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Effects of stimulating single acupoint and combination acupoints on diabetic gastroparesis: A randomised controlled trial study

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ABSTRACT

Background and aim: The most effective among the acupoints remains to be determined for treating diabetic gastroparesis (DGP). This study aimed to compare single and combination acupoints for their effectiveness in DGP.

Experimental procedure: A prospective, patient-assessor-blinded randomised controlled trial was designed to compare the efficacy of 8-week acupuncture at a single acupoint (Zhongwan, CV-12), combination acupoints (Zhongwan, CV-12 and Zusanli, ST-36), and a sham-acupoint, in 99 adults with DGP. The primary clinical outcome was measured using the Gastroparesis Cardinal Symptom Index (GCSI), while barium meal examination, fasting plasma glucose, the 2-h plasma glucose, short-form health survey (SF-36), and GCSI subscales were performed for evaluating secondary clinical outcomes. These results were analysed by two factorial analysis of variance (ANOVA) test, Chi-Square, Fisher Exact, Kruskal–Wallis tests and Tukey's Honest Significant Difference (HSD) test.

Results: After randomization, 97 patients completed the study. GCSI scores of all groups decreased during both post-treatment and the follow-up period, they were statistically significant compared to the baseline period ($p < 0.01$), but there was no significant difference among the groups ($p > 0.05$) during the post-treatment period. GCSI scores improved more in the combination acupoints group than in the single acupoint group which was better than the sham group after treatment. During the follow-up period, the same trend was observed.

Conclusions: Among patients with DGP, the combination acupoints were more beneficial compared with single and sham acupoints.

Trial registration number: NCT02452489.

1. Introduction

In recent years, there has been a notable increase in the prevalence of diabetes mellitus globally. Until 2019, the overall prevalence of diabetes stood at approximately 9.3 % worldwide, with approximately 40 % being attributed to type 1 diabetes mellitus and 30 % to type 2 diabetes mellitus.[1–3] According to a recent report by the International Diabetes Federation (IDF), the global prevalence of diabetes is projected to further rise to 10.2 % by the year 2030 and 10.9 % by the year 2045.[1] Approximately 50 % of individuals with diabetes experience delayed gastric emptying, a condition closely associated with diabetic gastroparesis (DGP).[4] Diabetic gastroparesis is a disorder of gastric motility

Abbreviations: DGP, Diabetic gastroparesis; GCSI, Gastroparesis Cardinal Symptom Index; MOS, Medical outcome study; ANOVA, Analysis of variance; IDF, International Diabetes Federation; GI, Gastrointestinal; RCT, Randomised controlled trials; SGL-A, Single acupoint group; COM-A, Combination acupoints group; SA, Sham-acupoint group; CRF, Case report forms.

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that occurs in diabetic patients.[5] It manifests with various symptoms, including delayed gastric emptying and upper gastrointestinal (GI) symptoms, without any mechanical obstruction, and may yield abnormal results in gastric emptying tests[6] which can significantly impact the patients' quality of life.[7]

The current treatment approach for DGP primarily involves alleviating symptoms using allopathic medicines like domperidone,[8] relamorelin,[9] and metoclopramide.[10,11] This focus on symptom relief is due to the complex interplay between glycaemic control and gastric emptying,[12–14] which makes addressing the condition challenging. However, due to the adverse effects associated with allopathic drugs, many patients with DGP are turning to complementary therapies as an alternative approach.[15–17]

Recent studies have demonstrated the effectiveness of acupuncture in treating DGP.[18–21] Notably, a clinical study compared acupuncture with domperidone in patients with DGP,[22] further supporting its efficacy. While combination acupoints are commonly preferred by clinical acupuncturists, single acupoint therapy remains applicable for improving specific symptoms of certain diseases, such as using Zhongwan (CV-12) for chronic atrophic gastritis[23] and Zusanli (ST-36) for constipation, among others.[24] However, few randomized controlled trials (RCT) have compared the effectiveness of single acupoints with combination acupoints, making this research area noteworthy.

Our previous study confirmed different therapeutic effects of stimulating ST-36, CV-12 acupoint, or their combination in DGP rat models.[25] To provide more scientific evidence for the clinical application of acupuncture therapies, we conducted an 8-week RCT to establish the differences in efficacy between single acupoints (CV-12) and combination acupoints (CV-12 and ST-36). To the best of our knowledge, this is the first RCT to compare the effectiveness of different acupuncture treatments for patients with DGP, and it includes a follow-up assessment to further enhance the study's validity.

2. Materials and methods

2.1. Study design and experimental paradigm

This study was a clinical trial designed as a randomised, parallel, three-arms, multi-center study. The research was approved by the ethics committee of the Changchun University of Chinese Medicine. (Identifier: CCZYFYLL2014-043). Written informed consent was obtained from all patients in the study. The study has been registered in ClinicalTrials.gov which is provided by the U.S. National Library of Medicine (Identifier: NCT02452489). And the calculation process for the sample size is as follows:

$$n = \frac{\left[u\alpha\sqrt{2p(1-p)} + u\beta\sqrt{p1(1-p1)+p2(1-p2)}\right]^2}{(p1-p2)^2}$$

According to the formulas, "n" represents the sample size, "p_1" and "p_2" are sample proportions, $p = (p_1 + p_2)/2$ is the sample average proportion. "u_α"and "u_β" represent the corresponding critical values from the standard normal distribution.

Between December 2016 and April 2018, we recruited patients with DGP from three different clinical centers in China: Jilin, Hunan, and Shandong. Each center conducted a stringent screening process in line with the established inclusion and exclusion criteria. As a result, 99 eligible patients were enrolled in the study and randomly divided into three groups, with 33 patients in each group: Single acupoint group (SGL-A): Patients received acupuncture stimulation at Zhongwan (CV-12) of the ren meridian. Combination acupoints group (COM-A): Patients received acupuncture stimulation at Zusanli (ST-36) of the stomach meridian and Zhongwan (CV-12), which are commonly used for DGP treatment. Sham-acupoint group (SA): Patients received sham acupuncture at the junction of the deltoid and biceps. During the course of the study, two patients from the control group dropped out, leaving a total of 97 patients who continued their participation (Fig. 1). Our trial comprised several stages, spanning from Week 0 to Week 8. Week 0: Trial initiation and pre-enrollment phase begins. Participants are selected for the study. Week 1–4: Treatment phase. The actual intervention or treatment is administered to the enrolled participants. Week 8: Follow-up assessment. Evaluation of the participants' progress and outcomes after the treatment phase.

