

Original Article

A study on healing of peptic ulcer disease after eradication of helicobacter pylori infection

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Abstract

There is intimate connection between peptic ulcer & *Helicobacter pylori* infection. But some uncertainties still surround the relationship between status of *H. pylori* infection and extent & time required for ulcer healing. This prospective observational study was carried out in the department of Gastroenterology, BSMMU, Dhaka from January 2007 to January 2008 to determine whether the successful eradication of *H. pylori* leads to adequate ulcer healing. To see the pattern of endoscopic findings in patients still having *H. pylori* infection after standard triple therapy for *H. pylori* were also a objective. Eighty nine consecutive patients, aged 15-60 years and of both genders, coming to the gastroenterology outpatient department with the symptoms suggestive of peptic ulcer disease and dyspepsia were included and *H. pylori* status was defined as positive if both rapid urease test & histopathology were positive. As found in this study, *H. pylori* was associated with 90% of duodenal ulcers and 80% of gastric ulcers. *H. pylori* eradication rate was 69%. Healing rate of duodenal ulcer and gastric ulcer after standard triple therapy for 14 days were 80% and 78% respectively. Adequate ulcer healing was achieved in this study despite relatively low eradication rate. Follow-up for additional period is required for recurrence of ulcer in

patients whose peptic ulcer disease had resolved but could not attain *H. pylori* eradication and *H. pylori* eradicated patients who are still having ulcer at endoscopy.

Key words : Peptic ulcer disease, *H. pylori*, triple therapy

Introduction

The term peptic ulcer disease is used broadly to include ulcerations and erosions in the stomach and duodenum from a number of causes. Regardless of the inciting agent, the role of acid and pepsin in the genesis and perpetuation of mucosal injury remains a unifying aspect of the pathogenesis of peptic ulcer disease.¹ Development of H2-receptor antagonist drugs and the subsequent development of proton pump inhibitor drugs led to major changes in the management of peptic ulcer disease but the first isolation of *Helicobacter pylori* in 1982 by Marshall and Warren has revolutionized the pathophysiology and concept of treatment of peptic ulcer disease and also transformed it from a chronic recurrent disease to a curable one.²⁻⁴

Helicobacter pylori is a slow growing micro-aerophilic, highly motile, gram negative spiral bacterial organism that chronically infects the stomach of more than half of the human population and represents the major cause of gastroduodenal pathologies.⁵ There are considerable differences in *H. pylori* prevalence between high-and low-income countries and ranges from less than 10% to more than 80%.⁶ The prevalence of *H. pylori* infection has diminished in developed world due to improved sanitation and living conditions but its prevalence is very high in Bangladesh. About 92% have been found to be seropositive for *H. pylori* antibody in a study carried out on adult male by Ahmed et al.⁷ In another study, conducted on Bangladeshi children by ICDDR scientists have shown that, 60% are infected by the age of three months and 80% are infected by three years of age.⁸

Both gastric and duodenal ulcer diseases are strongly related to *H. pylori*. In initial reports from all over the world in the first decade after the discovery of *H. pylori*, approximately 95% of duodenal ulcers and 85% of gastric ulcer occur in the presence of *H. pylori* infection.^{9,10} Other studies have found that 90% and 70% of cases of duodenal ulcer and gastric ulcer respectively were attributed to *H. pylori* infection.¹¹ Several cohort studies estimated that the lifetime risk for ulcer disease in

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H. pylori-positive subjects is 3 to 10 times higher than in H. pylori-negative subjects and that 10 to 15% of H. pylori-positive subjects developed ulcer disease during long-term follow-up. These data came from studies in developed areas of the world.^{9,10,12} For developing countries, an endoscopic survey showed a point prevalence of 11.9% duodenal ulcer and 3.5% gastric ulcer among individuals above the age of 15 years in Bangladesh.¹³ Despite the strength of this association, there is argument based on the fact that H. pylori infection is common in normal individuals, and that the prevalence of duodenal ulcer is far lower than that of H. pylori infection. In most patients H. pylori does not cause symptoms and the infection often persists without any clinically evident disease. However, only 10–20% of H. pylori-infected patients develop severe diseases during their lifetime including peptic ulcer disease.^{9,10}

