Response to *Helicobacter pylori* Eradication Triple Therapy in Peptic Ulcer Disease Patients on Curcumin Supplement According to different ABO Phenotypes

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Abstract

**Background:** *Helicobacter pylori* infection is one of the most predominant causes of peptic ulcer disease. There was a correlation between *H. pylori* infection and ABO phenotypes in peptic ulcer disease patients. Curcumin has anti-*H. pylori* effect due to its anti-oxidant, anti-inflammatory, anti-microbial, and anti-carcinogenic effect.

**Patients and Methods:** This study is a prospective randomized interventional open-label study which designed to show the potential benefit of adjuvant curcumin therapy in peptic ulcer disease Iraqi patients with different ABO phenotypes. The patients were allocated into two groups, group (1) treated with standard triple *H. pylori* eradication, and group (2) treated with curcumin capsules as adjuvant with the standard triple therapy for two weeks. The ABO phenotypes detected by Anti ABO and Anti-D monoclonal kit and the *H. pylori* infection was detected at the baseline and after 6 weeks of completion treatment course.

**Results:** highly significant improvement in *H. pylori* eradication after addition adjuvant curcumin to standard *H. pylori* eradication triple therapy compared to standard triple therapy alone(*P*<0.01) for patients holding blood group AB phenotypes (*P*<0.01) and significant improvement for patients holding blood group O phenotypes (*P*<0.05) reach up to (100 %) after 6 weeks from the intervention starting point. Besides, there was improvement in *H. pylori* eradication for patients holding blood group A and B phenotypes with adjuvant curcumin therapy, though no significant (*P*>0.05). This study showed no significant difference in BMI among ABO phenotypes (A,B, AB, and O) for both groups 1 and 2 patients after 6 weeks from the intervention starting point(*P*>0.05).
Conclusion: Use of adjuvant curcumin with standard triple therapy produced improvement in *H. pylori* eradication for all patients with different ABO phenotypes. Also, use of curcumin with triple therapy produced non significant increase in BMI compared to triple therapy alone among different ABO blood groups patients.

**Keywords:** Peptic ulcer disease, *Helicobacter pylori* infection, Curcumin, Triple therapy
Introduction

Peptic ulcer disease still one of the main prevalent unresolved medical problems affecting numerous patients of both genders in a wide range of age worldwide[1]. There are several predisposing factors for PUD that may be involved in the pathogenesis of the disease. *Helicobacter pylori* infection is one of the most predominant causes of PUD. Approximately all the DUs and up to two-thirds of the GUs reveal positive *H. pylori* infection[2]. At least 50% of the population worldwide are infected by *H. pylori*[3]. Although *H. pylori* is known to produce an extensive, non-invasive inflammatory reaction in the gastric mucosa[4]. Colonization of the stomach with *H. pylori* often causes an inflammation of the stomach lining that may evolve toward chronic gastritis, peptic ulcer, gastric mucosa-associated lymphoid tissue (MALT) lymphoma, and gastric cancer[5,6].

There was a correlation between *H. pylori* infection and ABO phenotypes in peptic ulcer disease patients diagnosed by upper gastrointestinal endoscopy[7]. Eradication of *H. pylori* decrease the recurrence of peptic ulcer disease (both gastric and duodenal ulcers), improves healing rates for duodenal ulcers, and prevents recurrent ulcer haemorrhge[8]. Increasing difficulties in the conventional *H. pylori* eradication triple-therapy due to antimicrobial resistance, undesirable side effects, incomplete cure, cost of the antibiotic regimens, noncompliance among the patients, and few other factors, promote a critical need to develop new non-antibiotic antibacterial agents to eradicate *H. pylori* that are safe, highly effective, low cost and have specific cellular targets[9]. Experimentally, combination of herbal medicines with standard antiulcer drugs produced a synergistic effect against peptic ulcer disease, and could be used as an alternative therapy for treating certain gastric ulcer and preventing recurrence[10]. Curcumin is a yellow pigment extracted from rhizome of *Curcuma longa* (C. Longa) used commonly as a spice and food-coloring agent[11]. It is a lipophilic polyphenol, is nearly
insoluble in water, but is quite stable at acidic pH of stomach[12]. Curcumin is widely used in herbal medicine because it possess many pharmacological properties[13]. Curcumin display antiulcer activity by attenuating different ulcerative effectors including gastric acid hypersecretion, myeloperoxidase activity, total peroxides, IL-6, and apoptotic incidence, along with its inhibitory activity for pepsin[14]. Curcumin has anti-\textit{H. pylori} effect due to its anti-oxidant, anti-inflammatory, anti-microbial, and anti-carcinogenic effect[15].

