Chinese Herbal Medicines as Complementary Therapy for Helicobacter Pylori-associated Gastroduodenal Ulcers: A Systematic Review and Meta-analysis

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ABSTRACT
Objectives: To evaluate the efficacy and safety of Chinese herbal medicines as complementary drugs used to treat Helicobacter pylori (HP)-associated gastroduodenal ulcers.

Methods: All randomized controlled trials (RCTs) listed in the PubMed, EMBASE, Cochrane Library, CNKI, WanFang, VIP and SinoMed databases that were published in English or Chinese were searched, and the retrieval time range was from database inception to December 31, 2018. A comprehensive meta-analysis of all publications was performed with RevMan 5.3 software, and the quality of the evidence reported in the results of meta-analysis was analyzed with GRADEprofiler software (version 3.6.1). Dichotomous data were analyzed by calculating odds ratios and 95% confidence intervals (CIs). Outcome measures included the HP clearance rate and percentage of adverse effects.

Results: Eight trials with 919 participants were included in this meta-analysis. Compared with the effects of single drug therapy on HP-associated gastroduodenal ulcers, according to the statistical analysis, odds ratios for the HP clearance rate and percentage of adverse effects of Chinese herbal medicines administered as complementary medicines combined with drugs were 3.10 (95% CI, 2.21, 4.36, P<0.01) and 0.28 (95% CI, 0.15, 0.52, P<0.01), respectively, and the differences were statistically significant. According to the GRADE analysis, the quality of evidence for the HP clearance rate and percentage of adverse effects were both very low.

Conclusions: Compared with simple drug therapy, the combination of Chinese herbal medicines with drugs more effectively eliminates HP and alleviates adverse reactions. However, the currently available evidence was of low quality and therefore inadequate to justify a strong recommendation for using Chinese herbal medicines as complementary drugs in the treatment of HP-associated gastroduodenal ulcers.

Keywords: Chinese herbal medicines, complementary therapy, gastroduodenal ulcer, Helicobacter pylori

Introduction
HP is an important human pathogen and classed as a human carcinogen. HP is the principal cause of chronic gastritis and HP-induced gastritis is considered the...
most important risk factor for peptic ulcers. HP infection also exerts additive effects on the risk of peptic ulcer bleeding. A meta-analysis showed relatively stable HP recurrence rates over the past two decades, but the rates varied across different regions. In Asia, the prevalence of HP often exceeds 50%. Currently, the treatment of HP is becoming more challenging due to an increase in antibiotic resistance. In the Asia-Pacific region, the overall mean prevalence of primary HP resistance was 44% for metronidazole, 17% for clarithromycin, 18% for levofloxacin, 4% for tetracycline, and 3% for amoxicillin. Although a longer duration of use of antibiotic therapy is associated with a higher HP eradication rate, a higher risk of adverse effects is also observed. In addition to replacing antibiotics and optimizing the management of HP infection, HP therapy should be based on patterns of local and individual antimicrobial resistance when possible to improve the therapeutic effect on HP. However, some complementary and alternative therapies have been administered as an adjuvant treatment for HP infection, particularly herbal therapy.

Chinese herbal medicines have been used for a many years to treat gastrointestinal diseases in the clinic. Many herbal products possess an anti-HP activity and gastroprotective action. Although the mechanism of HP resistance is incompletely understood, some herbs have been proven to inhibit essential HP enzymes, modulate the host immune system, and attenuate inflammation. Currently, evidence that herbal medicines statistically significantly improve HP eradication is unavailable, and most herbal medicines are applied as a supplement to antibiotic therapy. Chinese herbal medicines have been reported to play a role in assisting antibiotic therapy and alleviating adverse reactions. However, no high-quality meta-analysis has been published on the effectiveness and safety of Chinese herbal medicines in the treatment of HP-associated gastroduodenal ulcers to date. We conducted a systematic review and meta-analysis to evaluate the clinical efficacy of Chinese herbal medicines as a complementary therapy and to assess the differences in HP clearance and adverse effects.

