10 Effect of Curcumin on Severity of Functional Dyspepsia: a Triple Blinded Clinical Trial

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Abstract

Background

Functional dyspepsia is the main cause of upper abdominal discomfort affecting 5–10% of the world population. Despite various therapeutic approaches, up to 50% of patients with functional dyspepsia seek alternative treatments. In the present study we evaluated the effect of curcumin supplementation along with famotidine therapy on severity of functional dyspepsia. A total of 75 patients with functional dyspepsia according to Rome III criteria were allocated into intervention (N = 39) or control (N = 36) groups. The intervention group was treated with a combination of 500 mg curcumin and 40 mg famotidine daily for 1 month. The control group received placebo and 40 mg famotidine. Severity of dyspepsia symptoms was determined using the Hong Kong questionnaire at baseline, after the 1 month treatment and after a 1 month follow-up. The presence of *H. pylori* antigens in the stool samples was also investigated in all subjects. No significant difference was

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observed between intervention and control groups in biochemical indices, severity of dyspepsia and rate of *H. pylori* infection. A significant decrease was observed in severity of dyspepsia ($p < 0.001$) and rate of H. *pylori* infection ($p = 0.004$) immediately after the treatment and follow-up in the curcumin intervention group. This study indicated that curcumin therapy could be a favorable supplementation in the symptom management of functional dyspepsia. Moreover, curcumin could help efficient eradication of *H. pylori* in these patients.

Keywords

Functional dyspepsia · Curcumin · *H. pylori*

10.1 Introduction

Functional dyspepsia is the main cause of upper gastrointestinal tract discomfort manifested by abdominal fullness, heartburn, nausea, belching, acid taste and upper abdominal pain [1, 2]. It is a relapsing and remitting condition that affects 5–11% of population worldwide [1]. It is estimated that the financial burden of drugs in dyspepsia is about £450 million in the United Kingdom [3]. Based on Rome III criteria, functional dyspepsia is defined as chronic presence of early satiation, postprandial fullness, epigastric pain or epigastric burning, in endoscopy-negative patients [2, 4]. Genetic background and psychological distress are the most important factors related to this condition that evoke an inflammatory response and further clinical symptoms [1]. Some proposed treatments for functional dyspepsia are *H. pylori* eradication [5], acid-suppression [3], and administration of pro-kinetic agents [3], antidepressants [6–9] and herbal supplements [10, 11]. Due to increasing dissatisfaction with conventional therapeutic approaches in functional dyspepsia, almost 50% of patients seek alternative treatments [12]. Hence, more effective and yet safer agents are required to treat functional dyspepsia.

Curcumin is a yellow pigment derived from turmeric. A wide range of its pharmacological effects have so far been been reported for this dietary safe phytochemical [13–21]. Furthermore, clinical studies have indicated that curcumin supplementation could positively affect symptoms related to the gastrointestinal tract including epigastric pain, post-prandial fullness, bloating, belching and nausea. However, no improvement in *H.pylori* eradication has been shown thus far [22]. Similarly, curcumin treatment could efficiently improve some gastrointestinal diseases such as peptic ulcer, Barrett's esophagus, non-alcoholic fatty liver disease, irritable bowel syndrome (IBS), pancreatitis, ulcerative colitis and gastrointestinal cancers [23–33].

Evidence of curcumin efficacy on treatment of functional dyspepsia is scarce. Here we aim to investigate the effect of curcumin on improving of functional dyspepsia according to Hong Kong score and *H. pylori* eradication rate.

10.2 Materials and Methods

10.2.1 Subjects

Adult subjects were selected from the outpatient unit of Gastroenterology clinic of Baqiyatallah Hospital (Tehran, Iran) with symptoms of dyspepsia and qualified as candidates for upper gastrointestinal endoscopy. Eligible patients diagnosed with functional dyspepsia according to Rome III criteria [2] were enrolled in the study. Gastrointestinal structural abnormalities were ruled out by upper gastrointestinal endoscopy. Exclusion criteria were liver and renal dysfunction, chronic disease, previous anti-helicobacter therapy, malignancies, deterioration of dyspepsia and other related complications during the study period. The study design was approved by the institutional ethics committee and was conducted as per the Helsinki declaration. Written informed consent was taken from all of participants. The Hong Kong index of dyspepsia severity was recorded prior to intervention, at the end of the study and after a follow-up for 1 month. Blood samples were obtained in order to measure the fasting blood sugar (FBS), hemoglobin (Hb), triglycerides (TG), cholesterol (Chol), low density lipoprotein (LDL), high density lipoprotein

(HDL), aspartate aminotransferase (AST), alanine aminotransferase (ALT) and *alkaline phosphatase* (ALP). Stool samples were collected for assessment of *H. pylori* antigen prior to treatment, after the 1 month treatment and 1 month of follow-up periods. The patient flow chart is shown in Fig. 10.1.

