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***Clinical Trials Study***

**Effects of daily telephone-based re-education before taking medicine on *Helicobacter pylori* eradication: A prospective single-center study from China**

Wang CH *et al*. Telephone guidance for *H. pylori* eradication

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**Abstract**

**AIM:** To investigate the effects of daily telephone-based re-education (TRE) before taking medicine for the eradication of *Helicobacter pylori* (*H. pylori*) on the compliance and the eradication rate in a Chinese patient population.

**Methods:** A prospective, physician-blinded, randomized, controlled clinical study was conducted. The patients were randomly assigned to receive TRE every day before taking medicine (TRE group) or no TRE (control group). The patients in the TRE group received regular instructions before taking medicine for the eradication of *Helicobacter pylori* (*H. pylori*) during the entire course of treatment through telephone calls. The patients in the control group received detailed instructions at the time of seeing a doctor for the guidance. The primary outcome was the eradication of *H. pylori* eradication rate after treatment. The secondary outcomes includedthe clinical remissions after treatment, adverse events, compliance, and patients’ satisfaction.

R**esults:** A total of 140 patients were randomized, 70 to the TRE group and 70 to the control group. As the primary outcome, the *H. pylori* eradication rates in the TRE and control groups were 62.7% and 71.2% in per protocol analysis (*p* = 0.230), and 52.9% and 52.9% in intention-to-treat analysis (*p* = 0.567), respectively. As the secondary outcomes, there were no significant differences in the patients’ satisfaction between the test groups (good, 79.7% *vs* 76.9%; fair, 13.6% *vs* 19.2%; poor, 6.7% *vs* 3.9%, for the TRE group and control group, respectively (all *p* > 0.05); the rates of adverse effects were 15.2% and 63.5% in the TRE and control groups, respectively (*p* < 0.001); the compliance rates in the TRE and control groups were 85.7% and 74.3%, respectively (*p* = 0.069).

**Conclusion:** Daily TRE before taking medicine had no significant impact on the patients’ compliance, satisfaction, or *H. pylori* eradication, but reduced the rate of adverse events.

**Key words**: *Helicobacter pylori*;Eradication; Telephone re-education; Compliance; Adverse events

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**Core tip:** Compliance is an important factor affecting *Helicobacter pylori (H. pylori)* eradication. The present study is the first attempt to evaluate the telephone re-education (TRE) in *Helicobacter pylori* (*H. pylori*)treatment in China. The daily TRE neither improved the eradication rate nor the patients' compliance or satisfaction, but decreased adverse effects. Meanwhile, adverse effects may not be the main reason for poor compliance. Our results suggest that compliance is not the important reason for a deceased *H.* *pylori* eradication rate in China.

Wang CH, Liao ST, Yang J, Li CX, Yang YY, Han R, Chen DF, Lan CH. Effects of daily telephone-based re-education before taking medicine on *Helicobacter pylori* eradication: A prospective single-center study from China. *World J Gastroenterol* 2015; In press

**INTRODUCTION**

*Helicobacter pylori (H. pylori)*are a pathogen that infects more than 50% of the human population, resulting in high healthcare costs worldwide[1]. Though some of the *H.* *pylori*-positive individuals may remain asymptomatic through their life span, the infection can cause chronic gastritis in almost 100% of infected individuals, even resulting in severe diseases, such as atrophic gastritis, peptic ulcer disease, and gastric cancer[2]. Recently it has been revealed that poor compliance is often seen in patients undergoing treatment for the eradication of *H.* *pylori*[3]. Poor compliance and bacterial resistance are two major factors that cause the eradication rates of *Helicobacter pylori* (*H. pylori*) to decrease to an unacceptable level (≤ 80%)[4,5].

Compliance in *H.* *pylori* treatment has a great influence on treatment failures in antibiotic-sensitive patients and on the development of antibiotic resistance[6]. Multiple factors such as complexity and duration of the treatment can affect the patients’ compliance. Several methods had previously been tried to enhance patients’ compliance with instructions for *H.* *pylori* treatment, but the results are inconsistent. Adjuvant treatment (especially with probiotics) can improve the compliance[7].

Taking phone interview on the last day of therapy and returned pill counting can improve patients’ compliance, but attempts to increase compliance may have no impact on the treatment outcomes[8]. The doctor-patient relationships, including the relations with pharmacists and nurses, can also play an important role in improving compliance and eradication of *H. pylori*[9]. In addition, structured aftercare and follow-up often help improve the compliance and subsequent *H.* *pylori* eradication rate[10,11].