2.2. Participants

2.2.1. Diagnostic criteria

The diagnosis of gastroparesis according to the following criteria[6]:

(1) The patient has clinical symptoms including nausea, vomiting, early satiety, postprandial fullness, bloating, and upper abdominal pain or;
(2) A 4-h gastric emptying scintigraphy test shows objective evidence for the presence of gastric emptying delay.

The diagnosis of diabetes according to "Executive Summary: Standards of Medical Care in Diabetes—2014" criteria[26]:

(1) A1C is more than 6.5 % or;
(2) Fasting plasma glucose (FPG) is more than 7.0 mmol/L or;
(3) 2-h plasma glucose is more than 11.1 mmol/L during an oral glucose tolerance test (OGTT) or;
(4) A random plasma glucose is more than 11.1 mmol/L in patients with classic symptoms of hyperglycemia or hyperglycemic crisis or;
(5) The absence of unequivocal hyperglycemia needs to be confirmed by repeat testing.

2.2.2. Inclusion criteria

Participants eligible for enrollment in this study had to meet the following criteria: they must have met the diagnostic criteria for gastroparesis and diabetes, be aged between 18 and 65 years, and could belong to any gender. Additionally, they should have experienced diabetic gastroparesis symptoms for more than 3 years. Participants using glucose-lowering medications (except Alpha-glucosidase Inhibitors) based on diet, exercise, or a combination of both were required to have a stable drug dose for at least 3 months. Those who had not participated in other clinical trials for the past 3 months before our enrollment were eligible to participate. Informed consent was obtained voluntarily from all participants. During the screening, participants were required to have fasting plasma glucose (FPG) higher than 7.0 mmol/L and 2-h plasma glucose (2h PG) higher than 13.6 mmol/L.

2.2.3. Exclusion criteria

Participants were excluded from the study if they met any of the following criteria: patients with reflux esophagitis, functional dyspepsia, or postoperative gastroparesis. Those with acute liver dysfunction or renal dysfunction, severe cardiovascular and cerebrovascular diseases, or a history of severe complications such as diabetic ketoacidosis and hyperosmolar hyperglycaemic non-ketonic coma were also excluded. Additionally, individuals who were pregnant or lactating, had a history of malignant tumors, or suffered from digestive tract diseases causing peptic ulcer bleeding or other organic lesions were not eligible to participate. Patients who had been on α-Glucosidase Inhibitors treatment in the last 4 weeks were also excluded from the study.

2.3. Randomization and blindness

After the participants were assigned to their respective groups, random numbers were generated following the random coding procedure, and the trial concluded after all the planned observations were completed. The randomization sequence was conducted by the China

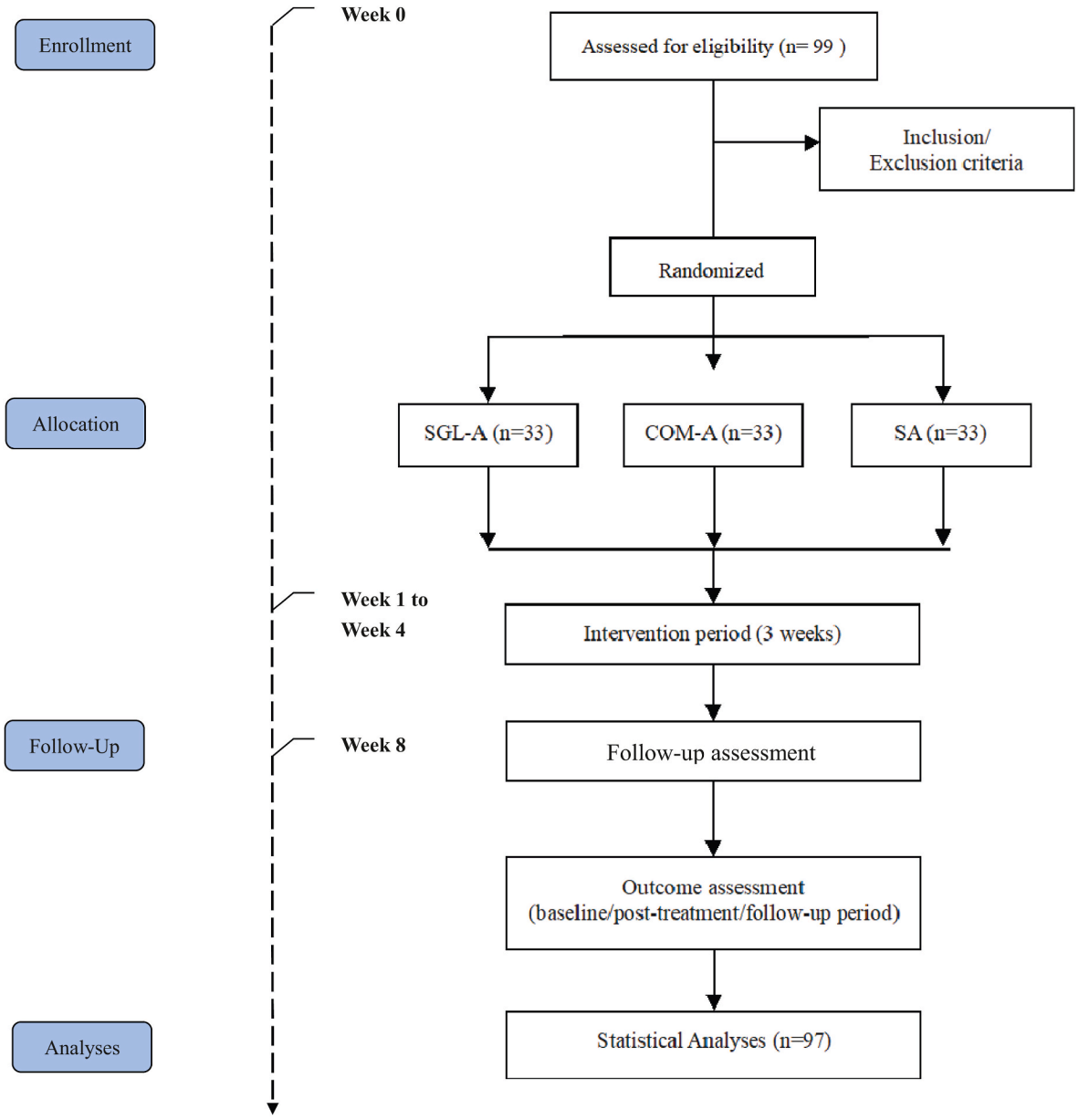

Fig. 1. Flow chart of study design.

