MEDICO RESEARCH CHRONICLES
ISSN NO. 2394-3971
DOI No. 10.26838/MEDRECH.2023.10.1.671
Contents available at www.medrech.com

Efficacy of *Helicobacter Pylori* Eradication in *Helicobacter Pylori* Positive Functional Dyspepsia Patients-A Double-Blind, Randomized, Placebo-Controlled Trial

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ARTICLE INFO | **ABSTRACT** | **ORIGINAL RESEARCH ARTICLE**

Article History
Received: October 2022
Accepted: January 2023
Key Words:
Helicobacter pylori, functional dyspepsia.

Multiple etiopathogenesis have been proposed for functional dyspepsia. But no conclusive mechanisms have been established yet. Many studies reported that *H. pylori* produce dyspeptic symptoms without any macroscopic lesion in the gastroduodenal mucosa. Some studies also reported that eradication of H. pylori relieves the symptoms of functional dyspepsia. The main objective of this double-blind randomized placebo controlled clinical trial was to see the response of *H. pylori* eradication in the management of '*H. pylori* positive functional dyspepsia'. We conducted the study on *H. pylori* positive functional dyspepsia patients visiting the gastroenterology OPD and see the effects of *H. pylori* eradication on their symptom resolution. Consecutive 59 *H. pylori* positive functional dyspepsia patients were randomly assigned to receive either Anti *H. pylori* therapy (Levofoxacin, Amoxicillin and Omeprazole) or placebo for 14 days. *H. pylori* status was assessed by ^{13}C urea breath test for inclusion into the study and 2 months later for eradication status along with symptom resolution. 23 patients receiving Anti *H. pylori* therapy and 17 receiving placebo were available for analysis. Two months after completion of therapy 56.5% patients resolved their symptoms who received Anti *H. pylori* therapy. On the other hand, 47.1% patients who received placebo

relieved their dyspeptic symptoms. Dyspeptic symptom resolution was also not statistically significant when comparison made between *H. pylori* eradicated and non- eradicated subjects irrespective of their treatment regimen (p=0.102). So in this study we found that there is no relationship between *H.pylori* eradication and resolution of dyspeptic symptoms in patients with functional dyspepsia.

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2023, www.medrech.com

INTRODUCTION

The word 'Dyspepsia' is derived from the Greek words 'dys' (difficult) and 'pepse' (digestion) [1]. Dyspepsia is not a diagnosis rather it refers to a heterogeneous group of symptoms including epigastric pain, postprandial fullness, early satiation, anorexia, belching, nausea and vomiting, upper abdominal bloating, and even heartburn and regurgitation [2]. Dyspepsia is a common medical disorder encountered not only by gastroenterologists but also by physicians in a variety of other fields. The condition is common worldwide, with 20-40% of the world's population affected depending on the definition used [3]. According to an unpublished thesis work done by Jayanta chowdhury in 2008 in BSMMU, the prevalence of dyspepsia in rural community of Bangladesh was 61.9% [4]. On the other hand, according to Pervin et al [5] the prevalence of dyspepsia among general population of Bangladesh ranges from 8-41% [5]. Patients with dyspepsia have a normal life expectancy, [6] but a markedly reduced quality of life along with emotional distress and impaired vitality [7]. Peptic ulcer disease, acute gastritis, esophagitis, hepatic, pancreatico-biliary diseases and gastrointestinal malignancies are the most important gastrointestinal causes of organic dyspepsia. Functional dyspepsia is a relapsing and remitting disorder and is the most common cause of dyspepsia. The current standard for the diagnosis of functional dyspepsia is the Rome III criteria [8]. According to ROME III criteria, functional dyspepsia must include one or more of the symptoms of a. bothersome postprandial fullness b. early satiation c. epigastric pain d. epigastric burning and no evidence of structural disease (at upper GI endoscopy) that is likely to explain the symptoms. These criteria should be present for the last 3 months with symptom onset at least 6 months prior to diagnosis [9]. Organic and functional dyspepsia cannot be reliably distinguished by symptoms only. In most cases, the cause of dyspepsia can be identified by upper GI endoscopy, a test that generally shows that less than 10% of patients with dyspepsia have a peptic ulcer, less than 1% have gastroesophageal cancer, and more than 70% have functional dyspepsia. Given that upper gastrointestinal endoscopy is associated with a relatively low rate of identification of organic disease, it is neither desirable nor realistic to perform this test in all patients with dyspepsia [8]. *H. pylori* is a slow growing micro-aerophilic, highly mobile, gram-negative spiral organism that chronically infects the stomach of more than half of the human population of the world and represents the major cause of gastroduodenal pathologies [10]. Due to the lack of satisfactory treatment in functional dyspepsia, an antibacterial therapy for those patients who have both functional dyspepsia and *H. pylori* infection may be relevant. Emerging data have shown that *H. pylori* eradication has a small but statistically significant effect on functional dyspepsia symptoms [11]. It has been calculated that *H. pylori* eradication is associated with a 10% therapeutic gain as compared to placebo, with a NNT of 14, and that symptoms improvement ultimately occurs in nearly 40% of eradicated patients [12].