China is among the countries with a high prevalence of *H. pylori* infection with a rate of 50%-80%. Several factors may affect the compliance of *H.* *pylori* treatment in Chinese patients such as lack of detailed guidance on drug administration, lack of detailed instruction or consultation from gastrointestinal doctors due to busy schedule, misunderstanding of or concerns over the side effects of Western medicine, and preference of use of the traditional Chinese medicine due to beliefs of having fewer adverse effects[12]. Therefore, there is an urgent need for improving the compliance of *H.* *pylori* treatment in China.

Telephone re-education (TRE) is often used to improve treatment compliance[6], but has not been well studied in China. We hypothesized that compliance of the *H. pylori* patients and its eradication rate could be improved by TRE every day before taking medicine, reminding the patients of the detailed information related to the time and dose of medicines, answering the patients’ questions, and comforting and encouraging them to continue the treatment. The purpose of the present study was to evaluate the effects of the intervention with TRE on the rate of *H.* *pylori* eradication and on other clinically relevant outcomes, such as the clinical symptoms after treatment and treatment-related adverse effects.

**MATERIALS AND METHODS**

***Patients***

The present study employed a prospective, physician-blinded, randomized, controlled single-center study design, and was conducted in consecutive outpatients at the Department of Gastroenterology of Daping Hospital, Chongqing, China, from September 2014 to November 2014. The study protocol and informed consent form were reviewed and approved by the Ethics Review Committee of Daping Hospital, Third Military Medical University, Chongqing, China [Approval No. (2014) 06], and the study was registered with Chinese Clinical Trial Register (ChiCTR-TRC-14005193). Each of the patients provided a written informed consent before enrolment to the trial.

Patients were randomized to either the TRE or control group at the time of first clinical visit, by using a computer generated random number kept in a sealed opaque envelope. At least two telephone numbers for each of the patients or their relatives living together were recorded for the TRE. All patients were instructed not to tell physicians and/or investigators about their preparation method and when they received instructions in any time of the study (before, during and after the procedure)

The inclusion criteria were as follows: (1) outpatients aged 18-60 years with chronic gastritis or gastroduodenal ulcer; (2) confirmed diagnosis of *H.* *pylori* infection by at least one of the following methods: 13C-urea breath test, histology, rapid urease test or bacterial culture; (3) An indication of *H. pylori* eradication treatment; and (4) ability and willingness to participate in the study.

The exclusion criteria were as follows: (1) advanced chronic disease that would not allow the patient to complete follow-up or attend visits; (2) allergy to any of the drugs used in this study; (3) previous gastric surgery; (4) pregnancy or breastfeeding (female participants with childbearing potential were required to use medically accepted contraception for the duration of the study); (5) alcohol or drug abuse; (6) previous *H.* *pylori* eradication treatment; and (7) taking antibiotics or bismuth salts within two weeks before the study.

***Intervention***

The patients in the TRE group received detailed instructions at the time of seeing a doctor for the guidance of clinical medication and reexamination at four weeks after the treatment. The detailed instructions of rational drug use and periodic review were given by another doctor through telephone call every day before taking medicine. The 10-d treatment was the triple therapy, including esomeprazole (AstraZeneca Pharmaceutical Co, London, United Kingdom; Lot H20046379; 20 mg/12 h), amoxicillin (Zhuhai Union Pharmaceutical Co. ltd., Zhongshan, China, H44021351; 1 g/12 h), and clarithromycin (Shanghai Abbott Laboratories Co. Ltd., Shanghai, China, J20050067; 500 mg/12 h). Symptom relief drugs including gastric mucosal protective drugs, cardiovascular drugs, and other medications were allowed to be used in both groups when needed. At four weeks after treatment, the patients received telephone calls to schedule reexamination through 13C-urea breath test to confirm eradication.

The patients in the control group received detailed instructions at the time of seeing a doctor for the guidance of clinical medication and reexamination at four weeks after treatment. The treatment plan was identical as that in the TRE group.

