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Efficacy of compound *Lactobacillus acidophilus* tablets combined with quadruple therapy for *Helicobacter pylori* eradication and its correlation with pH value in the stomach: a study protocol of a randomised, assessor-blinded, single-centre study

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ABSTRACT

Introduction *Helicobacter pylori* (Hp) is an important pathogenic factor for chronic gastritis, peptic ulcer, gastric cancer, gastric mucosa-associated lymphoid tissue lymphoma and other diseases. In China, the Hp infection rate is high, but the eradication rate is decreasing. A large number of literatures have shown that the addition of *Lactobacillus acidophilus* can improve the Hp eradication rate and reduce the side effects of antibiotic treatments. At present, the exact mechanism and curative effect of *L. acidophilus* in the eradication of Hp have not yet been determined, and the conclusions obtained from relevant meta-analyses at home and abroad are different. Thus, it is very necessary and urgent to further complete a high-quality, clinical, randomised controlled trial research. If this study is successful, it can provide a new idea and a plan for Hp eradication therapy.

Methods and analysis This study is a prospective, randomised controlled, single-blinded, parallel-design trial. We will randomly assign 526 adult patients (≥18 years but <70 years) with Hp confirmed positive by the kit for 14C-urea breath test. Eligible subjects were randomly divided into two groups (group A and group B), with 263 subjects in each group. Group A is a quadruple therapy group, while group B is an *L. acidophilus* tablets combined with quadruple therapy group. All patients were examined by gastroscopy, and 50 patients in each group will be placed under gastric pH monitor. The Hp eradication rate is the primary outcome. The secondary outcomes include gastric pH situation and adverse drug reactions.

Ethics and dissemination The study protocol has been approved by the Clinical Research Ethics Committees of Chongqing University Cancer Hospital and Chongqing Cancer Hospital (2018[012]). The results from this trial will be submitted for publication in peer-reviewed journals and will be presented at national and international conferences.

Trial registration number ChiCTR17014185; Pre-results.

Strengths and limitations of this study

- The trial design is prospective, assessor-blinded and randomised controlled, with a large sample size of 526.
- The kit for 14C-urea breath test has the advantages of simplicity, rapidity, accuracy, no pain, no trauma and no cross-infection.
- *Lactobacillus acidophilus* is expected to become a new method for precisely eradicating *Helicobacter pylori*.
- In different stages of this study, special personnel will be assigned to take charge of related work.
- The subjects were unable to perform blind methods due to limitations in the characteristics of the study.

INTRODUCTION

As we all know, *Helicobacter pylori* (Hp) is an important pathogenic factor for chronic gastritis, peptic ulcer, gastric cancer, gastric mucosa-associated lymphoid tissue lymphoma and other diseases, and has also been recognised by the WHO as the first type of pathogenic factor for gastric cancer. Hp infection is currently considered an infectious disease[1] and patients should be given eradication therapy.[2]

Hp is one of the hot spots in the field of gastroenteropathy. It has been a long time for anti-Hp research in our country. In the 1990s, the two or three regimens of Hp eradication treatment experienced a brilliant period of 90% or higher eradication rate. In recent years, however, the eradication rate has been decreasing, especially in many developed areas and urban populations. The triple therapy, once known as the 'gold

standard', has an eradication rate that can only reach about 70%,[3] and had to be removed from the recommended first-line treatment programme. Even with the currently recommended quadruple regimen[4 5] of proton pump inhibitor (PPI) + colloidal bismuth + two antibiotics, it is difficult to achieve an Hp eradication rate of 85% in many populations (85% is the basic requirement for internationally accepted eradication rates for recommended regimens). From 2013 to 2014, the Hp resistance rate of 740 patients in 11 provinces and cities of China was investigated by the Hp group of the digestive diseases branch of the Chinese Medical Association: the double resistance rate of antibiotics was 23.47% and the triple resistance rate was 12.91%.[6] The choice and substitution of antibiotics are limited in our country, and it is difficult to select antibiotics rationally in empirical treatment. At present, there is little room for improvement, whether in the number of combined drugs, dosage or the course of treatment. With the increase of Hp resistance to antibiotics, some of the previous Hp eradication rates of the programme will also be reduced. Therefore, it is imperative to develop a new method to precisely eradicate Hp.

