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Special Topic for 973 Program

Observation on the efficacy of moxibustion for chronic gastritis and a clinical study of moxibustion's effects on serum brain-gut peptides

艾灸治疗慢性胃炎的疗效观察及对血清脑肠肽影响的临床研究

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Abstract

Objective: To investigate the efficacy and mechanisms of moxibustion-based treatment of chronic gastritis (CG), and to provide an objective basis for treating CG using moxibustion.

Methods: A total of 61 CG patients were divided into an herbal cake-partitioned moxibustion group and a mild-warm moxibustion group. In both treatment groups, bilateral Tianshu (ST 25), Zhongwan (CV 12) and Qihai (CV 6) were selected for moxibustion. Before and after treatment, all the enrolled patients' gastrointestinal disease-related traditional Chinese medicine (TCM) syndrome scores and visual analog scale (VAS) scores were measured, and the changes in the serum levels of the brain-gut peptides ghrelin, somatostatin (SS) and motilin (MTL) were observed.

Results: There was no statistically significant difference between the two groups in the clinical efficacy rate ($P>0.05$). After treatment, the gastrointestinal disease-related TCM syndrome scores and VAS scores were reduced to varying extents in both groups, the intra-group differences were statistically significant (all $P<0.01$). In both groups, the serum levels of ghrelin and MTL increased and the serum levels of SS decreased after treatment (all $P<0.01$). And there were no serious adverse events occurred.

Conclusion: Both herbal cake-partitioned moxibustion and mild-warm moxibustion are effective for CG; these two therapies exhibited similar therapeutic efficacy of epigastric discomfort or pain. And both the two therapies act to anti-inflammation, promote the recovery of gastric mucosa and improve the gastric motility, which is possibly their crucial action mechanism in treating CD.

Keywords: Moxibustion Therapy; Gastritis; Point, Tianshu (ST 25); Point, Zhongwan (CV 12); Point, Qihai (CV 6); Mechanism

【摘要】目的：探讨艾灸治疗慢性胃炎的疗效与机制，为艾灸治疗慢性胃炎提供客观依据。**方法：**将 61 例慢性胃炎患者分为隔药饼灸组和温和灸组。两组治疗均选双侧天枢、中脘、气海施灸。治疗前后所有入选病例均进行胃肠疾病中医证候评分、视觉模拟评分(visual analog score, VAS)，并检测血清促生长素、生长抑素(somatostatin, SS)和胃动素(motilin, MTL)含量的变化。**结果：**隔药饼灸组与温和灸组治疗慢性胃炎总有效率差异无统计学意义($P>0.05$)。治疗后，两组胃肠疾病中医证候评分、VAS 评分均明显降低，与本组治疗前均有统计学差异(均 $P<0.01$)。两组治疗后血清促生长素、MTL 升高，SS 降低，治疗前后比较均有显著性差异(均 $P<0.01$)。并且在治疗期间无不良事件发生。**结论：**隔药饼灸与温和灸均是治疗慢性胃炎的有效方法，两者在改善腹部不适和胃痛方面疗效相当。隔药饼灸与温和灸在抗炎、促进胃粘膜修复和改善胃动力方面起重要作用，该作用可能是其有效治疗慢性胃炎的重要机制。