**PATIENTS AND METHODS**

**Study design:**

The present study is a prospective randomized interventional open-label study which designed to show the potential benefit of adjuvant curcumin therapy in PUD patients with different ABO phenotypes who attended the Endoscopy unit of Baghdad Teaching Hospital/Medical City. The study was conducted between November 2015 up to June 2016.

**Patients:**

Forty two patients (27 female and 15 male) were enrolled in this study with age range between (17-70) years. Patients were enrolled in the study after signing a written consent, the ethical approval was released by scientific committee of the hospital.

Patients were allocated into two groups, group (1) include (20) patients treated with standard triple \textit{H. pylori} eradication therapy [clarithromycin (500 mg) tablets (Limassol ,Cyprus) + esomeprazole (20mg) tablets (Astrazeneca , Sweden) + amoxicillin (1g) capsules (Bristol, UK)] all to be given twice daily for two weeks duration, which represent the control group, and group2 include (22) patients treated with curcumin (500mg) capsules given three times daily for two weeks as adjuvant with the standard triple \textit{H. pylori} eradication therapy[15], which represents the interventional group.

**Methods:**

**Diagnosis of \textit{Helicobacter pylori} infection:** The \textit{H. pylori} antigen rapid test device (feces) (ABON, China) is used for detection of \textit{H. pylori} in both group 1 and 2 patients at the baseline and after 6 weeks of completion treatment course.

**Detection of ABO phenotypes**
Anti ABO and Anti-D monoclonal kit (Spinreact, Spain) is used for detection of different ABO phenotypes in both group 1 and 2 patients.

Statistical analysis

The (SPSS) system was used for statistical analysis. Different tests were used for comparison between study parameters, where data expressed as percent and (mean \( \pm \) SD) and considered not significant if \( P > 0.05 \), significant if \(*p < 0.05\), and highly significant if \(**P < 0.01\). Paired \( t \)-test was utilized to compare between the pre- and post- treatment variable, and two sample \( t \)-test was utilized to compare the pre or post treatment variable between group 1 and group 2.

RESULTS

- Demographic and disease characteristics of \textit{H. pylori} infected patients

Table (1) demonstrates the demographic and disease characteristic for (42) \textit{H. pylori} positive patients including 27 female (64.29\%) and 15 male gender (35.71\%) with age range 17-70 year. No significant statistical difference was found between both study groups in respect to age, body mass index (BMI), genders, family history, Smoking habit, duration of symptoms, and Rh factor phenotype \( (P>0.05) \).

Demographic and disease characteristics of \textit{H. pylori} infected patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Study groups</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group1( ( n=20 ))</td>
<td>Group2( ( n=22 ))</td>
</tr>
<tr>
<td>Age(years):</td>
<td>39.40 ± 11.77</td>
<td>44.36 ± 15.11</td>
</tr>
<tr>
<td>Range(years):</td>
<td>20-63</td>
<td>17-70</td>
</tr>
<tr>
<td>BMI kg/m(^2)</td>
<td>26.89±5.27</td>
<td>26.54±4.22</td>
</tr>
<tr>
<td></td>
<td>n</td>
<td>%</td>
</tr>
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<td>--------------------------</td>
<td>-----</td>
<td>-----</td>
</tr>
<tr>
<td>Gender:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>12</td>
<td>60</td>
</tr>
<tr>
<td>Male</td>
<td>8</td>
<td>40</td>
</tr>
<tr>
<td>Family history</td>
<td></td>
<td></td>
</tr>
<tr>
<td>positive</td>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td>Negative</td>
<td>18</td>
<td>90</td>
</tr>
<tr>
<td>Duration of symptoms:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 1 (years)</td>
<td>15</td>
<td>75</td>
</tr>
<tr>
<td>1-5 (years)</td>
<td>5</td>
<td>25</td>
</tr>
<tr>
<td>&gt; 5 (years)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Smoking habit</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>3</td>
<td>15</td>
</tr>
<tr>
<td>Negative</td>
<td>17</td>
<td>85</td>
</tr>
<tr>
<td>Rh factor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>17</td>
<td>85</td>
</tr>
<tr>
<td>Negative</td>
<td>3</td>
<td>15</td>
</tr>
</tbody>
</table>

Data presented as Mean ±SD, (n) is number of patients and (%) is percentage.

Chi-square test for numerical values to compare between group 1 and group 2 where,
NS: Not significant ($P>0.05$).

