



Diabetic gastroparesis: what can complementary and alternative medicines do?

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Abstract: Diabetic gastroparesis (DGP) is a complication of long-standing diabetes mellitus (DM) and a chronic motility disorder of the stomach. Up to 50% of patients with type 1 and 2 DM have the gastrointestinal manifestations, especially delayed gastric emptying (GE). And DM accounted for almost one-third of all cases of gastroparesis. The most common symptoms of DGP include postprandial fullness, early satiety, nausea, vomiting, bloating, and abdominal pain, which markedly lead to poor quality of life. Therapeutic strategies in western medicine for DGP involve dietary modification, the control of blood glucose, medications that stimulate gastric motor activity, anti-emetic and prokinetic drug therapy, and nonpharmacological measures. However, the limited effectiveness and the side effects of the strategies above mentioned may be restricted for their applications sometimes. Complementary and alternative therapy like Chinese herbs, acupuncture, moxibustion, and massage has been widely used for thousands of years and there are an increasing number of studies in DGP about them, suggesting that Chinese medicine could bring multiple benefits in the treatment of refractory nausea and vomiting and also help to alleviate abdominal distension with fewer side effects. Here, we focus on the general treatment strategies of complementary and alternative therapy, as discovered through PubMed and CNKI in English and Chinese publications, respectively.

Keywords: Diabetic gastroparesis (DGP); complementary and alternative therapy; traditional Chinese medicine (TCM); acupuncture

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Introduction

Diabetic gastroparesis (DGP), as a complication of long-standing diabetes mellitus (DM) and a chronic motility disorder of the stomach, has become more common for the high prevalence of the glucometabolism disorder. The percentage of DGP in patients with type 1 and 2 DM is up to 50%, and DM accounted for almost one-third of all cases of gastroparesis (1). The most common symptoms of DGP include postprandial fullness, early satiety, nausea, vomiting,

bloating, and abdominal pain, which markedly lead to poor quality of life, and the concomitant anxiety and/or depression are also disturbing half of the patients with DGP. Some people may even demonstrate refractory DGP, such as severe, persistent nausea and vomiting, resulting in malnutrition, dehydration, electrolyte disturbances, poor glycemic control, diabetic ketoacidosis, and increased healthcare utilization (2,3). The increasing frequency of emergency department visits and/or high hospitalization

rates undoubtedly lead to a heavy economic burden on the health care system (4,5).

The characteristics of the DGP in physiopathology is the delayed gastric emptying (GE), which can be documented with scintigraphy, the criterion standard and the most widely used method (>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), a wireless motility capsule or 13 C-breath tests (6,7). And scintigraphy is the best way to assess GE and is becoming the criterion standard and the most widely used method. When results from tests of GE are inconclusive, measurements of gastric accommodation, such as single-photon emission computed tomography (SPECT) or MRI, are also showed. However, for the demand for specialized laboratories and radiation exposure in scintigraphy testing, it is not flexible for every patient to accept the method. Usually, the gastroparesis is based on clinical judgment rather than established criteria in practice. Therefore, gastroparesis cardinal symptom index (GCSI) has also been introduced for quantifying the severity and characteristics of gastroparesis symptoms reported by patients, which can be reflected more subjectively. And the GCSI has been reported showing excellent reliability and validity (8).

Pathogenesis and treatment in western medicine

The pathogenesis of DGP has been related to hyperglycemia, autonomic neuropathy, and enteric neuromuscular inflammation. The disordered metabolism and hormonal disturbances caused by DM may also contribute to impaired gastric tonicity and antral contractions (6). Autonomic neuropathy dysfunction has been proved as the major mechanism for DGP (9). More recently, there is emerging evidence for disturbances in the enteric nervous system (i.e., enteric neurons and ICC) and smooth muscle myopathy (10). Although there have been advances in understanding the mechanisms and pathophysiology of DGP, there are still substantial gaps in knowledge. Therefore, individualization of therapy is currently best achieved by carefully identifying functional impairment rather than cellular mechanisms.

Focusing on delayed GE, the cardinal pathophysiological process in DGP, the therapeutic strategies involves dietary modification, glycemic control, medications that stimulate gastric motor activity, antiemetic drug therapy, and nonpharmacological measures such as endoscopic or

surgical intervention or gastric electrical stimulation (11). However, the effectiveness of the strategies above mentioned may be limited and may be restricted for their side effects sometimes.