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Chronic gastritis (CG) refers to chronic inflammation of the gastric mucosa, which can be caused by many internal and external factors. CG is a common disease in clinical gastroenterological practice. The incidence rate of CG among individuals over 35 years of age is 80.9%[1], the prevalence of CG, especially chronic atrophic gastritis generally increases with age[2] and the endoscopic detection rate for CG is 80%-90%[3]. Based on endoscopic pathology, two major types of CG can be identified: non-atrophic (superficial) gastritis and atrophic gastritis. The symptoms of both types of CG are nonspecific but frequently include epigastric discomfort or pain, fullness with distention or nausea, belching, and acid reflux accompanied by loss of appetite, among other dyspeptic symptoms. Without early prevention and treatment of CG, atrophy, intestinal metaplasia, atypical hyperplasia, or even cancer may occur in the lamina propria glands of the gastric mucosa, severely impacting patients' daily life. Moxibustion is a process by which the thermal properties of mugwort leaves are used to stimulate acupoints on skin surface; the resulting signals can be transmitted to certain receptors to activate and adjust higher nervous functions, enhance the immune system, and mobilize the body's own systems to block persistent disease processes[4]. During moxibustion, most patients experience the phenomena of local hyperthermia, itching and swelling, and propagated sensation along the meridians at moxibustion sites or in the regions of lesions[5]. Moxibustion uses the warmth of mugwort leaves and the fiery heat of the moxibustion process itself to warm the meridians and dispel cold; warm yang to resolve dampness; and promote the circulation of qi to relieve pain. By stimulating the meridian qi, moxibustion can regulate body functions through nerves, body fluids, the endocrine system, and the immune system, thereby helping to relieve epigastric pain, recover spleen and stomach function, and regulate qi activity in CG patients[6-7]. Previous studies have demonstrated that moxibustion can reduce inflammatory stimuli not only by increasing blood flow and net Na^+ outflow while decreasing H^+ back diffusion in the gastric mucosa[8] but also by inhibiting the pro-inflammatory immune cytokines interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α), while promoting the anti-inflammatory cytokine IL-10[9-10]. In this manner, moxibustion can contribute to the repair of gastric mucosal damage. The pathogenesis of CG has not yet been completely elucidated. Studies have demonstrated that the brain-gut peptides can peripherally regulate gastrointestinal motility through humoral pathways or by functioning as neurotransmitters in the enteric nervous system and can centrally stimulate or inhibit gastric motility by influencing the vagal loop. Motilin (MTL) can significantly stimulate gastric motility in both the peripheral and enteric nervous systems. Somatostatin (SS) only exhibits excitatory effects on gastric motility within the central nervous system. Ghrelin is structurally similar to MTL and can stimulate gastrointestinal motility in various ways, such as by inducing the migrating motor complex and accelerating gastric emptying,

The treatment of CG by traditional Chinese medicine (TCM) begins with the internal causes of a loss of regulation of qi activity. In combination with compatible drugs, TCM can make the best use of approaches such as repressing the liver and supporting the spleen, promoting blood circulation to remove blood stasis, and regulating qi to eliminate dampness; in this way, TCM can play a key role in gastrointestinal motility function by causing the spleen qi to ascend and the stomach qi to descend and by regulating the liver and spleen together[11-12]. Moxibustion uses a unique meridian theory in which the meridian qi is stimulated at acupoints on the skin surface; through percutaneous absorption, moxibustion can activate the meridians to stop pain, regulate qi and blood, and enhance the immune functions. Therefore, this non-pharmacological treatment can avoid hepatic first-pass effects and the gastrointestinal burden caused by oral drugs. CG patients were the study subjects of this investigation. By establishing an herbal cake-partitioned moxibustion group and a mild-warm moxibustion group, the effects of herbal cake-partitioned moxibustion and mild-warm moxibustion on CG patients with respect to gastrointestinal disease-related TCM syndrome scores, visual analog scale (VAS) scores, and serum levels of the brain-gut peptides ghrelin, SS, and MTL were observed. Using this approach, the clinical efficacy and effector mechanisms of the different moxibustion treatments for CG were explored, providing a scientific basis for the clinical application of moxibustion for treating CG and the possible mechanisms involved in moxibustion's effects.

1 Clinical Material

1.1 Research objective

This study investigated the clinical efficacy of two different moxibustion methods, herbal cake-partitioned moxibustion and mild-warm moxibustion, for the treatment of CG and the possible underlying effector mechanisms involved in the treatment of CG by moxibustion.

1.2 Patient inclusion

All patients in this study were treated in the Department of Gastric Diseases of Shanghai Research Institute of Acupuncture and Meridian, the Department of Acupuncture and Moxibustion of Yueyang Hospital of Integrated Chinese and Western Medicine, Shanghai University of Traditional Chinese Medicine, or the Outpatient Clinic of Lingling Community Health Service Station.

