Original Article

Comparison of Efficacy of Four Different Helicobacter Pylori Eradication Regimens among Helicobacter Pylori Positive Peptic Ulcer Disease Patients

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ABSTRACT:

Introduction*: Helicobacter pylori has high prevalence in Bangladesh and the eradication rates of helicobacter pylori varies among different antibiotic combinations. It's not known which regimen is most effective. In this study effort was made to find out the efficacy of different drug regimens against helicobacter pylori in peptic ulcer disease patients.* ***Methods****: This is a prospective, open-label randomized study, done in the department of Gastroenterology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, from March 2013 to March 2014. A total of 112 patients underwent index endoscopy. Among them 52 patients were diagnosed as cases of peptic ulcer disease having Helicobacter Pylori infection by rapid urease test (RUT) and/or polymerase chain reaction (PCR). These 52 patients were randomized into 4 groups to receive EAT (esomeprazole+amoxicillin+tetracycline), EAL (esomeprazole+amoxicillin+levofloxacin), ETL (esomeprazole+tetracycline+levofloxacin) and ECA (esomeprazole+clarithromycin +amoxicillin) for 14 days. Follow up endoscopy and repeat RUT/PCR tests for helicobacter pylori was done after 2 months. Patients are declared eradicated who became negative for helicobacter pylori by both methods.* ***Results****: In total 47 patients presented at two months follow up, which included 13 patients in the EAT group, 11 in the EAL group, 11 in the ETL group and 12 in the ECA group. 72.7% of ETL group were cured and they were followed by EAL (63.6%). The cure rate for EAT and ECA stood at 53.8% and 50% respectively. Chi-square value is 2.33 and p value is 0.5 which is not significant. The eradication rates for* H. pylori *infection by intention-to-treat analysis for EAT was 53.8% (7/13), ECA 46.2% (6/13), EAL 53.8% (7/13) and ETL 61.5% (8/13) and P value is 0.94, which is statistically non-significant.* ***Conclusions****: In this study each of the regimens fell considerably short of the 80% intention–to-treat eradication rate. On the other hand, present study results did not bring any conclusion regarding which treatment regimen was superior or in other*

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words there was no definitive statistically significant helicobacter pylori treatment regimen which was superior to others.
***Keywords**: Helicobacter pylori, eradication rates, antibiotics and helicobacter pylori, rapid urease test*

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INTRODUCTION:

Helicobacter pylori, a gram-negative bacteria, found in half of the population of the world, was first isolated by Warren and Marshall in 1983.[1] A study conducted in Bangladesh had shown that 60% of the children were infected by the age of 3 months and 80% were infected by the 3 years of age.[2] On the other hand, about 92% of the adults had been found to be seropositive for H. pylori in Bangladesh.[3]

In 1994, Helicobacter pylori was classified as a type 1 carcinogen by international agency for research on cancer.[4] It is the primary cause of peptic ulcer disease, gastric carcinoma and mucosa-associated lymphoid tissue lymphomas.[5] Eradication of Helicobacter pylori has been shown to prevent the recurrence of peptic ulcer disease and reverse gastric atrophy. It's a precursor of gastric cancer and some localized low-grade gastric lymphomas.[6] Therefore, a safe and effective eradication regimen for this infection is imperative. [7]

The eradication rate was between 30-74% in most studies of Bangladesh [8,9,10,11]. In a study done in Bangladesh, H pylori eradication rate with Metronidazole, Amoxicillin and Omeprazole group was 58.3% compared to 78.6% with Levofloxacin, Amoxicillin and Omeprazole group.[11] In another study, antibiotic resistance to Helicobacter pylori was seen in Bangladesh and the result showed 77.5%, 15%, 10% and 6.6% of isolates were resistance to metronidazole, tetracycline, clarithromycin and amoxicillin respectively.[12]

Levofloxacin has proved to be very effective against Helicobacter pylori infection in several trials in different countries.[13,14,16] Levofloxacin may be used as a substitute for Clarithromycin in either a standard triple or sequential regimen. A large study comparing the antibiotics in either regimen shows a clear advantage to Levofloxacin in both combinations. Per-protocol cure rates for triple therapy were 66% for Omeprazole–Clarithromycin–Amoxicillin compared with 83% for Omeprazole–Levofloxacin–Amoxicillin and 81% for Omeprazole–Amoxicillin–Clarithromycin–Metronidazole vs. 85% for Omeprazole–Amoxicillin–Levofloxacin–Metronidazole, with no difference in compliance rates or adverse events.[15] The literature from Asia also seems to support Levofloxacin as a good alternative first-line therapy. A study on a triple regimen showed per-protocol eradication rates of 78% for standard Clarithromycin-containing therapies compared with 83% for a Levofloxacin-based regimen.[16] Another study from the Middle East looked at whether combining Clarithromycin and Levofloxacin in the same regimen could be effective and found a

