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Effects of Quince syrup on clinical symptoms of children with symptomatic gastroesophageal reflux disease: A double-blind randomized controlled clinical trial

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ABSTRACT

Objective: The aim of this study was to evaluate the efficacy of Quince syrup in pediatrics with symptomatic gastroesophageal reflux disease (GERD).
Method: Participants (n = 80) were randomly assigned to the Quince group (0.6 cc/kg/day) or the Omeprazole group (1 cc/kg/day). Age specific questionnaires were used to assess the frequency and severity of the GERD symptoms. Mean of cumulative symptom score (CSS) at weeks 4 and 7 were compared with baseline.
Results: The mean CSS value was significantly decreased from baseline in each treatment group without statistically significant differences between them. Although the mean CSS value among infants and young children was slightly decreased in the Quince group at week seven, this value was increased among children aged 5–18 years in both treatment groups without significant differences.
Conclusion: Despite the effectiveness of Quince syrup in reducing symptoms in all pediatrics age groups, no significant differences were observed in comparison with the control group.

1. Introduction

Gastroesophageal reflux disease (GERD) is a chronic and the most common esophageal disorder in children of all ages, defined as the passage of gastric contents into the esophagus with annoying symptoms or complications [1,2]. Heartburn, regurgitation/vomiting, refusing feeding, excessive crying, and abdominal pain are often associated with GERD in infancy through adolescence which can cause failure to thrive, recurrent pneumonia, apnea, and erosive esophagitis [3–5]. Although the prevalence of GERD is not well studied in pediatrics, prevalence of its symptoms varies about 1.8% through 25% [6,7].

Transient lower esophageal sphincter (LES) relaxation is the predominant cause of GERD in all ages but ineffective clearance of the esophagus, sluggish emptying of the stomach, increased acidity, and reduction of salivation are considered as other etiological factors [8–10]. Although diagnostic testing such as upper gastrointestinal series, esophagoscopy with biopsy, and esophageal pH monitoring are available to confirm the diagnosis of GERD, most patients are treated empirically with dietary changes, lifestyle modifications, and antacids or prokinetic agents for symptom relief [3,9,11,12].

Despite the lack of evidence to support the effectiveness of proton pump inhibitors (PPIs) in infants with symptomatic GERD, its prescriptions has increased 11-fold since 2002 and PPIs like

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omeprazole are prescribed as the first-line in medical treatment of GERD [13–17]. Nevertheless, some serious complications such as vitamin B12 deficiency, hemolytic anemia, neutropenia, intractable cough and bone loss have been shown to be associated with the use of omeprazole [18–22].

Nowadays, complementary and alternative medicine (CAM) becomes more popular in societies [23–26], and Traditional Persian Medicine (TPM), as a part of CAM, has many approaches or drugs for treatment of gastroesophageal disease symptoms [27,28]. The cardinal symptoms and clinical manifestations of GERD-like conditions such as regurgitation of sour material (Joshā-e Hāmiz), heartburn (Horqat, laz') and inflammation (Iltihāb) were described by Persian physicians many years ago [27,29–31]. Heated extract of Quince (*Cydonia oblonga* Mill.) belong to the rose family (Rosacea) is one of the TPM syrups used for treatment of GERD [27,32]. It has been used as a gastric tonic and ulcer healing agent traditionally, and increases the LES tonicity, as well [29,33–35]. Accordingly and based on the main etiology of GERD, we hypothesized that it could be helpful as a new remedy of GERD in pediatrics due to its tonic effect on stomach and LES. Therefore, this study was conducted to evaluate the efficacy, safety and tolerability of Quince syrup in the treatment of patients aged 0–18 years with symptomatic GERD.

2. Methods

2.1. Study design

This was an outpatient, double-blind, randomized, parallel treatment groups study that compared the Quince syrup with omeprazole syrup in children aged 0–18 years old, with symptomatic GERD. The trial was carried out in Emam Reza polyclinic, Shiraz, Iran. All patients were visited by a paediatrics gastroenterologist; if they had the inclusion criteria, they would be enrolled in the trial.

All of the patients had a clinical diagnosis of symptomatic GERD. In this study, patients who were younger than 60 months were categorized as infants and young children and received an age specific questionnaire with six questions. Older participants were categorized as older children and adolescents and received a questionnaire with 8 questions. A baseline individual symptoms score (ISS) and cumulative symptom score (CSS) were obtained to compare the efficacy of the drugs.

