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Treatment of hyperemesis gravidarum accompanied by metabolic disorders by modified Liujunzi decoction, acupressure combined with rehydration

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We aimed to assess the therapeutic effects of modified Liujunzi decoction, acupressure combined with rehydration on hyperemesis gravidarum (HG) (spleen and stomach weakness syndrome) accompanied by metabolic disorders. Two hundred pregnant women admitted from January 2019 to June 2022 were divided into an observation group (n=100) and a control group (n=100) using a random number table. The control group was given rehydration, on the basis of which modified Liujunzi decoction and acupressure were utilized for the observation group. Both groups were treated for 7 d. The total effective rate was higher in the observation group than that in the control group. Blood potassium and sodium levels increased in both groups after treatment, which were higher in the observation group ($p<0.05$). The observation group had a higher negative conversion rate of urinary ketone body than that of the control group ($p<0.05$). The scores of physical symptoms and worsening factors, fatigue, mood and restriction as well as total score of Nausea and Vomiting of Pregnancy Quality of Life decreased in both groups after treatment, which were lower in the observation group ($p<0.05$). No adverse reactions occurred in the control group during treatment, while 1 case of skin allergy and 1 case of stomach distension occurred in the observation group. Modified Liujunzi decoction, acupressure combined with rehydration can effectively and safely restore the electrolyte balance, shorten the time to recovery, alleviate the clinical symptoms and improve the quality of life of patients with HG accompanied by metabolic disorders.

Keywords: Acupressure, Decoction, Hyperemesis gravidarum, Metabolic disorder, Rehydration

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Hyperemesis gravidarum (HG) is a severe form of nausea and vomiting during pregnancy, typically occurring in the first trimester (before 12 weeks), but it can persist throughout the pregnancy in some women. When severe, HG may lead to dehydration, water-electrolyte imbalances, and metabolic disturbances, such as fat metabolism abnormalities, which can endanger both maternal and fetal health[1]. A hallmark of HG is excessive fat mobilization, resulting in the accumulation of intermediate products like acetone, which can manifest as positive ketone bodies in urine. This metabolic shift may disrupt the acid-base balance, lead to electrolyte imbalances, and potentially result in renal failure[2]. Thus, HG is often accompanied by significant metabolic disorders.

In clinical practice, the most common treatment for HG-associated metabolic disturbances is rehydration with glucose to address dehydration, regulate the acid-base balance, and correct electrolyte imbalances, thus relieving vomiting and nausea[3]. However, rehydration alone often fails to prevent relapse of symptoms once treatment is discontinued, and HG tends to recur. Consequently, it is important to explore more sustainable treatment approaches. From a traditional Chinese medicine (TCM) perspective, HG is categorized as a form of “pregnancy obstruction”, primarily associated with weakness of the spleen and stomach[4]. In *Jing Yue's Collected Works*, it is noted that "morning sickness mainly results from stomach deficiency and qi stagnation, and failure of descending of qi movement may induce nausea"[5]. This highlights the central role of digestive weakness and the reversal of stomach qi in the pathogenesis of HG.

Liujunzi decoction, a TCM remedy, is historically used to address spleen and stomach qi deficiency, as well as phlegm and qi stagnation[6]. The decoction has been shown to alleviate chemotherapy-induced anorexia through its four main components, *i.e.*, ephedrine hydrochloride, ginsenoside Rg1, hesperidin, and jujuboside A[7]. Modifying Liujunzi decoction by adding complementary components may

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further enhance its effectiveness by invigorating the spleen, harmonizing the stomach, descending adverse qi and relieving vomiting[8].

Acupressure, another prominent TCM therapeutic modality, involves stimulating specific acupoints along meridians to regulate organ function and alleviate clinical symptoms[9]. The Neiguan acupoint, located on the Jueyin Pericardium Meridian of Hand, is particularly beneficial for harmonizing the stomach, descending counterflow qi, and promoting overall balance within the body. Stimulation of this acupoint is effective in alleviating vomiting and nausea by facilitating the flow of qi through the triple energizer[10]. The Zusanli acupoint, situated on the Yangming Large Intestine Meridian of Hand, regulates qi, promotes blood circulation, and harmonizes the stomach, making it particularly useful for treating nausea and vomiting in pregnant women[11].

Hence, this study evaluated the combined therapeutic effects of modified Liujunzi decoction, acupressure, and rehydration on treating HG accompanied by metabolic disorders, particularly in patients with spleen and stomach weakness syndrome. By exploring this multi-faceted approach, we aimed to provide valuable clinical evidence for a more holistic and sustainable treatment for HG.

