Efficacy of Probiotics as Adjuvant to the Standard Triple Therapy for the Treatment of Helicobacter Pylori-Associated Peptic Ulcer Disease: A Randomized-Control Trial

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Helicobacter pylori (H. pylori) is a major cause of peptic ulcer disease (PUD), which needs effective eradication of the organism to heal ulcers and prevent a recurrence. In recent years, increasing resistance of *H. pylori* to clarithromycin and amoxicillin have decreased peptic ulcer cure rate following treatment with standard triple therapy worldwide. The addition of probiotics with standard triple therapy has shown excellent efficacy in *H. pylori* eradication and has appeared to be an alternative treatment strategy. This study aimed to assess the efficacy of standard triple therapy plus probiotics for *H. pylori* eradication and ulcer healing compared to standard triple therapy alone. This double-blind, randomized placebo-controlled clinical trial included 158 with endoscopically proven *H. pylori*-positive PUD who were randomly allocated equally into two groups; Group A was treated with standard triple therapy plus probiotics, and Group B was treated with standard triple therapy plus placebo for 14 days. The outcome was evaluated at the end of treatment (14th day) (symptoms plus adverse events) and after 60 days of treatment completion (*H. pylori* eradication and ulcer healing). One hundred forty four (144) study subjects (73 in Group A and 71 in Group B) completed the study. Significantly higher *H. pylori* eradication rate (82.2%vs. 67.6%, p=0.043) and ulcer healing rate (92.3% vs. 60.0%, p=0.049) were observed in the standard triple therapy plus probiotic group than the standard triple therapy plus placebo group. Early relief of epigastric pain was also seen among patients getting probiotics than the placebo in addition to standard triple therapy (42.3% vs. 15.1%, p<0.001).The addition of probiotics significantly improves the *H. pylori* eradication rate and ulcer healing rate among the patients getting standard triple therapy. Further large-scale, multi-center studies are needed to recommend routine use of probiotics with standard triple therapy for *H. pylori* eradication.

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Key words: *H. pylori*, Peptic ulcer disease, Triple therapy, Probiotics, Ulcer healing, Eradication

Introduction

Peptic ulcer disease (PUD) develops when the protective mechanisms of the gastrointestinal (GI) mucosa, such as mucus and bicarbonate secretion, are overwhelmed by the damaging effects of gastric acid and pepsin. Peptic ulcers occur mainly in the stomach (gastric ulcer, GU) or proximal duodenum (duodenal ulcer, DU)[1]. The incidence of PUD and its complications varies worldwide and has changed dramatically over the past few decades. Approximately 10.0% of the population experience PUD in a certain period during the life time[2]. The discovery of *Helicobacter pylori (H. pylori)* as a major etiological factor in the disease pathogenesis changed the management of PUD. In a study, *H. pylori* were found in >70.0% of patients suffering from gastroduodenal ulcers[3]. Currently, proton-pump inhibitors (PPI) are the primary drugs used in PUD management. PPI-based standard triple therapy is considered the standard treatment for *H. pylori*-associated PUD, which showed an eradication rate of 88.0% in clarithromycin-sensitive strains[4]. Unfortunately, Clarithromycin failure is rising worldwide, as reported in several studies[5,6,7].

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In a recent study, the eradication rate after standard clarithromycin-based triple therapy is reported below 80.0%[8]. The use of probiotics with standard triple therapy has attracted attention as an alternative approach for increasing *H. pylori* eradication rates and thereby increasing the regimen's efficacy for ulcer healing[9]. Probiotics are living or attenuated nonpathogenic microorganisms that have many potential beneficial effects on health. Probiotics increase the resistance of the gastric barrier and thereby inhibit the growth of *H. pylori* and its adherence to gastric epithelium[10,11,12,13]. Probiotics possess broad-spectrum antimicrobial activity and have inhibitory effects on the planting and growth of *H. pylori* on the gastric mucosa. In addition, probiotics also inhibit inflammatory and immune responses after *H. pylori* infection[14]. A recent meta-analysis has proven the beneficial role of supplemental probiotics in eradication therapy by demonstrating the higher cure rates and eradication of *H. pylori* for co-therapy with probiotics versus standard agents alone[15].

We conducted this randomized control trial to assess the efficacy of standard triple therapy plus probiotics for *H. pylori* eradication and ulcer healing compared to standard triple therapy alone.

