Helicobacter pylori ERADICATION BY LEVOFLOXACIN BASED TRIPLE THERAPY IN PATIENTS WITH PEPTIC ULCER DISEASE

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Abstract

Background : Clarithromycin resistance globally has challenged the success of conventional Clarithromycin based triple therapy for *Helicobacter Pylori* eradication. Levofloxacin has primarily been considered as a second-line treatment but may also be used as primary therapy. Recently, some studies have evaluated its efficacy as a valid alternative to standard antibiotics as first-line therapy for *H. pylori* infection. This study was intended to assess the eradication success of Levofloxacin based first-line triple therapy and also to see it's compliance & adverse effect profile.

Materials and methods : This non-randomized single-arm clinical trial was carried out in the Department of Gastroenterology, BSMMU from March 2016 to March 2017 involving 123 *H. pylori*-positive patients with endoscopically proven peptic ulcer disease to assess the eradication success of levofloxacin based first-line triple therapy and also to see its compliance and adverse effect profile. *H. pylori* status were detected by urea breath test. Patients were treated with amoxycillin 1 gm 12 hourly, levofloxacin 500 mg 12 hourly and omeprazole 20 mg 12 hourly for 14 days and were followed-up at 2 months after completion of therapy for repeat urea breath test.

Results: A total of 97 patients returned for follow-up. Male proportion was 63.41% and female was 36.58% with the median age of 57 years. On intention-to-treat analysis, the eradication rate of *H. pylori* was 65.85% and on per-protocol analysis, it was 83.50%. Total 15.44% patients developed adverse effects, all were mild to moderate in nature. One patient discontinued treatment because of epigastric pain and vomiting.

Conclusion: Levofloxacin-based therapy was effective, well-tolerated and compliance was excellent; but the eradication rate was not satisfactory.

Key words
Peptic ulcer disease; *Helicobacter pylori;* Levofloxacin; Eradication; Side effects.

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Introduction

Helicobacter pylori is a human pathogen that causes chronic active gastritis in all colonized subjects. This can lead to peptic ulcer disease, atrophic gastritis, gastric adenocarcinoma and MALT (mucosa associated lymphoid tissue) lymphoma[1]. *H. pylori* infection is a crucial factor in the multistep carcinogenic process evolving through acute gastritis, chronic gastritis, gastric atrophy, intestinal metaplasia and dysplasia before developing gastric adenocarcinoma. Eradication cures gastritis and can alter the progression to long-term complications or recurrence of disease[2]. Several meta-analyses showed significant improvement of gastric atrophy after eradication[3,4].

At least 50% of the world's human population has *H. pylori* infection[5]. Studies suggest that infection rates vary according to geographic region, but the number of infected people has persisted or even increased over the past three decades because of population growth and because of reinfection and recrudescence due to unsuccessful eradication[6]. Prevalence of *H. pylori* is very high in Bangladesh, about 92% of adult have been found to be sero-positive for *H. pylori*[7]. The annual reinfection rate was 13%[8].

Although *H. pylori* culture is the gold standard, according to Maastricht V/Florence consensus report for the management of *Helicobacter pylori* infection, Urea Breath Test (UBT) is the best approach to the diagnosis of *H. pylori* infection with high sensitivity, specificity and excellent performances[2,9].

The currently recommended first-line therapy for *H. pylori* infection is Proton Pump Inhibitor (PPI) amoxicillin and clarithromycin[2,10]. But the eradication rate of the standard triple therapy is gradually decreasing. There are several explanations but the most important is the increase in *H. pylori* resistance to clarithromycin. Clarithromycin resistance rates are increasing in all regions of the world and this threatens the viability of clarithromycin based triple therapies[2,10]. Clarithromycin resistance rates have now reached up to 50% in China[11]. Metronidazole resistance is also common in *H. pylori* and overall metronidazole resistance is found to be 47.22% with as high as 75% in Africa[12].

The Maastricht V/Florence Consensus Report on the management of *H. pylori* recommended either a bismuth-containing quadruple therapy or levofloxacin containing triple therapy after failure of PPI-clarithromycin-amoxicillin triple therapy[2]. Meta-analysis of Randomized Controlled Trials (RCTs) found similar efficacy but PPI-levofloxacin-amoxicillin triple therapy had a lower incidence of side effects[13].