***Trial outcomes***

The primary outcome was the eradication of *H.* *pylori* at four weeks after treatment. The eradication of *H. pylori* was confirmed by the 13C-urea breath test. The secondary outcomes included the compliance, clinical symptoms remission after treatment, adverse events, and patients’ satisfaction. The satisfaction of the patients were evaluated and recorded using a ten-point scale (poor, 1-4; fair, 5-7; good, 8-10) based on questionnaire in a physician-blinded fashion. (How this scale was calculated? based on questionnaire? if yes, what were the questions and was this questionnaire validated or not?)

***Calculation of sample size***

The sample size calculation was performed by assuming a 25% difference in the rate of the *H.* *pylori* eradication after treatment. The rate of standard triple therapy in China was about 75%. We calculated that at least 116 patients were needed for the study by using a significance level (α) of 0.05 and a power of 80% with a two-tailed test. However, from our previous experience, approximately 20% of patients may withdraw from the trial or loss to follow-up. We estimated that a total of 140 patients would be sufficient to detect a significant difference in the primary outcome.

***Statistical analysis***

The intention-to-treat (ITT) and per-protocol (PP) analyses were used to assess the primary outcome. Categorical variables were analyzed using χ2 tests or Fisher’s exact test, as appropriate. Continuous variables were expressed as means with SD and analyzed using Student’s *t*-test. Analyses were performed with SPSS software V.19.0 for Windows. A *p* value of < 0.05 was considered statistically significant.

**RESULTS**

***Patients’ characteristics***

We screened 286 outpatients with *H.* *pylori* infection; 146 of them were excluded (82 met exclusion criteria and 64 were unwilling to participate in the study); 140 were randomized to the TRE group (*n* = 70) or the control group (*n* = 70). Eleven subjects in the TRE group and 18 in the control group withdrew themselves from the study or were lost to follow up for various reasons including a busy schedule, remission of symptoms and stopping medication in treatment process, unsatisfying efficacy, giving up treatment, adverse events, and others. There was no significant difference in the number of patients lost in the follow-up between the two groups (11 *vs* 18, *p* = 0.069). Finally, 59 in the TRE group and 52 in the control group completed the treatment for the eradication of *H.* *pylori*.

The baseline characteristics of the patients in both groups were well balanced (Table 1), with no significant differences between the two groups.

***Outcomes of treatment***

In the PP analysis of the primary outcome, the *H.* *pylori* eradication rates of the TRE and control groups were 62.7% (37/59) and 71.2% (37/52) (*p* = 0.230), while in the ITT analysis, the rates were 52.9% (37/70) and 52.9% (37/70) (*p* = 0.567), respectively.

There were no significant differences in the symptoms after treatment were found between the two groups (all *p* > 0.05; Table 2). The rate of adverse effects in the TRE group was significantly lower than that of the control group (*p* < 0.001; Table 3). The taste disorder was significantly lower in the TRE *vs* the control group (6.8% *vs* 53.8%, *p* < 0.001)

The compliance rate in the TRE group (84.3%) was slightly higher; however non-significant than that of the control group (74.3%; *p* = 0.069). The results of patients’ satisfaction are shown in Table 4. There was no significant difference in patients satisfaction between the two groups (*p* > 0.05).

**DISCUSSION**

The triple therapy as a traditional standard care is widely used in China, but the eradication rate is decreasing due to various reasons such as drug resistance, *p*oor compliance, high bacterial loads, and genic polymorphisms of cytochrome P450 proteins 2C19 (CYP2C19)[2,13-15]. Therefore, the standard triple therapy does not reach the acceptable threshold of 80% eradication rate in most contexts[5,16]. Most researches have focused on the antibiotic resistance. In fact, improving compliance is relatively simple and less costly compared with other measures to improve the therapeutic outcome. The improvement in compliance can be accomplished through education. In the present study, the *H. pylori* eradication rates in the TRE and control groups were 62.7% and 71.2% (PP), and 52.9% and 52.9% (ITT), respectively.

Failure to comply with the anti-Helicobacter therapy (AHT) requirements by the patient often results in treatment failure[6,17]. In a previous study, patients with good compliance had a higher AHT effectiveness (96%) than those with low compliance (69%)[17]. The major reason for poor compliance was the development of an adverse event during the course of AHT[18], and the adverse events were found to be different with different AHT regimens[19]. In our study, the rates of adverse effects were 15.2% and 63.5% in the TRE and control groups, respectively. The reasons for the difference may be a result of telephone follow-up every day, including timely resolve, comfort and relief of the symptoms among the TRE patients. The studies with a seven-day AHT regimen have shown 41% frequency of adverse effects, which provoked cessation of therapy in 3%-10% of the patients[20]. If the treatment time is prolonged to 10-14 d, the development of adverse effects can be seen in more than half of the patients[21].