Methods

This randomized, double-blind, placebo-controlled clinical trial was conducted at the Department of Gastroenterology of Bangabandhu Sheikh Mujib Medical University, Bangladesh, from October 2014 to October 2015. One hundred fifty eight (158) patients aged between 18 to 60 years having endoscopically proven PUD with the presence of *H. pylori* evidenced by positive Urea Breathe Test (UBT) were included in this study. The exclusion criteria were pregnancy, pre-treatment with anti-ulcerants including PPIs within two weeks before the study, patients receiving clarithromycin for any reason within the previous two months, patients known to be allergic to any of the medicines used in the triple therapy regimen, regular use of non-steroidal anti-inflammatory drugs (NSAIDs) or steroids, chronic renal or hepatic disorders and neoplastic disease. The eligible study subjects were randomly allocated into two groups; Group A was treated with standard triple therapy (Omeprazole 20mg bid, Clarithromycin 500mg bid and Amoxicillin 1gm bid) plus probiotics (multi-strains) for 14 days and Group B was treated with standard triple therapy as mentioned plus placebo for the same duration. Then the outcome was evaluated clinically (relief of epigastric pain plus adverse events) on the 14th day and after 60days (eradication rate of *H. pylori* infection and ulcer healing rate) of completion of treatment with upper GI endoscopy and UBT. Eradication of *H. pylori* was defined by negative UBT. The study protocol got ethical approval by the Institutional Review Board (IRB) of Bangabandhu Sheikh Mujib Medical University, Bangladesh (Memo no: BSMMU/ 2015/ 3938 dated:15-03-2015). All participants signed the informed consent before enrollment.

Statistical analysis was done using the Statistical Product and Service Solutions version 26.0 software (IBM Corp Released 2019 IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp). The categorical variables were represented as percentages and measurable variables as the mean±standard deviation (SD). Student's 't' test and Chi-square test were performed to compare the variables between different groups as applicable. A p value of ≤ 0.05 was considered statistically significant.

Results

A total of 158 subjects (age 35.05±11.16 years, female 34.0%) having PUD were recruited. Six from Group A and 8 from Group B were lost to follow-up and 144 study subjects (73 in Group A and 71 in Group B) completed the study. Study subjects in Group A and Group B were similar in age, gender, occupational status, economic status, smoking habit and duration of symptoms (Table I). The two groups also had the identical endoscopic appearance of mucosal abnormality (Table II).

At follow-up on the 14th day of treatment, the frequency of epigastric pain was significantly lower in Group A than Group B (15.1% vs. 42.3%, $p<0.001$) [Not shown in the tables]. After 60 days of treatment completion, more subjects in the placebo group had positive UBT results compared to the probiotics group (32.4% vs. 17.8%, $p=0.043$), which indicates that eradication of *H. pylori* was achieved in 82.2% of subjects in the probiotics group (Group A) and 67.6% of subjects in the placebo group (Group B) (Figure 1).

Table I: Demographic and clinical characteristics of the study subjects (N=144)

Characteristics	Group A	Group B	p value
	Mean±SD	Mean±SD	
Number of subjects	73	71	0.074
Female [n (%)]	24 (32.9)	25 (35.2)	0.768
Mean age (years)	35.01±12.69	35.15±9.43	0.940
Mean BMI (kg/m^2)	22.10±1.62	22.80±2.19	0.104
Smoker [n (%)]	29 (39.5)	28 (38.7)	0.919
Duration of symptoms (months)	9.16±6.85	9.02±6.19	0.901

Table II: Endoscopic findings of the study subjects

Mucosal abnormality	Total (N=144) n (%)	Group A (n=73) n (%)	Group B (n=71) n (%)	p value
Ulcer	28 (19.4)	13 (17.8)	15 (21.1)	0.615
Erosion	116 (80.6)	60 (82.2)	56 (78.9)	

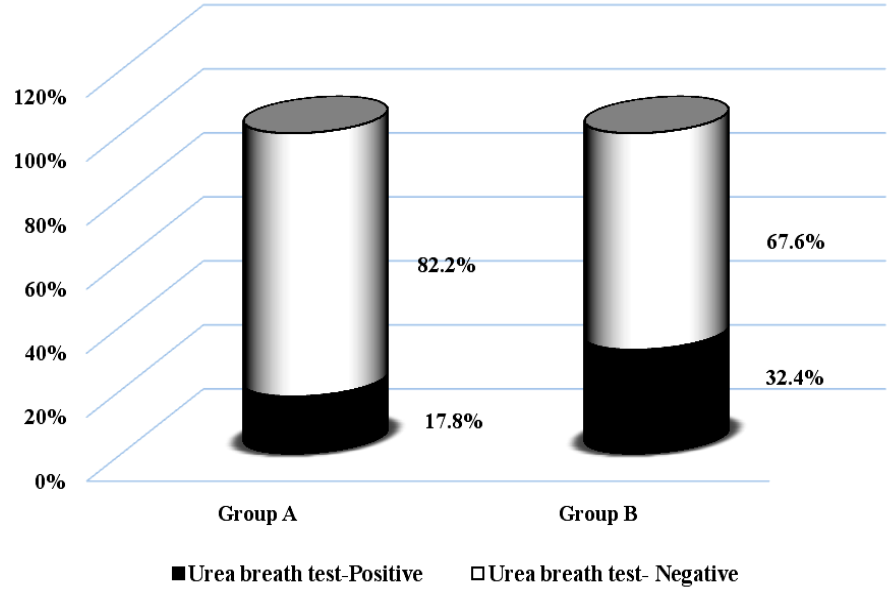

Figure 1: UBT result of Group A and Group B after 60 days of completion of treatment

A significantly higher ulcer healing rate was observed in Group A than Group B, evidenced by lower frequencies of ulcers and erosions 60 days after completion of treatment (Table III). In addition, both eradication of *H. pylori* and healing of mucosal abnormality were achieved significantly more in probiotics group than placebo group (78.1% vs. 49.3%, p<0.001).