Academy of Chinese Medical Sciences, responsible for the random allocation and data management throughout the study.

Considering the uniqueness of acupuncture therapy, blinding the patients was not feasible in this study. Therefore, a blinding method was employed for assessment, where a third party, unaware of the group assignments, conducted the efficacy evaluations. Additionally, during the data summarization phase, blind statistical analysis was applied to ensure the authenticity and reliability of the research results.

2.4. Interventions

2.4.1. Acupuncture and groups

Acupuncture therapy is a traditional Chinese medical practice that involves the insertion of thin needles into specific acupoints on the body. These acupoints are believed to be connected through pathways or meridians that influence the flow of energy (Qi) in the body. Stimulating these acupoints could help to balance the body's energy and promote health. In this clinical study, patients were assigned to different groups which were mainly divided into the true acupuncture groups (SGL-A and COM-A) and the sham group. The acupoints used were as follows: CV-12 and bilateral ST-36. These acupoints were chosen according to the "*Illustrations for the location of acupoints*" (GB/T12346-2006).[27] Single acupoint group chose CV-12 which is a specific acupoint. Combination acupoints chose bilateral ST-36 which are often used with CV-12 as He-Sea-Front-Mu Point Combination based on the Traditional Chinese theory as well as literature search.[28,29] The sham group chose a sham acupoint located at the junction of the deltoid and biceps.[30,31] (Fig. 2).

2.4.2. Acupuncture procedures

Acupuncture was administered by acupuncturists with more than 3 years of clinical experience and valid TCM licenses and was based on the "*Science of acupuncture and moxibustion*".[32] All subjects in the study were prescribed glimepiride as the foundational medication to ensure glucose stability. Acupuncture treatments were administered for 30 min per day, five days a week, with two days of rest, over a period of three weeks. During the treatment sessions, disposable acupuncture needles (Suzhou, Hwatuo Acupuncture Needle, China, 0.38*50 mm) were used to stimulate specific acupoints such as CV-12 or ST-36, or NA, aiming to elicit

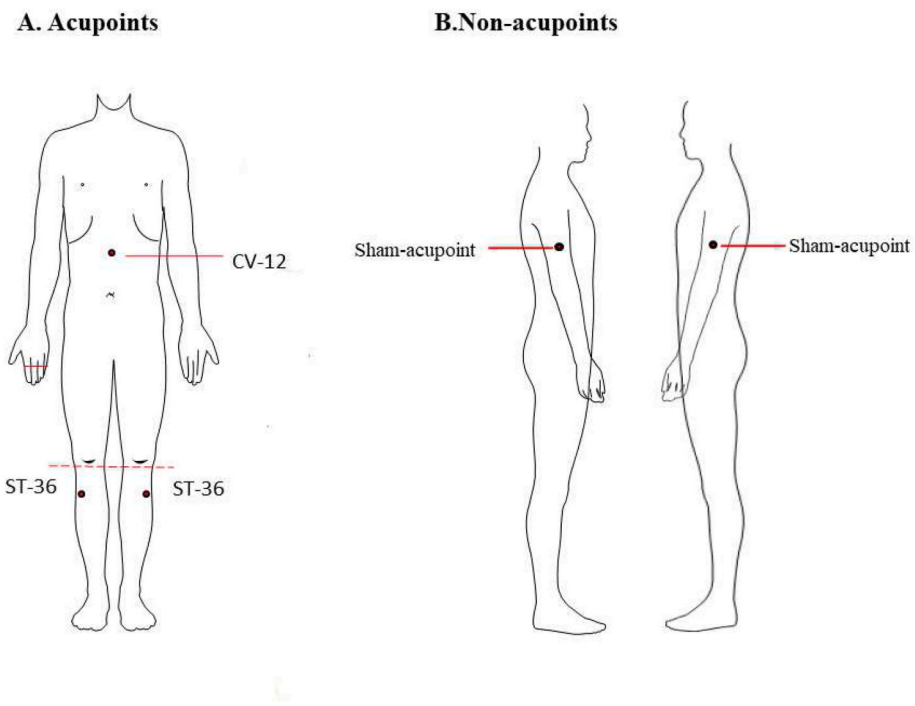

Fig. 2. Locations of acupoints and sham-acupoint.
A: The location of the acupoints in SGL-A and COM-A. B: The location of the acupoints in SA.

the essential "De-Qi" sensation. "De-Qi" is a significant concept in Traditional Chinese Medicine and acupuncture practice, referring to a unique and characteristic sensation that patients may experience during acupuncture treatment.[33] It encompasses sensations like heaviness, numbness, tingling, warmth, or a dull ache in or around the stimulated acupoints. In addition to the primary acupuncture needles, "auxiliary needles" made of silver (Suzhou, Hwatuo Acupuncture Needle, China, 0.18*13 mm) were also inserted about 1 cm away from CV-12 or ST-36, or NA. These auxiliary needles were connected to an electro-acupuncture machine (Suzhou Medical Appliance Factory, China) set at a frequency of 2Hz/1002 Hz and a dense-dispersed intensity of 1.0 MA to maintain the "De-Qi" sensation.

Of note, after the conclusion of our trial, participants in the SA group would receive true acupuncture therapy.

2.5. Measurements

2.5.1. Outcome assessment

2.5.1.1. Primary outcome. The primary clinical outcome was assessed using the Gastroparesis Cardinal Symptom Index (GCSI). The evaluation of GCSI took place at three specific time points: baseline, post-treatment, and during a follow-up period after enrollment. GCSI is a measurement tool that incorporates nine subscales, namely early satiety, gastric distension, post-prandial fullness, bloating, loss of appetite, eating less, nausea, abdominal bulge, and vomiting. Patients with more severe symptoms, as determined by clinicians, tended to report higher scores on the GCSI total score, indicating greater symptom severity.[34]

2.5.1.2. Secondary outcomes. The secondary clinical outcomes included the upper GI barium study, short-form health survey (SF-36), GCSI subscale, and glucose monitoring. The SF-36 is a questionnaire used to assess quality of life, and its total score ranges from 0 to 100 scales, with lower scores indicating a poorer quality of life. The SF-36 evaluation was conducted at baseline, post-treatment, and during follow-up periods after enrollment. It consists of eight dimensions to assess various aspects of well-being. Barium studies are commonly used in gastrointestinal radiological examinations. The upper GI barium study primarily focuses on observing the movement of barium through the gastrointestinal tract over a period of 4 h after ingestion. In addition, glucose monitoring serves as an objective measure for patients with diabetic gastroparesis, helping to track and assess blood glucose levels during the course of the study.

