Effect of modified Sanhuang Xiexin Tang plus additional herbs combined with "standard triple therapy" on Helicobacter pylori eradication

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Abstract

OBJECTIVE: To determine the effectiveness of modified Sanhuang Xiexin Tang (SHXXT) plus additional herbs (MSAH) combined with "standard triple therapy" for eradication of Helicobacter pylori (H. pylori) and amelioration of related symptoms in comparison with standard triple and standard quadruple therapies.

METHODS: From October 2015 to May 2016, we recruited patients with dyspepsia symptoms confirmed to have H. pylori infection by the $^{13}$C urea breath test in our outpatient clinic. Patients were randomly divided into three treatment groups: Nexium® standard triple therapy (group A; EAC); Nexium® standard quadruple therapy (group B; EBAC); or Nexium® standard triple therapy combined with MSAH (group C; EAC+MSAH). Comparisons of H. pylori eradication and symptom amelioration rates were made among the three groups at 2 or 6 weeks after group assignment.

RESULTS: There was no difference in H. pylori eradication rates between groups B (EBAC) and C (EAC+MSAH) ($P = 0.486$), and eradication rates in groups B and C were significantly higher than that in group A (EAC) ($P_{A vs B} = 0.001; P_{A vs C} = 0.003$). There was no difference in the total symptom score among the groups before treatment. In all groups, the total symptom scores after treatment (2 or 6 weeks after group assignment) were significantly lower than those before treatment ($P < 0.001$ for all). However, group C (EAC + MSAH) demonstrated superior total symptom scores and symptom amelioration rates than groups A (EAC) and B (EBAC). Group B also demonstrated better scores and rates than group A. There was no difference in symptom amelioration rates at 2 and 6 weeks within each group.

CONCLUSION: There is no difference between MSAH combined with standard triple therapy and standard quadruple therapy containing bismuth with regard to H. pylori eradication rate. However, MSAH combined with standard triple therapy has a higher symptom amelioration rate and therefore appears to be an ideal treatment scheme for H. pylori eradication.

Keywords: Helicobacter pylori; Disease eradication; Symptom assessment; Sanhuang Xiexin Tang

INTRODUCTION

Helicobacter pylori (H. pylori) infection is closely related to the occurrence of chronic gastritis, peptic ulcer and gastric cancer. H. pylori eradication is an impor-
tant aspect of gastritis treatment to prevent peptic ulcers and reduce the incidence of gastric cancer. First-line therapy for H. pylori recommended by the Maastricht IV Consensus Report comprises antibiotics and a proton-pump inhibitor, referred to as "standard triple therapy." Recently, the prevalence of antibiotic resistance has drastically increased, gradually reducing the eradication rate of clinical therapy for H. pylori. Bismuth agents along with standard triple therapy comprise "standard quadruple therapy" to improve the H. pylori eradication rate. The standard quadruple therapy is sufficient in clinical settings and has been widely used. However, bismuth agents may lead to adverse reactions such as bismuth encephalopathy, osteoarthritis and kidney function insufficiency. Therefore, bismuth agents must be prescribed with care for patients with renal function insufficiency or in the elderly, women and children. According to a consensus in 2012 in China, Traditional Chinese Medicine (TCM) is one alternative to Western Medicine worth exploring for H. pylori treatment, and some TCMs have been reported to improve the H. pylori eradication rate. One such formula is Sanhuang Xie Xin Tang (SHXXT), described by Zhang Zhongjing in "Synopsis of Golden Chamber". This traditional prescription may exert anti-inflammatory and gastroprotective effects in H. pylori-induced gastric inflammation. In vitro experiments conducted by Xiao et al. confirmed that SHXXT combined with moxicillin has an obvious inhibitory effect on H. pylori. Further clinical studies have shown that SHXXT combined with Western Medicine can improve the H. pylori eradication rate. In this study, we adjusted the proportion of rhubarb and Rhizoma Coptidis in SHXXT and added other TC-Ms to invigorate the spleen and increase appetite in order to improve indigestion symptoms. We refer to the final preparation as "modified SHXXT with additional herbs (MSAH)." We designed MSAH to suppress and kill H. pylori, as well as improve patients’ clinical symptoms. Based on the above information, we speculate that MSAH may replace bismuth agents, forming a "new quadruple therapy" to help improve the H. pylori eradication rate and provide superior improvement of symptoms compared with standard triple and standard quadruple therapies. In this study, we evaluated the effect of MSAH on H. pylori eradication and amelioration of indigestion symptoms in comparison with standard triple and quadruple therapies.