90% eradication rate for a combined Clarithromycin–Levofloxacin–
Esomeprazole regimen compared with 85% for Levofloxacin–Amoxicillin–Esomeprazole and 79% for Clarithromycin–Amoxicillin–Esomeprazole with no difference in the incidence or severity of adverse events.[17] In our country, Ahmed et al conducted the study and found eradication of Helicobacter pylori was 78.6% with levofloxacin, amoxicillin and omeprazole therapy.[11]

In Bangladesh several trials had been conducted in the past with different regimens to treat Helicobacter pylori. In most of the studies in Bangladesh eradication rate for Helicobacter pylori was between 30% to 60%. [9,10] As there is still lack of effective treatment regimen for Helicobater pylori in Bangladesh, it is now very much required to find appropriate drug regimen against the Helicobacter pylori for our population. In our study, we used four different drug regimens against Helicobacter pylori. The regimens were as follows- EAT (esomeprazole +amoxicillin +tetracycline), EAL (esomeprazole+ amoxicillin+levofloxacin), ETL (esomeprazole +tetracycline + levofloxacin) and ECA (esomeprazole+ clarithromycin+amoxicillin). These drugs would be given for 14 days. In the present study effort was made to find out the efficacy of the above mentioned drug regimens to eradicate the Helicobacter pylori in peptic ulcer disease patients.

METHODS AND MATERIALS:

This was a prospective, open-label randomized study done in the department of Gastroenterology, BSMMU, Shahbag, Dhaka, from March 2013 to March 2014, among the patients who had undergone an upper GIT endoscopy for dyspeptic symptoms. Inclusion criteria were, age between 18 to 69 years, Helicobacter pylori infected (positive by rapid urease test or PCR) and evidence of gastric and/or duodenal erosions and/or ulcer in upper GIT endoscopy. Exclusion criteria were, previous *H. pylori* eradication treatment or use of proton pump inhibitors, H 2 -receptor antagonists, bismuth preparations, and antibiotics in the previous 2 weeks, concomitant anticoagulant, nonsteroidal anti-inflammatory drugs, or ketoconazole use previous surgery of the esophagus and / or the upper gastrointestinal tract (with the exception of appendectomy, polypectomy, and cholecystectomy), severe or unstable cardiovascular, pulmonary, or endocrine disease, clinically significant renal or hepatic disease or dysfunction, hematological disorders or any other clinically significant medical condition that could increase risk, malignant disease of any kind during the previous 5 years, drug, alcohol, or medication abuse within the past year, severe psychiatric or neurological disorders; and pregnant or nursing women.

An estimated sample size of 76 subjects in each therapeutic group would give an 80% power to detect a difference of 15% for the eradication rate among each study group. With a 10% drop out rate we have to recruit at least 84 patients for each group. (Calculated by Power and precision-4, statistical software). Due to time constraints

and budget limitations, study groups were limited to 10 patients for each group.

Purposive type of non-probability sampling was done. History taking and clinical examination were done before endoscopy of upper GIT. Upper gastrointestinal endoscopy was done using a standard forward viewing endoscope.

In this study, an ulcer in the gastrointestinal tract was defined as a break in the lining of mucosa with appreciable depth at endoscopy and erosions were breaks in the surface epithelium that did not have perceptible depth. The term peptic ulcer disease would be broadly used to include both the ulceration and erosion in the stomach and duodenum.

Rapid urease test and/or PCR were done in all patients. During endoscopy, two gastric biopsies were collected from each patient from the antrum and the body. With the biopsy sample, rapid urease test (CLO test) was done. PCR were preformed from two pieces of gastric tissue obtained (from body and antrum) on the same day.

Therapeutic regimen:

13 patients were included in each group.

Group A: treated with EAT (Esomeprazole 20 mg twice daily +Amoxicillin 1 g twice daily, Tetracycline 1000 mg twice daily) for 14 days.

Group B: treated with EAL (Esomeprazole 20 mg twice daily +Amoxicillin 1 g twice daily, Levofloxacin 500 mg once daily) for 14 days.

