ORIGINAL ARTICLE

GMJ.2017;6(2):102-109
www.gmj.ir

Received 2016-12-07
Revised 2017-03-12
Accepted 2017-04-17

DOI: 10.22086/GMJ.V6I2.772

Effects of Iranian Traditional Medicine Remedies *(Apium Graveolence and Trachyspermum Copticum)* on Modifying the Quality of Life in Patients with Functional Dyspepsia: A Double-Blind Randomized Clinical Trial

Maryam Azimi [1,2], Mohammad Javad Zahedi [3]✉, Mitra Mehrabani [2], Haleh Tajadini [2,4], Farzaneh Zolala [5], Mohammad Reza Baneshi [5], Rasool Choopani [6], Fariba Sharififar [2], Ali Asadipur [2], Mehdi Hayatbakhsh [3], Bijan Ahmadi [3]

[1] Department of Traditional Medicine, School of Traditional Medicine, Kerman University of Medical Sciences, Kerman, Iran
[2] Herbal and Traditional Medicines Center, Kerman University of Medical Science, Kerman, Iran
[3] Gasteroenterology and Hepatology Research Center, Kerman University of Medical Science, Kerman, Iran
[4] Neuroscience Research Center, Institute of Neuropharmacology, Kerman University of Medical Science, Kerman, Iran
[5] Health Research Center, Institute for Futures Studies in Health, Kerman University of Medical Science, Kerman, Iran
[6] Department of Traditional Medicine, School of Traditional Medicine, Shahid Beheshti University of Medical Science, Tehran, Iran

Abstract

Background: Functional dyspepsia (FD) is common digestive diseases affecting patients' quality of life (QOL). Recently, improving the patients' QOL is being considered as an important therapeutic objective; several studies have shown that traditional medicine is influential for FD patients improvement. The purpose of the present research was to investigate the effectiveness Iranian traditional medicine remedies on the QOL of patients with FD. **Materials and Methods:** Through double-blind randomized clinical trial, our research patients were categorized into three groups followed as AT group(*Apium graveolence* 250 mg and *Trachyspermum copticum* 250 mg, twice daily), placebo (cornstarch, 500 mg, twice daily), and (omeprazole 20 mg, daily)for a duration of one month and followed up for another one month. The patients' QOL was measured by Nepean Dyspepsia Index short-version questionnaire at the baseline, 4 and 8 weeks after treatment onset. **Results:** The patients QOL of AT group after 4 weeks was found to have improved significantly in comparison to those of omeprazole and placebo groups. The statistical difference between omeprazole and placebo groups was not significant. After 8 weeks, the difference between AT and placebo groups remained significant whereas the same was not clear between AT and omeprazole. **Conclusion:** Regarding our results, AT remedies could prove the FD patients' QOL more than omeprazole or placebo; therefore, it can be used as an adjuvant therapy for treatment of the disease. **[GMJ.2017;6(2):102-109] DOI: 10.22086/GMJ.V6I2.772**

Keywords: Functional Dyspepsia; *Apium Graveolence*; *Carum Copticom*; Quality of Life

Tel/Fax: +98 71 36474503
PO Box 7193616563
Email:info@gmj.ir

✉ **Correspondence to:**
Mohammad Javad Zahedi, Gasteroenterology and Hepatology Research Center, Kerman University of Medical Science, Kerman, Iran
Telephone Number: +983433122050
Email Address : Zahedimj@yahoo.com

Introduction

The most common gastrointestinal disorders are functional disorders of digestive system, approximately including 50% of the related patients [1]. Functional dyspepsia (FD) is among functional disorders of the digestive system considered as major problems of community healthcare due to its high prevalence [2]. Around 25% of citizens are reported to have experienced symptoms related to dyspepsia at least 6 times a year, with only 10-20 percent of them have referred to a physician. FD compromises about 60% of dyspepsia, and, according to ROME III criteria, involves such characteristics as having more than two symptoms of early satiety, postprandial fullness, epigastric pain or burning not due to organic or metabolic causes, lasting for more than three months and at least 6 months from the time of diagnosis [3]. However, dyspepsia can be diagnosed by more than four main symptoms including epigastric pain, epigastric burning, postprandial fullness, early satiety, excessive belching, bloating, nausea, and vomiting. FD is divided into postprandial syndrome and epigastric pain syndrome, which often overlap [4].

