Adjunctive Therapy with Curcumin for Peptic Ulcer: a Randomized Controlled Trial

A. Khonche1, O. Biglarian1, Y. Panahi1, G. Valizadegan1, S. S. Soflaei1, M. E. Ghamarchehreh1, M. Majeed4, A. Sahebkar2, 3

Affiliations
Affiliation addresses are listed at the end of the article

Abstract

Background: Curcumin, the bioactive ingredient of turmeric, has been shown to improve the treatment of peptic ulcer (PU) in animal studies. However, clinical studies confirming this effect of curcumin have been scant.

Objective: To assess the efficacy of adjunctive therapy with curcumin on the eradication of Helicobacter pylori infection and severity of dyspepsia in patients with PU.

Methods: In this randomized double-blind placebo-controlled parallel-group trial, patients diagnosed with PU were assigned to standard H. pylori eradication triple therapy with clarithromycin (500 mg b.i.d.), amoxicillin (1000 mg b.i.d.) and pantoprazole (40 mg b.i.d.), and randomized to receive either curcumin (500 mg/day) or placebo as adjunct to standard treatment. Severity of dyspepsia symptoms was evaluated using the Hong Kong dyspepsia index (HKDI). Eradication of H. pylori infection was assessed using the urea breath test (UBT) at 4 weeks following the end of treatment.

Results: Adjunctive therapy with curcumin was associated with a greater improvement of dyspepsia symptoms according to the HKDI score (change score: −12.90±2.81 vs. −9.60±3.39 in the curcumin and control group, respectively; p<0.001). The number of subjects whose dyspepsia was resolved during the course of treatment was significantly higher in the curcumin (27.6%) vs. placebo (6.7%) group (p=0.042). Nevertheless, the results of UBT test showed equal rate (73.3%) of H. pylori eradication in the study groups. Curcumin was safe during the course of trial.

Conclusion: Addition of curcumin on top of the standard anti-helicobacter regimen in patients with PU is safe and improves dyspepsia symptoms but has no enhancing effect on the eradication of H. pylori infection.

Introduction

Peptic ulcer (PU) is a common disease that involves stomach and first part of small intestine causing defects in gastrointestinal mucosa. The global prevalence of PU is more than 4% [1]. Around 10% of the world population has been estimated to experience gastric or duodenal ulcer in their life time [2]. Helicobacter pylori is the main pathologic cause of PU [3] and is one of the most important causes of gastric cancer [4]. Around 65–95% of gastric and 50–75% of duodenal ulcers are causally related to H. pylori infection [5]. Upper abdominal pain, abdominal fullness, gastroesophageal reflux and nausea are the most common symptoms of PU, and are jointly known as dyspepsia. PU might be complicated by upper abdominal bleeding and gastric or duodenal perforation [1]. Standard treatment for H. pylori-positive PU is triple therapy with 2 antibiotics and a proton pump inhibitor (PPI) for 14 days; however, the eradication of H. pylori is still a challenge. The maximal eradication rate of the standard regimen is 85% and more than 15% of H. pylori-positive patients must shift to bismuth-containing quadruple therapy for 2 weeks [6].

Curcumin is a yellow polyphenolic pigment obtained from turmeric rhizome. It is a nutraceutical with documented safety and numerous pharmacological effects such as antioxidant, antimicrobial, anti-fungal, anti-inflammatory, anti-angiogenic and pro-apoptotic properties [7,8]. Several lines of evidence have indicated the efficacy of curcumin supplementation against several human diseases such as anxiety and depression [9,10], osteoarthritis [11,12], metabolic syndrome [13], dyslipidemia [14–16], non-
alcoholic fatty liver disease [17,18], atherosclerosis [19,20], chronic complications due to sulfur mustard intoxication [21-24], solid tumors [25], colorectal cancer [26] and inflammation [27,28].