Group C: treated with ETL (Esomeprazole 20 mg twice daily +Tetracycline 1 g twice daily, Levofloxacin 500 mg once daily for 14 days).

Group D: treated with ECA (Esomeprazole 20 mg twice daily +Clarithromycin 500 mg twice daily, amoxicillin 1 gm twice daily) for 14 days.

All the patients were randomized to receive one of the four treatment regimens. The primary outcome of the study was the eradication of H. pylori infection. Follow-up was done 8 weeks after giving the first treatment.

At the cessation of Helicobacter pylori eradication therapy all anti-secretory agents and antibiotics were discontinued and rapid urease test and PCR for Helicobacter pylori were performed at 8 weeks after the initial therapy to evaluate for complete eradication. Compliance and side effects of the regimens were assessed. Compliance was defined as consumption of > 90% of the prescribed drugs and was determined by pill counts.

All “adverse effects” were assessed by the questionnaire. The adverse effects included anorexia, nausea, taste disturbance, dizziness, abdominal pain, diarrhea, headache, and skin eruption.

Patient was labeled as Helicobacter pylori eradicated if in follow up visit patient became negative for helicobacter pylori by both PCR and RUT.

All data was recorded on standard data sheet. The analysis was performed with the

SPSS software. Differences between dichotomous variables were evaluated with the chi square test. *P* values less than 0.05 was considered significant.

The eradication rate was evaluated for each drug regimen by the per-protocol (PP) analysis based on the number of patients that completed the study, and by an intention-to-treat (ITT) analysis that took into account all of the patients, including those who dropped out because of severe adverse effects, those who had poor drug compliance, and those who were lost to follow-up.

RESULTS:

A total of 112 patients were underwent index endoscopy. Of them 52 patients were diagnosed as a case of peptic ulcer disease having Helicobacter Pylori infection by rapid urease test and/or PCR. These 52 patients were randomized into 4 goups to receive EAT (esomeprazole +amoxicillin +tetracycline), EAL (esomeprazole + amoxicillin +levofloxacin), ETL (esomeprazole +tetracycline +levofloxacin) and ECA (esomeprazole + clarithromycin +amoxicillin).

In total 47 patients presented at two months follow up, which included 13 patients in the EAT group, 11 patients in the EAL group, 11 patients in the ETL group and 12 patients in the EAC group. The mean age was found 36.95 ±8.43 years. The highest number of patients were seen in 30-49 years' age group. There were 26 males and 21 females. The ratio of male to female participants in the study was 1.2:1.

Table I: Percentage of patients became RUT negative following different treatment regimens.

	Total RUT positive before treatment	Total RUT negative after treatment	Percentage of RUT negative after treatment	P value
EAT	11	7	63.6	0.90
ECA	12	6	50	NS
EAL	10	9	90	
ETL	9	9	100	
	42	31		

RUT- Rapid Urease test, NS- Not significant

Table II: Percentage of patients who became PCR negative

	Total PCR positive before treatment	Total PCR negative after treatment	Percentage of PCR negative after treatment	P value
EAT	9	4	44.4	0.99
ECA	6	3	50	NS
EAL	8	4	50	

ETL	5	2	40	
	28	13		

PCR- Polymerase chain reaction, NS- Not significant

Table III: Per protocol analysis: Comparison of eradication (RUT& PCR both negative) of H pylori following different types of treatment.

	EAT	ECA	EAL	ETL	Chi square test P value
Eradication	7 (53.8%)	6 (50%)	7(63.6%)	8 (72.7%)	χ^2= 2.33
Not eradicated	6 (46.1%)	6 (50%)	4(36.3%)	3 (27.2%)	P-Value =0.50 (NS at p < 0.05)
Total	13	12	11	11	

Table IV: Intention to treat: Comparison of eradication (RUT&PCR both negative) of H pylori following different types of treatment.

	EAT	ECA	EAL	ETL	Chi square test P value
Eradication	7 (53.8%)	6 (46.2%)	7 (53.8%)	8 ((61.5%)	χ^2= 0.35
Not eradicated	6 (46.1%)	7 (53.8%)	6 (46.2%)	5 (38.5%)	P-Value = 0.94 (NS at p < 0.05)
Total	13	13	13	13	

Table IV shows distribution of the comparison of eradication following different types of treatment of H. pylori positive cases. Intension to treat was done to calculate the study subjects who did not appear in the follow up. The eradication rates for *H. pylori* infection by intention-to-treat (ITT) analysis for EAT was 53.8% (7/13), ECA 46.2% (6/13), EAL 53.8% (7/13) and ETL 61.5% (8/13) and P value was 0.94 which was non-significant at <0.05 level.

