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Original Article

Curative effect of Weierkang pills on chronic atrophic gastritis: a clinical study

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Abstract: *Objective:* To assess the efficacy of Weierkang Pills (WEKP) on chronic atrophic gastritis (CAG) patients on evidence based diagnostic and therapeutic criteria and try to explore optimal duration of WEKP. *Methods:* A total of 82 patients met the criteria were assigned to receive WEKP for either 3 months or 6 months. Observation of pathology changes were considered as primary outcome, changes of symptoms and endoscopic findings were considered as secondary outcomes. *Results:* Both groups showed an improvement inpathology and symptoms. Effective rate of pathology: in 3-month treatment group, inflammation regression rate was 26.2%, mucosal atrophy and intestinal metaplasia regression rate was 61.9% and in 6-month treatment group, which was up to 42.5% and 67.5% respectively. But there were no significant differences between two groups (p=0.12, p=0.60). Effective rates of symptoms were 65.2% and 85.3% in 3-month treatment group and 6-month treatment group respectively, and significant differences were found between two groups (p=0.003). *Conclusion:* WEKP treatment could obviously improve symptoms of chronic atrophic gastritis, and long-term duration is prior to short-term duration. Besides, it could block and even reverse the progress of CAG to GC to some extent in pathology aspect.

Keywords: Chronic atrophic gastritis, Weierkang pills, mucosal atrophy, intestinal metaplasia, clinical trial

Introduction

Chronic atrophic gastritis (CAG), induced by various causes, is a very common disease of the digestive tract and is an inflammatory condition characterized by the loss of gastric glandular [1]. It usually has a long duration of the illness, repeated attacks, and is an important precursor lesion of gastric carcinoma. The incidence of CAG increases with age, since the infection rate of *Helicobacter (H.) pylori* (HP) increases in old population and intestinal metaplasia has a relationship with aging. Although the exact prevalence rate is unknown, the Digestive Endoscopy Branch of Chinese Medical Association conducted a national multicenter cross-sectional study, 2014, which showed that the incidence of CAG is 17.69% (1573/8829) in all 33 centers [2]. Current treatments of CAG aim to relieve symptoms and improve inflammatory, but few method or western drugs have been proved to be effective for its prevention, treatment or even reversion.

Nowadays, many scholars pay attention to apply Traditional Chinese Medicine (TCM) to various diseases throughout the world. According to a large number of clinical studies [3-5], herbal drugs were verified to be an essential part of drugs that play an important role in the prevention and treatment of chronic diseases. Besides, it has been reported that, herbal drugs, such as Huang Qi, Jiang Huang were found to be associated with enhanced antitumor function in vivo and vitro studies [6, 7]. A clinical practice guideline of Chinese medicine for chronic gastritis recommended different kinds of herbs combination for corresponding patterns of Spleen and Stomach imbalance [8]. Chinese medicine was thought to take a holistic view to mediate attacking systems and self-regulation [9]. In recent decades, many efforts were made to evaluate the metabolomics and interaction of TCM [10, 11], and the active components of TCM was verified by modern technology.

Table 1. Criteria of symptoms assessment

	Scores			
Symptom	0	1	2	3
Epigastric pain	None	Sometimes	Usually but can be relieved	Durable and cann't be relieved
Poor appetite	None	Sometimes	Usually but can be relieved	Durable and cann't be relieved
Acid regurgitation	None	Sometimes	Usually but can be relieved	Durable and cann't be relieved
Gastric distention	None	Sometimes	Usually but can be relieved	Durable and cann't be relieved
Belching	None	Sometimes	Usually but can be relieved	Durable and cann't be relieved
Nausea	None	Sometimes	Usually but can be relieved	Durable and cann't be relieved
Emesis	None	Sometimes	Usually but can be relieved	Durable and cann't be relieved

Table 2. Criteria of pathology assessment

	Grade			
Pathology	0	1	2	3
Mucosal inflammation	None	<1/3 mucosal	1/3~2/3 mucosal	>2/3 mucosal
Loss of mucosal glands	None	<1/3	1/3~2/3	>2/3
Intestinal metaplasia	None	Mild	Moderate	Severe
Allotypic hyperplasia	None	Mild	Moderate	Severe

Note: The biopsy was mainly taken from gastric antrum, and other suspicious lesions were disposed separately. Specimens were deep enough to reach mucosa layer and all were under pathological examination for HP infection status. Eradication therapy would be given to the patients with HP positive before they participated this trial.