Materials and Methods

General data

The sample size was calculated using the following formula for comparing two proportions (or means), based on the expected difference in outcomes between the two groups and considering a predefined statistical significance level and power: $n = (Z_{\alpha/2} + Z_{\beta})^2 \times (2 \times \sigma^2)/\Delta^2$, where $Z_{\alpha/2}$ is the critical value for a two-tailed test at the chosen significance level (e.g. 1.96 for $\alpha=0.05$); Z_{β} is the critical value for the desired power (e.g. 0.84 for 80% power); σ^2 is the estimated population variance based on previous studies or a pilot study; Δ is the expected difference between the two groups (effect size). Assuming an expected difference in effective rates of 20% between observation and control groups, a significance level (α) of 0.05, and a power ($1-\beta$) of 80%, the calculated sample size per group was approximately 96. To account for potential dropouts or incomplete data, the final sample size was set at 100 participants per group.

Two hundred pregnant women with HG of spleen and stomach weakness syndrome accompanied by metabolic disorders admitted from January 2019 to June 2022 were selected and assigned to an observation group (n=100) and a control group (n=100) using a random number table. In the observation group, the women were aged 21-40 years old [mean: (28.40±1.44) years], and the body mass index was 22-26 kg/m^2 [mean: (23.80±0.94) kg/m^2]. The period of amenorrhea was 42-98 d, with a mean of (64.50±4.49) d, and the course of disease was 7-28 d, with a mean of (16.80±3.64) d. In the control group, the women were 20-39 years of age [mean: (27.90±1.69) years], and the body mass index was 21-26 kg/m^2 [mean: (23.40±1.25) kg/m^2]. The period of amenorrhea was 49-98 d, with a mean of (64.60±4.61) d, and the course of disease was 6-7 d, with a mean of (16.30±3.55) d. The baseline data had no significant differences between the two groups ($p>0.05$). This study was approved by the ethics committee of our hospital (approval No. GMH201901004). Written informed consent has been obtained from all subjects. The flow chart of subject enrollment is exhibited in (Fig. 1).

Diagnostic criteria

The included pregnant women met the diagnostic criteria for HG in *Obstetrics and Gynecology* (*9th Edition*)[12], and the diagnosis was confirmed by laboratory indicators. They also met the diagnostic criteria for pernicious vomiting in the *Criteria for*

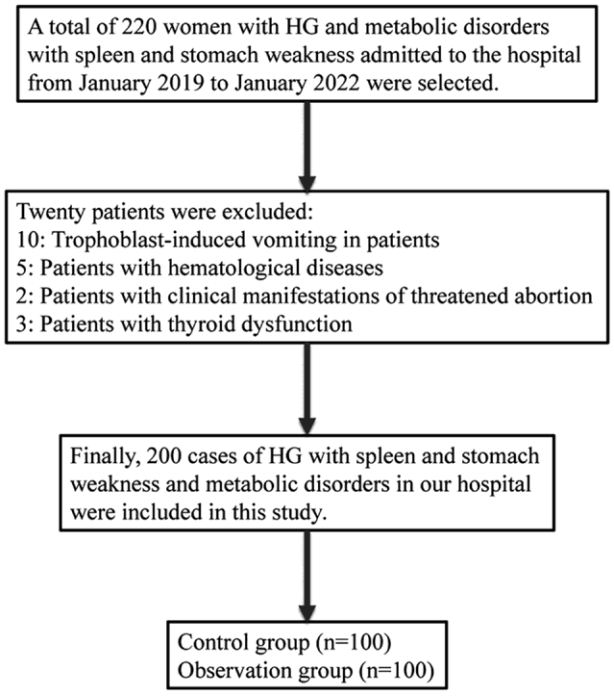

Fig. 1 — Flow chart of subject enrollment

Diagnosis and Therapeutic Effect of Diseases and Syndromes in Traditional Chinese Medicine[13], with spleen and stomach weakness syndrome: 1) primary symptoms: vomiting of sour or bitter fluid, and feeling sick when smelling oil, 2) secondary symptoms: thoracic fullness and rib-side pain, heartburn, and bitter taste in the mouth, and 3) tongue and pulse: light red tongue, slightly yellow coating, and slippery pulse.