2.2. Randomization and blinding

The participants were randomized after filling the consent written form, in two parallel groups. Quince syrup as the trial drug and omeprazole syrup for the control group were administered by a trained nurse in the clinic. The randomized list was prepared by using Random allocation software for parallel group randomized trials [36]. The study team including paediatric medical subspecialists, physician who delivered the drugs and statisticians were blind as to which patient belongs to which group; also, the patients were blind to the drug allocation. For this reason, omeprazole syrup was delivered in identically sized and colored bottles to match the Quince syrup.

2.3. Drug preparation

For this study, we used omeprazole syrup which was prepared in Faculty of Pharmacy, Shiraz University of Medical Sciences by omeprazole capsules (20 mg) as the control group which was purchased from Exir Pharmaceutical Co, (Brojerd, Iran) [37,38]. Each mL of the liquid concentrate, for oral administration, contains 2 mg of omeprazole. Inactive ingredients: flavor, sucrose and water.

The herbal medicine intervention used in this trial was an extract of Quince. Heated fresh juice of Quince fruit which was purchased from Barij Essence Pharmaceutical Co. (Kashan, Iran) was used for preparation of Quince syrup. The water extract of Quince was obtained from its pulp. A staff botanist visually identified fruits and their plants. The lot number for the Quince extract used in this study was # 3178-046-93/3. A voucher specimen was retained (#BC930834) and is kept at the manufacturer headquarters in Kashan, Iran. Heated extract of Quince fruit used in this trial was standardized to contain 67–77% dry residue (%w/w), specific gravity 1.312 g/ml, pH 3–4.5, refractive index 1.4250–1.4750, and Brix 67–77. Quince syrup was prepared in Faculty of Pharmacy, Shiraz University of Medical Sciences. It was prepared and prescribed by TPM guideline and each mL of the liquid concentrate, for oral administration, contains 600 mg of Quince extract. Inactive ingredients: sucrose and water. The percentages of quantified chemical constituents per each ml of Quince syrup was as follows: 0.37 mg (37%) water, 0.51 mg (51%) Quince extract, 0.12 mg (12%) sucrose. It was prescribed 0.3 ml/kg twice a day, after lunch and dinner, for 4 weeks. This dosage regimen was determined by referring to TPM books and usages of Quince extracts for the same indication [35,39]. Quality control tests including measurements of heavy metals and microbial contamination based on United States Pharmacopeia guidelines.

Patients in the control and trial groups of this study used both syrups bottled in 60 ml dark bottles and placed in the same containers.

2.4. Ethical considerations

This trial was reviewed and approved by the Ethics Committee of Shiraz University of Medical Sciences (registration number: CT-9370-7360) according to the guidelines of the Declaration of Helsinki (Hong Kong revision, 1983) and good clinical practice. A signed and dated parental/guardian or when applicable, participants informed consent forms were obtained for all cases. A recommendation for reporting randomized clinical trials as defined in the statement of Consolidated Standards of Reporting Randomized Clinical Trials (CONSORT) was used [40]. The trial protocol was registered in the Iranian Registry of Clinical Trials database under registration number: IRCT2015030921388N1.

2.5. Sample size and statistical analysis

The primary analysis was based on the intent-to-treat population. The sample size was calculated by considering one-sided significance level of 0.05, 0.80powers, and it was estimated to be 32 participants in each group. Therefore, due to a probable 20% withdrawal rate of the enrolled patients, 40 participants were selected for each group. Power of all parameters in this study which was calculated by NCSS, were more than 90%.

Changes from baseline in parameters were compared within treatment groups using Chi-square for demographic qualitative data and t-test for quantitative data, Paired t-test for weight and repeated measure ANOVA for comparison of treatment groups in different times. The significance value was set at $p \leq 0.05$. SPSS V. 22.0(SPSS Inc., Chicago, IL, USA) was used for all statistical analysis.

2.6. Inclusion criteria

Inclusion criteria for children who enrolled in this trial study were children that had at least two of the following five symptoms, at least for one month, without any improvement with routine treatments: Vomiting immediately after eating, restlessness between one to three hours after feeding, apnea and respiratory distress after feeding, poor weight gain or refusal to eat. Patients whose endoscopic result proved that they have GERD were also eligible for this study.