Hp is implanted on the surface of the gastric mucosal epithelial cells and covered by a mucus layer, which makes eradication difficult. It is difficult for most antimicrobial agents to penetrate directly through the mucus layer. PPI can effectively kill Hp by inhibiting gastric acid secretion and changing the pH value in the stomach. Therefore, all currently recommended eradication protocols contain PPI. Bismuth can penetrate the mucus layer and act directly on Hp, depositing on the cell wall of the Hp thalli, which leads to the rupture and death of Hp. In general, PPI and bismuth agents play an auxiliary and synergistic role in anti-Hp treatment, while antibiotics still play a central role. Current protocols for the eradication of Hp contain two antibiotics; however, large-dose combination of antibiotics can cause short-term changes in the intestinal flora,[7 8] which may lead to antibiotic resistance, antibiotic-related diarrhoea and severe *Clostridium difficile* infection, and the long-term safety of treatment is worrisome.

The acidic environment in the stomach (pH 2.0 or so) inhibited the growth of most bacteria, forming a unique flora structure and microenvironment in the stomach.[9 10] Once the structure of the flora in the stomach changes, an imbalance of the gastrointestinal microenvironment will lead to a disease.[11] Lactobacillus is the main microbial flora in the human stomach, and it can be successfully colonised in the non-acid region of the stomach. However, the infection site of Hp is also a non-acid-producing area, so lactobacillus can be used as natural enemies of Hp, inhibiting their growth.

In the Hp colonisation model experiment established with Mongolian gerbils, Hp colonisation can obviously competitively inhibit the growth of lactic acid bacteria and change the flora structure,[12] and after gastric perfusion with three strains of lactobacillus strains isolated from normal gerbil stomach the lactobacillus strains can clear Hp colonisation in the gerbil stomach in a short time (2 weeks), and the clearance rate reaches about 60%. Yaşar *et al*[13] have reported that *Lactobacillus acidophilus* combined with triple therapy can increase Hp eradication rates. 'The fifth consensus report on the treatment of helicobacter pylori infection' also indicates that studies have shown that supplementation with microecological agents during eradication of Hp may reduce the adverse effects of antibiotics on intestinal microecology.[14 15] Therefore, *L. acidophilus* used for anti-Hp treatment may improve the eradication rate of anti-Hp treatment and reduce the side effects of a large number of antibiotic treatment, and is expected to be a new method of accurate eradication of Hp.

At present, the exact mechanism and curative effect of probiotics in the eradication of Hp have not yet been determined, and the conclusions obtained from relevant meta-analyses are different in the world.[16 17] Whether probiotics (*L. acidophilus*) could improve the eradication rate of Hp or reduce the gastrointestinal side effects of Hp treatment remains to be confirmed, so it is very necessary and urgent to further complete high-quality clinical research.

There is also one thing worth noting: antibiotics are the core drugs in anti-Hp treatment. The minimal inhibitory concentration (MIC) of many antibiotics (eg, amoxicillin) to Hp depends on the pH value of the stomach, and the MIC increases when the pH decreases. The desired acid strength requires more than 16 hours of intragastric pH >5 within 24 hours. When amoxicillin was included in the regimen, an intragastric pH >6 could achieve better results. pH 5.0–5.5 is also the best pH for *L. acidophilus* growth. Therefore, it is necessary to accurately detect the pH level in the stomach and explore the most suitable pH range in the process of anti-Hp treatment.

METHODS AND ANALYSIS

We developed this protocol according to the Standard Protocol Items: Recommendations for Interventional Trials.[18] The trial is registered at the Chinese Clinical Trial Registry (www.chictr.org.cn) with identifier ChiCTR-INR-17014185.

Objectives

The purposes of this trial are to explore the clinical value of probiotic preparation compound *L. acidophilus* as an auxiliary treatment for Hp eradication and to find out the optimal pH value in the stomach for anti-Hp treatment.