Introduction of H. pylori eradication regimens have proved that eradication of this bacterium strongly reduce the risk of recurrent ulcer disease.^{12,14-17} In earlier days, this disease was a chronic, recurrent disorder with high morbidity, frequently requiring acid-suppressive maintenance therapy or surgery. Approximately 50% of patients with H. pylori-associated peptic ulcer disease suffered ulcer recurrence within 1 year. Eradication of H. pylori dramatically changes the natural course of ulcer disease and almost completely prevents ulcer recurrence.^{9,10,12} A meta-analysis including 24 randomized controlled trials and randomized comparative trials including 2,102 patients with PUD revealed that the 12-month ulcer remission rate was 97% for gastric ulcer, and 98% for duodenal ulcer in patients successfully eradicated of H. pylori infection, compared with 61% for gastric ulcer and 65% for duodenal ulcer in those with persistent infection.^{18,19}

While controversy continues regarding the place of treatment for H. pylori infection in non-ulcer dyspepsia and gastric cancer, the role of eradication therapy in the majority of patients with peptic ulcer disease is now firmly established. Recent studies have confirmed the low rate of duodenal ulcer recurrence following successful eradication and established a similar beneficial effect in gastric ulcer disease.^{20,21,22}

But some uncertainties still surround the relationship between status of H. pylori infection and ulcer healing. This study was carried out to determine whether the successful eradication of H. pylori leads to adequate ulcer healing. To see the pattern of endoscopic findings in patients still having H. pylori infection after standard triple therapy for H. pylori was also a objective.

Methods

This prospective observational study was carried out in the department of Gastroenterology, BSMMU, Dhaka from January 2007 to January 2008. Consecutive patients, aged 15-60 years and of both genders, coming to the gastroenterology outpatient department with the symptoms suggestive of peptic ulcer disease and dyspepsia i.e. upper abdominal pain, anorexia, vomiting, bloating, belching etc were initially enrolled for the study. Regular user of NSAID and steroid, patients with complicated peptic ulcer including active bleeding, perforation & pyloric stenosis, co-existing gastric carcinoma, pregnant & lactating mothers were excluded from the study. Patients unwilling or unable to undergo or having contraindication for upper GI endoscopy were also excluded from the study.

Their clinical history were noted and referred for upper GI endoscopy. Patients receiving proton pump inhibitors, H₂ receptor blocker, and antibiotic or bismuth compounds were advised to come for endoscopy after stopping the above-mentioned drugs for at least two weeks to avoid false positive/false negative result in rapid urease test. Selected patients underwent upper GI endoscopy in the department of Gastroenterology, BSMMU for possible findings of peptic ulcer disease. A total of 89 patients with endoscopic findings of peptic ulcer disease were finally enrolled for the study.

Ulcer was diagnosed at endoscopy, in the stomach or duodenum, when there was a mucosal break of diameter 5 mm or larger, covered with fibrin. Mucosal breaks smaller than 5 mm were considered as erosions.^{1,23}

Total four biopsy specimens, three from antrum, one from corpus were collected from the stomach of the patients who were found to have peptic ulcer disease. Endoscope and biopsy forceps were disinfected using 2% glutaraldehyde. Instruments were immersed in the solution for 15 minutes. Side channels were rinsed.

Rapid urease tests (RUT) were performed instantaneously with one of the four antral specimens using commercially available kit Pronto Labor^R at diagnosis of peptic ulcer disease. Results were available at the end of few minutes to 24 hours and noted in the data sheet. Three biopsy specimens, two from antrum and one from corpus were fixed in 10% buffered formalin and sent for histopathology, to be examined by an experienced histopathologist. They were stained with modified giemsa stain. The presence of spiral organism in any of the slides were considered positive for H. pylori.

H. pylori status was defined as positive if both RUT & histopathology were positive during diagnosis before treatment. For the confirmation of eradication, H. pylori status was considered to be negative when both these tests were negative. H.pylori positive patients were treated with 14 days course of triple therapy for H.pylori and were followed-up.

Patients were followed-up for compliance of drugs and side effects. Follow-up endoscopies were performed at least four weeks after completion of therapy. At least two weeks period, free of any proton pump inhibitors, H2 receptor blocker or antibiotics prior to follow up endoscopy were ensured. Improvement in the endoscopy findings were noted and compared with pre-treatment findings. Four biopsy specimens were collected from antrum and body of the stomach for rapid urease test and histopathology

Written informed written consents were obtained. The study protocol was approved by the ethical committee of BSMMU. Statistical analyses were done using SPSS.