Complementary and alternative therapy

Complementary and alternative therapy like Chinese herbs, acupuncture, moxibustion, and massage has been widely used for thousands of years and there are an increasing number of studies in DGP, suggesting that Chinese medicine could bring multiple benefits in the treatment of refractory nausea and vomiting and also help to alleviate abdominal distension with fewer side effects. Here, we focus on the general treatment strategies of complementary and alternative therapy, as discovered through PubMed and CNKI in English and Chinese publications, respectively.

Traditional Chinese medicine (TCM)

In TCM, DGP belongs to the painful abdominal syndrome, vomiting, and flaccidity of the stomach. Perennial diabetes or poor glycemic control may cause injury of the “qi” of spleen and stomach, resulting in dysfunction of the two organs in transformation and transportation, and what’s more, when earth is deficient, wood tends to become excessive, which may further bring about transverse attack of the liver-qi, leading to disorder of qi in descending and ascending, hence the appearance of DGP. The weakness of the spleen and stomach is the essential aspect of the disease, while stagnation of qi and reversed the flow of qi in the middle-jiao the superficial aspect. Therefore, it should be treated by regulating the flow of qi and promoting the function of the spleen and stomach (12). One of the most widely used decoction is Xiangshaliujunzi Decoction (XSLJZD), containing eight commonly used herbs (Panax ginseng, Rhizoma atractylodis macrocephalae, Poria, Radix glycyrrhizae, Pericarpium citri reticulatae, Pinellia tuber, Fructus amomi, and Radix Aucklandiae) for its function of tonifying qi and the spleen. XSLJZD has also been reported for its clinical evidence of the effectiveness in treating DGP. Tian *et al.* (13) in a systematic review, ten RCTs involving 867 patients, reported that XSLJZD could improve the GE rate and alleviated diabetic gastrointestinal symptoms, and could, therefore, be considered as an alternative method for the treatment of DGP.

Professor Lv (14) believes that the problem of DGP is mainly in the stomach, but it is most closely related to

the spleen. Spleen deficiency is the origin of DGP, and pathological products such as phlegm, blood stasis, and excessive fluid are also crucial factors in the pathogenesis of DGP. So deficient root and excessive superficiality are the characteristics of the DGP pathogenesis. So, Professor Lv thinks that there are three types of the syndrome in DGP: spleen deficiency with dampness retention, liver-stomach disharmony, and lack of stomach yin. The prescriptions mainly include XSLJZD, Chaihu Shugan powder, Maimendong decoction combined Zengye decoction.

Professor Nie (15) preferred to using the Banxia Xiexin Decoction (BXXXD) originated from the famous Shanghanlun work in treating functional gastrointestinal disease. And she firstly composed some new decoction such as Shuyu Xiexin decoction, Shengqing Xiexin decoction, and Jiangni Xiexin decoction, basing on the BXXXD. Shuyu Xiexin decoction is composed of BXXXD and Sini powder. It is adopted usually in the DGP related intensively with the sentiment, which may result from liver-qi depression in TCM. And the Shengqing Xiexin decoction consisted of BXXXD and Tongxie Yaofang decoction. DGP patients proving severe diarrhea are the ideal persons to apply the Shengqing Xiexin decoction. It is good at harmonizing the spleen and stomach, elevating clear qi to lower turbid qi. BXXXD plus Flos Inulae and semen perillae acutae are the Jiangni Xiexin Decoction. Professor Nie thought that Jiangni Xiexin Decoction is effective, especially for persistent vomiting in DGP patients. It has the effect of the soothing liver and harmonizing stomach and inversing phlegm reduction.