Table III: Comparison of follow up endoscopic appearance of upper GIT between Group A and Group B after 60 days of completion of treatment

Endoscopic appearance of upper GIT		Total (N=144)	Group A (n=73)	Group B (n=71)	p value
Ulcer (n=28)	Absent	21(75.0%)	12(92.3%)	9(60.0%)	0.049
	Present	7(25.0%)	1(7.7%)	6(40.0%)	
Erosion (n=116)	Absent	105(90.5%)	58(96.7%)	47(83.9%)	0.019
	Present	11(9.5%)	2(3.3%)	9(16.1%)	

This study's most common drug adverse effects were taste disturbance followed by diarrhea, dizziness and headache. The frequency of any adverse effect was significantly less in Group A than Group B at follow-up on the 14th day of treatment (13.7% vs. 32.4%, OR; 3.019, p=0.009).

Discussion

In this study, we observed the higher efficacy of probiotics than placebo when added to the standard triple therapy of PUD in early epigastric pain relief, *H. pylori* eradication rate and ulcer healing rate. Probiotics treated arm also had lower frequencies of adverse effects of drugs. *H. pylori* is the principal cause of peptic ulcer[16]. Long-term *H. pylori* infection is also a risk factor of chronic gastritis, gastric malignancy and mucosa-associated lymphoid tissue (MALT) lymphoma[17,18,19]. The effectiveness of *H. pylori* eradication therapy is mounting, suggesting the solid value for eradicating *H. pylori* in curing ulcers, preventing recurrence, and reducing complications[20]. *H. pylori* infection is observed among more than 80.0% of middle-aged adults in developing countries[21]. More than 90.0% of apparently healthy adults in Bangladesh are positive for antibodies to *H. pylori*[22]. Moreover, 84.0% of Bangladeshi children become infected with *H. pylori* by 6-9 years of age[23]. Various combinations of PPIs and antimicrobial agents have been designed to treat *H. pylori* infection. These regimens include triple therapy, bismuth-containing quadruple therapy, sequential therapy and concomitant therapy (non-bismuth quadruple therapy). PPI-based triple therapy is regarded as the mainstay of treatment for *H. pylori*-associated PUD. However, the cure rate following standard triple therapies suggested in previous and updated European guidelines decrease worldwide and are currently below 80.0%[8,24,25,26]. Adjuvant therapy with probiotics showed promising results regarding ulcer healing and eradicating *H. pylori* in recent studies[10,20,27,28]. Moreover, a meta-analysis of 14 randomized clinical trials demonstrated that the cure rates for standard agents used alone and eradication co‑therapy with probiotics were 74.8% and 83.6%, respectively[15]. In this study, after 60 days of completion of treatment, eradication of *H. pylori* was achieved in 82.2% in the probiotic group and 67.6% in the placebo group, which is quite similar to the findings of other studies[10,20,27]. This study finding is also consistent with a recently published systemic review by Szajewska et al., which showed an 80.0% *H. pylori* eradication rate after supplementation of *S. boulardii* to standard triple therapy[9]. High (100.0%) eradication rates were observed when bismuth and probiotics were added with triple therapy[28]. In this study, about 32.4% of patients experienced adverse drug effects in the control group treated with standard triple therapy, compared to 13.7% in the probiotics group. Though our study findings are consistent with some other study results, a higher frequency of adverse effects among patients treated with probiotics and standard triple therapy was observed by some authors[9,25]. Such varying observations may be due to ethnic differences in adverse reactions to drugs. This study had several strengths. It is a double-blind trial, so there is a meager chance of selection bias. *H. pylori* infection was detected by a standard UBT, which has very high sensitivity and specificity. The endoscopy was done by an expert GI endoscopist blinded to the regimen of therapy. The present study also had some limitations. The study sample size was relatively small and only included the adults. Long-term follow-up of the study subjects was beyond the scope of the current study.

Conclusion

The present study concludes that the standard triple therapy with probiotics is more effective in eradicating *H. pylori* and ulcer healing than standard triple therapy alone. The addition of probiotics also significantly improves the clinical symptoms and reduces antibiotic-associated adverse events. Further study with large sample size and a more extended follow-up period may be conducted to make a consensus decision regarding the routine use of probiotics with standard triple therapy.

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