International panel of clinical investigators on gastroduodenal functional disorders (Rome III) has also recommended *H. pylori* eradication in all infected patients with functional dyspepsia. They also suggested non- invasive testing followed by *H. pylori* eradication ('test and treat') in those patients with no alarm features, although many infected patients with FD may not gain symptomatic benefit [12]. Prevention of peptic ulcer onset, reduction of both cancer and lymphoma development in the stomach are other remarkable gains favoring *H. pylori* eradication in symptomatic patients [13]. At present there are no criteria to predict whether a patient with dyspeptic symptoms will respond to eradication therapy or not. But according to Asian consensus report on functional dyspepsia, where socio-economic conditions allow *H. pylori* testing and eradication should be part of the management strategy for all patients in Asia who present with dyspepsia [11]. The aim of this randomized study was to see whether the dyspeptic symptoms of *H. pylori* positive functional dyspepsia patients are improved by eradication of the organism. The other aspect of this study was to see the efficacy of Levofloxacin, Amoxicillin & Omeprazole based triple therapy in eradicating *H. pylori*.

MATERIALS AND METHODS

This double-blind parallel group randomized placebo-controlled trial was conducted in Department of Gastroenterology at Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh from March 2016 to March 2017. Signed informed consent was obtained from each patient before study enrollment and ethical approval was taken from the Institutional Review Board of the university. Their clinical history and examination findings were noted in the semi-structured data sheet. Consecutive dyspeptic patients of both sexes between the age range of 18-55 years attending the gastroenterology OPD of BSMMU in the time period of March 2016 to March 2017 were initially included in this study. Dyspepsia at least for more than 3 months with symptom onset ≥ 6 months were considered to include in the study. Functional dyspepsia was diagnosed on the basis of 'Translation and Validation of Enhanced Asian Rome 3 Questionnaires (EAR3-Q) in Bengali Language for Diagnosis of Functional Gastrointestinal Disorders' [14].

Relevant history taken along with thorough clinical examination was done to exclude possible organic causes of dyspepsia. Patients were then sent for upper GI endoscopy to exclude any macroscopic lesions. Endoscopy was done by (Olympus, Japan) 2 gastroenterologists of the department. Patients having any abnormalities in RBS, Serum Creatinine, TSH, serum electrolyte, liver function tests, plain X-ray abdomen and USG of W/A were excluded. Stool R/E was also done to exclude possible helminthiasis. Patients having no abnormalities in the above-mentioned investigations and fulfilling the diagnostic criteria of functional dyspepsia were sent for urea breath test for the diagnosis of *H. pylori* infection.

The *H. pylori* positive patients were then randomly assigned into 2 groups - Group A and Group B. Randomization was done by computer generated method. Group A patients were treated with 2 weeks anti *H. pylori* regimen containing Amoxycillin 1 gm 12 hourly, Levofloxacin 500 mg 12 hourly and Omeprazole 20 mg 12 hourly for 14 days. Group B patients were treated with placebo for same duration. Placebo were of similar size, shape, color, taste and number of medications to that of Group A drugs. The ingredient of placebo was carboxymethylellulose. The treatment regimen allocated to the 2 groups were labeled as 'Drug A' and 'Drug B' respectively. Both the patients and the investigator were blinded of the allocated treatment regimen (drug or placebo) for a particular group. Patients were instructed to report immediately for any adverse effects of

the allocated treatment regimen or deterioration of their current condition. They were asked to return with the bottle of the drugs at the end of the treatment to count & ensure compliance. Any adverse effect due to drugs was noted at the same time.

Patients of both groups were followed-up at 2 months after completion of therapy. Presence or absence of dyspepsia was determined at that time by 'Translation and Validation of Enhanced Asian Rome 3 Questionnaires(EAR3-Q) in Bengali Language for Diagnosis of Functional Gastrointestinal Disorders' [14]. Urea breath test was repeated at the same time in both groups for the presence or clearance of *H. pylori* infection [2]. Any PPI, if an individual patient was taking before the urea breath test was discontinued for at least 2 weeks before performing the test to avoid possible false negative result. Similar instruction was provided to the patients 2 months after completion of therapy to do a flawless urea breath test [2]. Drug Safety Monitoring Board of the Gastroenterology department of BSMMU closely monitored the research work during the study period.