- **Response of *H. pylori* infected patients to triple therapy alone and in combination with curcumin**

Table (2) and figure (1) showed the percentage of *H. pylori* eradication of both study groups 1 and 2 patients as follows:
In group 1 patients the mean percentage of \textit{H. pylori} eradication was (60\%) with standard triple therapy, while the mean percentage of \textit{H. pylori} eradication with triple therapy in combination with curcumin in group 2 patients was (95.45\%) after 6 weeks from the intervention starting point. Statistically high significant difference in \textit{H. pylori} eradication was presented between patients of study groups 1 and 2 ($P<0.01$) after 6 weeks from the intervention starting point and up ceiling for patients on triple therapy with adjuvant curcumin.

Response of \textit{H. pylori} infected patients to triple therapy alone and in combination with curcumin

<table>
<thead>
<tr>
<th>Study groups</th>
<th>Patients</th>
<th>\textit{H. pylori} eradication</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>n</td>
</tr>
<tr>
<td>Group 1</td>
<td>20</td>
<td>12 of 20</td>
</tr>
<tr>
<td>Group 2</td>
<td>22</td>
<td>21 of 22</td>
</tr>
<tr>
<td>$P$ value</td>
<td></td>
<td>0.003**</td>
</tr>
</tbody>
</table>

Data founded as (n) is number of patients and (\%) is percentage. Chi-square test used for numerical values to comber between the results of group1 and group 2 where,

\( (**)(P<0.01)\): Highly significant
Figure (1): Response of *H. pylori* infected patients to triple therapy alone and in combination with curcumin.

- **Effect of triple therapy alone and in combination with curcumin on *H. pylori* eradication according to ABO blood groups phenotypes**

Table (3) and figure (2) presented the percentage of *H. pylori* positive patients according to ABO blood group phenotypes as follows:

After 6 weeks from the intervention starting point, group 1 peptic ulcer patients holding blood group A presented with (66.67%), and O phenotypes presented with (57.14%) of *H. pylori* eradication after standard *H. pylori* eradication therapy, while patients with blood group B phenotypes presented with (80%) of *H. pylori* eradication but there was no eradication for patients with blood group AB. On the other hand, with curcumin adjuvant therapy, the mean percentage of *H. pylori* eradication in group 2 peptic ulcer patients was (100%) for blood group A, AB, O and (83.33) in patients with blood group B phenotype.

Statistically there was highly significant difference in mean percentage of *H. pylori* eradication between both study groups 1 and 2 patients holding blood group AB phenotypes (*P*<0.01) and significant difference for patients holding blood group O phenotypes (*P*<0.05) after 6 weeks from the intervention starting point. There was no significant difference in *H. pylori* eradication...
eradication for patients carrying blood group A and B phenotypes between both treatment regimens ($P > 0.05$).

Table (3): Effect of triple therapy alone and in combination with curcumin on *H. pylori* eradication according to ABO blood groups phenotypes  

<table>
<thead>
<tr>
<th>ABO phenotypes</th>
<th>Study groups</th>
<th>H. pylori eradication</th>
<th>H. pylori Eradication</th>
<th>P. value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group 1</td>
<td>Group 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>n (%)</td>
<td>N (%)</td>
<td>N (%)</td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>6 (30)</td>
<td>4/6 (66.67)</td>
<td>4 (18.18)</td>
<td>0.083 N.S</td>
</tr>
<tr>
<td>B</td>
<td>5 (25)</td>
<td>4/5 (80.00)</td>
<td>6 (27.27)</td>
<td>0.887 N.S</td>
</tr>
<tr>
<td>AB</td>
<td>2 (10)</td>
<td>0/2</td>
<td>3 (13.64)</td>
<td>0.000**</td>
</tr>
<tr>
<td>O</td>
<td>7 (35)</td>
<td>4/7 (57.14)</td>
<td>9 (40.91)</td>
<td>0.022*</td>
</tr>
<tr>
<td>Total</td>
<td>20 (100.00)</td>
<td>12 (60.00)</td>
<td>22 (100.0)</td>
<td>0.003**</td>
</tr>
</tbody>
</table>

Data presented as (n) is number of patients and (%) is percentage.

Chi-square test used for numerical values to compare between the results of group 1 and group 2 where,

N.S: Not significant ($P > 0.05$), (*) ($P < 0.05$): Significant, (**) ($P < 0.01$): Highly significant
- Effect of triple therapy alone and in combination with curcumin on body mass indices (BMIs) of *H. pylori* infected patients with different ABO phenotypes.

As presented in table (4) and seen in figure (3), there was statistical non-significant difference in level of mean BMI between the different blood groups (A, B, AB, and O) for both groups 1 and 2 patients at the baseline level (*P* > 0.05). After 6 weeks from the intervention starting point there was statistical non-significant increase in level of mean BMI for study groups 1 patients carrying blood group A, but for patients carrying blood group (B, AB and O) there was non-significant decrease in mean BMI (*P* > 0.05).

