HT4 receptor agonist, which has the dual effects of suppressing vomiting and promoting gastric motility, but the long-term application can cause irreversible delayed dyskinesia, so the recommended time limit is 12 weeks. Parkman

reported the safety and effectiveness of metoclopramide nasal spray and conventional oral tablets in the treatment of DGP. The results showed that at week 6 nasal spray 10mg (QID) for TSS (total symptom score) Is significantly better than oral tablets 10mg (QID) and has fewer side effects than oral tablets. The emergence of metoclopramide spray brings hope to the treatment of many patients who are difficult to take oral drugs due to nausea and vomiting[23]. A Mate analysis by Al-Saffar indicated that the risk of metoclopramide for delayed dyskinesia is less than 0.1%, which is lower than the estimated 1%-10% in the guidelines. Delayed disorders are more likely to occur after taking metoclopramide in elderly women, diabetic patients, patients with liver or kidney failure, and patients receiving concurrent antipsychotic medication[25].

In recent years, ghrelin receptor agonist relamorelin has been tested for clinical treatment of gastroparesis, and relamorelin has a powerful prokinetic effect. In clinical research, relamorelin is about 15-130-fold more potent than human ghrelin of promoting gastric motility, which seems to bring hope to the medical treatment of Gp[38]. In Phase I clinical trials, it has been shown that relamorelin can increase the frequency of distal antral motility contractions without significant effects on the amplitude of contractions and does not inhibit gastric self-regulation[39]. In phase II clinical trial, relamorelin was found to significantly improve gastric emptying, nausea, postprandial fullness, abdominal pain, and bloating in patients with DGP. But compared with the control group, the frequency of vomiting was not significantly different. In the trial, the patient developed adverse effects of hyperglycemia and diarrhea after medication but did not cause the drug to stop. Phase II trials have proven the efficacy and safety of relamorelin, but further validation is needed in later clinical trials[41].

Recently, some progress is reported on immunotherapy and cell transplantation in the treatment of refractory gastroparesis. Ashat selected 14 patients who were insensitive to drugs and surgical treatment and received at least 12 weeks of immunoglobulin injection (dose: 400mg/kg.w). After 12 weeks, all patients had a significant decrease in upper gastrointestinal symptoms and no adverse reactions were found, which proves that immunotherapy is feasible in the treatment of refractory gastroparesis. unfortunately, the experiment did not set up a control group[5]. Dadhic injected enteric nerve precursor cell (NPC) and Cajal interstitial cells (ICC) into an in vitro model of neuromuscular pyloric dysfunction in which NPC and ICC were missing. Isolated pyloric tissue restored neuromuscular function. This provides the possibility for stem cell transplantation to treat Gp [42].

Drugs	Mechanism	Gastric emptying	Effect on nausea and vomiting	Adverse reactions
metoclopramide	Dopamine D2 receptor antagonist, 5HT3 receptor antagonist, 5HT4 receptor agonist activity	acceleration	inhibition	tardive dyskinesia (<1%), extrapyramidal reactions, hyperprolactinemia, depression
domperidone	dopamine D2 receptor antagonist	acceleration	not obvious	Q-T interval prolongation, cardiac arrhythmia
Erythromycin, Azithromycin	Motilin receptor agonist	acceleration	inhibition	Drug resistance, prolonged QT interval, allergic reaction
Mosapride, revexepride, Prucalopride	5-HT4receptor agonists	acceleration	inhibition	Q-T interval prolongation
relamorelin	Ghrelin receptor agonist	acceleration	no effect	Increased blood sugar, diarrhea

Table 2: Gastric motility drugs classification

Traditional Chinese medicine treatment:

At present, there is no ideal treatment for Gp in Western medicine, but Chinese medicine has achieved a certain effect in the treatment of DGP. Chinese medicine believes that Gp is caused by the "weakness of the spleen and stomach". The main treatments include TCM syndrome differentiation, acupuncture, massage, acupoint application, etc. Professor Tong Xiaolin believes that DGP can be divided into an acute phase and a remission phase. The acute phase is treated symptomatically with Xiaobanxia decoction; the remission phase is treated with Sijunzi decoction[43]. Luo Xiaoqin reported on the effect of electroacupuncture on the gastrointestinal digestive function of rats. Acupuncture was performed on the "Zusanli" and "Taichong" acupoints in mice for 14 consecutive days. In the experimental group, the gastric emptying, small intestinal motility, and gastrin of the gastric antrum increased significantly, and the concentration of somatostatin decreased[44]. A randomized controlled trial by Chen Jun showed that acupuncture at Zusanli, Sanyinjiao, and other acupuncture points can treat PGS. On the 14th day, the experimental group observed gastric emptying, serum gastrin, and motilin concentrations increased significantly than before, and the patient's symptoms improved significantly[45]. Gu Jinghui's reported on the effect of Jianpixiaoji Chinese Herbs on DGP and motilin and gastrin levels. In the experimental group, Mosapride combined with Jianpixiaoji Chinese medicine was used

to treat DGP for 4 weeks. Compared with the control group, the patient's symptom score decreased, gastric emptying accelerated, and the levels of motilin and gastrin decreased[46]. These experiments indicate that electroacupuncture and Chinese medicine may improve gastrointestinal function through gastric emptying, gastrin, and somatostatin. In the treatment of 46 patients with PGS, metoclopramide was randomly divided into acupoint injection and intramuscular injection, and another 60 cases of DGP treatment were randomly divided into the acupuncture group and domperidone group. Experimental results have shown that acupuncture point injection is more effective than oral administration and has fewer side effects[47, 48]. Compared with Western medicine, traditional Chinese medicine has achieved certain effects in the treatment of DGP, and it has the advantages of non-invasive, cheap, less adverse reactions, and can significantly relieve symptoms in a short time. However, there is a lack of clinical research on big data and the mechanism of action of drugs. Its clinical application promotion and mechanism research need to be further improved. The integration of Chinese and Western medicine may be a potential method for the treatment of DGP in the future, which requires further exploration[49].

GES:

Entera was approved by the Federal Drug Administration (FDA) as a humanitarian device exemption in patients with chronic intractable (refractory) nausea and vomiting of diabetes or idiopathic gastroparesis in 2000[50]. GES began to be widely used in the clinical treatment of refractory gastroparesis. GES has two stimulation methods: (1) low-frequency stimulation or gastric pacing, which mainly promotes gastric emptying; and (2) high-frequency, low-energy gastric stimulation, which mainly improves upper gastrointestinal symptoms, but has little effect on gastric slow waves and gastric emptying. The latter is used in the clinical treatment of refractory gastroparesis[50, 51].

GES has been used clinically for more than 20 years, and its therapeutic effect is certain. Fred B et al. followed up for 8 years after the operation of 79 patients implanted with GES and carried out clinical symptoms such as nausea, vomiting, abdominal pain, upper abdominal fullness, early fullness, and upper abdominal fullness. According to the analysis of total symptoms (TSS), the TSS of 52 patients has been significantly improved, but the onset time is relatively long, usually from 6 months to 9 months. Over time, the efficacy may gradually increase[52]. Many clinical trials have shown that GES mainly reduces the frequency of nausea and vomiting in patients with refractory gastroparesis, and it also has a significant improvement in pain and quality of life[52-58]. A Mate analysis shows that GES is better than IGP and PSG for DGP[54]. In another clinical trial, the effect of GES on IGP and type 1 DGP was the most obvious by observing the change of cervical compound nerve action potential (CNAP)[58].

Although GES is currently a common surgical treatment for refractory gastroparesis, its specific mechanism of action is still unclear. At present, only GES can be observed to enhance the efferent activity of the vagus nerve, but it is not clear how to improve the symptoms of gastroparesis. There are the following conjectures: 1. The pulse of GES is transmitted to the subthalamic nucleus (STN), and then projected to the thalamus through the network structure, which has an inhibitory effect on the control mechanism of nausea

and vomiting; The sensitivity of swelling, thereby enhancing the gastric regulation function after meals, thereby improving the symptoms of GP; 3. Promoting pancreatic exocrine, mainly pancreatic elastase and pancreatic polypeptide, thereby reducing the symptoms of patients[54, 58-60].