10.2.2 Study Design

This study was performed as a randomized triple-blind placebo-controlled trial. Patients were randomly allocated into intervention or control groups. The intervention group received 40 mg famotidine and one capsule containing 500 mg curcuminoids (C3 Complex®, Sami Labs Ltd., Bangalore, India) after lunch for 30 days (n = 39). For the control group (n = 36), 40 mg famotidine and a placebo capsule were administered daily for the same period. The curcuminoid and placebo capsules were identical in size and shape. Each curcuminoid capsule also contained piperine (5 mg; Bioperine®, Sami Labs Ltd.), added for the purpose of enhancing bioavailability. The trial protocol was registered in the Iranian Registry of Clinical Trials (IRCT20080901001165N45).

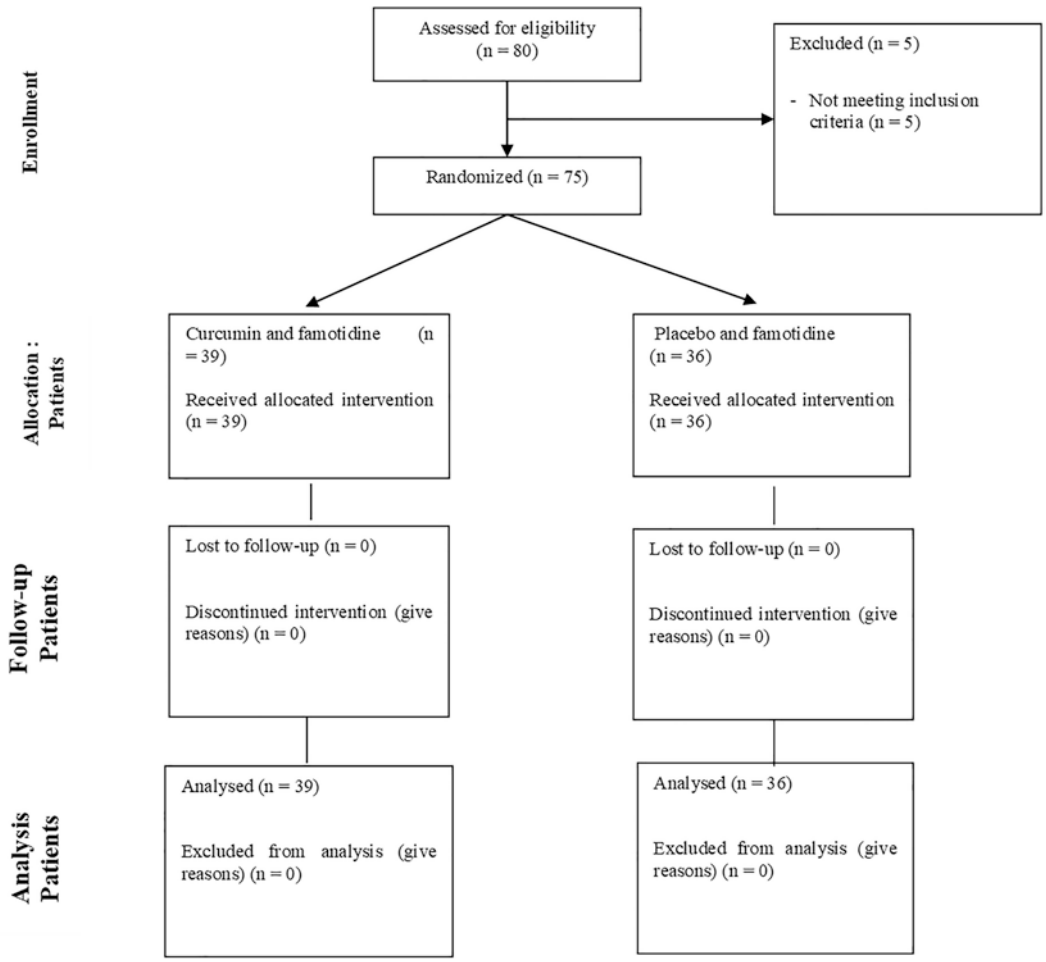

Fig. 10.1 Patient flow chart

10.2.3 Hong Kong Dyspepsia Index

Symptom severity of functional dyspepsia was determined using the Hong Kong dyspepsia index. The questionnaire consists of 12 items including stomach pain, upper abdominal dull pain, stomach pain before meals, stomach pain during anxiety, heartburn, upper abdominal bloating, vomiting, nausea, belching, acid regurgitation, feeling of acidity in the stomach and loss of appetite. Each item was scored from 1 (asymptomatic), 2 (mild symptoms that can be easily ignored), 3 (awareness of symptoms but easily tolerated), 4 (severe symptoms sufficient to interfere with normal daily activities) and 5 (incapacitating symptoms causing inability to perform daily activities and/or require days off work). Subsequently, all the above-mentioned scores were added together (from 12 to 60) to calculate the severity of functional dyspepsia [34].

10.2.4 Statistical Analysis

Data was analyzed using SPSS version 18 software. Data were reported as number and percent or median ± standard deviation. For analyzing categorical variables, the Chi-square test was used. Comparisons between groups were performed using independent Student's T-tests. For comparison of quantitative variables prior to treatment, immediately after and 30 days later, repeated measures analysis of variance (ANOVA) was used. P-values <0.05 were considered significant.

