

Combination of symptoms, syndrome and disease: Treatment of refractory diabetic gastroparesis

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Abstract

AIM: To assess effect of combination of symptoms, syndrome and disease on treatment of diabetic gastroparesis with severe nausea and vomiting.

METHODS: Professor Tong Xiaolin's clinical electronic medical records of patients who were treated between January 1, 2006 and October 1, 2012 were used as a database. Patients who met the inclusion criteria were enrolled. General information (name, sex and age), symptoms and blood glucose levels were obtained from the clinic electronic medical record, which was supplemented by a telephone interview. The patient-rated Gastroparesis Cardinal Symptom Index (GCSI) was used to evaluate the severity of the symptoms of gastroparesis. The effects of the treatment were assessed

by the change in the severity of the symptoms of gastroparesis and the change in blood glucose between the baseline levels and the post-treatment levels at 1, 2, 4, 8 and 12 wk.

RESULTS: Forty-five patients had a mean GCSI nausea and vomiting severity score of 4.21 ± 0.67 and a total GCSI score of 2.77 ± 0.63 before treatment. There was a significant improvement in the nausea and vomiting score at every return visit compared with the baseline score (1 wk: 3.02 ± 1.04 vs 4.18 ± 0.71 , $P < 0.001$; 2 wk: 2.32 ± 1.25 vs 4.16 ± 0.73 , $P < 0.001$; 4 wk: 2.12 ± 1.26 vs 4.12 ± 0.73 , $P < 0.001$; 8 wk: 1.79 ± 1.09 vs 4.24 ± 0.77 , $P < 0.001$; 12 wk: 0.69 ± 0.92 vs 4.25 ± 0.70 , $P < 0.001$). Twenty-five of the 45 patients had complete resolution of vomiting during the observation period (mean time to resolution was 37.9 ± 27.3 d). The postprandial fullness and early satiety subscale, bloating subscale and total GCSI scores were also improved. Finally, the blood glucose levels improved after treatment, although the change was not significant.

CONCLUSION: Use of the combination of symptoms, syndrome and disease to treat diabetic gastroparesis with refractory nausea and vomiting may be a new treatment option.

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Key words: Diabetic gastroparesis; Refractory nausea and vomiting; Traditional Chinese medicine; Treatment; Gastroparesis Cardinal Symptom Index

Core tip: Limited therapeutic options exist for the treatment of diabetic gastroparesis (DGP) with refractory nausea and vomiting. Traditional Chinese medicine (TCM) has supplied important complementary and alternative treatments. Professor Tong Xiaolin is an expert in the use of TCM for severe gastroparesis in China. The combination of symptoms, syndrome and disease is a concept that he incorporates into his clinical

cal practice. This article introduces how he uses this concept to treat DGP and assesses its effect by analysis of his clinical electronic medical records. It may provide a new treatment option for refractory disease associated with DGP.

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INTRODUCTION

Gastroparesis is a chronic motility disorder of the stomach that is characterized by delayed gastric emptying in the absence of mechanical obstruction. The cardinal symptoms include postprandial fullness (early satiety), nausea, vomiting and bloating^[1]. Gastroparesis is commonly found in patients with diabetes mellitus^[2] and can lead to weight loss, poor nutritional status and poor glycemic control. Common treatments for gastroparesis include erythromycin, metoclopramide, domperidone and cisapride^[3]. Some patients experience severe symptoms and therefore do not respond to traditional treatment modalities. These patients are unable to maintain sufficient oral nutrition and have frequent visits to the emergency room or are hospitalized^[4]. Nausea and vomiting, the most bothersome symptoms reported by patients^[5], contribute to electrolyte imbalance, dehydration and increased healthcare utilization^[6]. Diabetic patients with gastroparesis can experience severe nausea and vomiting with impaired glycemic control and nutritional status^[7-9].

The current treatment options for severe symptoms are surgery and gastric electrical stimulation (GES). These options both require hospitalization and are associated with a high cost and high risk of infection. Thus, new therapeutic options to alleviate severe nausea and vomiting are needed.

Traditional Chinese medicine (TCM) has been widely used in the treatment of diabetes mellitus in China and often provides a good curative effect. Professor Xiao-Lin Tong is one of the academic leaders in the field of TCM and is an expert in the use of TCM to treat severe gastroparesis in present-day China. He has worked in this field for > 30 years and has formed his own TCM theoretical system for diabetes and its complications.

A combination of symptoms, syndrome and disease is his primary concept for the treatment of diabetic gastroparesis (DGP) accompanied by severe nausea and vomiting, and is associated with good curative effects. The aim of this study was to evaluate his TCM method for the treatment of severe DGP and to introduce a new treatment option for clinicians by analyzing his clinical electronic medical records.