Functional diseases of digestive system have a lower quality of life (QOL) in comparison to other digestive diseases [4-9]. Lack of a standard medication for FD in addition to patients' chronic symptoms has resulted in an increase in conduction of studies on pathophysiology and medication of the patients [4-9].

FD is one of the major health problems, causing significant economic losses in many countries. This disease affects the patients' QOL. Since the patients' QOL varies according to the disease severity, the ROME II scholar recommend using QOL assessment tools in all clinical studies related to FD [10]. In a clinical study of FD patients, QOL is considered in second priority, along with diagnosing the patient's symptoms, for evaluation of response to medication [11]. In recent studies, nevertheless, there is an increasing tendency to use QOL assessment as the first criteria for assessment of responding to medication of diseases like FD [11-13].

The World Health Organization (WHO) definition of QOL is one's perception of his/her health status. It is a hidden variable assessed based on one's response to a set of standard questions [14]. In fact, QOL is a special expression of one's satisfaction, as well as a valuable milestone for societies and a subset of physical/mental health, satisfaction, personality, and environmental/social relations [15]. The QOL assessment of the patients involving with FD has become important as a therapeutic objective ever since 1990 [11, 16]. Relative limitations of common medications in controlling different symptoms of FD and the unknown nature of their exact mechanism has resulted in the tendency of the patients to use complementary and alternative medicine, including acupuncture and herbal medicine [13]. Therefore, several studies have so far been conducted in different countries based on the complementary and traditional medicines of each region, which is often related to the native plants of the very region. Most of the simple and combination medical plants of China, India, Australia, etc., have been found effective in previous studies [8, 17, 18].

One of the plants mostly used for gastrointestinal and dyspepsia diseases and vastly mentioned in Iranian traditional medicine (ITM) is the combination of *Apium graveolence* and *Trachyspermum copticum*. This drug can be prepared by an equal combination of *A. graveolence* and *T. copticum* and is one of the simplest combination drugs effective for all types of dyspepsia [19, 20].

According to previous studies, medicinal plants are more effective for patients when combined with one another [21]. Several studies have been conducted separately about the therapeutic effects of *A. graveolence* and *T. copticum*. Different therapeutic effects including antifungal, antioxidant, antibacterial, antiparasitic, analgesic, and carminative effects which reduce gastric irritation and antilipidemic have been described for these plants [22, 23]. However, there has been no clinical experiments so far on the effect of *A. graveolence* and *T. copticum* combination on FD.

This study was aimed to investigate the effect of *A. graveolence* and *T. copticum* (AT drug) as ITM remedies on the QOL of patients with FD.

Materials and Methods

Study Design and Participants

This randomized double-blind clinical trial was conducted at Kerman University of Medical Sciences, southeastern Iran. We include 180 FD patients who referred to Afzalipour Hospital during August 2015 to April 2016 according to the ROME III criteria and the diagnosis of gastrointestinal experts. Then, 150 of the patients were qualified to enter the study.

Sample Size

According to the parameters from the pilot study, the sample size was 42 patients. However, the final sample size was considered as 50 patients in each group.

Inclusion and Exclusion Criteria

All patients aged 18-60 years old with diagnosed according to ROME criteria were enrolled in the study were enrolled in the study. The exclusion criteria include pregnancy, breastfeeding, convulsion, active urinary tract infection, any severe side effects possibly relating to drug, simultaneous use of other chemical or herbal drugs related to symptoms of FD, intake anticoagulants, digestive ulcers or reflux, Irritable Bowel Syndrome (IBS), serious diseases like diabetes and cardiovascular diseases, Esophagus and gastrointestinal surgery, severe mental retardation, drug abuse, patient's unwillingness to continue the project, not filling out the consent form, and emergence of warning symptoms including sudden severe weight loss, anemia, blood in the stool, dysphagia, etc.

Randomization and Blinding

Randomization was done through minimization, in which 15 patients were divided into three intervention groups by random assignment of numbers 1, 2 and 3, and their multiples to subjects. Then, patients were purposively placed in these groups based on possible confounding factors namely age and gender, so as to match these three groups with respect to the mentioned factors.