Several in vitro and animal studies have revealed the inhibitory effect of curcumin on H. pylori [29-37], however clinical studies evaluating the efficacy of curcumin supplementation in PU have been scarce. To the best of our knowledge, only 2 previous clinical studies were available. In an uncontrolled clinical one, treatment with 3 non-antibiotics plus curcumin could eradicate H. pylori only in 12% of patients, though the reduction in PU symptoms with curcumin was significant [38]. The second study compared the efficacy of standard triple therapy and curcumin in H. pylori-positive patients. The results revealed that curcumin could not eradicate H. pylori infection but could ameliorate peptic ulcer symptoms [39]. However, no study has yet assessed the value of adding curcumin as an adjunct to standard anti-helicobacter regimen in the context of a randomized controlled trial. Here, we designed a randomized double-blind placebo-controlled clinical trial to investigate the effect of adjunctive therapy with curcumin on dyspepsia symptoms and eradication of H. pylori in patients diagnosed with PU.

Methods and Subjects

Subjects

This study was designed as a randomized double-blind placebo-controlled clinical trial. Participants were selected from patients (age range: 20-50 years) referring to the gastrointestinal endoscopy unit of the Baqiyatallah Hospital (Tehran, Iran) with gastric pain and symptoms of dyspepsia. Inclusion criteria were diagnosis of clean-based gastric or duodenal ulcers in gastroscopy and presence of H. pylori infection based on the rapid urease test on the biopsy specimens of antral mucosa. Exclusion criteria were history of receiving anti-helicobacter treatment, concomitant treatment with corticosteroids, chronic diseases, malignancies including gastric malignancy, and lack of adherence to the study protocol defined as non-compliance with the administered anti-helicobacter triple therapy, or changing the triple therapy regimen. 4 weeks following the end of treatment, urea breath test (UBT) with C14 was performed to evaluate eradication of H. pylori infection. UBT test was performed in a radioisotope laboratory with blinded staff to the study design and assigned interventions. The study protocol was approved by the Ethics committee of the Baqiyatallah University of Medical Sciences and written informed consent was obtained from the participants prior to the enrollment. The trial was registered at the UMIN Clinical Trial Registry (http://www.umin.ac.jp/ctr/) with the unique identification code of R000025483 UMIN000022106.

Study design

This study was a randomized double-blind placebo-controlled trial with a parallel-group design. Eligible patients were assigned to standard H. pylori eradication triple therapy with clarithromycin (500 mg b.i.d.), amoxicillin (1000 mg b.i.d.) and pantoprazole (40 mg b.i.d.), and randomized to receive either curcumin (Curcumin C3 Complex®, Sami Labs LTD, Bangalore, India; 500 mg/day) or placebo as adjunct to standard treatment. In order to improve the bioavailability of curcumin, 5 mg piperine (Bioperine®, Sami Labs LTD, Bangalore, India) was added to each 500 mg curcumin capsule [40,41]. Placebo capsules contained microcrystalline cellulose plus equal amount (5 mg) of piperine. C3 Complex® preparation that was used in the present study contained 3 major curcuminoids including curcumin, demethoxycurcumin and bisdemethoxycurcumin in a patented ratio. The purity of the product for the 3 major curcuminoids was determined using HPLC (supplementary files 1 and 2). Curcumin and placebo capsules were matched in color, shape and size.

Assessment of symptoms

Severity of dyspepsia symptoms was evaluated using the Hong Kong dyspepsia index (HKDI). HKDI consists of 12 items: stomach pain, upper abdominal bloating, upper abdominal dull ache, stomach pain before meals, stomach pain when anxious, vomiting, nausea, belching, acid regurgitation, heartburn, feel of acidity in stomach and loss of appetite). Each item was graded on a Likert scale with scores of 1 (asymptomatic), 2 (mild symptoms that can be easily ignored), 3 (awareness of symptoms but easily tolerated), 4 (severe symptoms sufficient to cause interference with normal daily activities) and 5 (incapacitating symptoms causing inability to perform daily activities and/or require days off work). A cut off score of ≥16 was used to categorize patients as dyspeptic and non-dyspeptic [42].

Statistical analysis

Statistical analyses were performed using the SPSS software version 20 (IBM Corp., Armonk, NY, USA Inc.). Data were expressed as mean±SD or number (%). Within-and-between-group comparisons were performed using Wilcoxon signed-ranks test and Mann-Whitney U test (for normally distributed data), respectively. Categorical variables were compared using Fisher’s Exact test. In all comparisons, a p-value of <0.05 was considered as statistically significant.

Results

From the initial 68 subjects who entered the study, 60 subjects (30 in each group) completed the study. 8 patients were lost to follow-up and did not refer to the study center for a final visit and UBT (Fig. 1).