10.3 Results

Total of 75 eligible subjects completed the study as shown in the patient flow diagram (Fig. 10.1). Baseline characteristics of participants are indicated in Table 10.1. Duration of functional dyspepsia as well as endoscopic findings, were not significantly different in the study groups. As shown in Table 10.2, none of the laboratory indices were different between two groups before or after intervention. The rate of *H. pylori* infection was decreased significantly in the intervention group (p = 0.004) in comparison to placebo, whereas no significant change in *H. pylori* was observed (p = 0.126) (Table 10.3). According to the Hong Kong questionnaire, dyspepsia severity index was decreased significantly in both groups (Table 10.4).

Comparison between different items of Hong Kong questionnaire is summarized in Fig. 10.2. Abdominal pain, belching and acid regurgitation were decreased in both the intervention ($p < 0.001$ for all three symptom scores) and control ($p = 0.033$, <0.001 and 0.022, for the respective symptom scores) groups. Upper abdominal dull pain ($p < 0.001$), stomach pain before meals ($p < 0.001$), stomach pain when anxious ($p < 0.001$), heartburn ($p < 0.001$), upper abdominal bloating ($p < 0.001$), nausea ($p = 0.033$) and feeling of acidity in stomach ($p < 0.001$) were decreased significantly in the curcumin group. Vomiting and loss of appetite were the only symptoms that did not change after treatment in both groups.

Table 10.1 Baseline characteristics of study groups

Characteristics		Case (N = 39)	Controls (N = 36)	P value
Age (years)		39.9 ± 8.6	37.2 ± 9.5	0.189
Sex (n%)	*Male*	19 (48.7%)	20 (55.6%)	0.359
	Female	20 (51.3%)	16 (44.4%)	
Functional dyspepsia duration (years)		4.21 ± 1.02	3.94 ± 0.88	0.140
Endoscopic findings	Esophagitis (%)	4 (10.3%)	1 (2.8%)	0.289
	Antral gastritis (%)	18 (46.2%)	22 (61.1%)	
	Pan gastritis (%)	7 (17.9%)	4 (11.1%)	
	Gastro-duodenitis (%)	10 (25.6%)	9 (25%)	

Results are expressed as mean ± standard deviation or number (percentage)