Results

On the basis of findings suggestive of peptic ulcer disease at endoscopy, 89 patients were included in the study. Of them, 67 were male and 22 were female with a male female ratio of 3:1. Age of the patients ranged from 21 to 60 years with a mean age of 38.08 years. The patients were mostly of average socio-economic condition (55 %). However, 27 % and 18 % of the patients belonged to low and high socio-economic conditions respectively.

Table-II: Endoscopic findings at enrolment

Endoscopic findings	Number of patients	H.pylori positive	H.pylori negative
Antral erosion with deformed bulb	31	26	5
Duodenal ulcer	19	18	1
Gastric ulcer	10	8	2
Antral erosion	18	17	1
Non-erosive gastritis	11	9	2
Total	89	78	11

Among these 78 H. pylori positive patients, 18 patients had duodenal ulcer and 8 had gastric ulcers. Antral erosion with deformed bulb, antral erosion, non-erosive gastritis were found in 26, 17 and 9 patients respectively. (Table-III)

78 H.pylori status positive patients were treated with 14 days course of triple therapy for H.pylori and were followed-up. In this study, half of the patients were treated with two weeks regimen of Omeprazole (20 mg, bd),

Among 89 patients, 79(88.76%) were positive and 10(11.23%) were negative for rapid urease test. H.pylori was detected in the biopsy samples of 80 (89.88%) patients and the rest (9) were histologically negative for H.pylori. 78 patients were positive for both rapid urease test and histopathology. These 78 patients were labeled as H.pylori status positive in the study, treated with anti-H.pylori therapy and subsequently followed-up. The remaining 11 patients were considered to be negative for Hpylori. (Table-I)

Table-I: H.pylori status before treatment

H.pylori Status		Number of patients	
Positive (both RUT and histopathology)		78 (87.64%)	
	RUT negative and histopathology negative	8	
Negative	RUT negative but histopathology positive	2	11 (12.36%)
	RUT positive but histopathology negative	1	

On upper GI endoscopy, among 89 patients who were enrolled for the study, 19 patients had duodenal ulcer and 10 had gastric ulcer. Antral erosion with deformed bulb, antral erosion, non-erosive gastritis were found in 31, 18 and 11 patients respectively. Among 19 duodenal ulcer patients, 18 (95%) were positive for H.pylori. On the other hand, 8(80%) were positive for H.pylori among 10 gastric ulcer patients.(Table-II)

Table-III: Endoscopic findings H. pylori positive patients before treatment

Endoscopic findings	Number of patients
Antral erosion with deformed bulb	26
Duodenal ulcer	18
Gastric ulcers	8
Antral erosion	17
Non-erosive gastritis	9
Total	78

Amoxicillin (1 gm, bd) and Metronidazole (400 mg, bd). For rest of the patients, two weeks regimen of Omeprazole (20 mg, bd), Amoxicillin (1 gm, bd) and levofloxacin (500 mg, od) were given. Fifty two patients returned for follow-up at least four weeks after completion of 14 days triple therapy.

Considering the endoscopic findings of the 52 patients who returned for follow-up, 15 patients had duodenalulcer and 9 had gastric ulcer. Antral erosion with

Table-IV: Endoscopic findings H. pylori positive patients before treatment who ultimately returned for

Endoscopic findings	Number of patients
Antral erosion with deformed bulb	13
Duodenal ulcer	15
Gastric ulcers	9
Antral erosion	9
Non-erosive gastritis	6
Total	52

follow-up deformed bulb, antral erosion, non-erosive gastritis were found in 13, 9 and 6 patients respectively. (Table-IV)

On upper GI endoscopy of 52 patients who returned for follow-up after completion of triple therapy, 38 patients were found to be normal. Four patients had duodenal ulcer and 2 had gastric ulcers, 2 had antral erosion with deformed bulb and 7 patients had only deformed bulb. On the basis of rapid urease test and histopathology, 16 patients were found still to be positive for H.pylori four weeks after completion of 14 days triple therapy. So, among 52 patients who returned for follow-up, eradication of H.pylori was observed in 36 (69%). There was eradication failure for the rest (16, 31%) of the patients.