1.3 Diagnostic criteria

1.3.1 Diagnostic criteria of TCM

The TCM-based diagnostic criteria were the pharmaceutical industry standards set forth in the *Criteria of Diagnosis and Therapeutic Effect of Diseases and Syndromes in Traditional Chinese Medicine*[13]. Upper central abdominal pain is the most common symptom; other symptoms include stuffiness and oppression, distension, belching and reflux; contributing factor include emotional disorders, improper diet, overexertion and cold attack.

1.3.2 Diagnostic criteria of Western medicine

The Western medicine-based diagnostic criteria were the pathological diagnostic criteria set forth in the Chinese Consensus on Chronic Gastritis in 2006[14]. Based on the endoscopic features, chronic gastritis can be divided into two basic types: non-atrophic (superficial) and atrophic. Non-atrophic gastritis may present with erythema (nodular, mosaic, striped), raised mucosa, hemorrhagic spot or plate, edema of mucosa and effusion. Atrophic gastritis is characterized by red and white striped mucosa with flattened and even disappeared folds and appearance of granular or nodular vessels.

1.4 Inclusion criteria

All included patients were required to satisfy the following conditions: Met with both TCM-based and Western medicine-based diagnostic criteria for CG; age ranged between 18 and 75 years, without limit on gender; volunteered to participate in this study and having signed an informed consent form.

1.5 Exclusion criteria

Subjects who met one or more of the following conditions were not included in this study: Who did not meet the inclusion criteria; pregnant or lactating women; patients with allergic constitutions and allergies to multiple drugs; patients whose conditions were complicated by severe dysplasia of the gastric mucosa or who had been diagnosed with a suspected malignancy by a pathological examination; patients with either a serious primary disease, such as a heart, brain, liver, kidney, or hematopoietic system disease, or a mental illness; and patients with tuberculosis, hepatitis, HIV, gonorrhea, or another infectious disease.

1.6 Discontinuation criteria

The experimental treatment was discontinued for patients who satisfied at least one of the following criteria: A lack of adherence to the tested treatment; a failure to execute the treatment protocol; the occurrence of additional severe complications or worsening of the disease condition during the treatment process.

1.7 Experimental grouping method

A simple randomized controlled investigative approach was utilized in this study. The enrolled patients were divided into an herbal cake-partitioned moxibustion group (n=30) and a mild-warm moxibustion group (n=31).

2 Treatment Methods

2.1 Acupoints

Zhongwan (CV 12), Qihai (CV 6) and bilateral Tianshu (ST 25) were selected for moxibustion.

2.2 Acupoint positioning

These three points were selected as the treatment acupoints for both the herbal cake-partitioned moxibustion group and the mild-warm moxibustion group. Acupoint positioning was based on the national standards of the People's Republic of China, which are set forth in *Nomenclature and Location of Acupuncture Points* (GB/T12346-2006).

2.3 Methods

2.3.1 Herbal cake-partitioned moxibustion group

The medicinal herbal cakes were produced by the following processes. *Fu Zi* (*Radix Aconiti Lateralis Preparata*), *Rou Gui* (*Cortex Cinnamomi*), *Mu Xiang* (*Radix Aucklandiae*), *Huang Lian* (*Rhizoma Coptidis*), *Dan Shen* (*Radix Salviae Miltiorrhizae*), *Hong Hua* (*Flos Carthami*), and *Bing Pian* (*Borneolum Syntheticu*) were ground into powder. A suitable amount of medicinal powder and rice wine were mixed at 5:6 to form a thick paste. Medicinal herbal cakes with a diameter of 28 mm and a thickness of 5 mm were created by pressing this paste into a special mold. Refined pure moxa sticks were selected (size: 17 mm × 200 mm, Nanyang Wolong Hanyi Moxa Factory, China).

During treatment, the moxa sticks were cut into moxa cones with a height of 16 mm and a weight of 1.8 g to perform herbal cake-partitioned moxibustion. Patients lay in a supine position during treatment. Moxa cones were placed on medicinal herbal cakes. After the moxa cones were ignited, moxibustion was performed by placing the herbal cakes on Zhongwan (CV 12), Qihai (CV 6) and bilateral Tianshu (ST 25). One cone refers to the dosage received when the burning of one moxa cone has naturally completed.

