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Prospective Randomized Trial of Esomeprazole versus Lansoprazole and Omeprazole Based Triple Therapy for H. Pylori Eradication in an Iranian Population

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Abstract

Background: Although triple therapy with one proton pump inhibitor (PPI) and two antibiotics for one week has been introduced as the treatment of choice, quadruple therapy in Iran is the standard treatment due to the organism's high resistance is related to Helicobacter pylori (H. pylori) organism.

Objective: Comparison of three different PPIs; esomeprazole, lansoprazole and omeprazole with a longer duration (10 days) for eradication of H. pylori in the Iranian population.

Methods and Materials: Two-hundred ninety-four patients with endoscopic evidence of peptic ulcer, non-ulcer dyspepsia, gastritis or acid reflux and confirmed H. pylori, either by histology or a positive urea test were randomly divided into three groups; namely, group I (98 patients) received omeprazole, clarithromycin and amoxicillin (OCA); group II (97 patients) received lansoprazole (LCA) and group III (98 patients) received esomeprazole (NCA) instead of omeprazole.

Response to treatment was defined as eradication of H. pylori confirmed by negative C14 urea breath test 40 days after treatment course completion.

Results: Per protocol (PP) eradication rate of H. pylori was 91.9 % for group I, 80.4 % for group II and 91.8 % for group III (P = 0.017). Intention to treat (ITT) eradication rate for groups I, II and III were 91 %, 78 % and 90 %, respectively (P = 0.012). The patients' compliance was 99 %, 97 % and 98 % and the adverse events were 36 %, 35 % and 14 % in these three groups, respectively (P = 0.614) (P = 0.001). Based on age and sex, eradication rate showed significant difference without considering various treatment protocols (P = 0.017 and 0.031, respectively). There was no difference in eradication rate between PUD and NUD patients (P = 0.166).
Conclusion: Both PP and ITT eradication rates were higher in the OCA and NCA treatment groups. Group III had the least adverse effects. Eradication by NCA regimen had less side effects but more cost compared to OCA regimen.

Introduction

First-line regimens for H. pylori treatment in Iran usually include a fourteen-day course of PPI, bismuth and two antibiotics.(1) However, selecting a regimen for eradication of H. pylori depends on several factors entailing existing antibiotic resistance, cost and patient tolerance. Geographic variations in the incidence of drug resistance have an impact on the success of eradication regimens. The disadvantages of this bismuth-based quadruple therapy include the high daily pill count and frequent side effects, which affect treatment compliance, as well as the high H. pylori resistance to nitroimidazole compounds observed in our country. In Iran, primary bacterial resistance to metronidazole, clarithromycin and furazolidone is about 37.5 %, 28 % and 5 %, respectively.(2) Furazolidone provides an excellent alternative to combined therapy for H. pylori eradication as a substitute for amoxicillin or metronidazole, resulting in good eradication rates in patients who have had failed treatment; however, its use has not become widespread due to the reported side effects. This drug can be a potential option in a rescue regimen with levofloxacillin and amoxicillin for refractory H. pylori eradication.(3) Consensus meetings on H. pylori have advised that the first line treatment should be a drug regimen that includes a PPI and two antimicrobial agents (clarithromycin + amoxicillin or clarithromycin + metronidazole). The triple therapy usually results in an eradication rate of higher than 80 %.(4) The aim of this study was to compare the efficacy of different PPIs such as esomeprazole (nexium), omeprazole and lansoprazole in combination with amoxicillin and clarithromycin in the first line eradication of H. pylori and to investigate the success of H. pylori eradication in our district. Considering the high rate of resistant H. pylori in this population, we implemented 10

days of treatment instead of the standard 7 days course.

Methods and Materials

We studied 294 patients, from February 2005 to March 2007. This study was approved by the ethics committee (grant NO: 107) at Jundishapour Ahwaz University of Medical Sciences and has been registered in IRCT (Iranian Registry of Clinical of Trials) as number IRCT201204043836N4. Written informed consent was obtained before starting the study. All the study group patients had endoscopic examination in the course of assessment for gastrointestinal symptoms such as weight loss, flatulence, dyspepsia, vomiting, heart burn or a history of gastric cancer in close relatives. In all patients two biopsies of the gastric antrum and two biopsies of the gastric body were studied for presence of H. pylori organisms by histology and urea test.