MATERIALS AND METHODS

Patients

Professor Xiao-Lin Tong's clinic electronic medical records were used as the database for this study. Patients who met the inclusion criteria and who were seen in the clinic between January 1, 2006 and October 1, 2012 were enrolled in this nonblinded study. The inclusion criteria were as follows: (1) documented diagnosis of DGP for > 1 year; (2) being refractory to conventional medical therapy such as antiemetics and prokinetics; and (3) a Gastroparesis Cardinal Symptom Index (GCSI) nausea/vomiting subscale severity score ≥ 3.5 ^[1]. Patients without follow-up, including those who did not return to professor Xiao-Lin Tong's clinic after the first visit and could not be contacted by telephone, were excluded. Patients with another planned intervention (such as placement of a gastric electrical stimulator) or a new medication for the treatment of severe gastroparesis were excluded. Finally, those patients with primary eating or swallowing disorders, including rumination syndrome, psychogenic vomiting and cyclic vomiting syndrome, or an active malignancy were also excluded.

Study protocol

General information (name, sex and age) and blood glucose levels were reviewed retrospectively from the clinical electronic medical records. The baseline and post-treatment symptoms were obtained from the clinical records and were supplemented by information obtained from a telephone interview. Patient evaluations were performed at 1-, 2-, 4-, 8- or 12-wk return visits. The symptoms of gastroparesis were evaluated using the GCSI, which uses a six-point scale ranging from none (0) to very severe (5)^[1]. The severity of each of nine symptoms was evaluated individually and grouped according to the three subscales (nausea/vomiting, postprandial fullness/early satiety and bloating) and by the total GCSI score. The severity of the symptoms of gastroparesis was the main standard used in evaluating the TCM therapy.

TCM as a therapy for severe DGP

Professor Tong Xiaolin writes a prescription according to the idea of a combination of symptoms, syndrome and disease. First, he chooses some herbs according to the patients' symptoms. Patients with severe DGP often experience vomiting and abdominal bloating as their main symptoms. Xiao-Banxia-Tang (consisting of *Pineliaternata* and ginger) and Suye-Huanglian-Tang (consisting of perilla leaves and *Rhizoma Coptidis*) were used as traditional antiemetic prescriptions. Zhizhu wan (consisting of *Fructus Aurantii Immaturus* and *Bighead Atractylodes rhizome*) was used as a traditional medication to relieve distention and other symptoms of abdominal bloating. Second, he selects some herbs according to the syndrome. In TCM theory, syndrome is the fundamental cause of the symptoms and can be established according to the types of symptoms. Patients with "excessive heat

Table 1 Change in nausea/vomiting subscale

Score follow-up (wk)	No.	Before treatment	After treatment	Before minus after	P value
1	33	4.18 ± 0.71	3.02 ± 1.04	1.16 ± 0.86	0.000
2	30	4.16 ± 0.73	2.32 ± 1.25	1.83 ± 1.33	0.000
4	27	4.12 ± 0.73	2.12 ± 1.26	2.00 ± 1.27	0.000
8	22	4.24 ± 0.77	1.79 ± 1.09	2.45 ± 1.06	0.000
12	12	4.25 ± 0.70	0.69 ± 0.92	3.56 ± 1.22	0.000

of the spleen and stomach” (symptoms of a bitter taste in the mouth and dry stool) were treated with Dahuang-Huanglian-Xiexin-Tang (consisting of *Rheumofficinale* and the rhizome of Chinese goldthread). Patients with “heat in the upper and cold in the lower” (symptoms of fulminant vomiting and cold pain in the stomach) were treated with Xiexin-Tang (consisting of *Pinellia ternata*, ginger, Rhizoma Coptidis, Radix Scutellariae, Rhizoma Zingiberis, ginseng and liquorice). Patients who experienced “deficiency-cold of the spleen and kidney” (symptoms of spitting or drooling, diarrhea, cold limbs and a deep thready pulse) were given Fuzi-Lizhong-Tang (consisting of ginseng, Bighead Atractylodes rhizome, Rhizoma Zingiberis and monkshood). Finally, as the primary index to monitor the diabetic disease process, the patient’s blood glucose level was also monitored. Rhizoma Coptidis, Rhizoma Anemarrhenae and Radix Trichosanthis were subsequently prescribed to control high blood glucose levels.