2.3.2 Mild-warm moxibustion group

Patients lay in a supine position during treatment. During moxibustion, the moxa cones were suspended approximately 3 cm above the acupoints (using moxa cones of the same quality and quantity as those in the herbal cake-partitioned moxibustion group) and ignited. The temperature was controlled at approximately 43℃ using infrared thermometers (Fluke Corporation, USA) monitored from time to time.

2.4 Treatment cycle

In both groups, one cone (about 25 min) was applied at each acupoint during every treatment. Treatments occurred once every two days, 3 times per week. Each course of treatment lasted four weeks, and each patient received 1 course of treatment.

2.5 Efficacy evaluation indicators

2.5.1 Gastrointestinal disease TCM syndrome score

The scoring table of gastrointestinal disease TCM syndrome, which was issued in 2003 by the Specialty Committee of Gastroenterology of the China Society of Integrated Traditional Chinese and Western Medicine at the Fifteenth Annual Gastroenterology Techniques Conference in Chongqing, was used to determine the TCM syndrome scores[15-16]. This table assigned integral values to 32 of the most common TCM symptoms of gastrointestinal diseases based on the 4 levels of none, mild, moderate, and severe.

The treatment efficacy evaluation system is introduced to evaluate the improvement of symptoms using the percentage of symptom score reduction (PSSR). The PSSR for a patient after treatment is calculated according to the following formula:

PSSR = (Symptom score before treatment − Symptom score after treatment) ÷ Symptom score before treatment × 100%.

Full recovery: Most of the symptoms disappeared, PSSR≥95%.

Good recovery: The symptoms significantly decreased or disappeared, PSSR≥75%, but <95%.

Moderate recovery: The symptoms decreased, PSSR ≥55%, but <75%.

No recovery: The symptoms without decreasing or decreased a little, PSSR<55%.

2.5.2 VAS scoring criteria

This study utilized the most common VAS to evaluate overall scores for the levels of epigastric discomfort of the examined CG patients before and after treatment. A 10 cm ruler labeled 0 and 10 at its two ends represented different levels from no pain symptoms to the most unbearable pain. Patients labeled the point on the ruler that was most representative of their intensity of discomfort. The distance between 0 and the labeled point was used as the value of the intensity score. The same method was used to perform scoring and objective evaluations both before and after treatment.

2.5.3 Detection of serum brain-gut peptide levels

Venous blood samples from the patients were collected before and after treatment and used to prepare serum sample, using enzyme-linked immunosorbent assay (ELISA) to detect the serum levels of the brain-gut peptides ghrelin, SS, and MTL.

2.6 Safety evaluation

The safety evaluation encompassed the following two types of safety considerations: vital signs, which included body temperature, respiration, heart rate, blood pressure, and liver and kidney function after treatment; and moxibustion abnormalities, which included skin burns, blisters, or other moxibustion-induced discomfort. All adverse events and adverse reactions were accurately recorded.

If an adverse event occurred after treatment, appropriate treatment was provided to patients. If extremely small blisters occurred after moxibustion, special treatments were not required; however, blisters with areas larger than 1 cm^2 were broken and treated with ointment.

2.7 Statistical methods

The SPSS 15.0 software package was used for data analysis and processing. Measurement data that were normally distributed (or approximately normally distributed) were presented as mean ± standard deviation ($\bar{x} \pm s$). Data with skewed distributions were presented as median (minimum, maximum) [M (min, max)]. For measurement data that were normally distributed (or approximately normally distributed) with homogeneous variances, paired-sample *t*-tests were used for inter-group comparisons of the pre-treatment and post-treatment values, whereas independent-sample *t*-test was used for between-group comparison. Data with skewed distributions were assessed using a nonparametric rank-sum test. With respect to evaluation criteria, α=0.05 and $P<0.05$ were used as the thresholds for statistical significance.

3 Results

A total of 61 patients were enrolled, and 60 patients completed the study (98%). One subject in the mild-warm moxibustion group did not complete the treatment due to a business travel; thus, there was a total of 1 lost case, and the final statistical analyses included 30 patients in each treatment group.