Exclusion criteria included previous treatment of H. pylori infection, previous use of any antibiotics or bismuth subcitrate or any PPI or H2 blockers within four weeks prior to endoscopy, use of NSAIDs for more than four weeks, history of allergy to medications, previous history of any gastric surgery, underlying diseases such as cirrhosis or uremia and pregnancy.

Patients were randomized to three groups using a computer regenerated code and each group was treated by the following medications for 10 days:

Group I (OCA): Omeprazole 20mg bid, clarithromycin 500mg bid and amoxicillin 1 gm bid.

Group II (LCA): Lansoprazole 30mg bid, clarithromycin 500mg bid and amoxicillin 1 gm bid.

Group III (NCA): Esomeprazole (nexium) 40mg bid, clarithromycin 500mg bid and amoxicillin 1 gm bid. The drugs which were be used in study where from AstraZeneca CO, Turky (nexium), Excel Life Science Ltd, London UK (lansocid), Abedi CO, Iran (Omeprazole).

Patients came to the clinic one week after completion of the treatment to be evaluated for any potential drug side effect and also to be checked for their compliance. To evaluate the efficacy of H. pylori eradication therapy, patients were examined with C14 urea respiratory test 40 days after completion of the treatment course. A questionnaire was used for each patient including the patient's symptoms, endoscopic findings, H. pylori status by urea test, pathology report and medication side effects. Each endoscopy was performed

by an experienced gastroenterologist and the findings were recorded then each recording was reviewed by two independent expert gastroenterology specialists. Side effects were systematically recorded throughout the study and were assessed using a checklist administered by a physician and described as

1-None or only mild: mild discomfort which did not interfere with the patients' normal daily activities

2-Intermediate: discomfort or side effects which interfered with the patients' normal daily activities.

3-Severe: side effects requiring cessation of treatment.

Data Analysis

A pilot study was carried out to determine the sample size. Based on the results with a confidence interval of 0.05 and statistical power of 90 % and after modification of the sampling, we assigned 99 H. pylori infected patients to each of the study groups. The results of pretest eradication rate in different treatment groups were calculated which were as follows: 90 % in group I (OCA), 68 % in group II (LCA) and 100 % in group III (NCA). Sampling was calculated based on the results of treatment groups I and II. Overall, the study started with a total population of 300; 100 patients in each group.

Patients were randomly assigned to three different treatment groups of OCA, LCA and NCA. We used Chi-square (X^2), Fisher's exact test and analysis of variance (ANOVA) for statistical analyses. Study outcomes including eradication of H. pylori, adverse events and compliance were compared using Chi-square (X^2) test. We used ITT analysis to compare eradication of H. pylori in all the patients in the three study groups without considering their compliance. In addition, we performed per-protocol analysis to compare the eradication for all the patients in the three different groups who finished the course of treatment. SPSS 13 for Windows (SPSS Inc., Chicago, Illinois) was used for statistical analysis.

Results

Three hundred patients with the mean ± SD age of 38.5 ± 12.5 years and confirmed H. pylori infection by histology and urea test were randomly assigned to three different treatment groups of OCA, LCA and NCA. Among these patients, one in the OCA group, three in the LCA group and two in the NCA group were excluded due to poor compliance. Clinical manifestations of patients who finished the course of treatment are described in Table 1.