It has been reported twenty years ago that "Weierkang Pills" (WEKP), a TCM drug, contains *Strychnosnux-vomica Linn* (Ma Qian Zi), *Codonopsispilosula* (Dang Shen), *radix trichosanthis* (Tian Hua Podwer), *Crataeguspinnatifida Bunge* (Shan Zha), *Ebony* (Wu Mei), *sauussureacostus* (Guang Mu Xiang) and so on, showed a certain effect on symptom improvement of CAG. It also has been assessed its safety both in animal experiment and clinical trial, but without advanced instruments and judgment criteriaat that time [12]. In this study, we try to demonstrate the effect of WEKP on CAG systematically. We set two groups to apply WEKP and try to explore optimal duration of WEKP.

Methods

Subjects & design

This current study is a population-based, self-controlled, prospective clinical trail. According to the Consensus on Chronic Gastritis in China (Shanghai 2012) [13] and the updated Sydney system [14], a total of 127 outpatients of GAG confirmed by endoscopic and pathologic examinations were recruited from March, 2014 to March, 2015 at Sir Run Run Shaw Hospital, Hangzhou, China. The participants were assigned into two groups. One group was designed to use WEKP for 3 months, while the other group was treated by WEKP for 6 months. *H. pylori*positive patients were first given *H. pylori* eradication treatment, and then enrolled with *H. pylori*negative atleast two weeks. The data including age, gender, previous and latter symptoms scores, endoscopic and pathological findings were analyzed.Written informed consents were provided by all patients. Besides, the trail has obtained agreement by Sir Run Run Shaw Hospital Clinical Trials and Biomedical Ethics Committee (No. 20140619-2) and has been registered in the Chineses Clinical Trial Registry (ChiCTR-IPR-16008996, http://www.chictr.org.cn/). This drugs were supplied by Huadong Pharmaceutical Ltd, Ningbo, China.

Diagnostic criteria

On the basis of the consensus on Chronic Gastritis in China (Shanghai, 2012) and the updated Sydney system, gastroscopy and biopsies for histological investigation were required to be done first. Then each biopsy was evaluated separately by two dependent pathologists as following items: mucosal inflammation, loss of mucosal glands, intestinal metaplasia and allotypic hyperplasia when patients were considered as eligible subjects who fulfilled the diagnosis of CAG.

Inclusion criteria: 1. Diagnosis of CAG according to the consensus on chronic gastritis in China (Shanghai, 2012) and the updated Sy-