3.1 The general condition of patients

The between-group comparisons in baseline characteristic, such as age ($P = 0.625$), gender ($P=0.563$) and disease duration ($P=0.532$) revealed no significant differences. Thus, the two groups were comparable (Table 1).

Table 1. Analysis of the general baseline conditions of the two groups

Group	*n*	Gender (case)		Age [M (min, max), year]	Disease duration [M (min, max), year]
		Male	Female		
Herbal cake-partitioned moxibustion	30	7	23	59.5 (25, 74)	3 (1, 15)
Mild-warm moxibustion	30	9	21	56.5 (30, 70)	4.5 (1, 13)
Statistical value		0.335[1)]		−0.488[2)]	−0.626
P value		0.563		0.625	0.532

Note: 1) x^2 value; 2) *Z* value

3.2 Gastrointestinal disease-related TCM syndrome score

The pre-treatment gastrointestinal disease-related TCM syndrome scores of the two groups were comparable, the difference was statistically inignificant ($P=0.893$). In the herbal cake-partitioned moxibustion group, the post-treatment TCM syndrome score was markedly lower than that before treatment, and the difference between before and after treatment was statistically significant ($P<0.001$). Similarly, in the mild-warm moxibustion group, the post-treatment TCM syndrome score was also markedly reduced relative to the pre-treatment score, and the difference between before and after treatment was statistically significant ($P<0.001$). And the difference value of gastrointestinal disease-related TCM syndrome score between the two groups was statistically insignificant after treatment ($P>0.05$), (Table 2).

3.3 VAS score

The pre-treatment difference of VAS score between the two groups was statistically insignificant ($P=0.834$). In the herbal cake-partitioned moxibustion group, the post-treatment VAS score was markedly lower than the pre-treatment VAS score, and the difference between the pre- and post-treatment was statistically significant ($P<0.001$). Similarly, in the mild-warm moxibustion group, the post-treatment VAS score was also markedly reduced relative to the pre-treatment VAS score, and the difference between pre- and post-treatment was statistically significant ($P<0.001$). And the difference value of VAS score between the two groups was statistically insignificant after treatment ($P>0.05$), (Table 3).

Table 2. Comparison of gastrointestinal disease-related TCM syndrome scores between the two groups ($\bar{x}\pm s$, point)

Group	*n*	Before treatment	After treatment	Difference between before and after treatment
Herbal cake-partitioned moxibustion	30	67.10±18.89	28.57±16.93[1)]	−38.53±15.05
Mild-warm moxibustion	30	67.83±23.08	28.87±15.22[1)]	−38.97±17.54

Note: Intra-group comparison, 1) $P<0.01$

Table 3. Comparison of the VAS scores between the two groups [M (min, max), point]

Group	*n*	Before treatment	After treatment	Difference between before and after treatment
Herbal cake-partitioned moxibustion	30	7 (4, 10)	2 (1, 6)[1)]	5 (−6, −2)
Mild-warm moxibustion	30	7 (4, 10)	2 (0, 6)[1)]	−5 (−8, −2)

Note: Intra-group comparison, 1) $P<0.01$

3.4 Comparisons of serum levels of brain-gut peptide indicators

Table 4 compares the serum levels of the brain-gut peptides ghrelin, SS, and MTL for the two groups of patients. The pre-treatment serum ghrelin levels of the two groups were comparable and did not significantly differ ($P>0.05$). In the herbal cake-partitioned moxibustion group, the post-treatment serum ghrelin levels showed a statistically significant difference ($P=0.003$) from the pre-treatment serum ghrelin. Similarly, the mild-warm moxibustion group also showed a marked statistically significant difference ($P=0.003$) between post-treatment and pre-treatment in serum ghrelin levels. These results indicated that both herbal cake-partitioned moxibustion and mild-warm moxibustion could effectively increase serum ghrelin levels. And the difference value of serum ghrelin between the two groups was statistically insignificant after treatment ($P>0.05$), demonstrating that herbal cake-partitioned moxibustion and mild-warm moxibustion produced similar changes in serum ghrelin levels after treatment.