Trial design and setting

This study was designed as a parallel control for two groups of equal samples. Group A will be treated with quadruple therapy alone, while group B will be treated with compound *L. acidophilus* tablets combined with quadruple therapy. This single-centre, double-blinded, randomised controlled trial is designed to evaluate the clinical efficacy and safety of probiotic preparation

compound *L. acidophilus* as a supplementary treatment for Hp eradication and to find out the optimal pH value for anti-Hp treatment. This study will be conducted in the Departments of Gastroenterology of Chongqing University Cancer Hospital and Chongqing Cancer Hospital in China.

Participant selection

Inclusion criteria

Participants will be enrolled if the following criteria were all met: (1) age above 18 and under 70 years; (2) patients with peptic ulcer and chronic gastritis caused by Hp infection were examined using the kit for 14C-urea breath test in the digestive department of Chongqing Cancer Hospital; (3) anti-Hp treatment has not been performed in the past; and (4) have signed the informed consent.

Exclusion criteria

We will exclude patients if any of the following criteria were met: (1) allergic to any one of rabeprazole sodium enteric-coated tablet, amoxicillin capsule, furazolidone tablet, bismuth potassium citrate capsule and compound *L. acidophilus* tablet; (2) digestive tract occupation or gastrointestinal active bleeding; (3) pregnancy and lactation; (4) those who had used drugs for eradication of Hp and related drugs; (5) gastroscopy contraindications; (6) existence of mental illness, which could make it difficult for the participant to cooperate; and (7) patients without self-judgement ability.

Sample size calculation

In this study, two groups of equal samples were designed for parallel control, and the eradication rate of Hp was proposed as the main outcome index. Therefore, the sample size estimation formula ($n_1=n_2=2\left[\left(Z_{\alpha/2}+Z_{\beta}\right)^2\pi\left(1-\pi\right)\right]/\delta^2$) for comparison of the two sample rates was used as the sample size required for theoretical calculation. In the above formula, n_1, n_2 are two groups of samples, Z_{β} is the standard normal distribution of bilateral test boundary value, $Z_{\alpha/2}$ is a unilateral test boundary value, and δ is the difference between the two groups of the overall probability. According to the published results of a meta analysis,[16] the eradication rate of Hp by probiotics combined with quadruple therapy is about 82.31%, while the eradication rate of Hp by quadruple therapy alone is about 72.08%. The allowable error (α) of the study is set at 0.05, the statistical efficiency (1-β) is 80%, the possible rate of lost to follow-up and the unqualified rate of the subjects during the study are 10%, and the theoretically required sample quantity is about 526 people; 263 people in each group can be obtained based on the EmpowerStats software.

Recruitment, randomisation and blinding

Subjects were recruited from patients confirmed to be Hp-infected by the kit for 14C-urea breath test. Investigators trained in the study will select 526 eligible applicants as subjects, in accordance with the process and with the authorisation of the lead investigator with regard to the inclusion and exclusion criteria. After eligible patients were identified, written informed consents will be obtained from the eligible patients, their next of kin or their legal representatives. At the same time, the investigators will collect the demographic and clinical characteristics of the 526 people, including sex, age, weight, contact information, drug allergy history, medical history (such as hypertension, diabetes and cardiovascular diseases, tumour history and so on), nearly 3 months of medication history and clinical symptoms. In this study, patients will be randomly divided into two groups—group A (quadruple therapy) and group B (probiotic combined quadruple therapy)—based on the random sequence of opaque envelopes generated and sealed by computer. First of all, all patients should be examined by electronic gastroscopy to get a clear diagnosis of peptic ulcer, chronic gastritis, and excluding gastrointestinal space occupation and active bleeding. At the same time, based on a random sequence of non-transparent envelopes generated and sealed by computer, 50 patients were randomly selected from each group. During gastroscopy, the pH monitor will be placed in the stomach and anti-Hp treatment was taken according to groups.

To increase the reliability of the conclusions deduced from the results of the study, the blind method was applied to endoscopic surgeons and data processing and analysis staff on the basis of a comprehensive evaluation of the feasibility of the study. However, due to the limitation in the nature of the study, the subjects could not apply the blind method.