Professor Tong proposed the thought of a “combination of symptom, syndrome, and disease” as a treatment guide for refractory DGP (16). He thought that the main aim of treatment for DGP patients is to relieve symptoms, such as recurrent nausea, vomiting, and fullness. Because the main symptoms are viewed as the fundamental factors in syndrome differentiation, the principal prescription should be related to the main symptoms (16,17). Xiaoban Xiatang (consisting of Pinelliaternata and ginger) combined with Suye Huanglian Tang (consisting of perilla leaves and Rhizoma Coptidis) is prescribed, and the decoction must be taken in small doses at short intervals. Zhizhu Wan (consisting of Fructus Aurantii Immaturus and Bighead Atractylodes rhizome) was also often used as a traditional medication to relieve abdominal bloating symptoms in DGP. When the symptoms above mentioned were mostly alleviated, Professor Tong performed “syndrome differentiation.” Patients with “excessive heat of the spleen

and stomach” were treated with Dahuang-Huanglian-Xiexin-Tang (consisting of Rheum officinale and the rhizome of Chinese goldthread). Patients with “heat in the upper and cold in the lower” were treated with Xiexin-Tang (consisting of Pinellia ternata, ginger, Rhizoma Coptidis, Radix Scutellariae, Rhizoma Zingiberis, ginseng, and licorice). Patients with severe symptoms and long duration may experience “deficiency-cold of the spleen and kidney” and were given Fuzi-Lizhong-Tang (consisting of ginseng, Bighead Atractylodes rhizome, Rhizoma Zingiberis, and monkshood), and the Fuzi Lizhong decoction is viewed as a fundamental prescription that may improve immune system function. The characteristics of “diseases” and the glycemic level also need to be considered (16,17). In his retrospective analysis, a six-year study, the “combination of symptom, syndrome and disease” method could alleviate the postprandial fullness and early satiety subscale, bloating subscale and total GCSI scores were also improved. Meanwhile, the blood glucose levels improved after treatment, although the change was not significant.

Zhang *et al.* (18) observed the curative effect of Xuanfu Daizhe decoction combined with compound azimtamide enteric-coated tablets in the treatment of DGP and explored its effect on gastrointestinal hormones and gastric motility. The changes of gastrointestinal hormone levels and electrogastrogram in the Xuanfu Daizhe decoction combined with compound azimtamide enteric-coated tablets group was significantly greater than that in the azimtamide enteric-coated tablets single group. The GE rate, plasma somatostatin (SS) level, gastric antrum frequency, and amplitude, gastric electrical rhythm showed the same trade. The plasma gastrin (GAS) and gastric motility of the two groups after treatment was significantly lower than that before, and the study group was significantly lower than the control group. Therefore, Xuanfu Daizhe decoction, combined with compound azimtamide enteric-coated tablets, is effective in the treatment of DGP and can significantly regulate the level of gastrointestinal hormones and improve gastric motility.

Acupuncture treatment

Acupuncture treatment exhibited a more significant effect on improving the symptoms of DGP and showed more safety and fewer side effects. Therefore, an increasing number of studies involving acupuncture treatment in DGP have been reported in recent years. For the dysfunction of the qi of spleen and stomach is the main pathogenesis, there

are some acupuncture points such as Zusanli, Zhongwan, Weishu, mainly chosen from the spleen channel and the stomach channel for promoting the function of the spleen and stomach.

Wang (12) observed the therapeutic effects of acupuncture on DGP. Eighty cases were divided randomly into three groups. In addition to the routine treatment for diabetes, 35 cases in the treatment group were additionally treated with acupuncture (main points: Zhongwan, Zusanli, Neiguan, Gongsun, Pishu, and Weishu. Adjunct points: for incoordination between the liver and spleen, Quchi, Yanglingquan, and Taichong were added; and for weakness of the spleen and stomach, Qihai, Guanyuan, and Sanyinjiao were used), and 25 cases in the control group 1 with domperidone, while 20 cases in the control group 2 with nothing. The experiment time is 25 days. The results showed that the total effective rate in the treatment group reached 94.2%, that in the control group 1 and control group 2 were 72% and 40%, respectively. The treatment group was showing a better therapeutic effect than the other two control groups ($P < 0.05$, $P < 0.01$). And it concluded that acupuncture gave better therapeutic effects on DGP in addition to the routine treatment for controlling blood sugar.

Zhuang *et al.* (19) compared the therapeutic effects of acupuncture (the main points are Zhongwan (CV 12) and Zusanli (ST 36) and mosapride in relieving DGP in their research, and it was found that the total effective rate was 95.0% in the treatment group and 83.3% in the control group. There was also a significant difference between the two groups ($P < 0.05$), and the side effect in the treatment group was less than that in the control group.