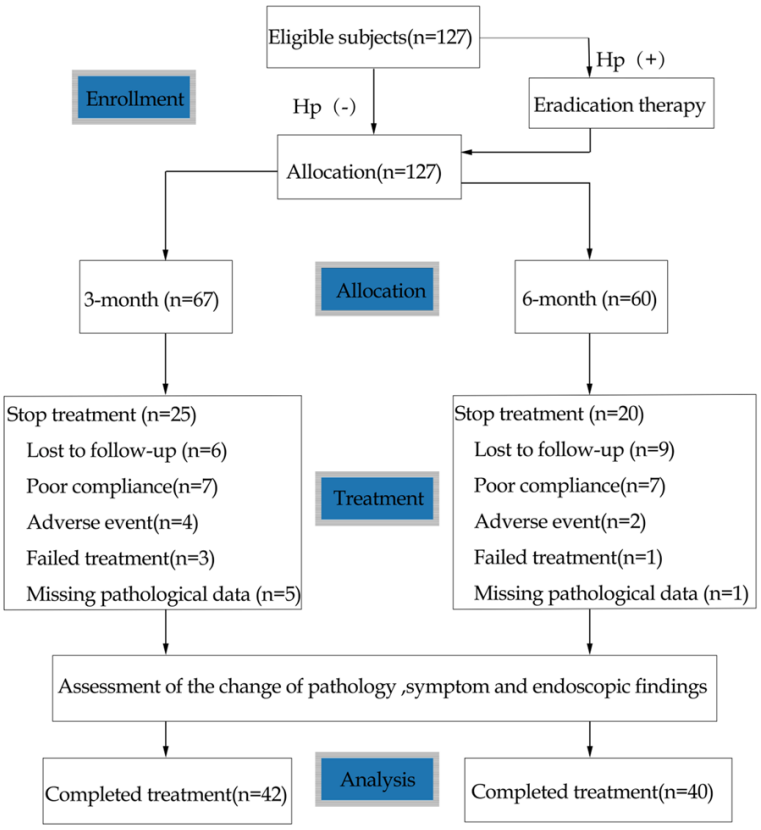

Figure 1. Flow chart of the patients with chronic atrophic gastritis in the clinical trial.

Table 3. Basic characteristics of the population

Baseline	3-month (n=42)	6-month (n=40)	*P* value
Age	55.96±9.17	57.10±6.92	0.526
Gender			
Male	20	23	
Female	22	17	0.387
Symptoms score	2.50±1.58	2.72±2.40	0.616

dney system. 2. Aged between 20 and 70 years old.

Exclusion criteria: 1. Gastric surgery history. 2. Combined with gastric carcinoma or other malignancy. 3. Ulceration, barrett's esophagus or other upper GI disease. 4. Having received acid inhibitors (H2 antagonists or proton pump inhibitors), promote power medicine (mosapride or domperidone, etc.) or gastric mucosa protectant for pury (teprenone, sucralfate, gefarnate, glutamine, rebamipide, bismuth, etc.) to treat CAG in the last two weeks before this trial. 5. Administration of non-steroidal anti-inflammatory, such as Aspirin, recently. 6. Severe comorbidities of heart, liver, kidney, lung or blood system. 7. Preparing for a baby, pregnant or lactating female patients. 8. Allergic to the trial tablets. 9. Unwilling to participate in this trail or unable to be followed up.

Test drugs and administration

The WEKP were manufactured by Huadong Pharmaceutical Ltd, Ningbo, China. The prescription for this pillhas obtained the approval of the SFDA for clinical studies only (Approval No. z10970120). Components of the tablet contain: *Strychnosnux-vomica Linn* (Ma Qian Zi), *Codonopsispilosula* (Dang Shen), *radix trichosanthis* (Tian Hua Podwer), *Crataeguspinnatifida Bunge* (Shan Zha), *Ebony* (Wu Mei), *sauussureacostus* (Guang Mu Xiang) and so on. Patients were randomized to two different durationgroups, in which they took 3 pills three times a day for 3 months, or for 6 months. A follow-up visit was scheduled after treatment.

Criteria for therapeutic effects

Pathological finding was treated as primary outcome, clinical symptoms and endoscopic findings were considered as secondary outcomes.

Observation of symptoms: The main symptoms were recorded respectively before and after the treatment, including epigastric pain, poor appetite, acid regurgitation, gastric distention, belching, nausea and emesis. The symptoms were scored in 4 grades: zero point for no symptoms, 1 point for the symptoms happening sometimes, 2 points for the symptoms happening usually but can be relieved by drugs, and 3 points for the symptoms happening continuously but cann't be relieved. The therapeutic effects were determined based on the total scores, shown in (**Table 1**).

Observation of pathology: Gastric glandular atrophy and hyperplasia were recorded respec-

Table 4. Response rate of two groups on pathology

Group	No.	Markedly effective	Effective	Ineffective	Effective rate (%)	*p* value	Markedly effective rate (%)	*p* value
Regression of inflammation								
3-month	42	0	11	31	26.2		0	
6-month	40	3	14	23	42.5	0.12	7.5	0.11
Mucosal atrophy and intestinal metaplasis								
3-month	42	9	17	16	61.9		21.4	
6-month	40	12	15	13	67.5	0.60	30	0.37

Note: No allotypic hyperplasia results were observed during this clinical trail.