Study protocol

Five hundred and twenty-six patients with peptic ulcer or chronic gastritis who were positive in the kit for 14C-urea breath test were randomly divided into group A or group B, with 263 patients in each group. All patients who participated in the study underwent electronic gastroscopy to clarify the diagnosis of peptic ulcer and chronic gastritis, while excluding digestive tract occupancy and active bleeding. Fifty patients in the two groups were randomly selected to be placed under gastric pH monitor to monitor gastric pH status. Then anti-Hp treatment will be carried out, and the specific medicine-taking methods in the different groups comprise the following steps:

- Group A (quadruple therapy): 20 mg rabeprazole sodium enteric-coated tablets were orally taken 1 hour before breakfast and dinner, 2 capsules of bismuth potassium citrate were orally taken 0.5 hours before breakfast and dinner, and 0.1 g furazolidone tablets and 1000 mg amoxicillin capsules were orally taken 0.5 hours before breakfast and dinner, respectively. The above medicines need to be taken continuously for 14 days. Patients with peptic ulcer should continue to take 20 mg rabeprazole sodium enteric-coated tablets before breakfast every day for 4 weeks. When all the drugs have been stopped for 1 month, the kit for 14C-urea breath test will be reviewed.

- Group B (probiotic combined quadruple therapy): 20 mg rabeprazole sodium enteric-coated tablets were orally taken 1 hour before breakfast and dinner, 2 capsules of bismuth potassium citrate were orally taken 0.5 hours before breakfast and dinner, and 0.1 g furazolidone tablets and 1000 mg amoxicillin capsules were orally taken 0.5 hours before breakfast and dinner, respectively. Take compound *L. acidophilus* tablets 1.0 g (*L. acidophilus* tablet is a compound tablet which contains 5×10^6 *L. acidophilus*) after breakfast, lunch and dinner, respectively. It is worth noting to take compound *L. acidophilus* tablets and antibacterial drugs with at least 2-hour interval. The above medicines need to be taken continuously for 14 days. Patients with peptic ulcer should continue to take 20 mg rabeprazole sodium enteric-coated tablets before breakfast every day for 4 weeks. When all the drugs have been stopped for 1 month, the kit for 14C-urea breath test will be reviewed.

During the trial, the investigators need to maintain close contact with the patient to dynamically master patient performance and provide guidance to the patient.

Study endpoints

Primary outcome

The main evaluation index is the eradication rate of Hp. The kit for 14C-urea breath test will be reviewed after anti-Hp treatment, and a negative result (<25) indicated that Hp had been eradicated. Eradication rate=number of negative cases/total cases × 100%.

Secondary outcomes

We will also measure intragastric pH: the capsule part of the pH detector is fixed on the gastric mucosa through the clamping seat, which can continuously record the gastric pH value, which is more than 96 hours during the anti-Hp treatment. Patients' symptoms are also an evaluation index: the investigators will record patients' symptoms such as nausea, vomiting, taste abnormalities, hiccups, abdominal pain, abdominal distension, diarrhoea, rash or increased symptoms during anti-Hp treatment.

Safety assessments

The investigator will record all adverse events related to anti-Hp therapy, such as nausea, vomiting, taste abnormalities, hiccups, abdominal pain, abdominal distension, diarrhoea, rash or increased symptoms on the case report form. That is to say, when an adverse event occurs, the investigator will record the symptoms and signs of the adverse reaction, duration (start and end date), severity, course, outcome, significance and any action taken in relation to the adverse event.

Data management

All original data will be recorded on the case report forms accordingly and signed by direct investigators. The completed case report forms will be sent to the head investigator (W-QC). Data collation is carried out independently by two persons with rich experience in data collation and analysis, and cross-checked by project and stage. Data entry will be doubly performed by two persons using the Excel V.2010 tool. More importantly, all processes associated with data access and analysis will be supervised by the Clinical Research Ethics Committees of Chongqing University Cancer Hospital and Chongqing Cancer Hospital.

Statistical analysis

In this study, the demographic and clinical characteristics of the patients will be summarised with mean, median and SD. The results of Hp eradication and safety are expressed in terms of the number of cases and percentage. The classification outcome indicators will be compared by non-parametric statistical analysis. If the relationship between Hp eradication rate and gastric pH value meets the bivariate normal distribution, Pearson's correlation analysis is selected, and if it is a non-bivariate normal distribution Spearman's correlation analysis is used. Non-parametric statistical analysis was used to compare the eradication rates of Hp with different pH values. Subgroup analysis will also be performed according to the specific disease type (peptic ulcer or chronic gastritis) included in the study, and a p value of <0.05 will be considered significant. All statistical analyses will be performed by blinded professional statisticians using SPSS V.13.0 for Windows.