2.6. Safety assessment

Any unexpected events or unusual sensations experienced during the acupuncture treatments would be recorded in case report forms (CRF), which included hematoma, broken needles, left needles, fainting, unbearable ache, severe post-acupuncture pain lasting 1 h, and infection.

2.7. Statistical analyses

All clinical data were commissioned to the Institute of Basic Research in Clinical Medicine, China Academy of Chinese Medical Sciences for analysis using SAS 9.4 and SPSS 24.0 statistical software. All data were reported as the mean with standard error (SE). For categorical demographic characteristics and baseline values, the chi-square test/analysis of variance (ANOVA) were used for comparing the data within and between-group comparisons; the ANOVA/Kruskal–Wallis/chi-square tests were used for the comparison of continuous data between groups and within groups. $p < 0.05$ was considered statistically significant. Missing data of primary outcome GCSI score were replaced using the last-observation-carried-forward (LOCF) method. Regarding the primary outcome GCSI score after the 4th week of treatment, it made a statistical description of the actual measurements and changes at all post-baseline time points according to the groups which include mean, standard deviation, median, 1st Quartile, *3rd* Quartile, minimum and maximum. If there was no interaction between centre and grouping ($p \geq 0.05$), then the interaction between baseline and grouping was eliminated from the model, and the modified mean corrected by Tukey's method was calculated, along with the difference between the modified mean and its 95 % confidence interval. A post-hoc analysis with Tukey's

Honest Significant Difference (HSD) test was employed when ANOVA indicated significant differences. This approach yielded adjusted group means, the disparities among these means, and their respective 95 % confidence intervals, all of which were calibrated using Tukey's method.

3. Results

3.1. Demographic characteristics at baseline period

The baseline status of all enrolled participants was evaluated before our combination study, to ensure concordance among groups. Finally, 97 DGP patients, including 33 SGL-A patients, 33 COM-A patients, and 31 controls, were enrolled in our final statistics. And 2 patients who did not enter for job reassignment and personal reasons. Table 1 shows the demographic characteristics during the baseline period. There was no significant difference among the three groups with respect to age, sex, disease history, medicine use history, course of disease, primary outcome, and secondary outcomes among the three groups ($p > 0.05$) and they were comparable.

3.2. Primary outcomes in different groups

The GCSI total score is usually used as the primary outcome to measure the symptoms of gastroparesis. During the post-treatment period, the GCSI scores of all three groups were significantly decreased compared to their respective baselines (Fig. 3) ($p < 0.01$); however, there was no significant difference among the SGL-A, COM-A, and SA groups. Moreover, during the follow-up period, GCSI scores of all three groups were significantly decreased ($p < 0.01$). According to the post-hoc analysis, the COM-A group exhibited significantly lower GCSI scores compared to both SGL-A and SA groups (COM-A vs SA: $p < 0.05$; COM-A vs SGL-A: $p > 0.05$; SGL-A vs SA: $p > 0.05$). Furthermore, the effect size also circularized between the three groups which could be seen in Table 2. According to our calculation, the main effect of group factor: $F = 1.046, p = 0.355 > 0.05$, indicating no statistically significant difference in GCSI scores among the SGL-A, COM-A, and SA. However, the main effect of the within-group factor: $p < 0.001$, indicating significant differences in GCSI scores at different stages. Also, interaction effect: $p = 0.148 > 0.05$, suggesting no interaction between time and grouping, meaning the effect of time does not vary significantly among the different groups.

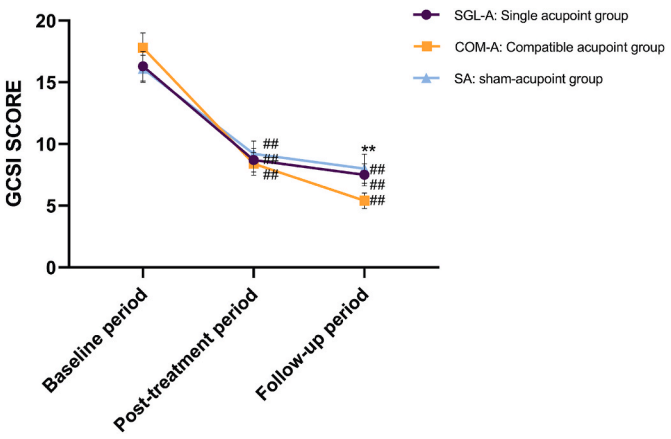

Fig. 3. GCSI scores during different periods.
Comparison of GCSI scores during different period. **: Significant difference among groups during the follow-up period ($p < 0.01$), with COM-A showing notably lower scores compared to SGL-A and SA (by Tukey's HSD post-hoc test). ##: Compared with baseline period, ($p < 0.01$ by ANOVA).

Table 2
Comparisons of GCSI Scores before and after treatment in three groups.

Group	Baseline period (Mean ± SEM)	Post-treatment period (Mean ± SEM)	Follow-up period (Mean ± SEM)	Within-Group F	Within-Group *p*
SGL-A (n = 33)	16.30 ± 1.23	8.68 ± 0.95	7.54 ± 0.88	50.936	<0.001*
COM-A (n = 33)	17.80 ± 1.18	8.36 ± 0.92	5.36 ± 0.63	47.850	<0.001*
SA (n = 31)	16.10 ± 1.09	9.16 ± 1.05	7.98 ± 1.17	29.000	<0.001*

**p < 0.01, comparison within the groups.

3.3. Secondary outcomes in different groups

3.3.1. Analysis of each factor of the GCSI scale

To investigate the variations in symptom regulation among different acupuncture therapies, we utilized the GCSI subscales, which are

Table 1
Baseline characteristics of patients in different groups.