The study groups were comparable in age, gender, anthropometric indices (weight, height and body mass index) and frequency of smoking habit (Table 1). The results of UBT test showed equal rate of H. pylori eradication in the study groups. In both groups, 22 out of the 30 subjects (equivalent to 73.3% of subjects) had their infection eradicated. Individual analysis of 12 items in the HKDI questionnaire revealed significant improvement of all dyspepsia symptoms, except vomiting, in both curcumin and placebo groups. Consistently, total HKDI score was found to be improved in both curcumin and placebo groups (p<0.001). Nevertheless, comparison of the magnitude of changes revealed greater improvements in upper abdominal dull ache (p=0.002), stomach pain before meals (pp=0.004), belching (p=0.028) and total HKDI score (p<0.001) in the curcumin vs. placebo group (Table 2).

At baseline, all subjects in the curcumin and placebo groups had HKDI scores of ≥16, suggesting a 100% prevalence of dyspepsia. In the curcumin group, 27.6% of subjects reached a score of <16 at the end of trial while in the control group only 6.7% of subjects were categorized as non-dyspeptic at the end of study. The number of subjects whose dyspepsia was resolved during the
course of treatment was significantly higher in the curcumin vs. placebo group (p=0.042) (Table 3). Curcumin was found to be safe and there was no report of any serious adverse event during the course of trial. There were 6 reports of adverse events including diarrhea (one subject in each group), headache (2 subjects in the curcumin group and one subject in the placebo group) and vertigo (one subject in the placebo group). These adverse events were mild or moderate and did not lead to premature study withdrawal.

Discussion

This study was designed with the aim of evaluating the efficacy of curcumin on the severity of dyspepsia and eradication of H. pylori in patients with PU. Our results revealed that adding curcumin to standard treatment of H. pylori-positive PU ameliorates dyspepsia symptoms significantly. However, such an adjunctive therapy does not have any enhancing effect on the H. pylori eradication rate. As expected, curcumin was safe and well tolerated in this study. This finding is consistent with numerous previous clinical studies and further supports consideration of curcumin as “generally recognized as safe” for human use.

The impact of curcumin on H. pylori has been the subject of several previous in vitro studies. It has been reported that curcumin suppresses IL-8 induction in H. pylori through inactivation of NF-kappaB. IL-8 has a key role in H. pylori pathogenesis [29]. These findings were confirmed by Foryst-Ludwig et al. in H. pylori-infected epithelial cells [31] and by Sintara et al. in rat model of H. pylori infection [36]. In an experimental study in mice, De et al. showed the efficacy of curcumin in eradicating H. pylori infection. In the same study, the beneficial effects of curcumin on healing of PU were shown [33]. In another animal study, Kundu et al. reported that curcumin supplementation can inhibit matrix metalloproteinases 3 and 9; 2 enzymes that are implicated in the pathogenesis of H. pylori. Interestingly, this effect of curcumin was stronger than that of the standard triple therapy [35]. Finally, another recent study on mouse model revealed that curcumin can inhibit all 84 up-regulated inflammatory cytokines and chemokines in H. pylori-infected mucosa [37].

With respect to clinical studies, only few human studies have explored the effects of curcumin in PU, and no study has yet assessed the impact of adding curcumin as adjunct to anti-helicobacter regimen in the context of a randomized controlled trial. Di Mario et al. treated 25H. pylori-positive patients with functional dyspepsia with the combination of pantoprazol, N-acetyl cysteine, lactoferrin and curcumin. All of the patients had functional dyspepsia. They found that after 7 days of treatment, only 3 patients were free of H. pylori but the severity of symptoms was reduced significantly [38]. Likely, Prucksunand et al. in a clinical phase II study found that treatment with turmeric (600 mg/day) for 4 weeks decreases PU symptoms. They showed that 76% of patients diagnosed with PU were free of ulcer 12 weeks after the treatment [43]. In spite of the promising findings, both of the aforementioned studies were limited in its single-arm design which makes it difficult to attribute the observed

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**Table 1** Baseline characteristics of the study groups.