Inclusion and exclusion criteria

The inclusion criteria were as follows: 1) pregnant women meeting the above diagnostic criteria, 2) those with 49-98 gestational days, 3) pregnant women with ketone positive urine and electrolyte disorders (low potassium, low sodium, etc.). The exclusion criteria involved: 1) pregnant women with vomiting due to trophoblastic diseases, 2) those complicated with hematologic disorders, 3) those with clinical manifestations of threatened abortion, or 4) those with abnormal thyroid function.

Methods for control group

The control group received rehydration treatment as follows: Ringer's fluid expansion, daily intravenous fluid supplement of 2500-3500 mL (5% or 10% glucose injection or 5% glucose sodium chloride injection; Guizhou Kelun Pharmaceutical Co., Ltd., China) plus 2 g vitamin C and 0.1 g vitamin B6, potassium and sodium supplement. Alkaline fluid was supplemented according to each binding force of CO_2. Urine volume was maintained at above 1000 mL.

Methods for observation group

The observation group was treated by modified Liujunzi decoction and acupoint massage on the basis of the control group. The prescription consisted of Codonopsis (10 g), poria cocos (10 g), stir-fried white Rhizoma (15 g), moxibustion licorice (6 g), tangerine peel (10 g), Faxia (10 g), stir-fried Shenqu (10 g) and Chinese yam (10 g). Bupleurum bupleurum (10 g), oyster (15 g) and scutellaria scutellaria (3 g) were added to the patients with irritable temper, bitter mouth and heartburn. Dried ginger (6 g) was added to those with stomach bleeding. Bletilla striata (6 g) was added to those with loose stool. Then 3 g ginger was added in 2000 ml of water to remove the residue of TCM drugs. The decoction (300 mL) was orally administered slowly in small portions, 1 dose/d. All herbs were provided by the TCM pharmacy in our hospital.

An operator alternately pressed the Neiguan acupoint (PC6) and Zusanli acupoint (LI4) until the patient felt slightly sore. Neiguan acupoint was located in the pericardium meridian and 2 Cun proximal to the wrist, between the flexor carpi radialis and the palmaris longus tendons. Zusanli acupoint was situated below the knee, on the tibialis anterior muscle, along the stomach meridian. The acupoint massage lasted for 7 days (5~10 min/time, twice/day).

Evaluation of treatment outcomes

On the 7th day after treatment, the treatment outcomes were assessed with reference to the *Criteria for diagnosis and therapeutic effect of diseases and syndromes in traditional Chinese medicine*[13]: 1) cured: disappearance of clinical symptoms such as vomiting, and no relapse after drug discontinuation, 2) improved: relief of clinical symptoms such as vomiting, but relapse after drug discontinuation, and 3) not cured: no relief of clinical symptoms.

Evaluation of recovery

The time to disappearance of clinical symptoms, length of hospital stay and time to return to normal biochemical levels were compared.

Measurement of blood potassium and sodium levels

Before treatment and on the 7th day after treatment, 3 mL of fasting peripheral elbow venous blood was drawn from each woman and centrifuged at 3,000 rpm for 6 min. Then the serum was harvested to detect potassium and sodium levels by the ion-selective electrode method.

Measurement of urinary ketone body

Before treatment and on the 7th day after treatment, urine specimen was collected from each woman to determine the ketone body by the dry-chemistry method.

Assessment of clinical symptoms and quality of life

Before treatment and on the 7th day after treatment, the clinical symptoms and quality of life of pregnant women were evaluated using Pregnancy-Unique Quantification of Emesis and Nausea (PUQE)[14] and Nausea and Vomiting of Pregnancy Quality of Life (NVPQOL)[15] scores. The PUQE scale included 3 dimensions (number of vomiting episodes, number of dry vomiting episodes, and length of nausea), with a total score of 3-15 points, and a higher score corresponded to severer clinical symptoms. The NVPQOL scale involved 4 dimensions (physical

symptoms and worsening factors, fatigue, mood, and restriction), with a total score of 30-210 points, and a higher score meant poorer quality of life.

Observation of adverse events

The incidence of skin allergies and stomach distension was recorded.

Statistical analysis

SPSS 24.0 software (IBM Inc., USA) was used for statistical analysis. All data were examined to be normally distributed using the Shapiro-Wilk test. The measurement data were expressed as mean ± standard deviation ($\bar{x} \pm s$) and analyzed by the independent samples *t*-test between groups and the paired samples *t*-test within groups. The count data were expressed as percentage and analyzed using the χ^2 test. The rank data were analyzed using the rank sum test. $p<0.05$ was considered statistically significant.