	Parameter	SGL-A	COM-A	SA	P-value
Basic information	Age(years) (Mean ± SEM)	52.1 ± 1.96	50.1 ± 1.79	49.4 ± 1.62	0.582
	Sex				0.397
	Male	11 (33.33 %)	16 (48.48 %)	12 (36.36 %)	
	Female	22 (66.67 %)	17 (51.52 %)	21 (63.64 %)	
	Disease history(years)	6 (18.18 %)	7 (21.21 %)	3 (9.68 %)	0.483
	Medicine use history(years)	1 (3.03 %)	0 (0.00 %)	0 (0.00 %)	1.000
	Course of disease(months)	68.7 ± 30.02	70.8 ± 49.00	67.2 ± 53.64	0.050
Primary outcome	GCSI total score (Mean ± SEM)	16.3 ± 1.23	17.8 ± 1.18	16.1 ± 1.09	0.528
Secondary outcome	GCSI Early Satiety	1.9 ± 0.22	2.3 ± 0.24	1.7 ± 0.26	0.397
(Mean ± SEM)	GCSI Gastric Distension	2.8 ± 0.20	2.9 ± 0.22	2.5 ± 0.25	0.536
	GCSI Post-prandial fullness	2.7 ± 0.23	2.9 ± 0.18	2.7 ± 0.22	0.844
	GCSI Bloating	2.4 ± 0.24	2.5 ± 0.21	2.4 ± 0.24	0.897
	GCSI Loss of appetite	2.0 ± 0.23	2.0 ± 0.21	2.1 ± 0.22	0.895
	GCSI Eating Less	1.8 ± 0.21	2.2 ± 0.20	1.9 ± 0.23	0.456
	GCSI Nausea	1.1 ± 0.19	0.9 ± 0.20	0.9 ± 0.22	0.628
	GCSI Abdominal Bulge	1.0 ± 0.27	1.9 ± 0.26	1.3 ± 0.26	0.243
	GCSI Vomiting	0.4 ± 0.15	0.2 ± 0.11	0.5 ± 0.19	0.385
	SF-36 score	232.5 ± 3.40	238.5 ± 2.44	235.5 ± 3.01	0.364
	X-ray barium discharge volume in 4 h(g)	2.5 ± 0.49	3.2 ± 0.77	2.7 ± 0.50	0.711
	fasting plasma glucose (mmol/L)	7.3 ± 0.13	7.3 ± 0.12	7.4 ± 0.27	0.982
	2-h plasma glucose (mmol/L)	9.9 ± 0.38	10.3 ± 0.36	9.5 ± 0.42	0.346

presented in Table 3 and Fig. 4. Although the SGL-A, COM-A, and SA groups did not exhibit statistically significant differences ($p > 0.05$), distinct trends in symptom regulation by these groups were still evident. During the post-treatment period, true acupuncture therapy demonstrated better performance than the SA group for four factors. Additionally, for early satiety, gastric distension, and post-prandial fullness, the COM-A group performed better than the SGL-A group. However, concerning bloating, the SGL-A group and COM-A group showed similar performance. Moreover, in terms of the performance of the two factors: loss of appetite and eating less, the SGL-A and SA groups had the same performance, and the adjustment ability was not as good as that of the COM-A group, while the effect of acupuncture therapies for nausea factor was just the opposite. In the case of abdominal bulge, the SGL-A group showed a better therapeutic effect, and the performance of the COM-A group and SA group showed a similar effect. However, the SA group showed a more substantial improvement in vomiting symptoms compared to the true acupuncture groups.

During the follow-up period, true acupuncture groups showed therapeutic advantages compared with the SA group in terms of 5 factors. Regarding the three factors of early satiety, bloating, and post-prandial fullness, the COM-A group was better than the SGL-A group. In the case of the abdominal bulge, SGL-A was better than the COM-A group, and for nausea, SGL-A and COM-A group showed similar therapeutic effect. In addition, for loss of appetite and bloating factors, the effects of the SGL-A and SA groups showed similar results, and the therapeutic effect was not as good as that of the COM-A group. For the factor of eating less, the COM-A group was better than the SA group and the SGL-A group. However, the SA group showed the same effect as the true acupuncture groups regarding vomiting. (Fig. 4).

3.3.2. Analysis of SF-36 scale

Fig. 5 displays the SF-36 total score compared among different groups. During the post-treatment period, only the COM-A group had statistical significance ($p < 0,01$). Although both SGL-A group and SA group showed decline, they were not statistically significant among the three groups. During the follow-up period, there were no significant differences among the groups.

3.3.3. Barium-meal x-ray

On the day of the experiment, patients were provided with a standard meal at 7:00 a.m., which included 200 ml of water, 80 g of instant noodles, 50 g of sausage, and special capsules (containing 20 purlins each, totaling 4 grains per capsule, with a total of 5 capsules). They were allowed to consume the meal within a 15-min timeframe. Following the meal, patients were given permission to stand, walk, and sit as needed. However, they were explicitly instructed not to sleep during the study period. Four hours after the meal, abdominal X-rays are taken, and an additional 4-h period is observed to calculate the remaining barium meal in the gastric region based on the abdominal X-ray results. The emptying rate can be calculated as (20 - number of stomach barium meals)/20 × 100 %. Fig. 6 displays barium-meal x-ray (4 h of excretion) among different groups. In general, the amount of barium meal had declined better in true acupuncture groups than SA group in both the post-treatment period and the follow-up periods. All groups improved after treatment compared with their baseline, but there was no significant difference among the three groups (Fig. 6). During the post-treatment period, there were statistically significant differences among groups. ($p < 0.05$). According to the post-hoc analysis, the COM-A group significantly outperformed the SA group ($p < 0.05$), and SGL-A group was significantly more effective than SA group ($p < 0.05$).

3.3.4. Glucose

Considering the fact that glucose is an important objective indicator to evaluate DGP, we conducted a related evaluation, though this study mainly focused on evaluating the effect of acupoints commonly used in digestive diseases. During the post-treatment period, the combination acupoints group had an obvious hypoglycaemic effect, though there was no improvement in both single acupoint group and control group (Fig. 7A). It is clear from the magnitude of the decline in Fig. 7B that true acupoints groups could better regulate 2-h plasma glucose, but it was not significant compared with their baseline period.

3.4. Adverse events

Adverse events associated with acupuncture clinical trials include signs, symptoms, or illnesses that are unintended or uncomfortable. There were no serious adverse events during the trial, and the adverse events included one case with a mild degree of adverse event, and the event did not persist. Based on the data presented in Table 4, only 1 patient experienced adverse events, while 96 patients did not have the uncomfortable symptom after treatment.