In order to improve the compliance of *H.* *pylori* eradication, detailed instructions of rational drug use and periodic review were provided by telephone call every day before taking medicine. A follow-up telephone call after initiation of therapy in a previous study suggested that although adverse effects were common between enhanced compliance program and control groups, most patients were able to complete 60% or more of the two-week regimen[20]. There was no statistically significant difference between the two test groups in the number of patients taking more than 60% of the medications, and the number of patients taking more than 90% of the medications; an enhanced compliance program further improved the percentage of medications taken[22].

However, similar studies found that the enhanced compliance had no impact on the treatment outcome and adverse effects were very common[8].

In the present study, TRE every day before taking medicine could not significantly improve the compliance or the *H.* *pylori* eradication rate. No statistically significant differences were found between TRE and control groups regarding the symptoms after treatment; however, the adverse effects in the TRE were significantly fewer than the control group. The results indicated that adverse effects might not be the major reason for poor compliance and less effectiveness in the eradication of *H.* *pylori*.

Although adverse effects are common in standard therapies, they are rarely severe. In our study, the adverse effects included taste disorder, diarrhea, skin rash, headache and sore throat. The most common adverse events reported in most studies are diarrhea, nausea, and vomiting. Using the standard first-line triple therapy, a multi-center study has found that the overall rate of adverse events was 53.3%[23]. The evidence supporting concurrent administration of probiotics to lessen the side-effects of triple therapy is still equivocal. While Kim *et al*[24] found that probiotics had no effect on the side-effect profile, but increased the rates of eradication, another study revealed that probiotics reduced side-effects and did not affect the eradication rate[25]. In our study, the adverse effects in the TRE group were significantly less than that of the control group, but the *H.* *pylori* eradication rates were similar between the two groups. Although the compliance increased in the TRE group, it was non-significant compared to the control group. Moreover, there were no differences in the satisfaction of patients between the two groups. It seems that the patients neither recognized the difference nor acknowledged the effects of the TRE. It is possible that daily telephone calling was exaggerated and perhaps made the patients feel uncomfortable. The effectiveness and acceptance of TRE may be dependent on the type of disease and the intervention. For instance, in a study conducted in China, it has been reported that TRE one day prior to colonoscopy improved the compliance, quality of bowel preparation, and the polyp detection rate[26]. Our results suggested that TRE may not be the best way to improve compliance in *H.* *pylori* treatment and that modifications of the TRE intervention may be required or other better approaches are needed.

In conclusion, the present study represented the first attempt to evaluate the TRE in *H.* *pylori* treatment in China. Although the daily TRE did not improve the *H.* *pylori* eradication rate, compliance, or patients’ satisfaction; however, it decreased adverse effects. Meanwhile, adverse effects may not be the main reason for poor compliance. Our results may help develop an effective plan for improving compliance and therapeutic outcome of *H.* *pylori* therapy.

**COMMENTS**

***Background***

Compliance with therapy is one of the most important factors in *Helicobacter pylori* (*H. pylori*) eradication. The effects of telephone re-education (TRE) daily before taking medicine for *H. pylori* treatmenton the compliance and the *H. pylori* eradication rate have not yet been studied in China.

***Research frontiers***

Most researches have mainly focused on the antibiotic resistance in the treatment for *H. pylori* eradication. Improving compliance is a relatively simple and less costly approach to improving the therapeutic outcome, compared with other measures.. The improvement in compliance can be accomplished through effective patient education program.

***Innovations and breakthroughs***

In the present study, an innovative TRE program was developed and evaluated in patients undergoing *H. pylori* treatment in China. The most important findings were that daily TRE before taking medicine reduced the rate of adverse events, but had no significant impact on the patients’ compliance, satisfaction, or *H. pylori* eradication rate.

***Applications***

The results from the present study suggest that compliance is not the main reason for a deceased *H.* *pylori* eradication rate in China. Additionally, adverse effects may not be the main reason for poor compliance. These results would help develop a more effective plan for improving compliance and therapeutic outcome of *H.* *pylori* therapy in China.