An examination of the serum SS levels before treatment in the two groups indicated that these levels were comparable ($P > 0.05$). In the herbal cake-partitioned moxibustion group, the post-treatment serum SS level differed markedly from the pre-treatment serum SS level, and this difference was statistically significant ($P < 0.001$). Similarly, in the mild-warm moxibustion group, there was a marked difference between post-treatment and pre-treatment serum SS levels, and this difference was also statistically significant ($P < 0.001$). These results indicated that herbal cake-partitioned moxibustion and mild-warm moxibustion could both effectively decrease serum SS levels. And the difference value of serum SS between the two groups was statistically insignificant after treatment ($P > 0.05$), demonstrating that herbal cake-partitioned moxibustion and mild-warm moxibustion produced similar changes in serum SS levels after treatment.

An examination of pre-treatment serum MTL levels in the two groups indicated that these levels were also comparable, the between-group difference was statistically insignificant ($P > 0.05$). In the herbal cake-partitioned moxibustion group, the post-treatment serum MTL level was markedly higher than that before treatment, showing a statistically significant ($P < 0.001$). Similarly, in the mild-warm moxibustion group, the post-treatment serum MTL level also showed a marked and statistically significant ($P < 0.001$) increase over the pre-treatment MTL level. These results indicated that both herbal cake-partitioned moxibustion and mild-warm moxibustion could effectively increase serum MTL level. And the difference value of serum MTL between the two groups was statistically insignificant after treatment ($P > 0.05$), demonstrating that herbal cake-partitioned moxibustion and mild-warm moxibustion produced similar changes in the serum MTL level after treatment.

Table 4. Comparisons of serum levels of the brain-gut peptides ghrelin, SS, and MTL between the two groups

Group	*n*	Time	Ghrelin [M (min, max), ng/L]	SS [M (min, max), μg/L]	MTL ($\bar{x} \pm s$, ng/L)
Herbal cake-partitioned moxibustion	30	Before treatment	1768.49 (1002.07, 8051.74)	9.61 (6.78, 91.03)	192.83±34.15
		After treatment	2334.22 (1009.52, 8642.04)[1)]	8.00 (3.46, 89.55)[1)]	278.54±55.77[1)]
		D-value	257.40 (−1633.74, 3562.28)	−1.46 (−21.05, 1.00)	85.71±52.95
Mild-warm moxibustion	30	Before treatment	1412.22 (1005.79, 8785.71)	9.81 (5.20, 89.08)	195.10±32.61
		After treatment	1721.94 (1018.94, 8558.55)[1)]	7.64 (3.86, 88.37)[1)]	278.75±54.98[1)]
		D-value	42.79 (−227.16, 1648.17)	−1.35 (−14.01, −0.09)	83.64±57.92

Note: D-value=Difference between before and after treatment; intra-group comparison, 1) $P < 0.01$

3.5 Safety assessment

One adverse event occurred during treatment in the herbal cake-partitioned moxibustion group. This event was mild burns during moxibustion and healed before the next treatment. No serious adverse events occurred.

4 Discussion

Our previous studies have confirmed that herbal cake-partitioned moxibustion at Zhongwan (CV 12), bilateral Tianshu (ST 25), and Qihai (CV 6) can effectively treat CG[17]. The results of this study indicated that in CG patients, both herbal cake-partitioned moxibustion and mild-warm moxibustion can not only effectively relieve abdominal pain and other symptoms but also increase the serum ghrelin and MTL levels and decrease the serum SS levels. We speculate that these effects may be important mechanisms in the effective treatment of CG.

