

COMPARATIVE STUDY BETWEEN METRONIDAZOLE, AMOXYCILIN, OMEPRAZOLE BASED THERAPY AND LEVOFLOXACIN, AMOXYCILIN, OMEPRAZOLE BASED THERAPY FOR HELICOBACTER PYLORI ERADICATION IN PEPTIC ULCER DISEASE

Ershad Uddin Ahmed¹ Razibul Alam² Fakhru Alam³ Chanchal Kumar Ghosh⁴ Subash Kanti Dey⁵ Hasan Masud⁶
Dewan Saifuddin Ahmed⁶ MMR Bhuiyan⁶ Abdur Rahim Miah⁶ Projesh Kumar Roy⁷ A S M A Raihan⁷

Abstract

Eradication should be the treatment of H. Pylori associated Peptic ulcer disease. But attempts at eradication in Bangladesh with different regimens have shown poor results. However, in Bangladesh there is no study with regimen containing Levofloxacin which has shown to be effective in several trials in different countries. So, this study was designed to find out the comparative efficacy of Levofloxacin 500 mg once daily plus amoxicillin 1 gm twice daily and Omeprazole 20 mg twice daily for 14 days (LAO) with Metronidazole 400 mg twice daily. Amoxicillin 1 gm twice daily and Omeprazole 20 mg twice daily for 14 days (MAO) for the eradication of H. Pylori in peptic ulcer disease patients in Bangladesh. This study was carried out in the Department of Gastroenterology, BSMMU, Dhaka. Seventy-eight H. pylori positive patients with endoscopically proven peptic ulcer were included in this study. 52 out of 78 patients completed the study. Of them H. Pylori was eradicated in 58.3% patients in MAO group and 78.6% patients in LAO group. Levofloxacin group had better H. Pylori eradication than Metronidazole group but difference in eradication between two groups was not statistically significant. The eradication rate found in this study parallels with the rates of most of the previous studies in Bangladesh but the rate is much lower than

those in developed countries.

Introduction

Peptic ulcer disease has been one of the major causes of morbidity for more than a century. The prevalence of duodenal ulcer and gastric ulcer was estimated to be 11.98% and 3.58% respectively in Bangladesh, which are much higher than in western countries¹. Peptic ulcer is the commonest disease associated with H. pylori infection. Among adults, about 92% have been found to be seropositive for H. Pylori antibody in our country². Eradication of H. Pylori in infected persons allow ulcer to heal and greatly reduces the chance of recurrence³. Proton pump inhibitor (PPI)-based triple therapy has been used as first-line treatment of choice for over a decade⁴. A combination of PPI 20mg, Clarithromycin 500 mg, and Amoxicillin 1 g or Metronidazole 400 or 500 mg, all given twice a day, is still recommended by the European Helicobacter Study Group⁴. Studies in Bangladesh have largely shown a low eradication rates (30-64%) using different H. Pylori eradication regimens and a higher rates of reinfection^{5,6,7,8}. Metronidazole resistance was found to be very high⁹. But Metronidazole resistance in vitro does not correlates with in vivo resistance⁸. Amoxicillin resistance is found to be low in Bangladesh⁹. Clarithromycin based regimens probably will not be suitable for our patients because of the high cost of the drug and increasing drug resistance (as high as 17%)¹⁰. In this Situation, finding of an alternate regimen which will be effective and cheaper has become important. Levofloxacin has been proved to be very effective against Helicobacter pylori infection in several trials in different countries^{11,12,13}. This drug is comparatively cheaper, have possible better drug compliance with a few adverse effects. Efficacy of two different levofloxacin-based triple therapies (associated with reabrazole and amoxicillin or nitroimidazole) have reported eradication rates higher than 90%¹¹. Another study on Levofloxacin based therapy (with Clarithromycin & Omerazole) as first-line treatment showed more effective than

1. Assistant Professor of Gastroenterology
Chittagong Medical College, Chittagong
2. Registrar of Gastroenterology
Dhaka Medical College Hospital, Dhaka
3. Assistant Professor of Medicine
Holy Family Red Crescent Medical College Hospital, Dhaka
4. Assistant Professor of Gastroenterology
Sir Salimullah Medical College, Dhaka
5. Resident of Neuromedicine
Mymensingh Medical College Hospital, Mymensingh
6. Associate Professor of Gastroenterology
Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka
7. Professor of Gastroenterology
Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka

Correspondence : Dr Ershad Uddin Ahmed

standard triple therapy (Clarithromycin, Amoxicillin, Omeprazole)¹². In Bangladesh, there is no study with regimen containing Levofloxacin and Omeprazole.