Statistical analysis was performed by SPSS software windows version 23. The student t-test was used to compare continuous variables between the groups. Difference between categorical variables was evaluated with the chi- square test. P values less than 0.05 was considered significant.

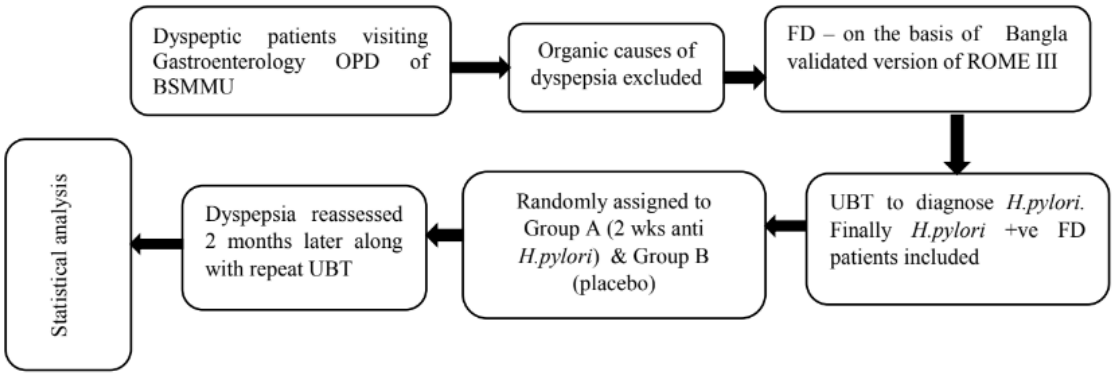

Figure-1: Flow Chart of the methodology.

RESULTS

Total 120 patients were expected to participate in the study but finally 59 '*H. pylori* positive functional dyspepsia' patients were available to analyses their outcomes. There was no statistically significant difference between the patients group receiving anti *H. pylori* therapy (group A) and placebo (group B) regarding their demographic characteristics. 7 patients from group A and 12 patients from group B were lost to follow up. So, 2 months after completion of therapy, 23 patients from group A and 17 patients from group B were available for analysis (Table-I).

Two months after completion of therapy, dyspepsia completely resolved in 13 (56.5%) patients of group A (Anti *H. pylori* therapy). No/partial improvement of dyspepsia occurred in 10 patients. On the other hand, in group B (placebo), 8(47.1%) patients had complete resolution of dyspepsia with 9(52.9%) patients having no/partial improvement 2 months after completion of therapy. No statistically significant improvement of dyspeptic symptoms occurred among the patients of group A receiving anti *H. pylori* therapy in comparison to group B patients who received placebo ($p=0.554^{)}$ therapy (Table-II).

Levofloxacin, Amoxicillin and Omeprazole based triple therapy was used to treat *H. pylori* infection in this study for group A patient. Two months after completion of therapy, *H. pylori* was eradicated in 16 (69.6%) patients of this group as evidenced by negative Urea Breath Test (UBT). On the other hand, two months after completion of therapy, 4(23.5%) patients achieved negative Urea Breath Test despite having placebo (*Figure-II*).

Among the total 40 patients of both groups who could be followed up, irrespective of their allocated treatment regimen (Drug/Placebo), total 20 (50%) patients achieved negative Urea Breath Test 2 months after completion of therapy. Among them 10 (50%) patients had complete resolution of dyspeptic symptoms. On the other hand, dyspepsia was resolved in 5 (25%) patients who did not achieve *H. pylori* eradication (Table-III). Dyspeptic symptom resolution was not significantly different between *H. pylori* eradicated and non-eradicated groups (p=0.102).

Table-I: Baseline characteristics of patients of FD treated with Anti *H.pylori* therapy and equivalent placebo.

Parameters	**Treatment group (n=23)**	**Placebo group (n=17)**
Age (years)		
Mean±SD	34.05±7.06	31.64±9.44
Range (years)	20 - 55	20 - 55
Males, n (%)	8(34.8)	7(41.2)
Females	15(65.2)	10 (58.8)
Smoker, Yes, n (%)	5(21.7)	4(23.5)

Table-II: Comparison between treatment group (group A) and placebo group (group B) based on resolution of dyspepsia at 2 months after completion of therapy.