MATERIALS AND METHODS

Patients
From October 2015 to May 2016, patients infected with H. pylori and diagnosed by the 13C urea breath test were enrolled in our outpatient clinic. The results of this test are represented as delta over baseline (DOB) values; DOB value > 4 indicates a positive result (i.e., patient is infected with H. pylori). Inclusion criteria were as follows: (a) positive for H. pylori infection by 13C urea breath test; (b) dyspepsia symptoms; (c) gastroscopy showed chronic gastritis or peptic ulcers; (d) age of 18-80 years (there was no limit on the sex ratio); and (e) had not been regularly treated for H. pylori infection. Exclusion criteria were as follows: (a) taking proton-pump inhibitors or H2-receptor antagonists 2 weeks before the study or taking bismuth or antibiotics 4 weeks before the study; (b) malignant ulcers and other malignant tumors; (c) history of gastric surgery; (d) pregnant or lactating; or (e) allergy to penicillin.

A total of 198 patients were screened [mean age (48 ± 12) years; range, 18-80 years].

Design
This was a prospective, parallel, open-label, randomized study approved by the ethics committee of Shengjing Hospital Affiliated to China Medical University (No. 2015 PS282K). All patients provided written informed consent.

Patients were randomly assigned to treatment group A (standard triple therapy; EAC: Nexium®, amoxicillin and clarithromycin), B (standard quadruple therapy; EBAC: Nexium®, bismuth potassium citrate, amoxicillin and clarithromycin) or C (EAC+MSAH). We recorded patients’ symptoms before treatment and 2 and 6 weeks after group assignment. The symptom score was calculated to indicate symptom severity at different timepoints. Comparisons of H. pylori eradication rate, symptom amelioration rate and side effects were made among the groups after the treatment period.

Randomization and blinding
Group allocation was performed using a random number table of 300 random numbers made by a random number generator (Stat Trek’s Random Number Generator). Numbers were randomly selected from within the range of 1 to 3 in the number table; numbers 1, 2 and 3 corresponded to groups A, B and C, respectively. Patients were grouped according to the numbers in the table corresponding to the selected order.

Neither the participants nor the investigator A should know which intervention was the more effective one. The investigator A should record and calculate the participants’ symptom score before and after the treatment, and he should record the participants’ side effects at the same time. The investigator B should record the participants’ age, sex, smoking habits, urban or rural residence, gastroscopy results and results of the 13C urea breath test (mean DOB values) before and after the treatment.

Interventions
Group A (EAC): A 14-day regimen of standard triple

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therapy with 20 mg b.i.d. Nexium® (batch no. H20046379; AstraZeneca Pharmaceutical Co., Ltd., Wuxi, China), 1000 mg b.i.d. amoxicillin (No. HC20090039; Hong Kong Federal Pharmaceutical Co., Ltd., Hong Kong, China) and 500 mg b.i.d. clarithromycin (No. H20031041; Jiangsu Hengrui Medicine Co., Ltd., Liyang, Jiangsu, China).

Group B (EBAC): A 14-day regimen of standard quadruple therapy with 20 mg b.i.d. Nexium®, 1000 mg b.i.d. amoxicillin, 500 mg b.i.d. clarithromycin and 600 mg b.i.d. bismuth potassium citrate (No. H20043059; Jichuan Pharmaceuticals Group Co., Ltd., Taixing, Jiangsu, China).

Group C (EAC + MSAH): A 14-day regimen of standard triple therapy combined with MSAH: 20 mg b.i.d. Nexium®, 1000 mg b.i.d. amoxicillin, 500 mg b.i.d. clarithromycin and MSAH (Dahuang (Radix Et Rhizoma Rhei) 5 g, Huangqin (Radix Scutellariae Baicalensis) 6 g, Huanglian (Rhizoma Coptidis) 8 g, Huangqin (Radix Scutellariae Baicalensis) 15 g, Chenpi (Pericarpium Citri Reticulatae) 10 g, Sharen (Radix Glycyrrhizae Preparata) 1 g, zhu (Endothelium Corneum Gigeriae Galli) 15 g, zhi (Radix Atractylodis Macrocephalae) 15 g and Zhi (Rhizoma Atractylodis Macrocephalae) 15 g and Zhi (Radix Glycyrrhizae Preparata) 10 g in dose per day divided into two, taken after being dissolved in liquid. Traditional Chinese Medicine was purchased from Beijing Kongrentang Pharmaceutical Co., Ltd., (Beijing, China).