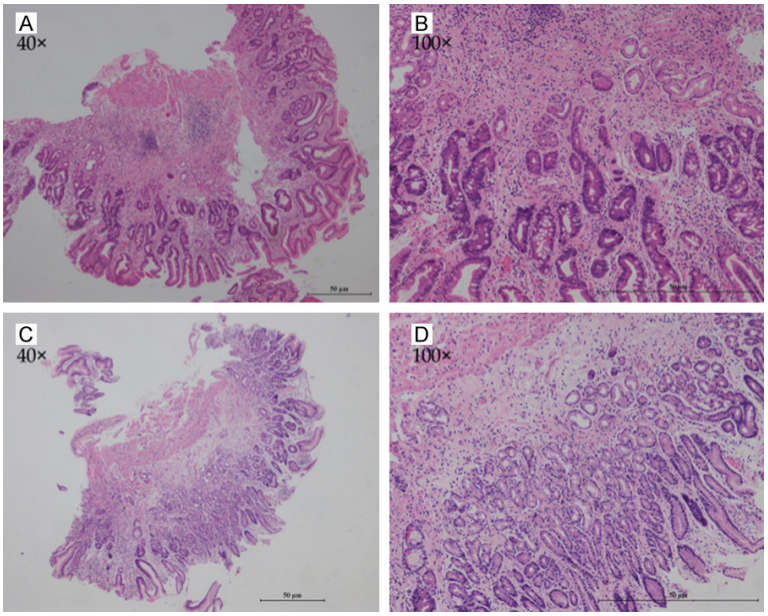

Figure 2. Pathological changes of chronic atrophic gastritis after treatment for 3-month group. Pathological findings were shown in (A and B) (before 3-month treatment) and (C and D) (after 3-month treatment).

tively before and after the treatment, including mucosal inflammation, the loss of mucosal glands (mucosal atrophy), intestinal metaplasia andallotypic hyperplasia. The symptoms were scored in 4 grades: zero point for no symptoms, 1 point for mild symptoms, 2 points for moderate symptoms, and 3 points for severe symptoms. The therapeutic effects were determined based on the total scores, shown in (**Table 2**).

The criteria for symptom therapeutic effects: Markedly effective: Disappearance or basic disappearance of clinical symptoms. Effective: Improvement or obvious alleviation of clinical symptoms, and the symptom score decrease ≥50%. Ineffective: no improvement or even aggravation of clinical symptoms, and the symptom score decrease <50%. Total effective rate referred to the sum of markedly effective rate and effective rate.

The criteria for pathologic therapeutic effects: Markedly effective: disappearance of active inflammation or improvement of inflammation for two grades, or improvement of the mucosal atrophy over two grades, or over two-grade improvement of mucosal atrophy accompanied with mild improvement of intestinal metaplasia and allotypic hyperplasia; or one-grade improvement of mucosal atrophy accompanied with improvement or disappearance of intestinal metaplasia and allotypic hyperplasia. Effective: improvement of inflammation for one grade, or mild improvement in any of the three, i.e., mucosal atrophy, intestinal metaplasia and allotypic hyperplasia. Ineffective: no pathologic improvement, or even the condition being worse. Total effective rate referred to the sum of markedly effective rate and effective rate.