***Terminology***

Daily TRE: The detailed instructions of rational drug use and periodic review were given to the patient by physicians through telephone call every day before taking medicine.

***Peer-review***

The authors conducted a new study to investigate the effects of daily TRE program before taking medicine on the compliance and the eradication rate in patients with the treatment for eradication of *H. pylori*. It is believed that this is the first study of this kind in China. The authors provided sufficient data to support their conclusion that daily TRE before taking medicine had no significant impact on the patients’ compliance, satisfaction, or *H.* pylori eradication, but reduced the rate of adverse events. The research is interesting and the study design and the results are clearly presented. Future large-scale studies should be conducted to develop an effective way to improve the outcome of *H.* *pylori* eradication therapy in China and other countries as well.

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**Table 1 Baseline characteristics of the patients included in this study**

|  |  |  |  |
| --- | --- | --- | --- |
| **Characteristics** | **TRE group**  **(*n* = 70)** | **Control group**  **(*n* = 70)** | ***p* value** |
| Sex(M/F) | 25/45 | 28/42 | 1.000 |
| Age (yr) | 42.9 ± 10.7 | 45.9 ± 9.2 | 0.098 |
| BMI (kg/m2) | 23.1 ± 4.0 | 23.7 ± 3.7 | 0.677 |
| Grade of education |  |  | 0.199 |
| Elementary school or no education | 5 (7.1) | 9 (12.9) |  |
| Higher than elementary school | 65 (92.9) | 61 (87.1) |  |
| Residence |  |  | 0.604 |
| Country | 8 (11.4) | 8 (11.4) |  |
| City | 62 (88.6) | 62 (88.6) |  |
| Digestive tract hemorrhage | 5 (7.1) | 3 (4.3) | 0.529 |
| Family gastric cancer history | 4 (5.7) | 2 (2.9) | 0.340 |
| Endoscopy results |  |  |  |
| Chronic gastritis | 55 (71.2) | 59 (84.3) | 0.257 |
| Peptic ulcer | 14 (20.0) | 10 (14.3) | 0.251 |
| *Helicobacter pylori* infection | 70 (100.0) | 70 (100.0) |  |

Values are expressed as mean ± SD, % or *n* (%). BMI: Body mass index; TRE: Telephone re-education.

**Table 2 Effects of telephone re-education on the symptoms after treatment o**f ***Helicobacter pylori* eradication *n* (%)**

|  |  |  |  |
| --- | --- | --- | --- |
| **After**  **treatment** | **TRE group**  **(*n* = 59)** | **Control group**  **(*n* = 52)** | ***p* value** |
| Pain | 14 (23.7) | 10 (19.2) | 0.367 |
| Burning sensation | 3 (5.1) | 5 (9.6) | 0.290 |
| Acid reflux | 4 (6.8) | 3 (5.8) | 0.571 |
| Nausea and vomit | 3 (5.1) | 1 (1.9) | 0.358 |
| Belching | 2 (3.4) | 3 (5.8) | 0.440 |
| Abdominal distension | 8 (13.6) | 2 (3.8) | 0.071 |
| Poor appetite | 1 (1.7) | 1 (1.9) | 0.720 |

**Table 3 Effects of telephone re-education on the adverse events after *Helicobacter pylori* treatment *n* (%)**

|  |  |  |  |
| --- | --- | --- | --- |
| **Adverse events** | **TRE group**  **(*n* = 59)** | **Control group**  **(*n* = 52)** | ***p* value** |
| Skin rash | 2 (3.4) | 0 (0.0) | NS |
| Headache | 1 (1.7) | 0 (0.0) | NS |
| Sore throat | 0 (0.0) | 2 (3.8) | NS |
| Taste disorder | 4 (6.8) | 28 (53.8) | < 0.001 |
| Diarrhea | 2 (3.4) | 3 (5.8) | 0.440 |
| Total | 9 (15.2) | 33 (63.5) | < 0.001 |

NS: Not significant.

**Table 4 Satisfaction of patients included in this study** ***n* (%)**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **TRE group** | **Control group** | ***P* value** |
| Satisfaction |  |  |  |
| Good | 47 (79.7%) | 40 (76.9%) | 0.452 |
| Fair | 8 (13.6%) | 10 (19.2%) | 0.290 |
| Poor | 4 (6.7%) | 2 (3.9%) | 0.401 |