This study was conducted in the double-blinded method. The drugs were equally packed and coded in Pharmacognosy Department of Kerman University of Medical Sciences. The person who coded the drugs did not have any role until the end of the intervention. Without any knowledge of the study objectives, the second person divided the patients into the three groups purposefully based on each patient's basic information, in order to have similar groups from the viewpoints of age and gender. Visiting and registration of the patient's information was done by a third person blind about drugs coding. Finally, the patient's information was analyzed by a fourth person blind about grouping and drugs coding.

Intervention

The selected 150 patients with FD were randomly entered into one of the three groups of the study based on inclusion/exclusion criteria and after a two-week screening. A500 mg capsule containing an equal amount of both seed powders of *T. Copticum* (herbarium number of KF1447) and *A. Graveolence* (herbarium number of KF1138) were administrated in the patients in AT group. The AT drug were prepared by Pharmacognosy Department at Kerman University of Medical Sciences. Microbiological and chemical tests of the ATdrug were performed by Barij Essence Pharmaceutical Company (No. 47/95/70). The dose of AT drug was prescribed 1gr per day including a 500mg capsule after breakfast and another one after dinner. In Placebo group, a 500mg capsule containing cornstarch powder was prescribed after breakfast and another one after dinner. In omeprazole group, a 20mg omeprazole (Abidi company, Iran) capsule was prescribed before breakfast daily. All the three groups took the drugs for one month and were then followed up for another month.

Data Collection

The QOL in the patients assessed by Nepean Dyspepsia Index (NDI) short questionnaire which is the specific tool to evaluate the QOL of the patients with FD. The questionnaire includes 10 questions designed by Talley *et al*. in 2001 in the form of 5 subsets (tension, interference with daily activities, eating/drinking, knowledge/control, work/study) [11]. Since a Persian versionof the questionnaire was not

available, it was translated, and its validity and reliability were calculated. In test-retest method, the Pearson correlation coefficient was obtained to be 0.83, and the Cronbach's Alpha coefficient was obtained as 0.9, which proves a high reliability of the Persian translation of the questionnaire. The validity of the questionnaire was verified through content validity method.

This questionnaire evaluates the effect of FD on QOL using 5-degree Likert Scale. The min and max scores obtained were 10 and 50, respectively. A higher score shows more effect of the disease on QOL and is expected to decrease along with the improvement in QOL. The questionnaire was filled out by the patients at the baseline, 4 and 8 weeks after treatment onset.

Ethical Issue

The Medical Research Ethics Committee of Kerman University of Medical Sciences approved the present study (code: IR.KMU.REC.1394.233). Also, this trial was registered in Iranian Registry of Clinical Trials (registration number: IRCT 2015092724228).

Statistical Analyses

Demographic data including age, sex, marital status, and education of the patients in all three groups were compared using the Chi-square test. The repeated measure test was applied to compare the variations of QOL in all three groups during the consecutive times. Statistical analysis of the results was performed by SPSS 23 and the P-values less than 0.05 were considered as significant.

Results

Each of the three groups included 50 patients. One of the patients in AT group was omitted from the study after two weeks due to the irregular drugs intake and the rest 49 patients successfully finished the treatment and the follow-up period. In placebo group, two patients due to the irregular drug intake, two patients due to drug intolerance (sensitive to gelatin shell of the capsule, diarrhea after taking the drug), two patients due to other drugs use related to dyspepsia, and one patient due to pregnancy were excluded from the study and the rest 43 patients finished the treatment and the follow-up period. In omeprazole group, two patients due to irregular drug intake, two patients due to other drug uses related to dyspepsia, and one patient due to drug intolerance (a severe headache after taking the drug) were excluded from the study and the rest 45 patients finished the treatment and the follow-up period (Figure-1).