Results

Treatment outcomes

The overall effective rate was higher in the observation group than that in the control group [92.00% (92/100) *vs*. 79.00% (79/100)] ($p<0.05$ (Table 1).

Recovery of both groups

Compared with the control group, the time to disappearance of clinical symptoms, length of hospital stay and time to return to normal biochemical levels were shorter in the observation group ($p<0.05$) (Table 2).

Blood potassium and sodium levels before and after treatment

Before treatment, there were no significant differences in blood potassium and sodium levels between the two groups ($p>0.05$). After treatment, they increased in both groups and were higher in the observation group than those in the control group ($p<0.05$) (Table 3).

Negative conversion of urinary ketone body after treatment

Before treatment, no significant difference was seen in the positive urinary ketone body between the two groups ($p>0.05$). After treatment, the observation group had a higher negative conversion rate of urinary ketone body than that of the control group [68.00% (68/100) *vs*. 55.00% (55/100)] ($p<0.05$) (Table 4).

Table 1 — Treatment outcomes [n (%)]

Group	Cured	Improved	Not cured	Total effective rate
Observation (n=100)	39 (39.00)	53 (53.00)	8 (8.00)	92 (92.00)
Control (n=100)	21 (21.00)	58 (58.00)	21 (21.00)	79 (79.00)
χ^2/Z		3.347		6.816
P		<0.001		0.009

Table 2 — Recovery of both groups ($\bar{x} \pm s$, d)

Group	Time to disappearance of clinical symptoms	Length of hospital stay	Time to return to normal biochemical levels
Observation (n=100)	3.67±0.94	6.74±2.06	4.28±2.03
Control (n=100)	4.08±1.27	9.16±3.15	7.36±3.31
t	2.595	6.430	7.932
P	0.010	<0.001	<0.001

Table 3 — Blood potassium and sodium levels before and after treatment ($\bar{x} \pm s$, mmol/L)

Time	Group	Blood potassium	Blood sodium
Before treatment	Observation (n=100)	3.02±1.03	131.58±8.36
	Control (n=100)	3.11±1.15	132.74±9.18
	t	0.583	0.934
	P	0.561	0.351
After treatment	Observation (n=100)	4.24±0.93[a]	142.26±6.92[a]
	Control (n=100)	3.95±0.88[a]	138.17±6.87[a]
	t	2.265	4.194
	P	0.025	<0.001

[a] $p<0.05$ *vs*. the same group before treatment.

Table 4 — Negative conversion of urinary ketone body after treatment [n (%)]

Time	Group	-	+	++	+++
Before treatment	Observation (n=100)	0	29 (9.00)	32 (22.00)	39 (22.00)
	Control (n=100)	0	31 (11.00)	34 (24.00)	35 (22.00)
	Z			0.527	
	P			0.598	
After treatment	Observation (n=100)	68 (68.00)[a]	20 (20.00)[a]	12 (12.00)[a]	0[a]
	Control (n=100)	55 (55.00)[a]	24 (24.00)[a]	19 (19.00)[a]	2 (2.00)[a]
	χ^2			2.050	
	P			0.041	

[a] $p<0.05$ *vs*. the same group before treatment.

PUQE scores before and after treatment

Before treatment, the difference in PUQE score was not statistically significant (p>0.05). After treatment, the score reduced in both groups, but it was lower in the observation group than that in the control group (p<0.05) (Table 5).

NVPQOL scores before and after treatment

Before treatment, there were no significant differences in the scores of physical symptoms and worsening factors, fatigue, mood and restriction as well as the total score of NVPQOL between the two groups (p>0.05). After treatment, they were lowered in both groups, but they were lower in the observation group than those in the control group (p<0.05) (Table 6).

Adverse events

No adverse reactions occurred in the control group during treatment, while 1 case of skin allergy and 1 case of stomach distension occurred in the observation group.

Discussion

According to the *Gist for Diagnosis and Treatment of Women's Diseases*, the spleen and stomach weakness is a leading cause of HG[16], as it leads to insufficient healthy qi, imbalances in yin-yang and qi-blood, and inability to properly descend stomach qi, resulting in nausea and vomiting[17]. The results of this study further validate these theories. The observation group, treated with modified Liujunzi decoction, acupressure, and rehydration, had a higher total effective rate and significantly lower PUQE and NVPQOL scores than those of the control group. Therefore, the combination therapy not only improved clinical outcomes but also enhanced the patients' quality of life. The treatment was well-tolerated, with only minor adverse effects (1 case of skin allergy and 1 case of stomach distension). These results demonstrate that the combined approach was both effective and safe, and patients showed high compliance with the treatment regimen.