Patients with severe vomiting or abdominal distension were re-evaluated in 7 d. Patients were advised to sip their medication (which was provided as a decoction) as tolerated if they experienced vomiting. After the severe symptoms were relieved, the return period was changed to 2, 4, 8 or 12 wk, according to the severity of their symptoms and their response to treatment. Patients took their TCMs twice daily and maintained regular clinic visits until the symptoms resolved.

Statistical analysis

Patient identification, data registration and data entry were performed by two clinicians. A third clinician checked the database for entry errors. All of the data were analyzed using SPSS 17.0 software (SPSS Inc., Chicago, IL, United States). The severity of the symptoms and blood glucose levels before treatment and at 1, 2, 4, 8 and 12 wk after treatment were compared using a paired *t* test. All data were presented as the mean ± SD, with *P* < 0.05 considered statistically significant.

RESULTS

Study population

Forty-five eligible patients were treated from January 1, 2006 to October 1, 2012. The treatment group comprised 32 women (71.1%) and 13 men (28.9%), with a mean age of 43.7 ± 15.3 years (range: 26-83 years). Of these, 24 patients (54.3%) were diagnosed with type 1

Table 2 Change in postprandial fullness/early satiety and bloating subscale scores

Follow-up (wk)	No.	Symptom	Before treatment	After treatment	Before minus after	P value
1	33	Fullness/early satiety	2.53 ± 1.00	2.08 ± 1.00	0.45 ± 0.60	0.000
		Bloating	1.23 ± 0.89	1.25 ± 0.80	-0.02 ± 0.59	0.882
2	30	Fullness/early satiety	2.48 ± 0.98	1.62 ± 0.95	0.86 ± 0.82	0.000
		Bloating	1.30 ± 0.89	1.03 ± 0.78	0.27 ± 0.77	0.069
4	27	Fullness/early satiety	2.64 ± 0.95	1.70 ± 1.18	2.00 ± 1.27	0.000
		Bloating	1.44 ± 0.84	1.06 ± 0.76	0.39 ± 0.66	0.005
8	22	Fullness/early satiety	2.82 ± 0.97	1.57 ± 1.09	1.25 ± 0.67	0.000
		Bloating	1.57 ± 0.81	0.91 ± 0.78	0.66 ± 0.66	0.000
12	12	Fullness/early satiety	2.81 ± 0.72	0.90 ± 0.77	1.92 ± 1.16	0.000
		Bloating	1.25 ± 0.92	0.33 ± 0.49	0.92 ± 0.76	0.002

diabetes mellitus, and 21 (45.7%) with type 2 diabetes mellitus. The mean duration of diabetes for the 45 patients was 11 years (range: 1-36 years), and the mean duration of gastroparesis was 30.6 ± 43.3 mo (range: 0.5-240 mo). Ten patients experienced chronic gastritis, eight had reflux esophagitis, and two presented with a history of incomplete intestinal obstruction. In addition, one patient had undergone a cholecystectomy, and one was diagnosed with gallbladder polyps. The 45 patients had a nausea/vomiting subscale severity score of 4.21 ± 0.67, a postprandial fullness/early satiety subscale severity score of 2.7 ± 0.97, a bloating subscale severity score of 1.38 ± 0.82, and a total GCSI score of 2.77 ± 0.63.

Change in symptom severity

The severity of the symptoms was evaluated before and after 1, 2, 4, 8 and 12 wk of treatment (Tables 1-3). This was a retrospective study based on Professor Tong’s clinical practice, therefore, patients may have had different follow-up periods according to the severity of their symptoms. Additionally, once the severe symptoms were relieved, a patient’s follow-up period may have been changed to 2, 4, 8 or 12 wk or even longer to limit the number of follow-up visits. Thus, many of the patients, due to great improvement in their symptoms after one or two follow-up appointments, did not return to the clinic within the 12-wk time frame. Consequently, most of their treatment records did not appear until after the 12-wk observation period. As a result, most of the patients in this study did not have treatment records representative of the five follow-up time points as the number of clinic visits decreased over time. Out of 45 patients, seven had follow-up consultations at each time point, and five had follow-up appointments at 1, 2, 4 and 8 wk. Four patients had follow-up appointments at 1, 2 and 4 wk, five had follow-up consultations at 1 and 2 wk, and five had follow-up appointments at 1 wk.