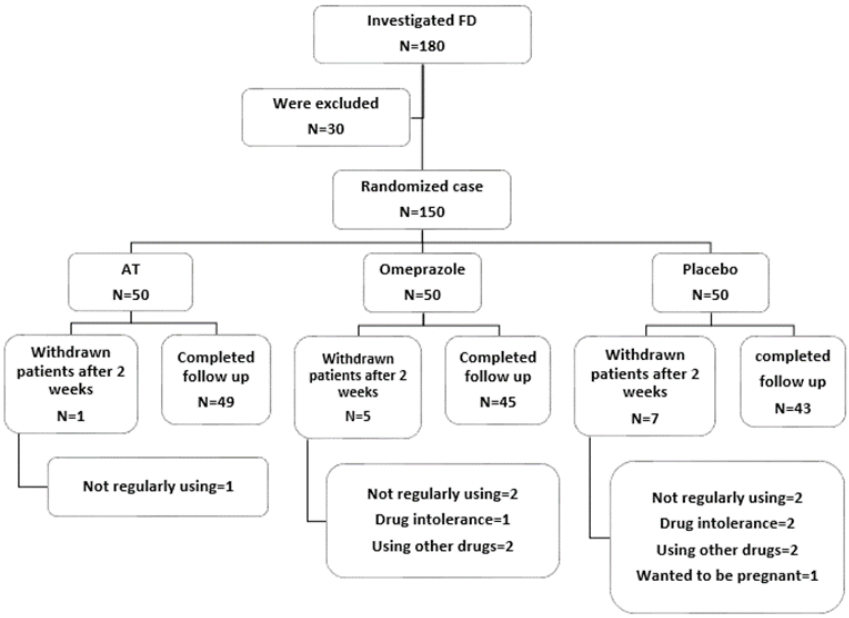

Figure 1. Flowchart of design and protocol of the study

Demographic Characteristics

In terms of gender, 67.7%, 62.8% and 62.2% subjects in the AT, placebo, and omeprazole groups were female, respectively. Also, 65.5%, 86.1% and 73.3% subjects in the AT, placebo, and omeprazole groups were married, respectively. In terms of age, 46.9%, 44.2% and 44.2% in the AT, placebo, and omeprazole groups were in the most common age group (31-45 years) in this study. In terms of educations,55.1%,39.5% and 42.2% in the AT, placebo, and omeprazole groups were in the most common educations group (academic education) in this study. There was no significant difference among three groups (P<0.05, Table-1).

The QOL of the Patients at the Baseline

At the baseline, the total NDI scores showed no any significant difference between three groups. Comparing the scores of 5 subsets of QOL revealed that except work/study section, there was not a significant difference among the subsets of the three group. Indeed, in the work/study section, there was a significant difference between AT group and placebo group (P<0.001), and omeprazole group (P=0.001). However, there was not a significant difference between omeprazole and placebo groups in the term of work/study section (P=1.00).

The QOL of the Patients After 4 Weeks

There was a significant difference between the total NDI score of the patients in ATgroup and the other two groups (P<0.001, Table-2). There was not a significant difference between patients in the placebo and omeprazole groups (P=0.63).

Regarding tension section, there was a significant difference between AT group and the other two groups, whereas there was not a significant difference between placebo and omeprazole (P=1.00). There was a significant difference between AT group and other two groups regarding all the 5subset of NDI.

The QOL of Patients After 8 Weeks

As the show in Table-2, there was a significant difference between the total NDI scores of

Table 1. Demographic Characteristics of Participants

Varibles	Sub group	AT group	Placebo group	Omeprazole group	P-value (At baseline)
Age (years)	18-30	15 (30.6%)	12 (27.9%)	16 (35.6%)	0.94
	31-45	23 (46.9%)	19 (44.2%)	18 (40%)	
	46-60	11 (22.4%)	11 (22.4%)	11 (24.3%)	
Sex	Male	16 (32.7%)	16 (37.2%)	17 (37.8%)	0.85
	Female	33 (67.3%)	27 (62.8%)	28 (62.2%)	
Marital status	Single	12 (24.5%)	6 (13.9%)	12 (26.7%)	0.30
	Married	37 (65.5%)	37 (86.1%)	33 (73.3%)	
Education level	Pre-hs diploma	5 (10.2%)	6 (14%)	8 (17.8%)	0.52
	Old school diploma	17 (34.7%)	20 (46.5%)	18 (40%)	
	Academic degree	27 (55.1%)	17 (39.5%)	19 (42.2%)	