Table 10.2 Changes in laboratory indices before and after intervention

Laboratory indices		Case (N = 39)	Controls (N = 36)	P value
FBS (mg/dL)	Before intervention	92.68 ± 14.08	94.32 ± 12.1	0.260
	After intervention	93.51 ± 14.02	91.45 ± 13.7	0.177
Hb (mg/dL)	Before intervention	13.24 ± 1.04	13.09 ± 1.12	0.482
	After intervention	13.78 ± 1.6	13.28 ± 1.8	0.550
TG (mg/dL)	Before intervention	124.4 ± 34.1	130.7 ± 44.2	0.178
	After intervention	118.3 ± 31.6	129.2 ± 38.9	0.099
Chol (mg/dL)	Before intervention	174.9 ± 37.1	183.1 ± 39.7	0.385
	After intervention	172.4 ± 31.2	183 ± 38.5	0.609
LDL (mg/dL)	Before intervention	116.2 ± 28.2	113.2 ± 33.4	0.595
	After intervention	109.3 ± 32.2	110.9 ± 28.7	0.761
HDL (mg/dL)	Before intervention	47.31 ± 11.42	46.14 ± 9.3	0.215
	After intervention	48.52 ± 10.5	46.99 ± 9.6	0.195
AST (mg/dL)	Before intervention	24.12 ± 13.2	23.58 ± 14.9	0.318
	After intervention	23.10 ± 11.9	23.46 ± 11.6	0.450
ALT (mg/dL)	Before intervention	21.65 ± 12.4	22.17 ± 11.3	0.351
	After intervention	21.19 ± 9.5	22.31 ± 11.9	0.182
ALP (mg/dL)	Before intervention	149.2 ± 68.3	168.9 ± 78.2	0.107
	After intervention	167.3 ± 53.5	192.2 ± 63.8	0.112

Table 10.3 Rate of positivity of *H. pylori* antigen prior to treatment, immediately after and 1 month later

H.pylori antigen	Case (N = 39)	Control (N = 36)	P value
Before intervention	29 (69.2%)	27 (75.0%)	0.580
After intervention	20 (51.3%)	24 (66.7%)	0.132
One month after intervention	18 (46.2%)	23 (63.9%)	0.095
P-value	0.004	0.126	–

Table 10.4 Changes in severity of dyspepsia prior to treatment, immediately after and 1 month later

Severity of dyspepsia	Case (N = 39)	Control (N = 36)
Before intervention	27.38 ± 2.63	28.19 ± 2.14
After intervention	19.46 ± 2.29	24.97 ± 2.29
1 month after intervention	15.77 ± 2.56	23.94 ± 2.82
P-value	<0.001	<0.033

10.4 Discussion

This study was designed to evaluate the efficacy of curcumin supplementation on improving the severity of symptoms in patients with functional dyspepsia. This study indicated that 500 mg of curcumin as adjunct therapy per day could improve the severity of functional dyspepsia according to Hong Kong score over a 30 day period and after 30 days of follow-up. Curcumin administration could efficiently ameliorate upper abdominal dull pain, stomach pain before meals, stomach pain when anxious, heartburn, upper abdominal bloating, nausea and feeling of acidity in the stomach. Furthermore, the current study indicated that curcumin administration could efficiently eradicate the *H. pylori* infection rate.

Curcumin is a natural polyphenol with anti-inflammatory properties comparable with some steroidal and non-steroidal compounds. It modulates inflammation through inhibition of cyclooxygenase-2 (COX-2), lipoxygenase (LOX), inducible nitric oxide synthase (iNOS), production of cytokines such as interleukin (IL)-6, IL-8, interferon-gamma (IFN-γ) and tumor necrosis factor-alpha (TNF-α), and through inactivation of transcription factors like nuclear factor kappa B (NF-κB), and activator protein 1 (AP-1) [35]. Experimental studies have supported the concept of curcumin effectiveness in *H. pylori* eradication [36, 37]. *H. pylori* adheres to the gastric epithelium and secretes virulence factors which, in turn, activate the pro-inflammatory pathways