Change in the nausea/vomiting subscale score: Table 1 shows the changes in the nausea/vomiting subscale

Table 3 Change in total Gastroparesis Cardinal Symptom Index score

Follow-up (wk)	No.	Before treatment	After treatment	Before minus after	P value
1	33	2.66 ± 0.65	2.13 ± 0.74	0.52 ± 0.48	0.000
2	30	2.64 ± 0.64	1.66 ± 0.76	0.99 ± 0.72	0.000
4	27	2.74 ± 0.65	1.63 ± 0.87	1.11 ± 0.69	0.000
8	22	2.88 ± 0.63	1.42 ± 0.81	1.45 ± 0.5	0.000
12	12	2.77 ± 0.51	0.64 ± 0.61	2.13 ± 0.74	0.000

score. The nausea/vomiting subscale scores after 1, 2, 4, 8 and 12 wk of treatment were significantly improved compared with the baseline score ($P < 0.05$). The patient symptom severity score also improved over time. Out of 45 patients, 25 had complete resolution of vomiting by 12 wk based on their medical records. The mean time to resolution was 37.9 ± 27.3 d (range: 7-90 d).

Change in the postprandial fullness/early satiety and bloating subscale scores: Similar improvements were found in the postprandial fullness/early satiety and bloating subscale scores (Table 2). The patient-reported symptom severity score also improved over time.

Change in overall symptoms: Table 3 shows that the total GCSI score significantly improved at all follow-up time points. The curative effect also increased as time progressed. The general feeling of well-being of the patients was then evaluated. The evaluation of overall well-being included sleep status, physical capacity and psychological status. Out of 45 patients, 43 reported that they "feel better after treatment". The mean time from the onset of treatment to this report was 19.6 ± 11.7 d (range: 2-56 d).

Change in blood glucose levels

Patients who were evaluated for DGP suffered from severe nausea or vomiting. The patients' symptoms were the primary focus, thus, their blood glucose levels were not always assessed. The fasting blood glucose levels were used to evaluate blood glucose levels (Table 4). As shown in Table 4, the blood glucose levels tended to improve with treatment.

DISCUSSION

DGP with refractory nausea and vomiting is a difficult clinical problem to resolve. Current treatment options for severe gastroparesis are limited because the pathogenesis of DGP is not completely understood^[10]. TCM has a long history of use as a complementary and alternative medicine. Many patients with incurable diseases such as severe DGP, especially in China, are advised to see a traditional Chinese doctor. However, there have been few reports that have evaluated the clinical efficacy of TCM treatments. This study was based on the nearly 6-year TCM clinical practice of Professor Tong. Twenty-five patients (54.3%) were diagnosed with type 1 diabetes mellitus, and 21 (45.7%) with type 2 diabetes mellitus.

Table 4 Change in fasting blood glucose level

Follow-up (wk)	No.	Before treatment	After treatment	Before minus after	P value
1	4	11.03 ± 3.04	6.85 ± 1.51	4.18 ± 2.53	0.046
2	4	9.30 ± 3.81	9.00 ± 2.63	0.30 ± 1.98	0.781
4	13	8.84 ± 3.81	6.67 ± 1.58	2.17 ± 4.19	0.087
8	7	7.33 ± 1.77	7.30 ± 2.73	0.03 ± 3.63	0.984
12	7	7.17 ± 2.38	7.80 ± 1.88	0.63 ± 2.69	0.560

These percentages reflect the lack of association between the two types of diabetes and the susceptibility to DGP. There were more female than male (33 women *v*s 13 men) patients with refractory nausea and vomiting, which suggests that women are more prone to severe DGP. This finding is consistent with previous reports that proposed that severe DGP may be related to a high estrogen level in women^[11-13].

The pathogenesis of DGP is not clear, and there is no standard evaluation for DGP. Most studies evaluate gastric emptying time because gastroparesis is defined as delayed gastric emptying. Radionuclide scanning at 15-min intervals for 4 h after the intake of labeled food is considered the gold standard for measuring gastric emptying^[9]. This test is relatively expensive, is associated with radiation exposure, and does not have a standardized application at different medical centers^[14]. In addition, completing a gastric emptying study in DGP patients with severe nausea and vomiting is difficult. Many reports show a poor correlation between improvement of the symptoms of gastroparesis and tests for gastric emptying^[15,16]. Severity of symptom and quality of life outcomes are needed for a better evaluation of the effectiveness of treatment^[17-20].

Patient-reported symptom severity is important in the evaluation of this disease and is the only measure that directly reflects each patient's experience with symptom severity, function and well-being. In clinical practice, clinicians rely on the patients' reports of their symptoms to manage DGP and to monitor the effectiveness of treatment. The GCSI is a widely used symptom standard in studies of gastroparesis^[21-23]. This scale was developed based on reviews of the medical literature, clinician interviews and patient focus groups and has been validated in patients with gastroparesis^[1,24]. The total GCSI score has been used as a standard to diagnose gastroparesis^[25]. We used the GCSI as the principal tool to evaluate patients with DGP and refractory nausea and vomiting. Glycemic control is an important part of the management of DGP^[26], therefore, we also monitored the blood glucose levels during TCM treatment. TCM greatly reduced the nausea/vomiting subscale score, postprandial fullness/early satiety subscale score, bloating subscale score and total GCSI score. There was a tendency toward improvement in blood glucose levels after treatment.