Dyspepsia resolution status	**Group A (n=23)**		**Group B (n=17)**		**P value**
	n	**%**	**n**	**%**	
Resolved	13	56.5	8	47.1	0.554
Not resolved	10	43.5	9	52.9	

Table-III: Comparison of dyspepsia resolution between *H. pylori* eradicated and non-eradicated groupirrespective of their allocated treatment regimen (drug/placebo).

Symptom resolution	**Eradication group (n=20)**		**Non eradication group (n=20)**		**P value**
	n	%	n	%	
Resolved	10	50.0	5	25.0	0.102
Not resolved	10	50.0	15	75.0	

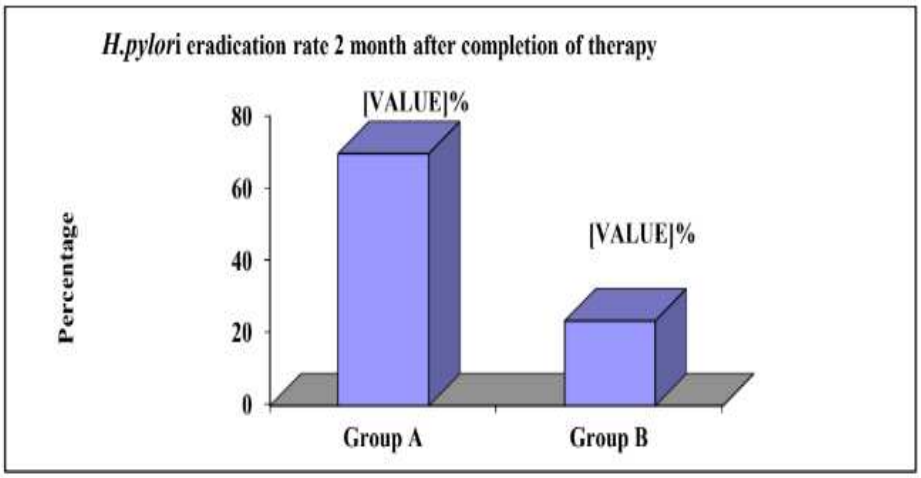

Figure-II*:* Bar diagram showing *H.pylori* eradication rate 2 month after completion of therapy (Group A took Anti *H.pylori* therapy and group B took placebo therapy).

DISCUSSION

Several studies have been carried out worldwide to assess the role of *H.pylori* eradication on functional dyspepsia with varying results. In our country, there is high prevalence of *H.pylori* infection with high recurrence rate. Tests and treat strategy is not routinely practised in Bangladesh. There is no structured guideline for eradication of *H.pylori* in functional dyspepsia patients in our clinical setting. Decisions are often made on individual basis. The main objective of this study was to see whether eradication of *H. pylori* improves the dyspeptic symptoms in *H. pylori* positive FD patients. But the results of this study revealed that dyspeptic symptom resolution does not depend upon *H.pylori* eradication status of these patients. Further evaluation is needed to identify the actual etiology of the disease. Bangla validated version of ROME III criteria for functional gastrointestinal disorders was used in this study for the diagnosis of functional dyspepsia and inclusion into the study. Similar criteria was used at the completion of therapy to see the symptom resolution and presence/absence of functional dyspepsia. So any partial improvement was not considered during assessment and analysis. After 2 months of therapy, total 20(50%) patients had *H. pylori* eradication irrespective of the allocated therapy(drug/placebo). Among these 20 patients, total 10 (50%) patients achieved symptom resolution. *H.pylori* was not eradicated in other 20(50%) patients. Among these *H.pylori* non eradicated group total 5(25%) patients had their symptom resolution. Statistically there was no significant difference in symptom resolution among those who were *H.pylori* eradicated and those who were not eradicated. A study conducted by Sodhi et al [15] also revealed that despite the eradication of *H.pylori* there was no significant symptom resolution in FD patients. Similar finding was also found in the study conducted by Talley et al [16] in which no significant difference of treatment success (defined as minimal or no dyspepsia) was found after 12 months of follow-up among those who were negative for *H pylori* (29%) and those who remained positive for *H pylori* (21%). On the contrary, a meta-analysis done by Du *et al* [17] analysing 25 RCTs with containing 5555 functional dyspepsia patients) revealed that *H. pylori* eradication therapy improves symptoms during long-term follow-up at ≥ 1 year but not during short-term follow-up at < 1 year. The study concluded that the decision to eradicate *H. pylori* in functional dyspepsia patients requires individual assessment. Levofloxacin, Amoxicillin and Omeprazole based triple