Study group 2 showed statistically non-significant increase in level of mean BMI for patients carrying blood group A and O, but non-significant decrease for patients carrying blood group B and no change in mean BMI for patients with blood group AB (*P* > 0.05). Again, there was no significant difference among ABO phenotypes (A, B, AB, and O) for both groups 1 and 2 patients after 6 weeks from the intervention starting point (*P* > 0.05).
Table (4) Effect of triple therapy alone and in combination with curcumin on body mass indices (BMIs) of *H. pylori* infected patients with different ABO phenotypes.

<table>
<thead>
<tr>
<th>ABO phenotypes</th>
<th>BMI(Kg/m2) of  group 1</th>
<th>ABO phenotypes</th>
<th>BMI(Kg/m2) of  group 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre treatment</td>
<td></td>
<td>Pre treatment</td>
</tr>
<tr>
<td></td>
<td>Post treatment</td>
<td></td>
<td>Post treatment</td>
</tr>
<tr>
<td></td>
<td>P-value</td>
<td></td>
<td>P-value</td>
</tr>
<tr>
<td>A</td>
<td>28.92</td>
<td>A</td>
<td>25.95</td>
</tr>
<tr>
<td>B</td>
<td>23.32</td>
<td>B</td>
<td>25.50</td>
</tr>
<tr>
<td>AB</td>
<td>26.70</td>
<td>AB</td>
<td>26.03</td>
</tr>
<tr>
<td>O</td>
<td>27.42</td>
<td>O</td>
<td>27.67</td>
</tr>
<tr>
<td></td>
<td>0.921&lt;sup&gt;N.S&lt;/sup&gt;</td>
<td></td>
<td>0.991&lt;sup&gt;N.S&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>0.911&lt;sup&gt;N.S&lt;/sup&gt;</td>
<td></td>
<td>0.973&lt;sup&gt;N.S&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>0.981&lt;sup&gt;N.S&lt;/sup&gt;</td>
<td></td>
<td>0.850&lt;sup&gt;N.S&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Statistically, independent *t*-test is used to compare between pre- and post-treatment results for different ABO blood groups where, N.S: Not significant.

Figure (3): Effect of triple therapy alone and in combination with curcumin on body mass indices (BMIs) of *H. pylori* infected patients with different ABO phenotypes.
Discussion

Infection of *H. pylori* is a worldwide problem in peptic ulcer disease patients with high risk for morbidity and mortality[19]. The most effective therapeutic regimen was evaluated by several studies to improving the *H. pylori* eradication rate [17-20]. This study is another attempt in this respect, though at a smaller scale, which might be (at least to best knowledge) the first attempt to investigate whether addition of Curcumin to the standard triple therapy will increase the eradication rate of *H. pylori* infection according to patients ABO blood group phenotypes.

The activity of curcumin alone in peptic ulcer disease was experimentally investigated previously *in vitro* as possessing antioxidant and anti-inflammatory properties, and to attenuating gastric hyper secretion (as a major pathology caused by *H. pylori* microorganism in gastric and duodenal ulcer), along with its inhibitory effect for pepsin was found[14]. Moreover, other *in vivo* and *in vitro* studies explored the inhibitory effect of curcumin against *H. pylori* growth, consequently eradicate *H. pylori* infection [21]. In clinical trial, curcumin supplement alone is still under investigation in which it is expected to play a potential role in suppressing *H. pylori* growth [22].

In the present study, and in many other, patients with peptic ulcer disease caused by *H. pylori* infection were mostly in a middle age of <50 years[23-25]. Female patients had the higher rate of infection with *H. pylori* microorganism, similar finding was found among Iraqi population in other studies[26], inversely, male gender were predominant to females in others[27,28].

Positive family history was correlated positively with *H. pylori* infection in previous studies. The *H. pylori* infections tend to distributed within families by close person-to-person contact[29]. Other data reported by Shokrzadeh, 2012 *et al.* showed that positive family history of peptic ulcer disease was seen in about 24% of *H. pylori* positive patients[30].

The most common *H. pylori* eradication regimen was the proton pump inhibitor (PPI)-based triple therapy (a PPI with two different anti-microbials)[31], which was studied on groups of Iraqi patients with other regimen as well[20,32]. The triple therapy for *H. pylori* improve ulcer healing, produce rapid relief for symptom, and decrease ulcer recurrence. However, failure of *H. pylori* eradication contributed by different host and bacterial factors, especially factors affecting
the bioavailability and metabolism of proton pump inhibitor [33], low patient compliance, particularly in elderly patients[34]. However, increasing antibiotic resistance - strains of \textit{H. pylori} especially for clarithromycin and metronidazole became the most contributing factor for treatment failure[33,35].