<table>
<thead>
<tr>
<th></th>
<th>Curcumin</th>
<th>Placebo</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>35.03 ± 9.29</td>
<td>35.10 ± 8.96</td>
<td>0.978</td>
</tr>
<tr>
<td>Female (%)</td>
<td>16 (53.3%)</td>
<td>18 (60.0%)</td>
<td>0.795</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>76.50 ± 10.53</td>
<td>74.60 ± 13.49</td>
<td>0.546</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>168.50 ± 8.50</td>
<td>166.37 ± 7.14</td>
<td>0.297</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.87 ± 2.28</td>
<td>26.79 ± 3.44</td>
<td>0.914</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>2 (6.7%)</td>
<td>3 (10.0%)</td>
<td>1.00</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± SD or number (%). BMI: body mass index.
In summary, findings of the randomized controlled trial suggested that although curcumin could not eradicate H. pylori, it could ameliorate PU symptoms possibly through reduction of gastric acid secretion.

Within-group comparison of dyspepsia symptoms in the study groups.

Table 2

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Curcumin Pre-treatment</th>
<th>Curcumin Post-treatment</th>
<th>Placebo Pre-treatment</th>
<th>Placebo Post-treatment</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stomach pain</td>
<td>3.67 ± 0.88</td>
<td>1.83 ± 0.38</td>
<td>&lt;0.001</td>
<td>3.57 ± 0.97</td>
<td>2.07 ± 0.45</td>
</tr>
<tr>
<td>Upper abdominal bloating</td>
<td>2.63 ± 1.10</td>
<td>1.40 ± 0.62</td>
<td>&lt;0.001</td>
<td>3.27 ± 1.05</td>
<td>2.20 ± 0.66</td>
</tr>
<tr>
<td>Upper abdominal dull ache</td>
<td>3.38 ± 0.62</td>
<td>1.57 ± 0.63</td>
<td>&lt;0.001</td>
<td>3.40 ± 0.67</td>
<td>2.10 ± 0.61</td>
</tr>
<tr>
<td>Stomach pain before meals</td>
<td>2.83 ± 0.79</td>
<td>1.40 ± 0.62</td>
<td>&lt;0.001</td>
<td>2.70 ± 0.79</td>
<td>1.80 ± 0.61</td>
</tr>
<tr>
<td>Stomach pain when anxious</td>
<td>2.33 ± 1.06</td>
<td>1.43 ± 0.57</td>
<td>&lt;0.001</td>
<td>2.77 ± 0.82</td>
<td>2.10 ± 0.71</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1.13 ± 0.43</td>
<td>1.03 ± 0.18</td>
<td>0.083</td>
<td>1.07 ± 0.25</td>
<td>1.00 ± 0.00</td>
</tr>
<tr>
<td>Nausea</td>
<td>2.00 ± 0.74</td>
<td>1.13 ± 0.35</td>
<td>&lt;0.001</td>
<td>2.07 ± 0.87</td>
<td>1.30 ± 0.47</td>
</tr>
<tr>
<td>Belching</td>
<td>1.67 ± 0.80</td>
<td>1.10 ± 0.31</td>
<td>0.002</td>
<td>1.47 ± 0.57</td>
<td>1.30 ± 0.53</td>
</tr>
<tr>
<td>Acid regurgitation</td>
<td>1.73 ± 0.74</td>
<td>1.33 ± 0.48</td>
<td>0.003</td>
<td>1.50 ± 0.68</td>
<td>1.23 ± 0.43</td>
</tr>
<tr>
<td>Heartburn</td>
<td>4.17 ± 0.79</td>
<td>1.97 ± 0.18</td>
<td>&lt;0.001</td>
<td>4.47 ± 0.51</td>
<td>2.40 ± 0.50</td>
</tr>
<tr>
<td>Feeling of acidity in stomach</td>
<td>1.87 ± 0.86</td>
<td>1.20 ± 0.41</td>
<td>&lt;0.001</td>
<td>1.63 ± 0.67</td>
<td>1.27 ± 0.45</td>
</tr>
<tr>
<td>Loss of appetite</td>
<td>1.83 ± 1.12</td>
<td>1.17 ± 0.38</td>
<td>0.001</td>
<td>2.00 ± 0.87</td>
<td>1.53 ± 0.57</td>
</tr>
<tr>
<td>Total score</td>
<td>29.41 ± 3.78</td>
<td>16.57 ± 1.59</td>
<td>&lt;0.001</td>
<td>29.90 ± 5.19</td>
<td>20.30 ± 3.14</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± SD