therapy was used in this study for eradication of *H.pylori*. The eradication rate of this regimen was 69.6%. According to the Maastricht III consensus report, the eradication rate should be ≥80% for any treatment regimen to be successful. But previous studies conducted in Bangladesh by using different regimens of anti *H.pylori* therapy could not achieve this level of eradication. The highest eradication rate (78%) was achieved by Ahmed et al [18] at BSMMU by using Levofloxacin, Amoxycilin and Omeprazole based triple therapy for 14 days. So a better anti H.pylori regimen should be sought for Bangladeshi patients. It has been observed in this study that, 2 months after completion of treatment, *H.pylori* was significantly more eradicated in group A(treated by levofloxacin based triple therapy) than in group B(treated by placebo) (69.6% vs 23.5%). This high eradication rate by placebo may be due to false negative urea breath test. Many similar studies in different part of the world evaluated *H.pylori* status by more than one tests (e.g. Rapid urease test, Histology). At 6 weeks, in a similar study conducted by Sodhi et al [15] the eradication rate of *H. pylori* by triple therapy and placebo group was 69.8% and 5.0% respectively. At 12 months, *H. pylori* eradication rate was 66.7% and 6.7% respectively. In that study, *H. pylori* infection was detected by rapid urease test and gastric biopsy; triple therapy consisting of Omeprazole, Clarithromycin and Amoxicillin was used. In HEROES trial (2011), one of the large clinical trial on this topic, the eradication rate at 1 year after therapy was 88.6% and 7.4% respectively in groups taking anti *H.pylori* and placebo for 10 days. *H.pylori* status was assessed by UBT and histopathology in that study. On the other hand, H.*pylori* eradication rate was relatively more in patients who took placebo in comparison to other studies of different countries. This may be due to false negative UBT report for variety of reasons. The monitoring of the patients should be more close and stringent to produce a reliable and flawless urea breath test report. More than one test (e.g. Stool Antigen test, Rapid Urease test or Culture) may also be employed to detect the infection. Symptoms were analysed irrespective of their *H.pylori* eradication status 2 months after completion of therapy in both groups receiving either anti *H.pylori* therapy or placebo. Dyspepsia resolved in 13 (56%) patients of group A (taking anti H.pylori therapy) and 8 (47%) patients of group B (taking placebo).There was no statistically significant difference regarding symptom resolution between these 2 groups. This finding is consistent with the study conducted in India by sodhi et al [15]. In that study, the symptom resolution at 1 month was 60.7% and 52.3% in the patient group taking anti *H.pylori* therapy and Placebo respectively. The same study also observed that at 1 year after therapy, the symptom resolution rate was 54.6% and 40% respectively. The difference in mean symptom score between this 2 group at 1, 3, 6, 9, and 12 months was not significant. The finding of the current study is also consistent with the randomized, double-blind, placebo-controlled study conducted by Talley et al [16] carried out on 278 *H.pylori* infected functional dyspepsia patients and followed up for 12 months. At 12 month 15% patients who took anti *H.pylori* therapy and 11% patients who took placebo had no dyspepsia. So there was no convincing evidence that eradication of *H pylori* relieves the symptoms of functional dyspepsia 12 months after treatment. On multivariate analysis, no significant correlation was found between any of the 6 selected variables (e.g. age, sex) and symptom resolution of dyspepsia in this study. In particular, the eradication of *H. pylori* infection did not correlate with the symptom resolution. In a previous study by McColl et al [19] duration of symptoms were independently related to resolution of symptoms in a multivariate analysis. The percentage of patients with resolution of symptoms decreased with increased duration of symptoms. No

significant drug adverse effect was observed in this study except few patients complaining of nausea. This single centre study had some limitations. The sample size was small. The study period was short. Functional dyspepsia was not assessed by any validated symptom scoring scale. A large number of patients (19/59, 32.2%) were lost to follow up which might have lessened the statistical power of the study. It was not possible to follow up the patients for long period of time; at least 1 year. The *H.pylori* eradication rate in placebo group was high (23.5%) which may be due to false negative urea breath test.

CONCLUSION

In conclusion, the study revealed that there is no relationship between *H.pylori* eradication (by Levofloxacin, Amoxicillin and Omeprazole regimen) and resolution of dyspeptic symptoms in patients with functional dyspepsia. A more potent anti *H.pylori* regimen in comparison to Levofloxacin, Amoxicillin and Omeprazole based triple therapy should be searched.

CONFLICT OF INTEREST: None.

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