Levofloxacin is a fluoroquinolone antibacterial agent with a broad spectrum of activity against Gram-positive and Gram-negative bacteria. Levofloxacin has, in vitro, shown to have remarkable activity against *H. pylori* and primary resistance to it is relatively infrequent when compared with metronidazole or clarithromycin[14,15]. Levofloxacin has primarily been considered as a second-line treatment but may be used as primary therapy also. Recently, some studies have evaluated its efficacy as a valid alternative to standard antibiotics as first-line therapy for *H. pylori* infection[16]. A large meta-analysis of 4,574 patients from 41 trials, including 16 trials in the first-line treatment and 25 trials in the second-line treatment revealed a cumulative eradication rate of 80.7% in the first-line treatment and 74.5% in the second-line treatment[17]. American College of Gastroenterology Clinical Guideline for the treatment of *Helicobacter pylori* Infection has recommended levofloxacin based triple therapy as one of the first-line regimens[18].

Prevalence and re-infection rate of *H. pylori* is very high in our country and there is no structured protocol for the management of *H. pylori* infection. Decision to treat as well as the drug regimens are often individualized and vary among physicians and specialties.

In the background of high antibiotic resistance and lack of effective antibiotic regimen with suitable eradication rate, this study was carried out to assess the eradication success of levofloxacin based first-line triple therapy and also to evaluate its compliance and adverse effect profile.

Materials and methods

This non-randomized single-arm clinical trial was carried out in the Department of Gastroenterology Bangabandhu Sheikh Mujib Medical University (BSMMU) from March 2016 to March 2017. Patients within 18-55 years of age and with a history suggestive of peptic ulcer disease were referred for upper Gastro-Intestinal (GI) tract endoscopy. Patients having either gastric erosion, gastric ulcer, duodenal erosion, duodenal ulcer or the combinations of lesions in upper GI endoscopy were initially included in the study. Biopsies were taken from all patients having gastric ulcer during endoscopy and sent for histopathology. Gastric malignancies were referred for appropriate treatment. Patients with alarm features e.g weight loss, anemia, vomiting, hematemesis/melena, dysphagia, palpable abdominal mass and patients with abnormal abdominal ultrasound e.g hepatosplenomegaly, ascites, gall stone disease, chronic pancreatitis were excluded from the study. Patients who took anti-*H. pylori* therapy within last 3 months were excuded. Patients with previous GI surgery, pregnancy or lactation were also excuded. Patients having abnormalities in blood tests e.g. anemia, raised Erythrocyte Sedimentation Rate (ESR) abnormal thyroid function test, abnormal transaminase values were excuded. Patients having concomitant significant comorbid illnesses e.g cardiorespiratory, renal, hepatic, neurological, pulmonary, metabolic, hematological and endocrine and suspected or confirmed malignancy were not considered for the study.

Patients with endoscopically proven peptic ulcer disease were sent for urea breath test for the diagnosis of *H. pylori* infection. Detection of *H. pylori* infection both during diagnosis and 2 months after

eradication therapy -was done by urea breath test. Consecutive 123 patients who were found to be positive for urea breath test were finally included in the study. They were treated with anti *H. pylori* regimen containing amoxycillin 1 gm 12 hourly, levofloxacin 500 mg 12 hourly and omeprazole 20 mg 12 hourly for 14 days. Patients were followed-up at 2 months after completion of therapy. Total 97 patients returned for follow-up. Urea breath test was again performed to ascertain the presence or clearance of *H. pylori* infection and 38 patients were found positive.

Patient were asked to discontinue PPI, if they had been taking any, for at least 2 weeks before performing urea breath test to avoid possible false-negative result. A similar instruction was provided to the patients 2 months after completion of therapy to have a flawless urea breath test.

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 strips of the drugs at the end of the treatment to count and ensure compliance. Any adverse effect due to drugs was noted at the same time. Signed informed consent was obtained from each patient before study enrollment.This study was performed in accordance with the Declaration of Helsinki, the International Conference on Harmonization Good Clinical Practice Guidelines. The study protocol was approved by the Institutional Review Board at Bangabandhu Sheikh Mujib Medical University.