Pan *et al.* (20) compared the clinical effectiveness of electroacupuncture (EA), monotherapy, and combination therapy involving the administration of EA and mosapride in diabetic patients with severe or mild symptoms suggestive of gastroparesis. A total of 56 patients with DGP were divided into two groups according to the GCSI score, including 33 in the mild group (GCSI score < 3.5) and 23 in the severe group (GCSI score ≥ 3.5). Patients receiving combination therapy with EA and mosapride demonstrated clinically significant improvements. Analysis of data from the mild subgroup showed that EA treatment specifically improved symptoms of nausea, vomiting, stomach fullness, excessive fullness, and bloating. They found that EA may be an option for improving mild symptoms in patients with DGP, whereas combination therapy involving EA and pharmaceuticals is required in patients with severe symptoms.

Li *et al.* (21) conducted a single-blind controlled crossover trial, 25 patients with DGP were randomly assigned to undergo 1 week of real acupuncture (RA) treatment followed by 1 week of sham acupuncture (SA) treatment, or vice versa, with a washout of 1 month in between. The acupuncture points used for RA included bilateral ST36 Zusanli, bilateral PC6 Neiguan, and CV12 Zhongwan. Before and after each intervention, gastric retention, the GCSI, fasting blood glucose (FBG), and HbA1c levels were all observed. They found that, compared with SA treatment, patients with RA treatment were associated with significantly greater reductions in gastric retention at 2 h and in GCSI score, although there were no significant differences in FBG and HbA1c levels. So 1 week of short-term manual acupuncture may be a better way to reduce gastric retention and to improve gastroparesis symptoms.

Massage treatment

Acupoint massage has been applied to improving symptoms in multiple diseases. It can improve the function of the organs by stimulating the body's meridians and acupoints. Some researchers are proving the effect of massage on DGP in recent years.

Zheng (22) conducted a study observing the effect of acupoint massage on DGP. He found that, compared with patients who used conventional Western medicine and routine care, patients treated with acupoint massage were always more effective and had shorter gastric solids emptying time. The results showed that acupoint massage could help the treatment of DGP by pressing, clicking, and acupuncture points to achieve the purpose of balancing yin and yang. In his research, the main acupoints included Feishu, Pishu, Weishu, Ganshu, Shenshu in the back and Zusanli, Gongsun, Shangjuxu, Xiajuxu and so on, which played a key role in reinforcing spleen and strengthening Qi.

In another study (23) including 136 DGP patients treatment with foot gastrointestinal reflex zone massage combined with Banxia Xiexin Decoction can effectively improve intestinal hormone secretion, enhance gastric motility, promote GE, and further improve the efficacy of western medicine.

In Liu's (24) study, they observed the effect of abdominal massage on GE time and clinical symptoms in 108 patients with DGP. They conclude that abdominal massage can effectively improve the symptoms of loss of appetite, abdominal distension, and upper abdominal pain in patients

with DGP, and the curative effect is better than western medicine (Mosapride citrate tablets).

Experimental studies

Although the mechanism of traditional Chinese medicine for treating DGP is still unclear, the current researches on the mechanism of the disease continue to emerge.

Gao *et al.* (25) summarized the national and international research on the mechanisms of acupuncture therapies for improving DGP and the pathogenesis of DGP over the past 10 years. The authors explored the mechanism of acupuncture underlying the improvement in DGP as follows: (I) the effect on autonomic nerves and neurons of the central nervous system; (II) improving restoration of the enteric nervous system; (III) the effect on Cajal interstitial cells; (IV) promoting gastrointestinal hormone disorder; (V) alleviating hyperglycemic state; (VI) the effect on gastric smooth muscle.

Liu *et al.* (26) observed the effect of point-moxibustion and electroacupuncture (EA) on gastrointestinal motility, and expression of endothelial nitric oxide synthase (eNOS) mRNA and angiotensin 2 (AT II) mRNA in gastric antrum in DGP rats, and explore the mechanism underlying improvement of DGP. “Zusanli” (ST 36), “Sanyinjiao” (SP 6), and “Liangmen” (ST 21) were chosen to be stimulated with moxibustion or EA. Both the two therapies can effectively improve gastrointestinal motility in DGP rats and promote the symptoms of delayed GE. Their mechanism may be related to the increase of eNOS mRNA expression and the decrease of AT II mRNA expression in the gastric antrum. And it has been proved that low levels of NOS can result in chronic angiopathy, and AT II may decrease the expression of eNOS mRNA. So, the moxibustion and EA may play a key role by regulating the above molecules in treating DGP.