Patient and public involvement

Patients/public were first involved in the research during the recruitment stage of the research process, and they can participate in the study voluntarily. Patients/public are not involved in the design of the study. They will not be asked to assess the burden of the intervention and the time required to participate in the research. In the randomised controlled trial, the burden of intervention and major research indicators need not be assessed by the patients themselves, but the safety (adverse reactions) of the patients during treatment needs timely feedback. Because it is a double-blinded experiment, our main research indicators are also measured by instruments, so experience and preferences will not affect the development of research problems and measurement of the results. At the end of the experiment, the final results will be fed back to the patient in the form of a report.

DISCUSSION

Hp infection is a chronic disease and is the main cause of chronic gastritis, with the highest infection rate in China. It initiates a series of pathogenic events, leading to atrophic gastritis, metaplasia, dysplasia and ultimately gastric cancer. Eradication of Hp can prevent the occurrence and development of gastric precancerous changes (atrophic gastritis, intestinal metaplasia). Removal of Hp infection in the stomach can greatly reduce the risk

of precancerous lesions and gastric cancer. Hp is very stubborn; once infected, it is difficult to cure, unless with regular treatment. The Maastricht V consensus and the fifth report on Hp infection management consensus in China recommended quadruple therapy containing PPI, bismuth and two antibiotics as a first-line treatment regimen for Hp eradication. At least two antibiotics are included in the currently recommended Hp eradication treatment regimen, at the same time, and the treatment course reaches 14 days. The application of the antibiotics can cause short-term change in the intestinal flora.[18 19] In Hp eradication treatment, the combination of two antibiotics in large doses may lead to intestinal flora imbalance, which may cause antibiotic-related diarrhoea, and if serious can cause *C. difficile* infection. A meta-analysis[19] of 1671 patients showed that approximately 5%–30% of the patients who received Hp eradication therapy were discontinued due to adverse reactions. *L. acidophilus* as a probiotic can reduce the secretion of micropathogenic bacteria toxin on the surface of the host mucosa, promote mucosal repair and help reduce the adverse reactions in Hp eradication therapy. Some studies[20] also show that *L. acidophilus* can inhibit Hp infection through competitive colonisation, which may improve the eradication rate of Hp.

In this study, we will compare the eradication rate of Hp and the incidence of adverse reactions between the compound *L. acidophilus* tablets combined with quadruple therapy and a simple quadruple therapy, and observe the relationship between pH value in the stomach and Hp eradication rate, explore the clinical value of probiotic compound *L. acidophilus* as an auxiliary scheme of Hp eradication therapy, find out the most suitable pH value of the stomach for anti-Hp therapy, and hope to explore a new method of precise eradication of Hp.

ETHICS AND DISSEMINATION

To guarantee the rights of all eligible patients during the study period, we will strictly follow the Declaration of Helsinki and the Chinese guidelines for good clinical practice.

During screening and recruitment, investigators must provide qualified candidates with the details of the study, such as the purpose, procedures and potential benefits and risks of the experiment, as well as the results of the study. At the same time, the investigator must let each participant know that he/she has the right to withdraw at any time during the study. Each patient or his authorised agent must give the written informed consent prior to participating in the practice. All written informed consent forms will be retained as part of the partial clinical trial documentation.

All participants will be informed that their personal information will only be used in this study and that all such information will not be used for other purposes. All processes will be performed according to the Chinese guidelines for good clinical practice. The results of the study will be submitted to peer-reviewed academic journals and will be presented at national and international conferences.

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Contributors WJ, W-QC, XT contributed to the protocol design and writing of the manuscript. W-QC is responsible for monitoring the processes of the trial. WJ, XT, W-QC are responsible for writing the manuscript and also managing and supervising the clinical research. All authors approved the final manuscript.

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Competing interests None declared.

Patient consent Obtained.

Ethics approval The study protocol has been approved by the Clinical Research Ethics Committees of the Chongqing University Cancer Hospital and Chongqing Cancer Hospital (2018[012]).

Provenance and peer review Not commissioned; externally peer reviewed.

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