Table 3
GCSI scores in subgroups during different periods.

Different time	Baseline period			Post-treatment period			Follow-up period			P-value	
GCSI factors	SGL-A (n = 33)	COM-A (n = 33)	SA (n = 31)	SGL-A (n = 33)	COM-A (n = 33)	SA (n = 31)	SGL-A (n = 33)	COM-A (n = 33)	SA (n = 31)	Post-treatment period	Follow-up period
1. Early Satiety	1.9 ± 0.22	2.3 ± 0.24	1.7 ± 0.26	1.2 ± 0.18##	1.2 ± 0.18##	1.1 ± 0.20##	1.0 ± 0.17##	0.8 ± 0.14##	0.8 ± 0.18##	0.2392	0.0508
2. Gastric Distension	2.8 ± 0.20	2.9 ± 0.22	2.5 ± 0.25	1.5 ± 0.18##	1.2 ± 0.15##	1.7 ± 0.19##	1.2 ± 0.16##	1.0 ± 0.14##	1.4 ± 0.23##	0.0162*	0.0286*
3. Post-prandial fullness	2.7 ± 0.23	2.9 ± 0.18	2.7 ± 0.22	1.6 ± 0.14##	1.5 ± 0.17##	1.7 ± 0.16##	1.4 ± 0.13##	1.0 ± 0.13##	1.5 ± 0.19##	0.4435	0.0925
4. Bloating	2.4 ± 0.24	2.5 ± 0.21	2.4 ± 0.24	1.3 ± 0.15##	1.3 ± 0.18##	1.5 ± 0.20##	1.2 ± 0.17##	0.7 ± 0.14##	1.2 ± 0.21##	0.4699	0.0552
5. Loss of appetite	2.0 ± 0.23	2.0 ± 0.21	2.1 ± 0.22	1.0 ± 0.16##	0.8 ± 0.14##	1.0 ± 0.20##	0.9 ± 0.16##	0.5 ± 0.12##	0.9 ± 0.18##	0.3098	0.3233
6. Eating Less	1.8 ± 0.21	2.2 ± 0.20	1.9 ± 0.23	1.1 ± 0.17##	1.0 ± 0.15##	1.1 ± 0.17##	1.0 ± 0.15##	0.6 ± 0.11##	0.9 ± 0.18##	0.0687	0.0150*
7. Nausea	1.1 ± 0.19	0.9 ± 0.20	0.9 ± 0.22	0.2 ± 0.10##	0.4 ± 0.13##	0.2 ± 0.08##	0.2 ± 0.08##	0.2 ± 0.08##	0.3 ± 0.15##	0.4293	0.2704
8. Abdominal bulge	1.0 ± 0.27	1.9 ± 0.26	1.3 ± 0.26	0.7 ± 0.19##	0.9 ± 0.17##	0.9 ± 0.20##	0.4 ± 0.15##	0.5 ± 0.13##	0.8 ± 0.19##	0.0035**	0.0024**
9. Vomiting	0.4 ± 0.15	0.2 ± 0.11	0.5 ± 0.19	0.1 ± 0.04#	0.1 ± 0.06	0.0 ± 0.03#	0.1 ± 0.06#	0.1 ± 0.07	0.1 ± 0.05	0.4293	0.2704

#$p < 0.05$, ##$p < 0.01$, (Kru.-Wal.), compared with baseline period;
*$p < 0.05$, **$p < 0.01$, comparison among the groups.