Statistics

SPSS 16.0 was used to perform all the statistical analyses. Continuous variables are expressed as mean ± standard deviation (SD) and categorical variables are expressed as frequencies (percentages). Student's t-test or Chi-square test was used to compare demographic data baselines and evaluate the response rate of symptom improvement and the pathological grades change between groups. $p<0.05$ was

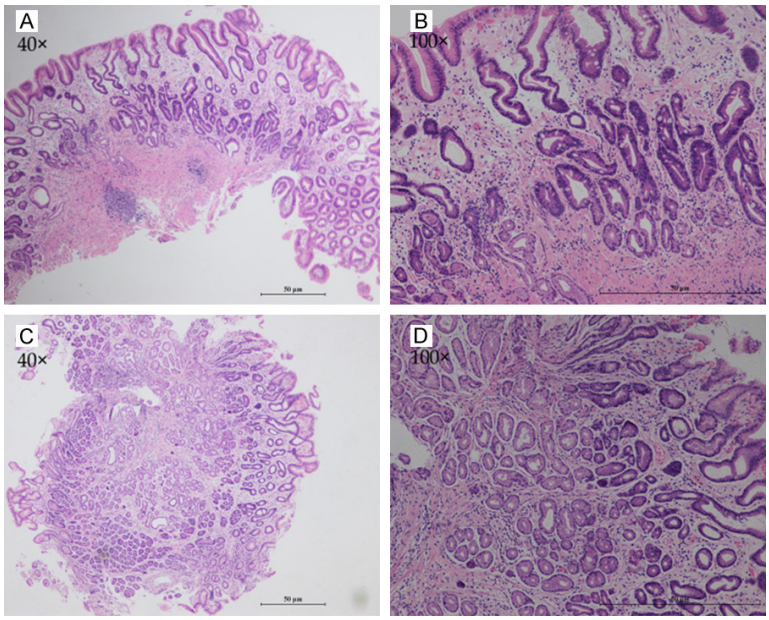

Figure 3. Pathological changes of chronic atrophic gastritis after treatment for 6-month group. Pathological findings were shown in (A and B) (before 6-month treatment) and (C and D) (after 6-month treatment).

Table 5. Changes of symptom scores (points, x±s)

Group	No.	Before treatment	After treatment
3-month	42	2.50±1.58	1.31±1.33[a]
6-month	40	2.72±2.40	0.52±0.99[a,b]

Note: [a]p<0.01 in-group comparison before and after treatment; [b]p<0.01, compared with 3-month treatment for WEKP.

assumed to be statistically significant for two-sided tests.

Results

Baseline

Finally, 82 patients completedthis trials, shown in (**Figure 1**). 42 patients (20 male, 22 female; mean age 55.96±9.17 years) were assigned to3-month treatment of WEKP group and 40 patients (23 male, 17 female; mean age 57.10±6.92) were assigned to 6-month treatment ofWEKP group. No statistical significance was found between two groups in baseline data (age, gender ratio and symptoms scores), shown in (**Table 3**).

Primary outcome evaluation

The total effective rate of inflammation, mucosal atrophy and intestinal metaplasia were 26.2%, 61.9% in 3-month treatment group and 42.5%, 67.5% in 6-month treatment group, but there was no significant difference between groups. The improvements of inflammation, mucosal atrophy and intestinal metaplasia after treatment were showed in **Table 4**. And the changes ofpathologic findings were shown in (**Figures 2** and **3**).

Secondary outcome evaluation

After treatment, both of two groups showed an obvious improvement in symptoms. The score values before and after the treatment were described in **Table 5**, both showing significant differences before and after WEPT treatment. For 3-month treatment, its total effective rate reached to 63.4% and markedly effective rate reached to 31.7%, while for 6-month treatment, its total effective rate reached to 85.3% and markedly effective rate reached to 61.8%, shown in **Table 6**. For between-group comparison, 6-month treatment had a more significant improvement in total symptom scores (p<0.01) and total effective rate (p<0.01). There was a significant difference in the gastric distention score between two groups (p<0.05), but no significant difference in the scores ofepigastric pain, poor appetite, acid regurgitation, belching, nausea and emesis was found. Changes of endoscopic findings were shown in (**Figure 4**).

Adverse reaction

During this clinical trail, 4 patients in 3-month group and 2 patients in 6-month group reported rash reaction after WEKP treatment, then they refused to further study.