Materials and methods

Data sources and searches

The PubMed (1970.01.01-2018.12.31, English), EMBASE (1967-2018, English), Cochrane Library (1997.1-2018.12, English), CNKI (1979.01.01-2018.12.31, Chinese), WanFang (1970-2018, Chinese), VIP (1989-2018, Chinese) and SinoMed (1970-2018, Chinese) databases were searched for RCTs. The searches were limited to the English and Chinese languages. Separate search strategies were designed for each database. Search strategies included MeSH, Emtree, Meth terms and free text, such as “Chinese herbal medicine”, “herbal”, “decoction”, “Chinese drugs”, “Chinese herbal drugs”, “herbal drugs”, “plant extracts”, “Helicobacter pylori” and “randomized controlled trial”. Because of relatively limited number of relevant publications in the actual search, the keywords “peptic ulcer” or “gastroduodenal ulcer” were not used. The EMBASE strategy is as follows:

#1 ‘chinese herbal medicine’/exp
#2 ‘herbal’
#3 ‘decoction’
#4 ‘chinese drugs, plant’
#5 ‘chinese herbal drugs’
#6 ‘herbal drugs, chinese’
#7 ‘plant extracts, chinese’
#8 ‘chinese plant extracts’
#9 ‘extracts, chinese plant’
#10 #1 OR #2 #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9
#11 ‘helicobacter pylori’/exp
#12 ‘randomized controlled trial (topic)’/exp
#13 #10 AND #11 AND #12

Study selection

The included studies were selected based on PICOS eligibility criteria using the population, intervention, comparators, outcomes and study design. The inclusion criteria are listed below. (1) Subjects with gastroduodenal ulcers who were HP-positive. Subjects with bleeding ulcers or gastric cancer were excluded. (2) Both experimental groups (Chinese herbal medicines combined with drug groups) and control groups (simple drug groups) received the first-line therapy regimens recommended in current Consensus Report when trials were performed. (3) The experimental groups simultaneously received Chinese herbal medicines, including single herbs, formulas or herbal products, oral decoctions, pills, powders or granules. (4) Randomized controlled and parallel trials were performed, regardless of whether blinding was adopted, and had a duration of at least one week. (5) The minimum outcome indicator was the HP clearance rate. The definition of the HP clearance rate must conform to the requirements of the current Consensus Report. Two independent reviewers determined whether the RCTs met the eligibility criteria. The reviewers screened the qualified studies in the order of title, abstract and full text. All publications were managed using EndNote X9 software (EndNote X9), and trials that were excluded in each step were recorded and the reasons were indicated. Discrepancies between reviewers were resolved by a third reviewer.

Data collection and assessment

The data were extracted and collected in specialized spreadsheets. The extracted contents included the demographic data of the participants, specific treatment measures, and the results of outcome indicators and
safety indicators. The outcome indicators are listed in the summary of findings (SoF) table and reasons for downgrading were provided by adhering to the GRADE guidelines. Discrepancies between reviewers were resolved by a third reviewer.

**Statistical analysis**

Mean values and standard deviations for continuous endpoints, counts and proportions for categorical endpoints were extracted. All statistical analyses were conducted with RevMan5.3 software. The results for dichotomous and continuous outcomes were reported as odds ratios or weighted mean differences and 95% CIs, respectively. The Mantel-Haenszel (statistical method) and fixed effect models (analysis model) were used to assess outcomes, and random effects analyses were considered when statistical heterogeneity was observed. The I² value was used to evaluate heterogeneity. If the I² value was high, a subgroup analysis or sensitivity analysis was conducted. After the subgroup analysis or sensitivity analysis, if I²>50%, the meta-analysis was discontinued. Forest plots visually showed effect estimates of the included trials. Funnel plots were used to assess publication bias when a sufficient number of studies were available.

**Results**

The process used to select the RCTs followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram. Seven hundred thirty studies were retrieved, and 8 studies were finally included after selection. The detailed screening process is illustrated in Figure 1. One of these trials was conducted in Japan and published in the English language [24], and the remaining trials were conducted in China and published in the Chinese language. Baseline data are shown in Table 1. The mean age of the included participants was 43.65 ± 12.56 years. The majority of the population in the included studies was male. Only 1 trial[27] was a multicenter RCT trial and the others were single-center trials. An Intention-To-Treat (ITT) analysis was performed in 2 trials. Chinese herbal medicines used in all included trials were formulas and administered orally, the herbal prescriptions of 6 trials were designed according to the ancient formulas by the researchers themselves, 1 trial[28] administered a patent Chinese medicine (capsule), and 1 trial[29] used a fixed ancient Chinese prescription.