Both the intention-to-treat analysis and per-protocol analysis were carried outwhile assessing the efficacy of *H. pylori* eradication by Levofloxacin based triple therapy. The 95% confidence interval was calculated for categorical variables and the mean±SD for quantitative variables. Patients who were lost to follow-up due to poor/noncompliance, adverse effect or others were excluded in per-protocol analysis. All statistical analyses were performed using the statistical software SPSS version 23.

Results

A total of 123 *H. pylori*-positive patients with peptic ulcer disease were included in the study and they were prescribed amoxycillin 1 gm 12 hourly, levofloxacin 500 mg 12 hourly and omeprazole 20 mg 12 hourly for 14 days. Patients returned after completion of treatment for the assessment of compliance of drugs and possible side effects. They were then asked for follow-up visit at 2 months after completion of therapy to assess for the clearance of *H. pylori* infection.

Among the total 123 patients, male proportion was 63.41% and female was 36.59% with the mean age of 57 years (Table I). Most of the patients were in their 50s and 60s. Thirty-five percent of the study population were smokers.

Table I : Demographic characteristics.

Patient characteristics		Results
Total number (ITT)		123
Sex	Male	78 (63.41%)
	Female	45 (36.58%)
Meanage		57 years
Smoking habit	Smoker	43(34.95%)

During the study period, 26 patients were lost to follow-up. Seven (7) patients did not complete the therapy deliberately. One (1) patient discontinued treatment due to nausea and epigastric pain. The rest 18 patients completed treatment but did not return at 2 months after completion of therapy for repeat urea breath test.

Total 97 patients were available for analysis at 2 months after completion of therapy. Among them, 58(59.80%) were male and the rest 39(40.20%) were female. Among 97 patients, 81(83.51 %) tested negative for *H. pylori* infection in urea breath test. Sixteen patients (16, 16.49 %) failed to clear the infection and remained positive in urea breath test. So, the eradication success was 83.51% (81/97) in per-protocol analysis. On the other hand, according to intention-to-treat analysis, the eradication rate of Levofloxacin based triple therapy was 65.85% (81/123) (Table II).

Table II : H. pylori eradication rate 2 months after therapy.

	H. pylori eradication rates	
	Intention-to-treat analysis (95 % CI)	Per-protocol analysis n (95 % CI)
Total no. of cases	123	97
Over all eradication	81 (65.85%)	81(83.50%)
Male	49/78(62.82%)	49/58 (84.48%)
Female	32/45(71.11%)	32/39 (82.05%)

There was no occurence of serious adverse effects, most were mild to moderate in intensity. One patient discontinued treatment because of epigastric pain and vomiting. Total 19 (15.44%) patients experienced adverse effects and there were some overlaps (Table III).

Table III: Adverse events.

Adverse event	Males (n =95)	Females (n=36)	Total
Nausea/Vomiting	5	2	7
Diarrhoea	3	1	4
Rash	1	2	3
Abdominal pain	-	1	1
Metallic taste	3	1	4
Total	12	7	19

Discussion

Considering the widespread and indiscriminate use of antibiotics, *H. pylori* resistance to antibiotics is common. Particularly, clarithromycin resistance is now at a level that, clarithromycin based first-line triple therapy is not recommended by some authority[19].

The eradication rate of *H. pylori* in this study with the triple therapy consisting amoxycillin 1 gm 12 hourly, levofloxacin 500 mg 12 hourly and omeprazole 20 mg 12 hourly for 14 days was 65% (Intention-to-treat analysis).

H. pylori prevalence and relapse rate is very high in Bangladesh[7,8]. In the context of increasing antimicrobial resistance, it has become difficult to formulate a suitable anti-*H. pylori* regimen and attain a satisfactory eradication rate. A number of studies have been carried out in our country with different combinations of antibiotics and PPI to assess *H. pylori* eradication rate. Other than Hasan MQ and colleagues (84.3%), none could attain a satisfactory eradication rate[20-21].