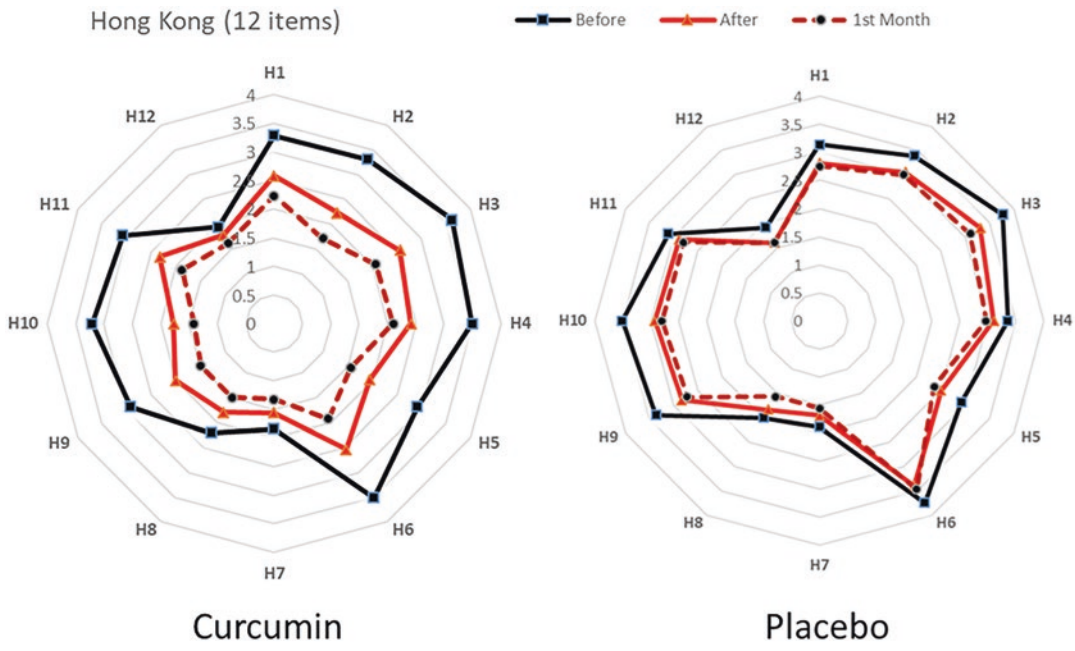

Fig. 10.2 Comparison between different items of hong kong questionarre in case and control group (H1: abdominal pain, H2: upper abdominal dull pain, H3: stomach pain before meals, H4: stomach pain when anxious, H5: heartburn, H6: upper abdominal bloating, H7: vomiting, H8: nausea, H9: belching, H10: acid regurgitation, H11: feeling of acidity in stomach, H12: loss of appetite)

causing gastric mucosal damage. Curcumin supplementation could significantly downregulate NF-κB and matrix metallopeptidase (MMP)-3 and MMP-9 activities which play roles in *H. pylori* infection [38–40]. Furthermore, an experimental study indicated that curcumin could suppress gastric inflammation caused by *H. pylori*-infection in mouse mucosa [31]. A comprehensive review by Sarkar et al. introduced curcumin as a potential treatment for *H. pylori* and its associated diseases [35]. On the contrary, some studies have found inconsistent results. Di Mario et al. studied 25 *H. pylori*-positive subjects with functional dyspepsia. The patients were treated with a combination of pantoprazol, N-acetylcystein, lactoferrin and 30 mg curcumin two times a day for 7 days. These therapies were not effective for *H. pylori* eradication [22]. In another study, the efficacy of curcumin was evaluated on *H. pylori* eradication in patients with *H. pylori*-positive peptic ulcers through a parallel-group design. Subjects were treated with 500 mg of curcumin daily plus a standard *H. pylori* medication (clarithromycin, amoxicillin, pantoprazole) for four weeks. In contrast with the current study, no significant effect was observed for *H. pylori* eradication [23]. These inconsistencies may be due to differences in curcumin dosage, duration of intervention, combination therapies and comorbidities across the studies. In addition, the source of curcumin also plays a role in its antibacterial activity. As shown by Vetvica et al. only some curcumin preparations have shown a good activity against *H. pylori* infection [40].

In contrast to the conflicting results related to the effects of curcumin on the rate of *H. pylori* infection, to our knowledge all available studies have found that curcumin attenuates the symptoms of dyspepsia. Di Mario et al. reported that curcumin decreased the overall severity of dyspepsia and some symptoms of dyspepsia including stomach pain, post-prandial fullness, bloating, belching and nausea up to 2 months after intervention [22]. Khonche et al. also reported significant alleviation of symptoms including upper abdominal dull pain, stomach pain before meals

and belching following curcuminoid supplementation [23].

10.5 Conclusions

The findings of this study revealed that adding curcumin as an adjunct therapy not only improves clinical symptoms of dyspepsia but also eradicates the rate of *H. pylori* infection. Considering the good safety profile of curcumin and its pleiotropic actions, it could be used as an efficacious agent in functional dyspepsia. However, additional larger and long-term investigations are needed to confirm these promising results and the potential role of adjunctive curcumin therapy in the management of functional dyspepsia. Finally, it seems that the presence of *H. pylori* infection is a confounding factor in functional dyspepsia and the efficacy of curcumin on *H. pylori* eradication was not fully established. The impact of the presence *H. pylori* infection on the efficacy of curcumin in ameliorating the symptoms of functional dyspepsia needs to be further scrutinized.

Conflict of Interest Muhammed Majeed is the founder of Sabinsa Corp. and Sami Labs Ltd. The other authors declare no competing interests.

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