The current treatment options for severe DGP are limited. The most widely used treatment reported is gastric electrical stimulation (GES), and although GES treat-

ment is effective^[27,28], it is expensive^[29] and poses risks of device infection, accidental deactivation by a magnetic field, and gastric perforation by the electrical leads^[30]. The endoscopic pyloric injection of botulinum toxin has also been used to treat severe gastroparesis^[31,32], but in patients who have vomiting as a major symptom, there was no predictable response to this treatment^[31]. In contrast, treatment with TCM is inexpensive and noninvasive.

TCM takes patient symptoms into account before the treatments are selected. Vomiting is often the most troublesome symptom in these patients, therefore, Xiao-Banxia-Tang combined with Suye-Huanglian-Tang was used to relieve the symptoms of vomiting. Xiao-Banxia-Tang effectively alleviates vomiting by inhibiting NK1 receptor activity, antagonizing motilin activity and releasing intestinal serotonin^[33-35]. Suye-Huanglian-Tang has also been used to treat intractable vomiting^[36-38]. The use of these two prescriptions may explain the rapid improvement in vomiting that we observed. Abdominal distention is a prominent symptom of DGP, and some reports^[39,40] have shown that abdominal bloating and fullness alone may be associated with DGP. Zhizhu wan is used to improve abdominal distention by enhancing gastrointestinal motility^[41,42]. Other Chinese medicines were added according to the syndrome presentation. This combined treatment may explain why the symptoms improved with prolonged treatment and why the curative effects increased over time. Modern medical findings were also applied to this TCM therapy. Chinese medicines that are known to lower blood glucose levels were used, including Chinese goldthread rhizomes^[43,44] and *Rhizoma Anemarrhenae*^[45-47]. Blood glucose levels were improved in the patients who were evaluated.

There is considerable documentation of TCM as a complementary and alternative medicine source. Although identifying the exact pharmacological composition of these medicines is difficult due to their complex components, their clinical activities cannot be ignored. The aim of this study was to evaluate a TCM treatment of DGP in patients with refractory nausea and vomiting and to provide a new treatment option for clinicians.

This is a large study of patients with severe DGP, but it has several limitations, including its retrospective nature and use of clinical electronic medical records supplemented with detailed telephone interviews to identify the patients' symptoms. Patients in this study did not undergo gastric emptying scintigraphy during treatment to determine whether there was a correlation between improved gastric emptying and relief of their symptoms. This study used the patients' symptoms to determine the clinical follow-up period, thus, the timing of the return visits of the patients was not consistent, and there was not an equal number of patients at every follow-up time point.

Despite the above limitations, we believe that this study offers a useful treatment option for DGP with refractory nausea and vomiting. Prospective studies are needed to better evaluate this form of TCM.

COMMENTS

Background

Diabetic patients with severe nausea and vomiting have impaired glycemic control and nutritional status. However, limited therapeutic options exist for the treatment of diabetic gastroparesis (DGP) with refractory nausea and vomiting. Finding new treatment options for this refractory disease is a complex clinical problem that needs to be solved.

Research frontiers

The most common treatment options for severe gastroparesis are surgery and gastric electrical stimulation, but these treatments require hospitalization and are associated with a high cost and high risk of infection.

Innovations and breakthroughs

Limited therapeutic options exist for the treatment of DGP with refractory nausea and vomiting. Based on nearly 7 years of clinical medical records, this study analyzed the effects of Professor Tong's treatment on this refractory disease and found significant improvement in nausea and vomiting as well as in other symptoms of gastroparesis. This study provides a new treatment option for clinicians.

Applications

The study results suggest that the use of the combination of symptoms, syndrome and disease model within the Traditional Chinese medicine (TCM) framework could be a treatment option for DGP with refractory nausea and vomiting.

Terminology

Syndrome is a specific diagnostic concept in TCM; it is a pathological summary of the location, cause, nature and condition of a disease at a certain stage and also describes a conclusion about the pathological nature of the disease.

Peer review

This manuscript provides a detailed data analysis to assess the effects of Professor Tong Xiaolin's methods in the treatment of DGP with severe nausea and vomiting. The use of combination of symptoms, syndrome and disease to treat DGP with refractory nausea and vomiting may be a new treatment option.

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