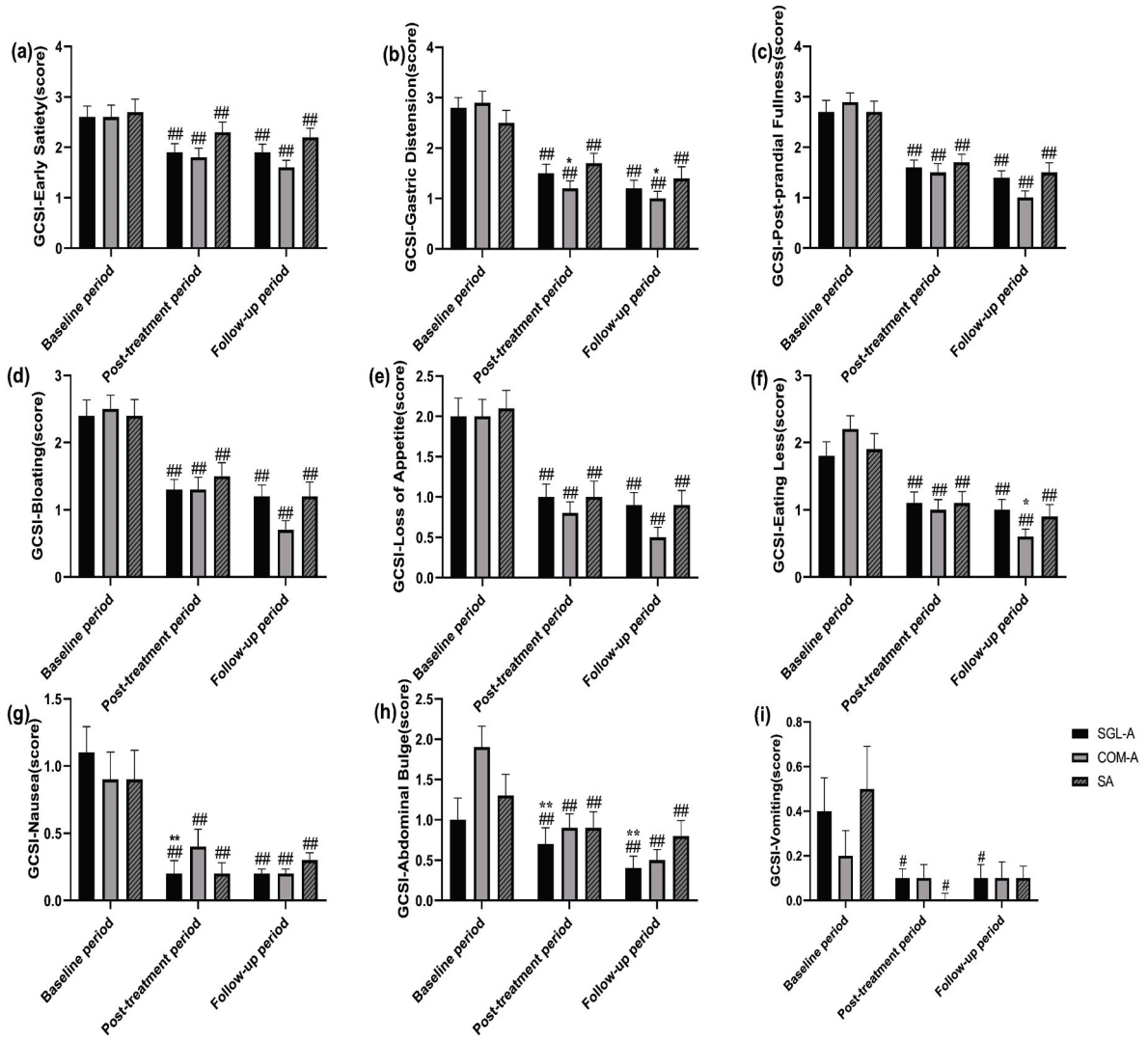

Fig. 4. GCSI scores in subgroups during different periods.
Comparison of GCSI scores in sub-factors during different period. (Kru.-Wal.). $^{*}p < 0.05$, $^{**}p < 0.01$, SGL-A or COM-A group vs. SA. $^{\#}p < 0.05$, $^{\#\#}p < 0.01$, compared with baseline period.

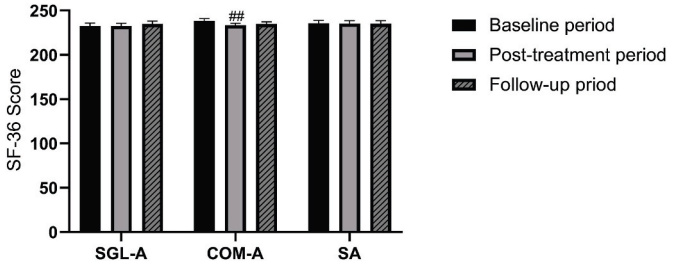

Fig. 5. SF-36 scale scores during different period.
Comparison of SF-36 scale scores during different period. $^{\#\#}$: Significant difference ($p < 0.01$ by ANOVA), compared with baseline period.

4. Discussion

In our clinical trial, acupuncture therapy showed significant regulatory effects on various digestive factors during the post-treatment and follow-up periods. However, it's important to note that not all comparisons between different acupuncture groups reached statistical significance. Despite this, the results indicate that acupuncture still had meaningful impacts on several digestive factors in the management of the condition. Moreover, stimulating combination acupoints appeared to alleviate more gastrointestinal discomfort and improve gastric emptying. We specifically targeted gastrointestinal acupoints (ST-36 and CV-12) and observed that stimulating the combination acupoints also led to a significant reduction in fasting plasma glucose levels and improvements in physical and psychological factors. This suggests that COM-A can systematically regulate the body, addressing both gastrointestinal symptoms and glucose levels, leading to longer-term therapeutic effects. Hence, the combination acupoints therapy appears more suitable for DGP patients with complex symptoms. Interestingly, our study also revealed noteworthy outcomes in the group receiving sham acupuncture. While initially designed as a placebo control, the sham treatment demonstrated a level of effectiveness that cannot be disregarded. The fact that sham electroacupuncture yielded similar results to true acupuncture therapies raises intriguing questions about the mechanisms at play. It is possible that non-specific therapeutic effects, such as the placebo response or the psychosocial aspects of the treatment, could be contributing to the observed outcomes. In our clinical trial, we utilized subjective rating scales, and from the research findings that the placebo effect does play a role in the treatment. Some studies have indicated that true acupuncture therapy could exhibit greater activation in the anterior cingulate gyrus and insula regions than

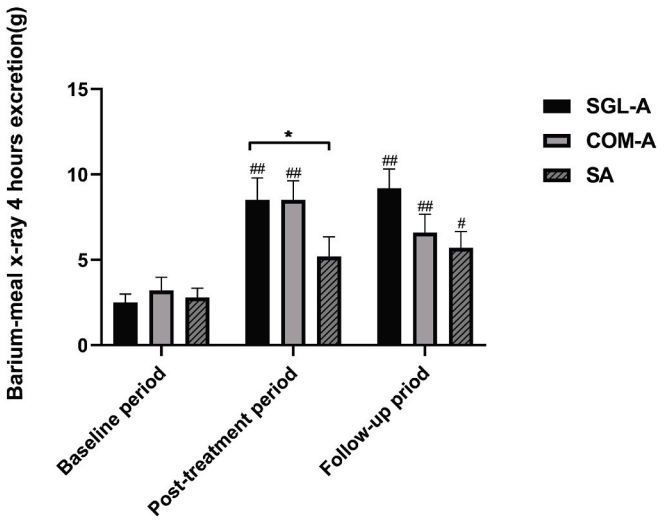

Fig. 6. Barium-meal x-ray 4 h excretion during different periods.
Comparison of Barium-meal x-ray 4-h excretion during different periods. $^{\#\#}p < 0.01$, $^{\#}p < 0.05$, compared with baseline period. *: Significant difference among groups during the post-treatment period ($p < 0.05$, by Chi-Square), with both COM-A and SGL-A proving more effective than SA (by Tukey's HSD post-hoc test).

phantom acupuncture without somatosensory tactile stimulation. However, based on our study results, the therapeutic effects of true acupuncture therapies are significantly superior to sham acupuncture. Similarly, a relative study focusing on the importance of selecting specific acupoints shows that acupuncture therapy is an effective method for the treatment of gastroparesis. It showed that the combination of CV-12 with ST-36 demonstrated the most promising effect in alleviating symptoms in patients with gastroparesis. Also, the GCSI scores of the combination of CV-12 with ST-36 group and control group after treatment and at follow-up were all significantly lower than those before treatment.[21] Hence, it can be said that the placebo effect does indeed have a certain impact, but when compared to true acupuncture therapy, there is still a difference in efficacy. Further investigations are warranted to delve deeper into the potential mechanisms underlying these intriguing findings.