For each regimen, amoxicillin and clarithromycin were taken 30 min after meals, and the other medicines were given 30 min before meals. All Western Medicines and TCMs were obtained from our hospital outpatient pharmacy.

Outcome measures

All patients underwent 13C urea breath testing before treatment and 4 weeks after treatment (6 weeks after group assignment). Patients’ symptoms were recorded before treatment and 2 and 6 weeks after group assignment. They were given a symptom score to indicate symptom severity at different times, according to the symptom scoring criteria, with reference to Glasgow Dyspepsia Severity Score.13 Comparisons among the groups were made after treatment with regard to the H. pylori eradication rate, symptom amelioration rate and side effects.

A score of 0 to 3 points was given to the following five symptoms: epigastric pain, abdominal distention, belching, nausea and sour regurgitation, with a maximum total score of 15 points. The following scoring criteria were used: 0, asymptomatic; 1, patients had memories of symptoms when reminded; 2, patients complained of symptoms, but symptoms did not influence their daily life and work; and 3, symptoms affected daily life and work.

The main index of curative effect was the amelioration rate of the total symptom score at 14 d after treatment (2 weeks after group assignment) and 4 weeks after treatment (6 weeks after group assignment). The total symptom score amelioration rate was calculated as follows: rate = ([symptom score before treatment − symptom score after treatment]/score before treatment) × 100%.

Statistical analysis

Statistical analyses were conducted using SPSS 22.0 (IBM Corp., Armonk, NY, USA). Data were analyzed using the χ2 test or t test. A value of P < 0.05 was considered statistically significant.

RESULTS

Comparison of basic characteristics

The flow diagram of this study design is depicted in Figure 1. A total of 198 patients were initially screened. All patients were randomly assigned to group A (n = 64), B (n = 68) or C (n = 66). One patient in group A and two patients in group B dropped out because of poor compliance, and one patient in group C was lost to follow-up. Therefore, 194 patients were included in analyses; 75 were male and 119 were female (mean age (47 ± 12) years; range, 18-80 years). There were no statistically

![Diagram](image-url)
significant differences in age, sex, disease classification (gastroscopy results and total symptom score before treatment), result of the $^{13}$C urea breath test (mean DOB values), smoking habits and urban or rural residence among groups (partially shown in Tables 1 and 2). The three groups were therefore comparable.

**Comparison of H. pylori eradication rate among the three groups after treatment**

H. Pylori eradication rates in groups B (EBAC) and C (EAC + MSAH) were significantly higher than that in group A (EAC) ($P_{A \times B} = 0.001; P_{A \times C} = 0.003$). However, no significant difference was observed between groups B and C (Table 3).

**Comparison of total symptom scores and symptom amelioration rate among the three groups after treatment**

There were no differences in the total symptom score among the groups before treatment. Within each group, the total symptom score after treatment was significantly lower than that before treatment. In addition, 2- and 6-week symptom amelioration rates showed no differences. However, groups B (EBAC) and C (EAC + MSAH) demonstrated superior total symptom scores and symptom amelioration rates than group A (EAC) (Table 4). Moreover, group C (EAC + MSAH) showed better symptoms scores and symptom amelioration rates than group B (EBAC).

**Side effects**

Patients in group A (EAC) had no side effects. One patient in group B (EBAC) had mild and tolerable nausea, without suspending medication, and symptoms disappeared after the study. One patient in group C (EAC + MSAH) defecated more frequently than before (about 3 times/d), but did not suspend medication, and symptoms disappeared after the study.

**DISCUSSION**

SHXXT has been reported to inhibit gastric secretion, promote gastric muscle relaxation and also have anti-inflammatory and antioxidative effects. In this prescription, Dahuang (Radix Et Rhizaoma Rhei Palmati), Huanglian (Rhizoma Coptidis) and Huangqin (Radix Scutellariae Baicalensis) are the main extracts of the three components. Dahuang (Radix Et Rhizaoma Rhei Palmati) can damage DNA and thus directly kill H. pylori. The sterilization mechanism of Huanglian (Rhizoma Coptidis) maybe that it inhibits the oxidation process of intermediate products generated in glycolysis, especially deoxidization reaction, to restrain growth, thus killing H. pylori. In this study, we explored the clinical effectiveness of TCMs to eradicate H. pylori. Dahuang (Radix Et Rhizaoma Rhei Palmati) can cause diarrhea and Huanglian (Rhizoma Coptidis) has a similar effect. When the dosage of Huanglian (Rhizoma Coptidis) in SHXXT is higher than that of Dahuang (Radix Et Rhizaoma Rhei Palmati), the prescription’s bacteriostatic effect is improved by a higher content of Huanglian.