Table 3

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Curcumin</th>
<th>Placebo</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stomach pain</td>
<td>−1.83 ± 0.75</td>
<td>−1.50 ± 0.94</td>
<td>0.151</td>
</tr>
<tr>
<td>Upper abdominal bloating</td>
<td>−1.23 ± 0.90</td>
<td>−1.07 ± 0.74</td>
<td>0.366</td>
</tr>
<tr>
<td>Upper abdominal dull ache</td>
<td>−1.86 ± 0.69</td>
<td>−1.30 ± 0.65</td>
<td>0.002</td>
</tr>
<tr>
<td>Stomach pain before meals</td>
<td>−1.43 ± 0.82</td>
<td>−0.90 ± 0.66</td>
<td>0.004</td>
</tr>
<tr>
<td>Stomach pain when anxious</td>
<td>−0.90 ± 0.92</td>
<td>−0.67 ± 0.66</td>
<td>0.404</td>
</tr>
<tr>
<td>Vomiting</td>
<td>−1.00 ± 0.31</td>
<td>−0.07 ± 0.25</td>
<td>0.643</td>
</tr>
<tr>
<td>Nausea</td>
<td>−0.87 ± 0.73</td>
<td>−0.77 ± 0.63</td>
<td>0.625</td>
</tr>
<tr>
<td>Belching</td>
<td>−0.57 ± 0.77</td>
<td>−0.17 ± 0.38</td>
<td>0.028</td>
</tr>
<tr>
<td>Acid regurgitation</td>
<td>−0.40 ± 0.62</td>
<td>−0.27 ± 0.52</td>
<td>0.377</td>
</tr>
<tr>
<td>Heartburn</td>
<td>−2.20 ± 0.81</td>
<td>−2.07 ± 0.52</td>
<td>0.254</td>
</tr>
<tr>
<td>Feeling of acidity in stomach</td>
<td>−0.67 ± 0.71</td>
<td>−0.37 ± 0.56</td>
<td>0.087</td>
</tr>
<tr>
<td>Loss of appetite</td>
<td>−0.67 ± 0.84</td>
<td>−0.47 ± 0.73</td>
<td>0.380</td>
</tr>
<tr>
<td>Total score</td>
<td>−12.90 ± 2.81</td>
<td>−9.60 ± 3.39</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± SD

Clinical benefit to curcumin or turmeric. The third trial was a randomized one comparing the effects of standard triple therapy (omeprazole, amoxicillin and metronidazole) vs. turmeric tablet (containing an average of 40 mg curcumin) in H. pylori-positive patients with chronic gastritis. Following a 4-week treatment period, Koosirirat et al. found that H. pylori eradication and reduction of IL-8 mRNA expression were significantly higher in patients treated with standard medication compared with the turmeric group. However, this latter study was limited in not assessing clinical symptoms, and administration of a relatively small dose of curcumin. Besides, intestinal and hepatic glucuronidation has been suggested as a major reason for the low oral bioavailability of curcumin in the crude and unformulated forms. Therefore, in the present study we co-administered curcumin with piperine – the alkaloid extracted from black pepper or long pepper – which is a strong glucuronidase inhibitor with known bioavailability-enhancing effects on curcumin [40,41]. Finally, Kim et al. showed that turmeric extract reduces gastric acid via blocking H2 histamine receptors in an experimental rats model [44]. This finding is in line with the present results, and suggests that although curcumin could not eradicate H. pylori, it could ameliorate PU symptoms possibly through reduction of gastric acid secretion.

In summary, findings of the randomized controlled trial suggested that adding curcumin on top of standard H. pylori treatment regimen improves clinical symptoms of dyspepsia with apparently no effect on the eradication rate of H. pylori. Owing to the strong evidence on the safety and pleiotropic actions of curcumin in human use, this phytochemical could be considered as an efficacious adjunct in patients suffering from PU. However, future investigations are required to test the long-term efficacy of curcumin in patients with dyspepsia, especially with respect to the prevention of new H. pylori infections.

Acknowledgments

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Conflict of Interest

Muhammed Majeed is the CEO of Sabinsa Corporation and Sami Labs Ltd.

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