Considering the H.pylori status of the individual groups of patients based on endoscopic findings, 13 out of 38 endoscopically normal patients were still positive for H.pylori after eradication therapy. This number was 1 out of 3 patients of duodenal ulcer & 1 out of 2 patients of gastric ulcer. Among the 2 patients having antral erosion with deformed bulb after eradication therapy, 1 patient was still positive for H.pylori. (Table-V)

Table-V: Endoscopic findings H. pylori positive patients 4 weeks after completion of triple therapy

Endoscopic findings	Number of patients	H.pylori eradicated	Number of patients still positive for H.pylori
Normal	38	25	13
Duodenal ulcer	3	2	1
Gastric ulcers	2	1	1
Deformed bulb	7	7	
Antral erosion with deformed bulb	2	1	1
Total	52	36 (69%)	16 (31%)

Discussion

Mean age of the patients in this study was 38 years, males were predominant (75%) and most of the patients were from middle socioeconomic class (55%). These findings are more or less consistent with other studies in our country carried out on patients of peptic ulcer disease due to helicobacter pylori.^{7,8,24-26}

According to Maastricht III consensus conference – 2005, diagnosis is confirmed and treatment can be started if rapid urease test is positive.¹⁰ In the current study H.pylori status were considered to be positive if both rapid urease test and histopathology were positive.

The prevalence of H.pylori among endoscopically proven peptic ulcer disease in this study was 87.64%. Among the

duodenal ulcer patients, 95% was positive for H.pylori. It was 80% for gastric ulcer patients. Prevalence of Helicobacter pylori in asymptomatic population of Bangladesh, as studied by Ahmad et al in a pilot serological study, was 92%.⁷ Approximately 95% of duodenal ulcers and 85% of gastric ulcers usually occur in the presence of H. pylori infection.^{9,10} H. pylori infection was associated with 92% of duodenal ulcer and 90 % of gastric ulcer respectively in a study by Mokhlesur Rahman et al.²⁶ It was 64% for duodenal ulcers in another study by Morshed et al.²⁴ Our study also revealed, in accordance with other studies, similar association of H.pylori with duodenal and gastric ulcer.

H.pylori eradication rate in this study was 69%. According to Maastricht III Consensus Report, H.pylori

eradication should be more than 80% for any eradication regimen to be effective.¹⁰ But most of published studies in our country including this one failed to attain eradication rate more than 70%²⁴⁻²⁶

Healing rate of duodenal ulcer and gastric ulcer were 80% and 78% respectively in this study. Pooled data show that eradication therapy heals > 90% of duodenal ulcers and >85% of gastric ulcers, while individual studies repeatedly confirm that it is more effective at healing ulcers than conventional treatment with anti-secretory drugs.²⁰ In a study by Suzuki et al, the eradication rate of *H. pylori* was 84% in the gastric ulcer group and 89% in the duodenal ulcer group.²⁷ Mokhesur Rahman et al, in a Bangladeshi study on 200 patients with gastric/duodenal ulcer, found that the eradication rate after 8 weeks of anti helicobacter therapy were 86.5% for duodenal ulcer and 84.6% for gastric ulcer.²⁶ Ulcer healing rate was 75% in another study by MT Rahman et al.²⁵

There was no significant difference between the *H. pylori*-eradicated and *H. pylori*-uneradicated groups with regard to age, sex, location of gastric ulcer, size of ulcer, and stage of ulcer in the gastric ulcer patients. In the duodenal ulcer patients, there was also no significant difference between the *H. pylori*-eradicated and uneradicated cases.

An intimate connection that exists between peptic ulcer & *H. pylori* status; and causal link between the eradication of *H. pylori* and healing of peptic ulcers is well known. But adequate ulcer healing was achieved in this study despite relatively low eradication rate. Follow-up for additional period for recurrence of ulcer should have been done for patients whose peptic ulcer disease had resolved but could not attain *H. pylori* eradication. Prolong follow-up with upper GI endoscopy should have also been done for *H. pylori* eradicated duodenal ulcer & gastric ulcer patients to see whether healing occurs with additional PPI therapy.

It is obvious from this study that suitable eradication regimen of appropriate duration should be formulated to attain higher *H. pylori* eradication. Culture and urea breath test should be included to identify *H. pylori* infection. Long-term follow-up with large sample size should be arranged to study ulcer healing and recurrence specially for endoscopically normal uneradicated patients and also for duodenal/gastric ulcer patients who have attained eradication with standard therapy.

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