Based on available information, we adjusted the proportions of Dahuang (Radix Et Rhizaoma Rhei Palmati) and Huanglian (Rhizoma Coptidis) in SHXXT and increased other TCMs that have spleen-nourishing and Qi-regulating effects to improve the patient’s digestion symptoms, forming a new prescription named modified SHXXT with additional herbs (MSAH). In the new prescription, Huanglian (Rhizoma Coptidis), Dahuang (Radix Et Rhizaoma Rhei Palmati) and Huangqin (Radix Scutellariae Baicalensis), which serve as the principal components, should clear heat toxin, eliminate pathogens and dispel dampness, while simultaneously inhibiting H. pylori. Chenpi (Pericarpium Citri Reticulatae), Shaan (Fructus Amomi), Yanhusuo (Rhizoma Corydalis Yunnana) and Baishao (Radix Paeoniae Alba), which serve as assistants, should disperse stagnated liver Qi to relieve Qi stagnation and regulate the flow of Qi to relieve pain. Shanza (Fructus Crataegi Pinnatifidae), Chaojineijin (Endotrichium Cornium Gigeriae Galli) and Baizhu (Rhizoma Atractylodis Macrocephalae), which serve as complements, should promote digestion and invigorate the spleen.

**Table 1 Demographic and clinical characteristics of the 194 patients (± s)**

<table>
<thead>
<tr>
<th>Asignation</th>
<th>DOB values (n)</th>
<th>Smoking (n)</th>
<th>Urban or rural (n)</th>
<th>Sex (n)</th>
<th>Age (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4-40 &gt;40 Y N Urban Rural Male Female</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group A (n = 63)</td>
<td>43 20 12 51 42 21 27 36 47 ± 12</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group B (n = 66)</td>
<td>36 30 14 52 53 13 23 43 46 ± 12</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group C (n = 65)</td>
<td>40 25 16 49 48 17 25 40 48 ± 11</td>
<td></td>
<td></td>
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</tbody>
</table>

$\chi^2/F$ value 2.556 0.596 3.094 0.873 0.359

$P$ value 0.279 0.742 0.213 0.646 0.699

Notes: group A treated with standard triple therapy (EAC); group B treated with standard quadruple therapy (EBAC); group C treated with EAC + MSAH. Each $P$ value is the result of comparisons among three groups. There were no statistically significant differences in age, sex, result of the $^{13}$C urea breath test (mean DOB values), smoking habits and urban or rural residence among groups; Y: smoking; N: no smoking; EAC: Nexium, amoxicillin and clarithromycin; EBAC: Nexium, bismuth potassium citrate, amoxicillin and clarithromycin; MSAH: additional herbs.
In this study, we compared three different H. pylori eradication treatments: EAC, EBAC and EAC + MSAH. There were no significant differences in H. pylori eradication rates between the EAC + MSAH and EBAC groups. However, H. pylori eradication rates in these groups were significantly higher than that in the EAC group. Effects of alleviation of dyspepsia symptoms in the EBAC and EAC + MSAH groups were greater than those in the EAC group, and the EAC + MSAH group showed greater improvement than the EBAC group. Moreover, indigestion symptoms of patients in all three groups 2 weeks after group assignment were clearly improved compared with conditions before therapy, and the effect remained until 6 weeks after assignment. Although symptom alleviation at 6 weeks was greater than that at 2 weeks, the difference was not significant.

In conclusion, MSAH combined with standard triple therapy may be an alternative treatment for H. pylori eradication. This treatment may safely eradicate H. pylori and improve clinical symptoms without adverse side effects associated with drugs such as bismuth agents.

**REFERENCES**


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**Table 2 Gastroscopy results (n)**

<table>
<thead>
<tr>
<th>Assignation</th>
<th>Chronic gastritis</th>
<th>Peptic ulcers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A (n = 63)</td>
<td>51</td>
<td>12</td>
</tr>
<tr>
<td>Group B (n = 66)</td>
<td>53</td>
<td>13</td>
</tr>
<tr>
<td>Group C (n = 65)</td>
<td>55</td>
<td>10</td>
</tr>
</tbody>
</table>

Notes: group A treated with standard triple therapy (EAC); group B treated with standard quadruple therapy (EBAC); group C treated with EAC + MSAH. $\chi^2 = 0.476, P = 0.788$ among three groups. There were no statistically significant differences in gastroscopy results among groups. EAC: Nexium®, amoxicillin and clarithromycin; EBAC: Nexium®, bismuth potassium citrate, amoxicillin and clarithromycin; MSAH: additional herbs.