Disscussion

Gastric carcinoma refers to a multistep process, which contains a series of mucosal lesions, from superficial gastritis, chronic atrophic gastritis, intestinal metaplasia to dysplasia. Mostly, gastric carcinoma was diagnosed at advanced stage due to its atypical symptom,

Table 6. Improvement in symptoms and the total effective rate of two groups

Group	No.	Markedly effective	Effective	Ineffective	Effective rate (%)	*p* value	markedly effective rate (%)	*p* value
Total symtoms								
3-month	42	13	13	15	63.4		31.7	
6-month	40	21	8	5	85.3	0.003[c]	61.8	0.009[c]
Epigastric pain								
3-month	23	16	1	6	73.9		69.2	
6-month	18	15	1	2	88.9	0.422	83.3	0.382
Poor appetite								
3-month	5	4	1	0	100.0		80.0	
6-month	4	3	1	0	100.0	-	75.0	-
Acid regurgitation								
3-month	11	7	1	3	72.7		63.6	
6-month	16	13	1	2	87.5	0.353	81.3	0.340
Gastric distention								
3-month	19	6	7	6	68.4		31.6	
6-month	22	17	2	3	86.4	0.178	77.3	0.04[d]
Belching								
3-month	22	10	6	6	72.7		45.5	
6-month	17	12	2	3	82.4	0.676	70.6	0.188
Nausea								
3-month	4	4	0	0	100.0		100	
6-month	3	3	0	0	100.0	-	100	-
Emesis								
3-month	0	0	0	0				
6-month	1	1	0	0	100.0	-	100	-

Note: Compared with 3-month treatment for WEKP, [c]$p<0.01$, [d]$p<0.05$. Due to 7 trialed patients(1 for A group,6 for B group) didn't have obvious symptoms during all the observation, so 41/42 subjects data in the 3-month treatment group and 34/40 subjects data in the 6-month treatment group were calculated eventually in this comparison.

so it's essential to focus on the precursor lesion of gastric carcinoma. It has been proved worldwide that CAG is a precancerous lesion of the gastric cancer, and there is a positive correlation between the morbidity of CAG and gastric cancer [1].

China has a high morbidity of GAG and more and more Chinese people have been diagnosed as CAG, predisposing to intestinal metaplasia, dysplasia, and eventually gastric cancer. To block and even reverse the progress of CAG to GC, which is the key way to control disease and prolong life, is the main point we should focus on. However, in the clinical practice, few therapeutic drugs have been proved to be effective in current western medical system. Based on this concern, TCM is getting more and more attention as many of them have been proved to be effective on CAG [5, 15-17]. Its potential mechanism was reported that TCM can treat for atrophic gastritis through protecting the gastric mucosa, strengthening antioxidant, influencing cell proliferation and gene expression and mediating gastrointestinal hormones [4].

Twenty years ago, Professor Li CY *et al.* first reported the clinical and experimental study of Weierkang Pills (WEKP) on treating CAG. It showed that WEKP had a significant anti-inflammatory, strong spleen function and could promote the effect of atrophic glands regeneration and repair. In their study, the pathogenesis of CAG and the efficacy of WEKP was described in TCM theory. CAG was considered as an imbalance condition of spleen and stomach. Besides, a 550-clinical observation trail for WEKP performed by Wang LQ *et al.* [18], showed its total effective rate was up to 97%. But due to these researches lack of evidence-based medicine effective basis, there was still