In the present study, the eradication rate of \textit{H. pylori} was increased from (60%) with standard triple therapy alone up to (95.44%) after use of curcumin as adjuvant therapy. As monotherapy, the effect of curcumin against \textit{H. pylori} infection was previously studied and reviewed by other researches[9,36], meanwhile Di Mario, 2007 et al. showed that administration of 30 mg of curcumin b.i.d for 7 days, 20 mg of pantoprazole b.i.d, 100 mg of bovine lactoferrin b.i.d, and 600 mg of N-acetylcysteine b.i.d, cure only (12%) of dyspeptic patients infected with \textit{H. pylori}, while after 2 months there was a significant reduction in severity of overall symptoms[37]. This study might be a new trend for improving the eradication rate of \textit{H. pylori} infection with curcumin adjuvant to the (PPI)-based triple therapy, which alone showed (40%) eradication failure rate, while with adjuvant curcumin therapy the eradication failure rate was(4.55%)

The relationship between ABO blood group phenotypes and the incidence of peptic ulcer disease caused by \textit{H. pylori} infection had been investigated previously worldwide[38,39] and in Iraq[40,41].

In the present study, the percentage of \textit{H. pylori} eradication for patients holding blood group A, O, and AB was increased to (100% ) after the addition of curcumin to the standard \textit{H. pylori} eradication triple therapy. No matched studies were found that can interpret the exact role of curcumin on the \textit{H. pylori} eradication among different blood groups phenotypes patients.

There are specific phenotypic features related to PUD patients carrying ABO phenotypes, PUD patients carrying blood type A phenotype are most likely to develop gastric cancer secondary to GU[41].Those patients are characterized by acid hypo secretion, and low serum-pepsinogen level[42].On the other hand, PUD patients carrying blood group O are prone to have persistent colonization of \textit{H. pylori}[43] following the expression of Lewis antigens (Le$^b$) in gastric mucosa which act as a receptor for bacterial adhesion[44], expression of H-antigen on the gastro duodenal cells, acting as a receptor for \textit{H. Pylori}[44,45], the expression of blood group
antigen b-binding adhesion (babA) on the outer membrane of \( H. \text{pylori} \)[46], and cagA-positive virulent strain \( H. \text{pylori} \) colonize in both the corpus and antrum [47]. Moreover, patients with blood group O phenotype stimulate a higher inflammatory responses to \( H. \text{pylori} \) with higher levels of lymphocyte infiltration in the gastrointestinal mucosa[48], have low level of Von Willebrand’s factor (VWF)[49], high frequency of secretor status[48], and high gastric acidity[42] which reduces the efficacy of antibiotic therapy [50]. Accordingly, and all together, may explain the higher susceptibility of patients holding blood group A, AB, and O, phenotype for \( H. \text{pylori} \) eradication following curcumin adjuvant therapy.

globally; the distribution pattern for BMI changed within and between different populations according to socioeconomic status [51]. The ABO phenotypes and BMI have been considered as risk factors for certain diseases, some studies examined the effect of carrying a specific ABO phenotype on body mass index[52-54]. One study from India showed a correlation between the O blood group and obesity in children[55]. While other showed a prevalence of high body weight in patients with B blood group[56]. In contrast other study showed no relation between BMI and ABO phenotypes[57]. The beneficial effect of \( H. \text{pylori} \) eradication on BMI had been studied previously [58,59], while other study was not able to showed any effect [60]. In the present study addition of curcumin as adjuvant therapy produced non significant increase in BMI compared to triple therapy alone among different ABO blood groups patients. No matched studies were found that can explain the exact role of curcumin on the BMI among different blood groups phenotypes patients.

Increase in BMI after eradication of \( H. \text{pylori} \) may be due to improvement of some postprandial symptoms such as early satiety [58]. Other study showed that after \( H. \text{pylori} \) eradication there was a significant change in circulating meal- associated levels of ghrelin and leptin with subsequent effect on BMI[61]. While other cohort study showed no association between seropositivity of \( H. \text{pylori} \) with leptin level or BMI[60].

CONCLUSION

This study revealed that use of adjuvant curcumin with standard triple therapy produced improvement in \( H. \text{pylori} \) eradication for all patients with different ABO phenotypes. Also, use
of curcumin with triple therapy produced non significant increase in BMI compared to triple therapy alone among different ABO blood groups patients.

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