Aims and objectives

- To compare the efficacy of Metronidazole, Amoxicillin, Omeprazole with Levofloxacin, Amoxicillin, Omeprazole for eradication of H.pylori infection in patients with peptic ulcer disease.
- To find out an effective drug regimen for treatment of H.pylori infection.

Materials & method

This prospective comparative study was carried out in the department of Gastroenterology, BSMMU between June 2007 to July 2008. On the basis of findings suggestive of peptic ulcer disease on upper GI endoscopy, 89 consecutive patients were initially included in the study. Four biopsy specimens, three from antrum and one from body of the stomach were collected from each patient with endoscopically proven PUD for rapid urease test (RUT) and histopathology. 78 Patients turned out to be positive for H. pylori on the basis of positive results on both RUT and histopathology. They were finally included in the study. Out of 78 patients, every odd numbered patient received Levofloxacin based and every even numbered patient received Metronidazole based therapy for 14 days. Among them 38 patients received Metronidazole, Amoxicillin, Omeprazole(MAO) and another 40 patients received Levofloxacin, Amoxicillin, Omeprazole (LAO). Total 52 patients completed the study (24 of 38 MAO based and 28 of 40 LAO based therapy) and came for follow-up endoscopy & gastric biopsy four weeks after completion of therapy. H.pylori infection was considered to be eradicated if both RUT & histopathology were negative. To detect differences in H.pylori eradication rates, chi-square & Z test were employed. Odds ratio for achieving H.pylori eradication with 95% confidence interval was calculated. P value <0.05 was considered to be significant.

Results

Age of patients ranged from 21 to 60 years with the mean of 38.08 there were 67 (75.28%) male and 22 (24.72%) female patient. Among 78 patients, 26 patients dropped out from the study due to non-compliance, drug reaction, pregnancy and others (Table I). The rest 52 patients returned for follow-up four weeks after completion of 14 days triple therapy.

Table I : Patients information (n = 78)

Patients	No
Follow-up done	52
Drop out	26
Drug reaction	2
Pregnancy	1
Going abroad	2
Others	21
Total	78

On intention to treat analysis (ITT) which disregards compliance in MAO group 14 of 38 patients (36.84%) were cured of H. Pylori infection as determined by negative RUT and histopathology and in LAO group 22 of 40 patients (55%) were cured of H. Pylori infection as revealed by negative RUT and histopathology. On per protocol analysis in MAO Group 14 of 24 patients (58.3%) were cured of H. Pylori and in LAO group 22 of 28 patients (78.6%) were cured of H. Pylori. Eradication rate of H. Pylori between the two groups were not statistically significant (P value > 0.10) (Table II).

Table II : Comparison of MAO group us LAO group eradication analysis (per protocol)

Status	MAO group (n=24) No. (%)	LAO group (n=28) No. (%)	P Value
Present	10 (41.7)	6 (21.4)	>.10ns
Absent	14 (58.3)	22 (78.6)	>.10ns
Proportion of eradication(n=36)	14 (38.9)	22 (61.1)	

Z test/Chi-square test, ns- not significant

Discussion

The high efficacy of Clarithromycin based regimens in eradicating H. Pylori infection is well known. Nevertheless, resistance to Clarithromycin is increasing and resistance to this drug is always correlated with a reduction in therapeutic efficacy⁸. Efficacy of Clarithromycin based regimes in Bangladesh is not satisfactory¹⁴. But in this study, Metronidazole 400 mg tds, Amoxicillin 1 gm 12 hourly and Omeprazole 20 mg 12 hourly for 2 weeks achieved 58.3% H. Pylori eradication rate (14/24) and Levofloxacin 500 mg once daily, Amoxicillin 1 gm twice daily & Omeprazole 20 mg bd for 2 weeks achieved 78.6% H. Pylori eradication rate (22/28). Difference of eradication rate between these two regimens is not statistically significant and these eradication rates parallel with the rates of

previous studies in Bangladesh. Trials in different countries showed higher eradication rates with Levofloxacin based triple therapies, as the first line, 2nd line & as rescue therapy. In a study from Italy, with a seven day course of Rabeprazole 20 mg bd plus Levofloxacin 500 mg od and either amoxicillin 1 gm bd or tinidazole 500 gm bd Cammorota et al²³ showed eradication rates of 92% and 90% respectively. Bilardi et al found eradication rates with based triple therapy and with bismuth based quadruple therapy of 70% and 37% respectively¹⁵. Most trials showed, at one week the Levofloxacin based triple therapy achieved a 90% eradication rate with no major adverse effects. But from this study, it appears that adequate eradication rate is not achieved by any of the Levofloxacin based triple therapies. Since drug compliance was ensured, drug sensitivity, bio-availability of drugs, bacterial virulence factors and host factors may be the possible causes of the low eradication rates. Pre-treatment microbial sensitivity to drugs was not assessed. **Indiscriminate use of Fluoroquinolones in our country might be a possible cause of selection of drug resistant strains to this group of antibiotics.**