AT: *Apium graveolence* and *Trachyspermum copticom*

Table 2. Total QOL Scores at Baseline, 4 and 8 Weeks

Time	AT group (Mean ± SD)	Placebo group (Mean ± SD)	Omeprazole group (Mean ± SD)
Baseline	23.37 ±5.58	21.93 ±6.87	22.24 ±5.92
4 weeks	12.65 ±3.50	18.98 ±6.15	17.56 ±6.02
8 weeks	16.2 ±4.37	21.23 ±5.32	17.56 ±6.02

patients in ATand placebo groups (P<0.001), whereas the difference between ATgroup and omeprazole group was not significant (P=0.64). Also, there was a significant difference between patients in placebo and omeprazole group (P=0.004).
Regarding work/study subset, not any statistically significant difference observed in any of the three groups after 8 weeks.
In AT group, there was not any particular side-effect observed in patients except for a slight increase in bowel movements during the first three days of taking the drug.

Discussion

In the present study, the QOL of 150 patients with FD was investigated using the NDI questionnaire. In a randomized double-blinded study, the patients were intervened in three groups, i.e., AT, placebo, and omeprazole; the total score of the patients' QOL at baseline in the three groups was not significantly different. After 4 weeks and at the end of the intervention, the QOL of the AT group improved significantly in comparison to the other two groups, which was in line with findings in most of other similar studies [24, 25]. In a study by Mohtashami *et al*. (2015) on the effect of the honey-based formulation of Nigella Sativa on FD patients, the QOL significantly improved after the intervention, in comparison to the placebo group [26]. In another study by Ghoshegir *et al*. the results showed the total score of the patients' QOL in Pimpinella anisum group significantly improved after the intervention, in comparison to the placebo group [27].
Analysis of all the subsets (except for work/study part) showed that there was not a significant difference among the three groups at the baseline. At the end of the intervention and after 4 weeks, in all 5 subsets, there was a significant statistical difference among AT, placebo, and omeprazole groups, which was the sign of more effect of the AT than that of the other two. The difference between placebo and omeprazole was not significant at this stage. In a study by Jeung-Bae kim *et al*. on the effect of traditional medicine of Hiangsa-Pyeonwi San (HPS) on the QOL of the patients with FD, there was not any significant difference between the QOL of the patients after intervention in HPS and placebo groups, whereas the difference was a significant difference in some subsets such as eating/drinking and interference [28]. In another study by Talley *et al*. about the effect of amitriptyline and citalopram on FD patients, the total QOL in the drug groups improved significantly in comparison to that of the placebo group. There was a significant difference between drug and placebo groups in work/study subset, whereas the same was not significant in all other subsets [29].
One month after the end of the treatment and after 8 weeks, there was a significant difference in all subsets in comparison to placebo except for work/study part, whereas the same was not significant in omeprazole. The difference between placebo and omeprazole groups was significant except for eating/drinking and knowledge/control parts.
The total NDI score in most similar studies improved after the intervention of both drug and placebo, whereas the improvement difference in drug group was statistically significant in comparison to that of the placebo. More detailed results in the 5 subsets of NDI questionnaire of QOL were different in several studies; the subsets scores were not mentioned in most studies. Comparing to previous similar studies, the AT drug improves the QOL of the FD patients more efficiently, as observed in all 5 subsets of the present research. The decrease in the patients' QOL one month after the cessation of drug use in AT group occurred quicker than in placebo and omeprazole groups. Although the AT group was at a better level than the other two groups, it resulted in an insignificant statistical analysis for the comparison of AT and omeprazole. Further research is recommended to conduct to achieve more durability of this drug effect on the QOL of patients with FD.

Conclusion

This study was associated with some limitation, such as being a single center study, limited sample size and short follow-up period. Therefore, results of this study are not gen-

eralized to all FD patients. Nevertheless, AT drug proved to be capable of improving the QOL of patients with FD more effectively than placebo and omeprazole

Acknowledgements

This study was part of a Ph.D. dissertation (number: 95/10/27/88) supported by Kerman University of Medical Sciences.

Conflict of Interest

The authors declare that there is no conflict of interests.

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