Table 1. Demographic Data and Endoscopic Appearance of Patients in the Three Study Groups

Characteristics	**OCA Group N = 100**	**LCA Group N = 100**	**NCA Group N = 100**	**P value**
Age (year) (mean ± SD)	40.46 ± 13.066	36.26 ± 11.188	39.02 ± 8.59	0.055
Gender ($^{Male}/_{Female}$)	56/44	51/49	51/49	0.716
Endoscopic findings				
NUD	27 (27%)	31 (31%)	21 (21%)	0.166
Gastritis	29 (29%)	20 (20%)	17 (17%)	
Duodenal ulcer	24 (24%)	26 (26%)	34 (34%)	
Gastric ulcer	2 (2%)	0.00	4 (4%)	
Erosive gastritis	7 (7%)	12 (12%)	13 (13%)	
Erosive duodenal	8 (8%)	13 (13%)	7 (7%)	
Reflux	3 (3%)	6 (6%)	4 (4%)	

ITT analysis shows eradication of H. pylori was significantly higher in treatment groups OCA (91 %) and NCA (90 %) compared to LCA group (78 %) (P = 0.012) (Table 2). According to PP analysis, H. pylori eradications were 91.9 % in OCA, 80.4 % in LCA and 91.8 % in NCA groups. OCA and NCA treatment groups had higher eradications compared to the LCA group (P = 0.017) (Table 2).

Table 2. Eradication of H. Pylori and Treatment Results in OCA, LCA and NCA Groups

Eradication Rate	**Group OCA N = 100**	**Group LCA N = 100**	**Group NCA N= 100**	**P value**
Intention to treat	(91 %) $^{91}/_{100}$	$\frac{78}{100}$ 78 %	$\frac{90}{100}$ 90 %	0.012
Per protocol	(91.9 %) $^{91}/_{99}$	$\frac{76}{97}$ 80.4 %	$\frac{76}{97}$ 80.4 %	0.017
Compliance	99 % ($^{99}/_{100}$)	$\frac{97}{100}$ 97 %	$\frac{97}{100}$ 97 %	0.614
Adverse events	$^{36}/_{100}$	$^{35}/_{100}$	$^{14}/_{100}$	0.001

Based on Fisher's exact test, there was a statistically significant difference regarding H. pylori eradication between the two genders regardless of treatment protocols (P = 0.017). In female patients, H. pylori eradication was performed in 117 out of 140 (83.6 %), whereas in male patients it was 142 out of 152 (93.4 %). Based on age, patients were subclassified into two age groups of older than 45 years of age and equal to or younger than 45 years of age. H.

pylori eradication was significantly different between these two groups without considering the treatment protocol they used (P = 0.031). In the current study, 210 patients were younger than 45 and 84 of them were older than 45 years. In patients younger than 45, eradication rate was seen in 180 out of 210 individuals and in patients older than 45 years old, this was seen in 79 out of 84 patients. Fisher test showed that there was a significant difference between these two age groups (P = 0.31). The eradication rate among patients with peptic ulcer disease, erosive gastritis and erosive duodenitis was 94.2 % (N = 131); while 74.7 % (N = 59) of the patients with non ulcer dyspepsia had eradication of H. pylori (P = 0.00).

The most common side effect in all treatment groups was sensation of a bitter taste. The NCA group was associated with the least complication (P = 0.001) (Table 3).

Table 3. Side Effects in the Three Treatment Groups

Adverse Effect	**OCA group N = 100**	**LCA group N = 100**	**NCA group N = 100**	**P value**
Diarrhea	4 (4 %)	2 (2 %)	0.00	0.13
Dizziness	10 (10 %)	4 (4 %)	2 (2 %)	0.032
Bitter taste sensation	10 (10 %)	13 (13 %)	4 (4 %)	0.077
Headache	4 (4 %)	7 (7 %)	2 (2 %)	0.217
Anorexia	4 (4 %)	8 (8 %)	1 (1 %)	0.034
Non SA/ Vomiting	4 (4 %)	3 (3 %)	5 (5 %)	0.771