Considering levofloxacin based first-line triple therapy in Bangladesh, Ahmed EU et al in BSMMU in 2007 compared metronidazole, amoxycillin and omeprazole based triple therapy with levofloxacin, amoxycillinand omeprazole. Although the difference of eradication rates between two groups was not statistically significant, levofloxacin based therapy attained much higher rate of eradication (78.6% vs 58.3%)[21].

Meanwhile in Kashmir, India, Shah and colleagues achieved considerably high eradication rate of 85.5 % with 7 days levofloxacin based first-line triple therapy in a study involving 131 *H. pylori*-positive patients with gastroduodenal ulcers[19]. According to a Brazilian study by Silva FM and colleagues involving 66 *H. pylori*-infected treatment naïve peptic ulcer disease patients, 7 days triple therapy with lansoprazole, amoxicillin and levofloxacin achieved 73% eradication rate[22]. Cheng H and colleagues compared clarithromycin, amoxicillin and lansoprazole based therapy with amoxicillin, levofloxacin and lansoprazole based first-line therapy in a multicentre RCT in China. Although the difference was not statistically significant, levofloxacin based therapy achieved a higher eradication rate (82.4% vs 74.5%)[23]. On the other hand, after two consecutive failures of first and second-line eradication, 110 *H. pylori*-positive peptic ulcer disease patients in 14 secondary or tertiary medical centers in Korea received levofloxacin based third-line *H. pylori* eradication therapy for peptic ulcer disease. The overall eradiation rate was 71.6%[24]. In a recent study conducted in Iran involving 61 *H. pylori*-positive patients who had failed previous non-bismuth clarithromycin-containing first-line therapies, a high eradication rate of 91.8% was found after 14 days triple therapy with pantoprazole, amoxicillin and levofloxacin[25].

While assessing the adverse outcome, there was no event of serious adverse event in the current study. One patient discontinued treatment because of epigastric pain and vomiting. Overall occurrence of side effect was 15.44%. In the Indian study by Shah A and colleagues, overall prevalence of adverse effects was 17.6 % and most were mild to moderate in intensity. One patient discontinued treatment because of epigastric pain and vomiting[19]. On the other hand, 13.1% patients developed adverse effect in the Iranian study by Fakheri H and colleagues. Most common was anorexia (4.9%). Only 3.2% reported marked nausea and metallic taste, but no one stopped treatment due to the adverse reactions[25].

The ideal therapy for *H. pylori* eradication should be simple, safe, free from side effects with low cost and desired efficacy. It is well known since 'Maastricht IIIConsensus Report' that; treatment should achieve an eradication rate of ≥ 80%[26]. On the other hand, the Real-world Practice and Expectation of Asia-Pacific Physicians and Patients in *Helicobacter pylori* Eradication (REAP-HP) Survey demonstrated that the accepted minimal eradication rate of anti-*H. pylori* regimen in *H. pylori*-infected patients was 91%[27]. Similarly, the Kyoto Consensus Report on *Helicobacter pylori* Gastritis recommended an eradication rate of ≥ 90%[1].

Limitations
There were certain limitations in this study. The sample size was small. The Margin of error in the statistical analysis could have been less with large sample size. Too many patients (26) were lost to follow-up and it reduced the eradication rate in intention to treat analysis.

Conclusion
In our study, we used levofloxacin-based therapy as first-line therapy and showed that it is effective, well-tolerated, cheap, and compliance was excellent. But the eradication rate was not satisfactory, although it was consistent with the eradication rate from previous studies carried out in Bangladesh and elsewhere in the world.

Recommendation
This sorts of study to be done with large scales. Comparison with first-line therapy with culture and antibiotic sensitivity for *H. pylori* were also necessary for formulating an effective regimen and also for future references. Long term follow-up with evidence of ulcer healing should also have been done.

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Contribution of authors
MRA-Conception, design, acquisition of data, manuscript writing & final approval.
MSA-Data analysis, manuscript writing & final approval.
MAMS-Interpretation of data, critical revision & final approval.
MAO-Data analysis, interpretation of data, critical revision & final approval.
MZR-Acquisition of data, manuscript writing & final approval.
MAK-Design, critical revision & final approval.

Disclosure
All the authors declared no conflict of interest.

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