**Risk of bias**

The risk of bias for all studies is shown in Figure 2-3. Random sequence generation was assessed as an unclear risk of bias in 2 studies.[24][29]. None of the trials mentioned a placebo for Chinese herbal medicines. Because the binding of researchers and participants during the distribution of herbal formulas was not possible, all trials were open label. Allocation concealment and detection bias (blinding of outcome assessment) displayed an unclear risk of bias in all studies. None of these RCTs clearly reported allocation concealment or methods for blinding outcome assessments, which was the main reason for the judgement of an unclear risk of bias. One study did not report adverse effects after medication, which would increase the risk of attrition bias ( incomplete outcome data) [30]. Because the HP clearance rate is the key outcome indicator, which had been statistically detailed in all studies, reporting bias (selective reporting) and other sources of bias were considered to be low.

**Efficacy outcomes**

Through a systematic review, 8 trials were ultimately included in the statistical analysis (N=919 participants). Although the formulas used in each study were different, the heterogeneity (Chi²=8.73, P=0.27; I²=20%) was low, according to the statistical analysis, and data were centralized for a meta-analysis. The Mantel-Haenszel test (statistical method), fixed effect analysis (analysis model) and odds ratio (effect measure) were chosen as the methods for the analysis. Compared with drugs alone, odds ratios of the combination of Chinese herbal medicines and drugs in improving the HP clearance rate was 3.10 (95% CI, 2.21, 4.36; I²=20%) (Figure 4), and the difference was statistically significant (P<0.01).

**Safety outcomes**

Seven of the 8 trials had reported the adverse reactions and were included in the statistical analysis (N=809 participants). The Mantel-Haenszel test (statistical method), fixed effect analysis (analysis model) and odds ratio (effect measure) were chosen as the methods for this analysis as well. Compared with drugs alone, the odds ratio of the combination of Chinese herbal medicines and drugs for the percentage of adverse effects was 0.28 (95% CI, 0.15, 0.52; I²=0%), and the difference was statistically significant (P<0.01) (Figure 5). Among the 7 studies, the participants of 2 studies did not experience adverse reactions[25][26].

**Figure 5 Forest plot of the percentage of adverse effects**

**Quality of evidence**

Evidence was assessed with GRADE (the GRADE diagram is shown in Appendix). The quality of the evidence for the HP clearance rate and the percentage of adverse effects was low. The risk of bias of the studies was downgraded to an unclear or high risk: 2 trials did not mention specific randomization methods, no trials reported allocation concealment or methods for blinding outcome assessments, and 1 trial did not mention adverse reactions[30]. Imprecision is downgraded by most CIs overlapping the vertical line, and the broad CI of 1 trial[27] decreased the credibility of the outcome index. The data points for the effect size were all clus-
tered on one side of plot, the CIs of all trials overlapped, and the heterogeneity test was not statistically significant; therefore, the degradation of inconsistency was not considered. Indirectness is considered according to the PICO principle: Although some difference in the intervention measures were noted, the detection and methods for recording the outcomes were basically the same, and the difference in the outcome indicators was very small; thus, degradation was not considered. The number of trials included in this study was small and the total sample size was small. Therefore, publication bias existed, and the quality of the evidence was downgraded.

Discussion

HP persistently colonizes more than half of the global human population. Gastrointestinal ulcers caused by HP are very common in the clinic, and the associated pain, loss of appetite and hemorrhagic complications seriously affect the quality of life of patients. The removal of HP effectively inhibits the recurrence of peptic ulcers. PPI combined with antibiotics is an essential therapeutic regimen for the removal of H. pylori, but bloating, diarrhea, taste disturbances and epigastric discomfort are the most frequent side effects reported by patients taking these medicines. Chinese herbal medicines are able to regulate gastrointestinal function and reduce discomfort symptoms while assisting in clearing HP, which is worthy of clinical application. Therefore, an evidence-based analysis of the curative effect of Chinese herbal medicines on HP-related gastrointestinal ulcers is necessary.

According to the results of the meta-analysis, compared with the simple use of drugs, the odds ratio for the HP eradication rate in patients treated with Chinese herbal medicines combined with drugs is 3.10 (95% CI, 2.21, 4.36), which is greater than 1, and the total effect size is located on the right side of the vertical line. The efficacy of HP eradication in the experimental group appeared to be improved compared with the control group. The odds ratio for the percentage of adverse reactions was 0.28 (95% CI, 0.15, 0.52), which is less than 1, and the total effect size is located on the left side of the vertical line. The percentage of adverse reactions experienced by the experimental group was less than the control group. Compared with the simple use of PPI and antibiotics to eradicate HP, the combination of these drugs with Chinese herbal medicines is more likely to improve the HP clearance rate and reduce adverse reactions.