Discussion

According to a number of recent meta-analyses, even with the recommended regimens, H. pylori eradication failure is still seen in approximately 20 % of patients.(5) This issue is becoming a cause of concern owing to the indiscriminate use of antibiotics. H. pylori resistance is an important factor involved in the failure of treatment. The prevalence of primary resistance of H. pylori to clarithromycin has been reported to range from 2.2 to 24 % in different countries.(6) The prevalence of H. pylori resistance to metronidazole has been reported to range from 8 to 80 % in different countries.(7) The prevalence is much higher in developing countries (> 60 %) than in developed countries.(8) The prevalence of resistance to amoxicillin, tetracycline and rifampicin fortunately remains low. In most studies, it is less than 2 %, with the exception of Bangladesh

(6.6 %) for amoxicillin and Bulgaria (5.2 %) for tetracycline. The prevalence of primary resistance of H. pylori to quinolones has been reported to range from 2 to 22 % in different countries.(9, 10) The prevalence of quinolone resistance is reported relatively higher in Japan, Korea and Italy (15-22 %) and very low in Iran, China and Egypt (approximately 2 %).(11, 12) Resistance to quinolones is easily acquired and the resistance rate is relatively high in countries with a high rate of usage of these drugs. These findings suggest that regional-specific treatment regimens based on local antibiotic resistance may improve eradication rates. In developing countries where resistance to metronidazole is usually very high, furazolidone in combination with tetracycline, bismuth and PPI is very effective, safe and cost benefit. However, some adverse aspects related to the use of furazolidone as a rescue therapy for H. pylori infection should be noted, especially regarding its potential oncogenic risk.(10) Although there is an increasing trend for clarithromycin resistance, clarithromycin-based regimens remain the recommended first line option in regions with clarithromycin resistance below 20 %.(13) For patients with eradication failure to a first-line clarithromycin-based regimen, quadruple therapy regimen composed of bismuth subcitrate, tetracycline, metronidazole and an antisecretory agent (standard-dose PPI bid), administered 14 days or levofloxacin-based rescue regimens (levofloxacin-amoxicillin-PPI) constitute an encouraging second-line alternative.(14, 15) Assessment of H. pylori sensitivity to antibiotics may be useful only after failure of second-line therapy.(16) The alternative candidates for third-line therapy are quinolones, tetracycline, rifabutin and furazolidone; high-dose PPI/amoxicillin therapy has also shown promise.

The increase in gastric pH induced by antisecretory drugs is crucial in order to allow antibiotics to exert their optimal activity against H. pylori.(17) By increasing intragastric pH, antisecretory drugs allow the microorganism to reach the growth phase and become more sensitive to antibiotics such as amoxicillin. Moreover, PPIs exert an antibacterial action against H. pylori.(18) The resistance to amoxicillin is very rare, so high-dose dual therapy might be a promising option as an alternative treatment regimen. Because the standard recommended doses were more in esomeprazole, lansoprazole and pantoprazole, it might be expected that the use of these drugs instead of

omeprazole in triple therapy would achieve better H. pylori eradication rates. In addition, some PPIs including esomeprazole and rabeprazole were found to have minimal first pass metabolisms and underwent less hydroxylation by CYP2C19 than omeprazole.(19) Some studies suggested that esomeprazole provides better control of intragastric PH than omeprazole or pantoprazole and that is has high activity against H. pylori in comparison to other PPIs.

Our study showed that triple therapy with different PPI drugs have both ITT and PP variable results. The patients' compliance was 97 %. Eradication rate was above 78 %. Eradication in omeprazole and esomeprazole treatment groups was higher than lansoprazole group (ITT analysis 91 % and 90 % versus 78 %, respectively and PP analysis 91.9 % and 80.4 % versus 80.4 %, respectively). However previous studies have found various results. Ping-I Hsu et al. found that esomeprazole-based triple therapy demonstrated a higher eradication rate than pantoprazole-based regimen (ITT analysis 94 % versus 82 % and PP analysis 97 % and 84 %, respectively).(19) Another study did not detect that double-dose new generation PPIs have better H. pylori eradication rates and tolerability than omeprazole.(20) Choi et al. showed that the intention to-treat analysis showed no difference between the eradication rates of four PPIs; 64.9 % omeprazole, 69.3 % pantoprazole), 69.3 % rabeprazole and 72 % esomeprazole.(21) Javier P Gisbert et al. reported that double-dose esomeprazole may improve the H. pylori eradication compared to omeprazole-based therapy.(22) In a review article published by Laine with esomeprazole 40 mg qid, amoxicillin 1 g bid and clarithromycin 500 mg bid, obtained 77-78 % ITT eradication rates and 84-85 % per protocol eradication rates in duodenal ulcer in USA cases.(21) The mean cure rates of the same regimen (NCA) by ITT and PP were 82 % and 86 %, respectively in another study performed by Gisbert et al. in 2004 showing a highly effective eradication rate.(23) ITT analysis in a study by Wu et al. revealed a 89.4 % eradication for NCA and a compliance of 100 %.(24) Geographic variations in response to eradication treatment have been demonstrated and attributed to genetic difference in the metabolism of PPIs.