The pathophysiology of HG involves excessive ketone body production due to severe vomiting and diarrhea, resulting in ketonuria[18]. Under normal conditions, ketone bodies are metabolized by the liver and other tissues, but in the context of HG, the overload of ketones can overwhelm renal metabolism, leading to elevated urinary ketone levels. Moreover, electrolytes like potassium and sodium are crucial for maintaining cellular metabolism and acid-base balance, and abnormalities in their levels are common in HG patients with metabolic disorders. Potassium helps regulate osmotic pressure[19], while sodium play essential roles in maintaining the osmotic pressure of extracellular fluid, normal nerve and muscle functions[20]. These can serve as indicators of metabolic dysfunction in HG patients[21].

In this study, the observation group had a higher negative conversion rate of urinary ketone body and higher blood potassium and sodium levels than those of the control group, indicating that modified Liujunzi decoction and acupressure combined with rehydration effectively ameliorated the condition of patients with HG accompanied by metabolic disorders. The results may be attributed to the following reasons. Radix Aucklandiae, a key component of Liujunzi decoction, contains compounds like cosiuslacione and dihydrocostus lactone, which are capable of resisting the intestinal muscle spasm[22]. Rhizoma Pinelliae, another important herb in the formula, contains volatile oils and glutamates that exert a direct action on the central nervous system to inhibit vomiting[23].

Table 5 — PUQE scores before and after treatment ($\bar{x}$ ± s, point)

Group	Before treatment	After treatment	*t*	P
Observation (n=100)	14.16±1.28	10.39±1.03	22.947	<0.001
Control (n=100)	14.49±1.23	12.29±1.07	13.495	<0.001
t	1.859	12.793		
P	0.065	<0.001		

Table 6 — NVPQOL scores before and after treatment ($\bar{x}$ ± s, point)

Time	Group	Physical symptoms and worsening factors	Fatigue	Mood	Restriction	Total score
Before treatment	Observation (n=100)	48.48±7.25	20.89±2.55	39.16±5.03	56.89±4.03	165.32±5.57
	Control (n=100)	48.59±7.59	21.03±2.79	39.25±5.59	57.04±5.18	165.91±5.16
	t	0.105	0.370	0.120	0.229	0.777
	P	0.917	0.712	0.905	0.820	0.438
After treatment	Observation (n=100)	28.35±6.06[a]	13.89±2.06[a]	23.06±3.38[a]	32.06±4.87[a]	97.36±6.86[a]
	Control (n=100)	35.09±7.03[a]	16.48±3.02[a]	31.19±3.68[a]	45.06±5.88[a]	127.82±6.23[a]
	t	7.262	7.085	16.271	17.027	32.870
	P	<0.001	<0.001	<0.001	<0.001	<0.001

[a] p < 0.05 *vs*. the same group before treatment.

Furthermore, acupressure at the Neiguan acupoint may affect the release of endogenous morphine, modulate the secretion of motilin and gastrin, and regulate the gastric electrical rhythms, all of which contribute to the antiemetic effect of the treatment[24].

This study provides novel insights into the effectiveness of combining TCM with acupressure for managing HG, particularly in cases accompanied by metabolic disturbances. Nevertheless, this study is limited. Since this study was conducted in the COVID-19 period, there were difficulties in case management and collection, which may lead to bias. Therefore, further multicenter prospective studies with large sample sizes need to be carried out to verify the conclusion. Additionally, studies that examine the molecular mechanisms by which these treatments regulate gut motility, hormone secretion, and electrolyte balance can provide deeper insights into their therapeutic benefits.

Conclusion

In conclusion, modified Liujunzi decoction and acupressure combined with rehydration is effective and safe in restoring electrolyte balance, shortening the time to recovery, mitigating clinical symptoms and improving the quality of life of patients with HG accompanied by metabolic disorders.

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Conflict of Interest

The authors declare no conflict of interest.

Author Contributions

All authors played equal roles in the formulation of the study, sampling analysis and manuscript production.

Ethical Approval

This study was performed in accordance with the relevant ethics guidelines and regulations granted by Guiyang Maternal Hospital (No. GMH201901003).

Informed Consent

Written informed consent has been obtained from all subjects.

Data Availability

The data are available upon reasonable request from the corresponding author.

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