Lin *et al.* (27) conducted a study to observe the effect of electroacupuncture (EA) on the gastric interstitial cells of Cajal (ICCs) in a rat model of DGP. They found that, compared with the model group, the gastromucosal glandular and smooth muscle cells of the EA group were more regularly arranged, with fewer vacuoles; there was an increased cellular gap and the vacuolar degeneration on the gastric walls was mild. Compared with the blank group, DGP rats showed a reduced number of gastric ICCs, altered ultrastructural morphology, and a reduced number of cell organelles, particularly mitochondria. And EA may help to reverse the various pathological changes of gastric ICCs in

rat models of DGP. In DGP, the SMCs in gastrovascular layers, circular muscle nerve cells, and ICCs show varying degrees of damage. The glands were disorderly arranged, the cellular gaps were more large, the glandular cytoplasm was reduced and lightly stained, and vacuolar degeneration was apparent, which would have strongly affected their contraction and transmission functions.

Zhang *et al.* (28) also researched the effects of electroacupuncture on the ultrastructure of ICCs and the stem cell factor-kit signal pathway of gastric antrum in DGP Rats. The expressions of c-kit receptor protein and stem cell factor (SCF) mRNA were detected in DGP rats, and they found that EA at “Zusanli” (ST 36), “Liangmen” (ST 21) and “Sanyinjiao” (SP 6), etc. It can regulate blood glucose and improve gastrointestinal emptying in DGP rats. The mechanism may be related to up-regulating SCF mRNA, repairing ICC ultrastructure, restoring the pacing function, and improving gastrointestinal motility.

In Wu’s (29) research they found that electroacupuncture stimulation of “Zusanli” (ST 36), “Sanyinjiao” (SP 6) and “Liangmen” (ST 21) at 0.12, 0.24 and 0.36 mA can promote the gastrointestinal motility in DGP rats, which may be associated with its effects in enhancing RhoA/ROCK signaling in the gastric antral smooth muscle at different degrees.

Discussion

One important etiology of gastroparesis is DM. Notably, symptoms attributable to gastroparesis are reported by 5–12% of patients with DM. Obesity connected with type 2 diabetes was associated with an almost tenfold increase in the odds of reporting gastroparesis symptoms. The presence of presumed gastroparesis in patients with DM is associated with other complications, including retinopathy and peripheral neuropathy, higher mean levels of glycosylated hemoglobin. The effectiveness of western medicine strategies may be limited and be restricted for their side effects sometimes.

The research about complementary and alternative therapy in DGP is focusing on the comparison of monotherapy, such as TCM, acupuncture and massage, and combination therapy with the prokinetic drugs. Both the monotherapy and combination therapy are proving an advantageous effect on the treatment of DGP. So, the complementary and alternative therapy may bring multiple benefits in the treatment of refractory nausea and vomiting and also help to alleviate abdominal distension with fewer

side effects from the above studies. The pathogenesis of DGP in TCM has been related to the injury of the “Qi” of spleen and stomach, resulting in dysfunction of the two organs in transformation and transportation. So, the principle of the treatment for DGP is tonifying spleen and reinforcing Qi. And XSLJZD is the most commonly used decoction, which has a better effect on tonifying spleen and stomach. Some other decoctions are improving the symptoms of early satiety, nausea, vomiting, bloating, and abdominal pain, such as Banxia Xiexin decoction, Xiaobanxia decoction, etc. Meanwhile, as for the pathogenesis, the points such as Zusanli, Zhongwan, Weishu, are mainly chosen from the spleen channel and the stomach channel for promoting the function of the spleen and stomach.

Although there are some studies about the mechanisms of complementary and alternative therapy in DGP, they were still insufficient. Randomized controlled trials are undoubtedly required in future studies. So there will be lots of work to do and to explore the efficiency and the potential mechanisms of complementary and alternative therapy in DGP.

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