At present, GES still has many problems to be solved in the treatment of refractory gastroparesis. Firstly, at present, the optimal GES parameters for the treatment of special symptoms of refractory gastroparesis are still unclear, and the mechanism of its treatment is also unclear[58]. Secondly, according to current clinical trials, the onset of GES is slow, usually 6 months, and cannot quickly improve the patient's symptoms[52]. Thirdly, the service life of the gastric electrical stimulator in the body is usually about 5 years, then we need to perform a second operation to replace the stimulator[52]. Finally, the risk rate of infection, skin erosion, pain at the implantation site, and device displacement is 8.3% due to the implantation of gastric electrical stimulator and electrodes in the body[52, 61].

G-POEM:

In recent years, with the rapid development of endoscopy, endoscopic techniques have been used for the treatment of refractory gastroparesis, such as botulinum toxin injection, pyloric balloon dilatation, pyloric stent placement, and gastric peroral endoscopic myotomy (G-POEM)[62]. Gastric tissue biopsy of patients with gastroparesis of different causes found pyloric fibrosis and pyloric spasm. Endoscopic treatment is based on this pathophysiological change to treat refractory gastroparesis [63, 64].

G-POEM is a new endoscopy method based on the principle of the submucosal tunnel. Its appearance brings new directions to the treatment of patients with refractory gastroparesis. In a meta-analysis of 272 patients, it was found that its short-term efficacy and safety are very objective, and the total clinical effective rate was 84% after 12 months of observation. The improvement rate of gastric emptying reached 84% and the normal rate of gastric emptying reached 53%, but the incidence of postoperative adverse events also reached 14%[65]. Another meta-analysis also reported a similar view, with 83.9% of patients having significantly improved postoperative symptoms[66]. From the short-term safety and efficacy results, G-POEM is feasible and safe for the treatment of refractory gastroparesis and has potential first-line treatment value for some patients. Abdelfatah's long-term observation of G-POEM showed that 6 months (n=48), 12 months (n=32), 24 months (n=21) and 36 months (n=16) after GPOEM operation), their quality of life improvement rates were 73%, 65%, 51% and 45%. Its efficacy declines as the symptoms of gastroparesis continue, and experiments have also found that high BMI, taking psychotic drugs, and analgesics will reduce the efficacy of G-POEM[67].

The short-term efficacy of G-POEM is unquestionable, but its long-term efficacy needs further study. The incidence of abdominal pain, perforation, bleeding, and other adverse events after G-POEM operation reached 6%-19%. The longitudinal direction of the mucosal incision, the use of a hook knife, the use of a mucosal closure clip, and an experienced endoscopist can reduce the occurrence of such adverse risks[65, 68]. Although G-POEM is a promising GP method in terms of short-term efficacy, the indications for pyloric endoscopic therapy have not been clearly defined. There is currently no method for diagnosing pyloric spasm.

Pyloric dilatation measurement (Endoflip technique) may be a promising diagnostic method for evaluating the pyloric function and identifying gastroparesis with pyloric dysfunction, but further proof is required[62, 69].

CONCLUSIONS

In recent years, because of the establishment of animal models of Gp and the study of tissue biopsy of patients with Gp, we have made great progress in the treatment of Gp. However, at present, the clinical treatment is still based on the relief of symptoms, and there is still no drug discovery with fast efficacy and little side effects. The combination of traditional Chinese and western medicine has brought good results in the treatment of Gp, but its mechanism of action and adverse reactions of long-term treatment are not clear. Exploring new treatment methods for Gp, such as immunotherapy and cell transplantation technology, may bring new hope for the treatment of gastroparesis. G-POEM can achieve a curative effect in a short period during surgery, which gives us hope, but the long-term curative effect is not good. GES therapy has a slow onset and good long-term effects. In the future, we can combine the two to treat refractory gastroparesis. Perhaps only when the mechanism of gastroparesis can be fully explained can this disease be completely overcome.

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