The main forms of moxibustion include mild-warm moxibustion (also known as suspended moxibustion, in which a certain distance is maintained between the skin and the moxibustion sites), herbal cake-partitioned moxibustion (indirect moxibustion through a variety of different materials), and scarring moxibustion (moxibustion in which moxa cones are directly burned on the skin at acupoint locations to gradually cause suppuration and eventually form scars)[18]. Because of its simplicity to perform and known therapeutic effectiveness, mild-warm moxibustion is the most widely used form of moxibustion in clinical applications. Mild-warm moxibustion, which is based on the characteristics of mugwort leaves, cures disease through heat. The heat production in mild-warm moxibustion is relatively concentrated, and temperature variations at acupoints on the body surface during moxibustion exhibit relatively steady increases; producing fairly stable thermal stimulation sensations in the human body. Herbal cake-partitioned moxibustion is an indirect moxibustion approach that cleverly utilizes the synergistic effects of herbs and moxibustion therapy. In this study, for patients in the herbal cake-partitioned

moxibustion group, there was a significant decrease in the post-treatment gastrointestinal disease-related TCM syndrome score relative to the pre-treatment TCM syndrome score ($P<0.001$), indicating that the patients' relevant symptoms significantly improved after herbal cake-partitioned moxibustion treatment and that herbal cake-partitioned moxibustion can effectively treat CG. In the mild-warm moxibustion group, there was also a marked decrease in the post-treatment gastrointestinal disease-related TCM syndrome score relative to the pre-treatment TCM syndrome score; this decrease was significant ($P<0.01$), demonstrating that mild-warm moxibustion could also effectively treat CG. There were no significant difference between the herbal cake-partitioned moxibustion group and the mild-warm moxibustion group with respect to TCM syndrome score ($P>0.05$), suggesting that in these CG patients, the overall therapeutic effects of herbal cake-partitioned moxibustion and mild-warm moxibustion were similar. However, the two types of moxibustion exhibited different efficacies for patients with differing symptoms. With respect to the components of the medicinal herbal cake, *Fu Zi* (*Radix Aconiti Lateralis Preparata*) and *Rou Gui* (*Cortex Cinnamomi*) not only tonify fire and bolster yang but also dispel cold and relieve pain. Moreover, *Mu Xiang* (*Radix Aucklandiae*) and *Huang Lian* (*Rhizoma Coptidis*) can promote qi circulation and relieve pain; disperse stagnant liver qi and harmonize the stomach; and regulate the spleen and stomach while remove food stagnation. In addition, herbal cake-partitioned moxibustion is a yang-stimulating thermotherapy that can tonify, reinforce, and nourish yang; dispel cold; tonify the spleen; and strengthen the kidneys. As a result, herbal cake-partitioned moxibustion has excellent effects in treating CG that involves the stagnation of qi in the liver and stomach and/or deficiencies due to cold in the spleen and stomach. Mild-warm moxibustion uses pure moxa sticks for moxibustion; there is no direct contact with the skin; the height of the moxa sticks is relatively fixed; the heat is balanced; and the thermal energy is consistent and comfortable. This moxibustion technique uses the unique effect of moxa to warm and activate the meridians and regulates the function of the internal organs, therefore, mild-warm moxibustion has remarkable therapeutic effects with respect to warm the spleen and stomach, regulate qi, and promote stomach harmony.

Moxibustion and acupuncture both regulate meridian qi circulation through meridians and acupoints on the body surface. Through thermal stimulation, moxibustion can improve local microcirculation by not only warming and activating the meridians but also promoting qi flow and blood circulation. The key to achieving good analgesic effects through acupuncture and moxibustion is that acupuncture and moxibustion both stimulate the body's own inherent capabilities to adjust body functions towards normal levels. These techniques also effectively increase the availability of endogenous analgesic opioid peptides such as enkephalins, β-endorphin, and dynorphin[19]; reduce anti-opioid substances[20] to decrease the body's sensitivity to pain; and increase the pain threshold in the nerve centers corresponding to visceral organs, thereby alleviating visceral pain in accordance with the embryo containing the information of the whole organism (ECIWO) theory[21]. The results of this study indicated that the VAS scores significantly decreased after treatment in both the herbal cake-partitioned moxibustion group and the mild-warm moxibustion group; specifically, these scores decreased from 7 (5, 8) points prior to treatment to 2 (1, 3) points after treatment. These results demonstrated that both herbal cake-partitioned moxibustion and mild-warm moxibustion could effectively improve epigastric pain and produce analgesic effects.