Conclusion

H Pylori eradication as the mode of treatment for peptic ulcer disease in Bangladesh poses a problem unlike that of developed countries because of lower rates of eradication and higher rates of re-infection. The present study also did not show a satisfactory H. Pylori eradication rate. Therefore, H. Pylori eradication therapy with Metronidazole, Amoxicillin, Omeprazole and Levofloxacin, Amoxicillin, Omeprazole based regimens cannot be routinely recommended for Bangladeshi patient with peptic ulcer disease. Further studies involving large sample size representing all population of different socioeconomic status of the country are needed to find out a more effective therapeutic regimen for H. Pylori eradication.

References

1. Hasan M, Ali SMK, Azad Khan AK. Peptic ulcer in Bangladesh: an endoscopic survey. *Gut* 1985; 16:117
2. Ahmed MM, Rahman M, Rumi AK, Islam S, Huq F, Chowdhury MF et al. Prevalence of Helicobacter pylori in asymptomatic population-a pilot serological study. *Bangladesh Journal of Epidemiology* 1997; 7:251-254
3. Hopkins RJ, Giradi LS, Turney EA: Relationship between Helicobacter pylori eradication and reduced duodenal and gastric ulcer recurrence: A review. *Gastroenterology* 1996; 110:1244-1246
4. Malfertheiner P, Megraud F, O'Morain C, Bazzoli F, El-Omar E, the European Helicobacter Study Group (EHSO). Current concepts in the management of Helicobacter pylori infection: the Maastricht III Consensus Report. *Gut* 2007; 56: 772-781
5. Hildebrand P, Brandhar P, Rossi L, Pervin S, Rahman A, Arefin MS, et al. Recrudescence and re-infection with Helicobacter pylori after eradication therapy in Bangladeshi adults. *Gastroenterology* 2001;
6. Rahman MM, Hussein SMB, Ahmed Z, Siddique MAM, Hossain R, Uddin MN et al. A prospective study of three different Helicobacter pylori eradication regimens in the treatment of peptic ulcer disease. *Bangladesh Armed Forces Medical Journal* 2001/2002; 29:1-4
7. Rahan MT, Miah MAoy PK, Rasul K. Study of efficacy of 14 days triple therapy with furazolidone based regimen (furazolidone plus amoxicillin and omeprazole) in the eradication of Helicobacter pylori in patients with peptic ulcer disease in Bangladesh. *Bangladesh Journal of Medicine* 2003; 14:1-5
8. Khan MR, Rasul K, Hasan M. Helicobacter pylori eradication therapy for duodenal ulcer disease in Bangladeshi patients by two triple drug regimens: results of a clinical trial. *Bangladesh Journal. of Medicine* 2003;14:39-41
9. Nahar S, Mukhopadhyay AK, Khan R, Ahmad MM, Datta S, Chattopadhyay S, et al. Antimicrobial susceptibility of Helicobacter pylori strains isolated in Bangladesh. *J Clin Microbiol* 2004; 42: 4856-4858
10. Iovene MR, Romano M, Piloni AO, Prevalence of antimicrobial resistance in eighty clinical isolates of Helicobacter pylori. *Chemotherapy* 1999; 45: 8-14
11. Cammarota G, Cianci R, Cannizzaro O, Cuocol L, Pirozzi G, Gasbarrini A, et al. Efficacy of two one-week rabeprazole /levofloxacin-based triple therapies for Helicobacter pylori

- irriection. *Aliment Pharmacol ther.* 2000; 14:1339-1343
12. Nesta EC, Candelli M, Cremonini F, Ogetti V, Finizio R, et al. Levofloxacin-based triple therapy in first line treatment for *Helicobacter pylori* eradication: *Am J Gastroenterol* 2006; 101; 1985
 13. Nesta EC, Candelli M, Cremonini F, Cazzato IA, Dicaro S, Gabrielli M, et al. Levofloxacin-based triple therapy vs quadruple therapy in second-line *Helicobacter pylori* treatment: a randomized trial. *Aliment Pharmacol Ther* 2003; 18: 627-633
 14. L Savarino V, Mela GS, Zentilin P, Carrington M. 24-hour gastric pH and extent of duodenal gastric metaplasia in *Helicobacter pylori* positive patients. *Gastroenterology* 1997; 113: 741-745
 15. Bilardi C, Dulbecco P, Zentilin P, Reglioni S, Iiritano E, Parodi et al. A 10 days levofloxacin-based therapy in patients with resistant *Helicobacter pylori* infection: a controlled trial. *Clin Gastroenterol Hepatol.* 2004; 2: 997-1002