**Table 3 Helicobacter pylori eradication rate after treatment**

<table>
<thead>
<tr>
<th>Assignation</th>
<th>Eradicated (n)</th>
<th>Eradication rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A (n = 63)</td>
<td>40</td>
<td>63.5±2</td>
</tr>
<tr>
<td>Group B (n = 66)</td>
<td>58</td>
<td>89.2±2</td>
</tr>
<tr>
<td>Group C (n = 65)</td>
<td>56</td>
<td>86.1±2</td>
</tr>
</tbody>
</table>

Notes: group A treated with standard triple therapy (EAC); group B treated with standard quadruple therapy (EBAC); group C treated with EAC + MSAH. $\chi^2 = 0.476, P = 0.788$ among three groups. $^1P < 0.05$ A vs B; $^2P < 0.05$ A vs C; $^3P > 0.05$ B vs C. EAC: Nexium®, amoxicillin and clarithromycin; EBAC: Nexium®, bismuth potassium citrate, amoxicillin and clarithromycin; MSAH: additional herbs.

(Radix Glycyrrhizae Preparata), which serves as a guide, should benefit Qi to invigorate the spleen and reconcile various drugs in the prescription. Recent pharmacological studies showed that Dahuang (Radix Et Rhizoma Rhei Palmati), Huanglian (Rhizoma Coptidis) and Huangqin (Radix Scutellariae Batacensis) have anti-inflammatory effects and can inhibit H. pylori in vitro.13,14 Chenpi (Pericarpium Citri Reticulatae) has an obvious effect in promoting gastric emptying.14 Certain in vitro studies have confirmed that Chenpi (Pericarpium Citri Reticulatae) and Zhigancao (Radix Glycyrrhizae Preparata) both have an inhibitory effect on H. pylori.15,16 Sharen (Fructus Amomi) can promote digestive juice secretion and enhance intestinal movement.22 Yanhusuo (Rhizoma Corydalis Yanhusuo) has analgesic and antiulcer effects.23 Baisha (Radix Paoniae Alba) can act as an antispasmodic and analgesic. Shan-zha (Fructus Crataegi Pinutatifideae) and Chaojineijin (Endothelium Cornuem Gigeriae Galli) can promote digestion and adjust gastrointestinal function. Additionally, Chaojineijin (Endothelium Cornuem Gigeriae Galli) can enhance the activity of pepsin and pancreatic lipase. Baizhu (Rhizoma Arctacylodis Macrophyllae) have the effect of regulating bowel movements.23

**Table 4 Total symptom score and symptom amelioration rate after treatment (x ± s)**

<table>
<thead>
<tr>
<th>Assignation</th>
<th>Total symptom score before treatment</th>
<th>Total symptom score 2 weeks after treatment (amelioration rate, %)</th>
<th>Total symptom score 6 weeks after treatment (amelioration rate, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A (n = 63)</td>
<td>7.1±2.9</td>
<td>4.3±1.7* (34.5±22.2)</td>
<td>3.9±1.6* (38.5±24.0)</td>
</tr>
<tr>
<td>Group B (n = 66)</td>
<td>7.5±2.5</td>
<td>3.2±1.5* (51.0±27.7)</td>
<td>2.9±1.5* (55.3±25.8)</td>
</tr>
<tr>
<td>Group C (n = 65)</td>
<td>7.2±3.0</td>
<td>0.7±0.9* (89.5±13.3)</td>
<td>0.5±0.7* (92.5±9.5)</td>
</tr>
</tbody>
</table>

$^* F$ value: 0.202, $P$ value: 0.817

Notes: group A treated with standard triple therapy (EAC); group B treated with standard quadruple therapy (EBAC); group C treated with EAC + MSAH. $^*P < 0.05$, compared within the same period among groups ($P = 0.817$); $^bP < 0.05$, compared with before treatment; $^cP > 0.05$, compared with the total symptom score (amelioration rate) 2 weeks after group assignment; $^dP < 0.05$, compared with the same period in group A; $^eP > 0.05$, compared with the same period in group B. EAC: Nexium®, amoxicillin and clarithromycin; EBAC: Nexium®, bismuth potassium citrate, amoxicillin and clarithromycin; MSAH: additional herbs.