DGP is a chronic disease that may present with symptoms of both diabetes mellitus and functional gastrointestinal disorders.[35] Given the complexity of this condition, acupuncture therapies for DGP in China often adopt a systematic approach by combining multiple acupoints. Indeed, personalized treatment tailored to the specific symptoms experienced by individual patients is also administered in clinics. The efficacy of acupuncture therapy in DGP patients has been confirmed in various clinical trial studies.[18,36,37] Building on these, our study sought to identify the most effective acupoints for DGP treatment.

Previous investigations in treating digestive diseases have frequently employed the combination of local CV-12 and distal ST-36 as local-distal acupoint pairs. However, despite its widespread usage, the effectiveness of this particular acupoint combination, along with the underlying mechanisms, remains unclear. Our study aimed to shed light on these aspects to enhance our understanding of acupuncture's potential in addressing DGP and its associated symptoms. Although the combination acupoints can regulate multiple and broad indicators (both objective and subjective), we also found that stimulating the single acupoint (CV-12) could focus more on alleviating the symptom of stomach or belly visibly larger, and it can take effect in a short time. Additionally, stimulating the single acupoint (CV-12) could also relieve the symptoms of nausea or vomiting, but longer-term intervention is needed. The use of a single acupoint can not only avoid the abuse of needles and save resources in clinical practice but can also reduce the pain associated with using multiple needles. Therefore, patients with a single symptom should be prescribed a single acupoint treatment. As for our choice of non-acupoints, though, there are a lot of ways to choose non-acupoints (NA), such as a few "cm" or "cun" next acupoints ("cun" is Chinese units of length measurement) and NA far away from the acupoint. We cited the way of NA far away from the acupoint since the NA is next to the acupoint and has some limitations. Therefore, non-acupoints far away from the acupoints recognized in clinical trials were selected as controls.[30,31]

This clinical trial is the largest multicentre clinical trial for the acutherapy of DGP. The sample size as well as the multiple-centre aspect of the study may enhance its credibility. The design of our multi-arm research by including an SA group is more objective, which may exclude the false-positive results that could have been caused by the anticipation of the DGP patients. Moreover, the selected acupoints in this study relied not only on the clinical experience of our acupuncturists but also on the key literature.[38] In addition to multiple outcome factors, and objective parameters, subjective parameters have also been included in our study.

In the light of our findings, although SA showed some effects on the DGP treatment, the true acupuncture therapies presented better long-term, persistent, and clinically relevant benefits for DGP patients. The selected acupoints in this study were more specific to the digestive disease. More acupoints that may contribute to the hypoglycaemic effect should also be taken into account. In our study design, we could not

Table 4
Adverse events in three groups.

	SGL-A	COM-A	SA	P-value
No	32 (96.97 %)	33 (100.00 %)	31 (100.00 %)	1.0000
Yes	1 (3.03 %)	0 (0.00 %)	0 (0.00 %)	
Total	33	33	31	

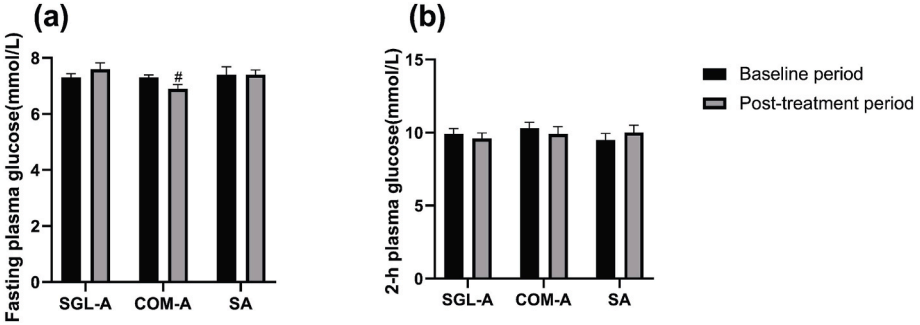

Fig. 7. Fasting plasma glucose and the 2-h plasma glucose.
Comparison of plasma glucose among groups. (a) Fasting plasma glucose; and (b) the 2-h plasma glucose. $^{\#}$: $p < 0.05$, compared with its own baseline period (by ANOVA).

include a positive control group. Only metoclopramide is approved by the FDA; however, its side effect involving tardive dyskinesia may be irreversible, especially for patients with hyperglycaemia. Furthermore, we used glimepiride as the hypoglycaemic agent, which may occasionally cause some side effects such as abdominal pain, vomiting, nausea, etc, however, according to a study that it could significantly accelerate gastric emptying in diabetic mice and the results mainly concentrated on was about the effect of acupuncture therapy for the DGP syndrome.[39] Additionally, owing to some complex situations during the clinical study, such as the compliance of the subject, our study was conducted only for two months.

A recent systematic review found that symptoms relief by stimulating acupoints may sustain for 2–3 months.[19] This suggests that a longer period for the follow-up observation should be evaluated for a sufficient and reasonable analysis in the future.

In summary, clinical acupuncture is considered one of the effective supplements for DGP treatment. Since the symptoms of patients are complex and variable, therapists should be more cautious in choosing acupoints, and combination acupoints should be considered more carefully and objectively when symptoms occur.

5. Conclusion

This study demonstrated that acupuncture has a therapeutic effect on DGP patients. In some cases, the effect of the single acupoint is better than the combination acupoints which has an obvious therapeutic effect only on the abdominal bulge. The combination acupoints can be more beneficial in the treatment of diverse symptoms or systemic regulation of diseases. Thus, our study will help in the better management of patients with DGP.

Authors 'contributions

RML and MH equally contributed to this article as the first author. RML and MH drafted and revised the manuscript. TL and FCW conceived the idea and designed the study. XWZ, MMS, JZC, XBW, XYW, and SMZ conducted the statistical calculation. All authors have read and approved the manuscript.

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Ethics approval and consent to participate

The whole research was approved by the ethics committee of the Changchun University of Chinese Medicine. Identifier was CCZYFYLL2014-043. All patients in the study obtained written informed consent. The study has been registered in ClinicalTrials.gov which is provided by the U.S. National Library of Medicine (Identifier: NCT02452489). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Data availability

The datasets used and/or analyzed after completing the current study will be available from the corresponding author upon reasonable request.

Conflicts of interest

This manuscript has not been published or presented elsewhere in part or in entirety and is not under consideration by another journal. All study participants provided informed consent, and the study design was approved by the appropriate ethics review board. We have read and understood your journal's policies, and we believe that neither the manuscript nor the study violates any of these. There are no conflicts of interest to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jtcme.2024.01.008.

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