

A Work on the Treatment of Traditional Chinese Medicine Combined with Proton Pump Inhibitor (PPI) Step-down on Non-erosive Reflux Disease

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Introduction

We have published an article in *Trials* journal to carry out a multicentered, randomized controlled clinical trial on the treatment role of Traditional Chinese Medicine (TCM) combined Proton Pump Inhibitors (PPIs) step-down in non-erosive reflux disease (NERD) [1]. NRED is the most popular type of gastroesophageal reflux disease (GERD), which is defined as “the presence of abnormal acid exposure time (AET) with or without reflux-symptom association on ambulatory reflux monitoring performed off anti-secretory therapy” by Rome IV consensus [2]. PPIs are the most effective strategies for NERD, however, about 50% of the NRED patients do not respond to the standard PPI dose and two-thirds of NERD patients have a recurrence of symptoms after stopping the PPI medication [3-5]. Besides, the usage of PPIs has been proven in relation to different kinds of diseases including spontaneous bacterial peritonitis and bacterial enteric infections [6]. Complementary and alternative approaches have been suggested for effective treatment of NERD [7,8]. Traditional Chinese Medicine (TCM) is one of the methods useful in NERD intervention which has been used in China for many years in NERD treatment. Lots of studies have proved that TCM has beneficial therapeutic effects in NERD [8-10]. It is a well-known adage from medical practice: “All drugs should be given in the lowest effective dose and for the shortest possible time.” However, a sudden stop of PPIs will cause physiological acid rebound and repeated symptoms, resulting in unsuccessful drug withdrawal. Therefore, our

research first put forward an innovative kind of tactic that TCM helps to reduce the gradient of PPIs and relieve the patient's symptoms.

TCM treated patients according to a complex network analysis based on the criterion that doctors make a diagnosis after a comprehensive assessment of the patient's symptoms, tongue, and pulse [11]. In our previous research, 6 hospitals from different provinces of China divided participants into three groups according to their different TCM syndromes which conforms to the basic criteria of TCM treatment [1]. Confirm the clinical research reporting standards: administrating treatment according to pattern differentiation [12]. The evidence-based medicine (EBM) has changed the concepts and the way of clinical decision-making since the 1990s, TCM researchers have worked on how to use the evidence to support decision-making [13,14]. There are four elements in a clinical question, participants (P), intervention (I), comparison (C), and outcomes (O) [15]. In the research, patients' selection criteria for NERD were made according to the China Consensus Opinion on Gastroesophageal Reflux Disease. The treatment history, compliance, and security strict adherence to the research standards [16]. Participants with the same TCM syndrome will be separated into the intervention group and the control group at a ratio of 1:1 [1]. The preparation of placebos used in the trial was made in a dosage form similar to that of the testing drug as possible [17,18] to reduce intervention bias. TCM physicians from

different hospitals received professional training. Besides, different groups of patients are distinguished, and more personalized schemes are formulated.

In clinical research, blinding is necessary for human behavior to be influenced by what we know or believe [19]. The blinding in controlled trials, and particularly "double-blind," usually refers to keeping participants, those involved with management, and those collecting and analyzing data unaware of the treatment assignment, so that they would not be influenced by what they know, avoiding overestimating the test results [20-22]. In the trial, we followed the requirements strictly according to the established SOP guidelines. All codes were kept in the Good Clinical Practice (GCP) Centre of Xiyuan Hospital [1]. Besides, the protocol received approval from the Ethical Review Committee Auditing and written informed consent forms were provided for eligible participants. The above design enhances the reliability of the results.

During the treatment of NERD, interventions should satisfy psychosocial and physical aspects related to the disease process. In the previous clinical trial, both the visual analog scale (VAS) for heartburn along with regurgitation and the major symptoms scale were used as the primary outcomes [1]. VAS has been used for decades to evaluate the effects of various therapies for its ability to detect minute changes. VAS makes it easy for any cognitive participants to understand the parameters and respond to clinician instructions [23]. However, different candidates have different perceptions of feelings, VAS threshold, and the subjective distinction between what they deem simply an unpleasant sensation versus clinically relevant feelings [23]. The secondary outcomes including PPI withdrawal rate and symptoms recurrence rate, scales about minor symptoms, health-related quality of life, mental health, and TCM syndromes help us avoid the above distractions.

PPIs are widely used in upper gastrointestinal disease treatments characterized by excessive acid production. PPIs have a side effect, prescribers should evaluate every patient and prescribe the shortest PPIs period [24]. There are two weeks of acid reflux after stopping PPI treatment, which affects about 44% of the volunteers [25]. Slowly decreasing the dose of PPIs in two or four weeks shows the reduction of rebound symptoms risk [26]. The combination of TCM and PPI application can improve other related symptoms when improving the efficacy, and it is not easy to bounce back and have small side effects.

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