Previous study has demonstrated that moxibustion exerts its effects through its warm-dredging or heat-promoting effects[22]. Certain scholars regard thermal effects as the key aspect of moxibustion[23-24]. During moxibustion therapy, thermal stimulation affects are not only the epidermis but also the subcutaneous and muscular layers; by activating various receptors in the skin and muscle layers, moxibustion affects the biological activities of the nervous system, tissues, and cells. Brain-gut peptides, which include ghrelin, MTL, and SS, are widely distributed throughout the gastrointestinal tract. Studies have revealed that ghrelin is the third known endogenous ligand [in addition to growth hormone-releasing hormone (GHRH) and SS] that regulates the secretion of growth hormone (GH) from the pituitary gland. Ghrelin is currently the only known humoral orexigenic factor. Through an endothelin-mediated mechanism, ghrelin can stimulate the release of nitric oxide. Moreover, ghrelin can protect the gastric mucosa through central and peripheral pathways; it may also activate neuropeptide γ in the arcuate nucleus of the hypothalamus to increase gastric motility and food intake, promote appetite, and up-regulate gastric acid secretion[25-26]. The coordination between SS and ghrelin can inhibit the release of endogenous somatotropin release inhibiting factor (SRIF), directly or indirectly increasing GH and protecting gastric mucosa. In patients with Helicobacter pylori-positive chronic atrophic gastritis, the appropriate reduction of SS can weaken the inhibitory effects of SS on gastric motility, reduce blood flow in the gastric mucosa, and prevent ulcers. Significant reductions in SS, which may be caused by the

decreased SS secretion from D cells in the pyloric glands, can cause changes such as atrophy of the gastric mucosal glands. Furthermore, increases in MTL can accelerate gastrointestinal motility and gastric emptying, reduce stomach capacity, and relieve epigastric fullness, early satiety, nausea, and other symptoms of functional dyspepsia. In cases of glandular atrophy, intestinal metaplasia, dysplasia, or inflammation, MTL will increase the secretion of the neural and humoral factors to promote gastrointestinal motility[27]. The results of this study demonstrated that the serum levels of ghrelin and MTL exhibited statistically significant increases ($P < 0.01$) after treatment by either herbal cake-partitioned moxibustion or mild-warm moxibustion. These results indicated that herbal cake-partitioned moxibustion and mild-warm moxibustion could both effectively increase the serum levels of ghrelin and MTL in CG patients. The release of ghrelin contributes to relieving inflammation, reducing gastric acid secretion, repairing and protecting the gastric mucosa, promoting food intake, improving antropyloric coordination[28-29], enhancing motility and emptying, and improving dyspeptic symptoms. The observed increases in the serum MTL levels indicated that moxibustion could enhance gastrointestinal motility, improve gastrointestinal contractility, strengthen phase III activity during digestion, promote the gastric emptying of solids and liquids, and improve functional dyspepsia symptoms. In addition, after treatment with herbal cake-partitioned moxibustion or mild-warm moxibustion, the serum SS levels were markedly decreased relative to the pre-treatment serum SS levels; this decrease was statistically significant ($P<0.01$), indicating that both herbal cake-partitioned moxibustion and mild-warm moxibustion could effectively decrease serum SS levels. This reduction in the serum SS level could weaken the inhibition of gastrin release by SS, thereby indirectly increasing blood flow to the gastric mucosa, promoting mucosal repair, improving microcirculation, and contributing to the recovery of gastrointestinal function. The external treatment effects of herbal cake-partitioned moxibustion and mild-warm moxibustion could increase the endogenous serum levels of ghrelin and MTL and decrease the serum levels of SS; these effects may be important mechanisms in the moxibustion-based treatment of CG and the regulation of gastrointestinal functions.

In conclusion, this study demonstrated that both herbal cake-partitioned moxibustion and mild-warm moxibustion are effective methods for treating CG; thus, this investigation provided a reliable theoretical basis for the clinical use of herbal cake-partitioned moxibustion and mild-warm moxibustion in treatment of CG.

Conflict of Interest

The authors declared that there was no potential conflict of interest in this article.

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Statement of Informed Consent

Informed consent was obtained from all individual participants included in this study.

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