According to the GRADE analysis, the level of evidence for this review is very low. The quality of the 8 trials was low, which basically did not meet the reporting requirements of the CONSORT statement. The reported methods, particularly the estimation of sample size, allocation concealment and implementation of randomization and the blinding method, lacked detailed descriptions. An ITT analysis was not mentioned in most of the included trials when reporting the results. However, after comparing the number of people included in each trial with the same number of people analyzed in the results, an ITT analysis was considered adopted in these trials. When extracting the data from the studies, in addition to the HP clearance rate and the occurrence of adverse reactions, other mentioned outcome indicators were meaningful but difficult to be included in the present meta-analysis. First, clinical efficiency was evaluated by combining three indicators: the mucosal ulcer recovery observed during gastroduodenoscopy, the HP eradication effect and the relief of the severity of participants’ clinical discomfort symptoms. This indicator was judged by recording the number of participants presenting each of the following four grades of recovery: cured, obviously effective, effective and ineffective. The comprehensive efficacy of each intervention group was evaluated using this indicator. Unfortunately, only 4 included trials mentioned this indicator. Due to the strong subjectivity in the determination of the obviously effective grade and effective grade, the different consensus reports referenced by each trial, and the differences in the detailed rules for each grade formulated by each trial, the heterogeneity was very large, and thus a meta-analysis was not conducted. Second, 5 of the included trials reported the recovery of the gastroduodenal mucosa. One used continuous data (scores), and the other four adopted dichotomous data (efficiency); additionally, the referenced consensus reports and the detailed evaluation rules also differed, making the outcome data difficult to combine and analyze. TCM symptom complex scores were reported in 4 included studies, which were used to record the scores of specific symptom in TCM terms. This index also has the problems of different data types, reference consensus reports, scoring rules and item formulation. For example, in the formulation of items, the descriptions of gastrointestinal pain differed and were: epigastric pain, stomach pain, abdominal burning pain and abdominal distension pain. The location and nature of these types of pain were different and were unable to be analyzed together. The aforementioned problems are mainly attributed to the lack of a unified consensus or reference standard, which is also related to the subjectivity of the indicators described above. In contrast, the HP clearance rate and the percentage of adverse reactions are objective data and are easily counted.

Although the level of evidence is very low, the conclusion of the review still suggests that Chinese herbal medicines have a certain role in the treatment of peptic ulcers caused by HP. Currently, TCM clinicians in China tend to believe that peptic ulcers caused by HP are closely related to the damp-heat factor, and thus they prefer to administer herbal medicines that possess the
functions of clearing heat and eliminating dampness. However, various types of Chinese herbal compounds are being used, whose functions include invigorating qi and spleen, activating blood circulation and removing blood stasis, and clearing heat and removing dampness. The clearing heat and eliminating dampness functions were used in most trials. Due to the small number of publications included in the present study, the tendency to use common functions in formulas was unable to be conclusively confirmed.

Only two of the included trials clearly indicated the TCM syndromes of participants, namely, the mixed cold and heat syndromes, using the herbal medicine of wet and hot syndromes using self-designed prescriptions. The use of Chinese herbal medicine is closely related to the syndromes of the disease. According to the theory of TCM, peptic ulcers associated with HP in patients with different syndromes should result in different symptom characteristics, and therefore different prescriptions will be used. However, most of the trials did not report TCM syndromes, which reduced the credibility of the trial, and may also reduce the efficacy of TCM in statistical analyses due to the confounding factors of various syndromes. Therefore, clinicians should focus on designing the study according to syndrome types to conduct proper clinical trials of TCM, reduce the heterogeneity of participants’ baseline data and improve the credibility of the outcome results.

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Conflict of interest

The authors have no competing interests to declare. Funding agencies and any external organizations were not involved in the design of the review or preparation of the manuscript. All authors read and approved the final manuscript.

Contributors

Tang XD and Wang FY designed the study and served as mentors. Lv L, Ma XX, Yin XL, Xie JY, Wu HM, Li X, Ma JX, Ma W, and Zhang M were involved in data extraction and collation.

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