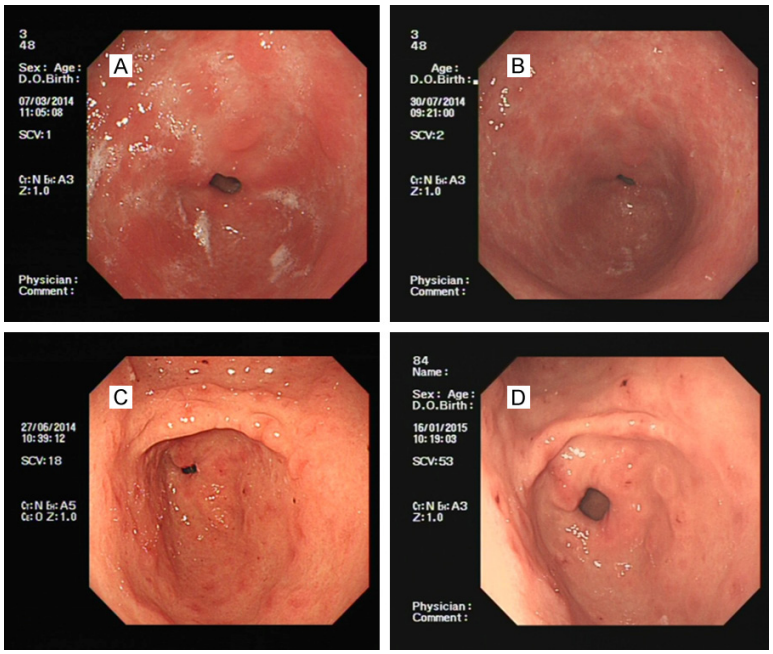

Figure 4. Endoscopic changes of chronic atrophic gastritis before and after treatment. The changes of endoscopic findings were shown in (A and B) (for 3-month treatment), (C and D) (for 6-month treatment).

no break through progress and extensive identity. What is more, with the rapid changes of diet structure, the disease has also changed. It was reported that individual dietary intakes act was associated with different stages of precancerous lesions. Interestingly, milk was found significant positive association with atrophic gastritis and intestinal metaplasia [19]. And the knowledge to the causes of human cancer has been changed all the time with advanced studies [20]. To address these issues, we proposed to carry out the post-marketing clinical trials of WEKP again, to demonstrate the effect of WEKP on CAG systematically.

Referring to the Consensus On Chronic Gastritis in China (Shanghai, 2012), our study demonstrated that two groups of WEKP could both improve symptoms of CAG, and 6-month treatment is superior to 3-month treatment ($p< 0.05$). The response rate of symptoms improvement was up to 63.4% for 3-month and 85.3% for 6-month. To our knowledge, patients often focus more on their physical symptoms,which can influence their daily life and work seriously. WEKP has demonstrated a markedly effective rate to relieve symptoms of CAG, corresponding with previous report conducted by Wang [18]. The inflammation regression rates of WEKP were 26.2% for 3-month treatment and 42.5% for 6-month treatment, respectively. Intestinal metaplasia was reported to have more than a ten-fold high risk to develop to gastric cancer. The response rate of mucosal atrophy and intestinal metaplasia for two groups were 61.9% and 67.5%, separately. Our data showed WEKP could block and even reverse the progress of CAG to GC to some extent.

It was suggested that long-term treatment of WEKP can significantly improve the clinical symptoms caused by CAG but no noteworthy difference in disappearance rate of pathological change compared with short-term treatment for WEKP. WEKP as a kind of TCM has two-way regulatory effects in TCM theory and its unique advantages enhance the therapeutic effects with little side effects.

Conclusion

Our study exhibited a systematic result on the efficacy of WEKP for treating chronic atrophic gastritis patients. WEKP could be used as a kind of potential effective agents for CAG. But our study was limited by lacking patent control and failed to carry out mucosa marking targeting biopsy (MTB). A multi-center clinical study of WEKP on CAG will be designed as a double-blinded, randomized, controlledtrial by using MTB technology and the mechanism of WEKP will be clarified in our later plan.

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Disclosure of conflict of interest

None.

Authors' contribution

Shujie Chen made substantial contributions to the conception and design of this study; Lan Zhao and Hua Chu performed the experiment; Lan Wang analyzed and interpreted the data; Lan Wang and Jiamin He wrote the manuscript; Shujie Chen revise the manuscript for important intellectual content; Shujie Chen give final approval to submit the manuscript for publication.

Ethics statement

The study was reviewed and approved by Ethic Committee, Sir Run Run Shaw Hospital, College of Medicine, Zhejiang University.

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