DISCUSSION:

H. pylori has been identified as the most important risk factor for peptic ulcer disease. [18.19] However, the choice of the optimal regimen for H. Pylori eradication is debated.[20] The efficacy of standard triple therapy, using amoxicillin, clarithromycin and omeprazole varies from 76% and 90%.[21] But the emergence of resistance of the organism to clarithromycin has urged the researchers to look for alternatives to standard triple therapy.

A total of 52 patients were included in the study but after drop out of 5 patients 47 patients were included in the per protocol analysis. Age range was between 20 to 69 years. It was observed that the majority, 19 patients were from 30 to 39 years, whereas 1 patient was from 60 to 69 group. The mean age was found 36.95 ±8.43years. However, in another study by Ahmed et al the mean

age for H. Pylori infection was 30.33 years in Bangladesh.[22] Among the 42 patients in the study, majority (23, 54.8%) patients were male and 19(45.2%) patients were female.

In current study, according to the per protocol analysis EAT was given to 13 patients, ECA was given to 12 patients, EAL and ETL both were given to 11 patients.

However, RUT of the studied patients before treatment was positive among 42 patients. Among 42 positive cases of RUT 31 cases became negative (73.8%) and 11 were still positive after the treatment.

On the other hand, among the 47 patients who came for follow up, 28 patients were initially PCR positive for H. Pylori and negative cases were 18. Among the 28 positive cases 13 (46.42%) cases ultimately became PCR negative whereas 15 patients (53.57%) still remained PCR positive.

There was wide difference (73.8 % versus 46.42%) between the percentage of the patients who became RUT and PCR negative after eradication therapy. In a study done in India in 2014, also showed a wide difference of post treatment output of PCR and RUT after giving H. pylori therapy as RUT positivity dropped from 81.8% to 12% after therapy whereas the value for the positive PCR test dropped from 100% positivity to 92%.[23]

The eradication rate for H. Pylori infection by per protocol analysis versus intention to treat analysis for EAT group was 53.8% (7/13) versus 53.8% (7/13), ECA group was 50% (6/12) versus 46.2% (6/13), EAL group was 63.6% (7/11) versus 53.8% (7/13) and for ETL group was 72.7% (8/11) versus 61.5% (8/13). However, Gisbert et al, (2007) studied the efficacy of Levofloxacin based therapy as the first line therapy for H. Pylori and found eradication rates of 85% under per protocol analysis.[24] On the contrary, clarithromycin based therapy for eradication of H. Pylori showed mixed picture as the eradication rates varied widely (25% to 60%).[25,26] In our country, Ahmed et al, conducted the study and found eradication of Helicobacter pylori was 78.6% with levofloxacin, amoxicillin and omeprazole therapy.[11] On the other hand, in 2004 Nahar et al, had done the culture sensitivity for H .pylori in Bangladesh and found 90% H .pylori was sensitive to clarithromycin, 85% was sensitive to tetracycline and 93.4% was sensitive to amoxicillin.[12]

Nevertheless, in the current study each of the regimens fell considerably short of the 80% intention–to-treat eradication rate that is considered the minimal acceptable levels as recommended in the Maastricht guidelines. So it appears that adequate eradication rate was not achieved by any of the four regimens namely- EAT, EAL, ETL and ECA though ETL groups reached highest percentage of H. pylori eradication. But statistically, among the four anti Helicobacter regimens used in the study no drug group was superior to each other as Chi square value was 2.33 and P value was 0.5 for per protocol analysis and chi square and P value was 0.35 and 0.94 for intention to treat analysis. So the study result did not bring any conclusion regarding which

treatment regimen was statistically superior to each other.

CONCLUSION:

Unlike developed countries, Helicobacter pylori eradication therapy for peptic ulcer disease in Bangladesh poses a problem because of lower rates of eradication. The present study also did not show a satisfactory eradication rate and no regimen used in this was proved to be more effective than other. The principal reasons may be due to small sample size and inappropriate antibiotic usage leading to emergence of new drug resistance in the community. However other factors like bioavailability of drugs, bacterial virulence factor and host factors may be the possible causes of lower eradication rates.

We recommend, further study including large number of study population, encouraging the patients for drug compliance and pretreatment microbial culture sensitivity to drugs may be done for appropriate antibiotics.

The **s**ample size was small. Pretreatment microbial sensitivity was not seen in the study. And endoscopic findings were not homogenous.

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