Although most of H. pylori-related diseases are associated with male gender, the role of gender as a risk factor for H. pylori infection is still debated. Three groups had comparable mean

age, gender and endoscopic findings. Our study showed a correlation between the rate of eradication of H. pylori and gender among our patients (P = 0.017) which was also revealed in a study conducted by Cai et al. in a PPI, metronidazole and amoxicillin triple therapy for a week. There was a 68.1 % eradication rate in men and a 57 % eradication rate in women. Of course women had a lower eradication rate due to prior use of metronidazole for vaginal infection.(25)

We have found that the eradication rate of H. pylori was higher in the patients younger than 45 years old (P = 031) which is in contrast to Cai et al.'s study, in which no association was detected between the eradication rate and age.(26) All patients, but six (three in the LAC group and two in the NCA group and one in the OCA group) complied with the eradication therapies and took more than 90 % of the assigned tablets. The three groups displayed similar compliance rates (99 % versus 97 %; P = 0.6).

The three patient groups tolerated the treatment well and exhibited comparable adverse event profiles and frequencies (Table 4).

Bitter mouth was the most common adverse effect in the three groups (4 % in NCA, 13 % in LCAand 10 % in OCA). The less seen side effect occurred in the NCA group (P = 001). However, in Choi et al.'s study, similar to our study, side-effects were more common in the esomeprazole-based triple therapy group than in the other groups (P < .05).(22) In Wu et al.'s study, the adverse events were reported as 3.83 % in the NCA treatment group.(24) Conflicting results have been reported regarding whether patients with non-ulcer dyspepsia (NUD) response differently to H. pylori eradication treatment compared with patients with peptic ulcer disease (PUD). This difference between patients with NUD and PUD may influence the efficacy of eradication therapy. In our study, the difference in eradication rate was observed between PUD and NUD patients (94.2 % versus 74.7 %; P = 0.00).

Conclusion

The present study showed that triple therapy with a PPI base and two antibiotics; clarithromycin and amoxicllin have an eradication rate more than 78 % in our area. These regimens were well tolerated with a 97 % compliance in our patients with different PPIs. We prefer omeprazole and esomeprazole to lansoprazole in triple therapy for eradication of H. pylori. Esomeprazole is an expensive drug in iran, but has less

side effects in comparison with omeprazole. We suggest future studies with assessment of CYP2C19 for evaluation of the efficacy of different PPIs in eradication of H. pylori in Iran.

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Table 4: Side Effects in Three Treatment Groups:

Advers Effect	OCA group N=100	LCA group N=100	NCA group N=100	P value	NCA group N=100
Diarreha	4 (4%)	2 (2%)	0.00	0.13	0.00
Dizziness	10 (10%)	4 (4%)	2 (2%)	0.032	2 (2%)
Bitternes	10 (10%)	13 (13%)	4 (4%)	0.077	4 (4%)
Head ache	4 (4%)	7 (7%)	2 (2%)	0.217	2 (2%)
Anorexia	4 (4%)	8 (8%)	1 (1%)	0.034	1 (1%)
Non SA/ Vomiting	4 (4%)	3 (3%)	5 (5%)	0.771	5 (5%)

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