

## Treatment of *Helicobacter pylori*, Comparison of three Regimens, a double Blind Randomized Trial

Abu Safieh Yasser F, Yamin Haneen

Abu Safieh Yasser F, Yamin Hanin, Specialized Arab Hospital, Internal Medicine and GI Department, affiliated with School of Medicine, An-Najah University, Nablus, Palestine

Correspondence to: Yamin Haneen, MD, Specialized Arab Hospital, Internal Medicine and GI Department, affiliated with School of Medicine, An-Najah University, Nablus, Palestine. [dr.haneenya@gmail.com](mailto:dr.haneenya@gmail.com)

Received: March 7, 2013

Revised: May 18, 2013

Accepted: May 21, 2013

Published online: July 21, 2013

### ABSTRACT

**AIM:** To compare the effectiveness of standard triple, sequential, and concomitant therapies for eradication of *Helicobacter pylori* in a randomized, double-blinded, comparative clinical trial conducted in Palestine.

**METHODS:** Patients who underwent upper endoscopy for a clinical indication and tested positive for rapid urease test (RUT) were included, written consent was signed, and randomly allocated into three groups: **Group A** received the conventional Triple therapy; Esomeprazole 40 mg OD, Amoxicillin 1g and Clarithromycin 500 mg both given BID for 10 days; **Group B** received Sequential therapy; Esomeprazole 40 mg OD and Amoxicillin 1g BID for 5 days then Esomeprazole 40 mg OD, Clarithromycin 500 mg BID and Tinidazole 500 mg BID for another 5 days; and **Group C** received Concomitant therapy; Esomeprazole 40 mg OD, Amoxicillin 1g, Tinidazole 500 mg and Clarithromycin 500 mg all given BID, for 10 days. Stool antigen was done 4 weeks after completion of treatment. Binary logistic regression and  $X^2$  test with ( $P < 0.05$ ) were used as appropriate to compare the eradication rates.

**RESULTS:** Six hundred and seventy three (673) patients were tested by (RUT), of whom 242 patients (36%) had a positive RUT, 203 patients were included in the study and 163 patients completed the study. In Per Protocol analysis, the overall eradication rate was 73%. The eradication rates were 70.2%, 70.9% and 77.2% in Groups, A, B, and C respectively. Although the eradication rate achieved by the concomitant therapy was higher than both sequential and triple therapy, these differences were not statistically significant.

**CONCLUSION:** The eradication rates were low with the three protocols. The three protocols are equal as first line treatment of *H. pylori*. The sequential and concomitant therapies were not superior to

triple therapy. New regimens that are more effective, with a higher eradication rate need to be developed.

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**Key words:** *Helicobacter pylori*; Eradication therapies

Yasser F AS, Haneen Y. Treatment of *Helicobacter pylori*, Comparison of three Regimens, a double Blind Randomized Trial. *Journal of Gastroenterology and Hepatology Research* 2013; 2(7): 699-702 Available from: URL: <http://www.ghrnet.org/index.php/joghr/article/view/436>

### INTRODUCTION

*Helicobacter pylori* infection causes peptic ulcers, gastric mucosa-associated lymphoid tissue lymphoma (MALT lymphoma), and gastric cancer<sup>[1]</sup>. Standard treatments for *H. pylori* infection that have been endorsed by U.S. and European authorities rely on clarithromycin or metronidazole in conjunction with other antibiotics and acid inhibitors<sup>[2,3]</sup>. The prevalence of clarithromycin and metronidazole resistance has increased substantially in recent years, and there has been a corresponding decrease in the eradication rate for *H. pylori* infection<sup>[4]</sup>. Eradication rates in most Western countries have declined to unacceptable levels. Eradication therapy fails in approximately 1 in 5 patients<sup>[5]</sup>. A simple and short treatment regimen that would return eradication levels to those seen at the advent of *H. pylori* treatment is urgently needed<sup>[5]</sup>. Such a regimen should have high efficacy against clarithromycin-resistant and metronidazole-resistant strains of *H. pylori* because these strains are increasingly encountered in routine clinical practice. One successful approach to the problem of clarithromycin resistance has been to administer the drugs sequentially<sup>[6,7]</sup>. The initial experiments with "sequential therapy" prescribed the dual therapy combination of amoxicillin and a PPI twice a day for 5 days followed by another 5 days of the PPI, plus clarithromycin and tinidazole/metronidazole. This approach has been compared with PPI amoxicillin plus clarithromycin triple therapy and repeatedly been shown to be superior<sup>[6-8]</sup>. The difference between the two approaches was related to improved results with clarithromycin resistant strains<sup>[6,7]</sup>. One potential problem with sequential therapy is that it is relatively complex requiring the patient to switch from a dual to a triple

therapy at mid point<sup>[6,9]</sup>. It was therefore proposed that the same four drugs (a PPI, clarithromycin, metronidazole, and amoxicillin) can be given concomitantly as a non sequential 4-drug, 3-antibiotic non-bismuth containing quadruple therapy to overcome this problem<sup>[10,11]</sup>. Interestingly, the efficacy of this therapy regimen was equivalent to sequential therapy in some studies<sup>[12,13]</sup>. Several studies in various countries have proven its efficacy with eradication rates above 90 %<sup>[14,15]</sup>. With application of this regimen the treatment could even be shortened to 5 days<sup>[15]</sup>. These therapies have not formally been tested in Palestine where *H. pylori* infection is high, The aim of this study was to compare the efficacy of standard triple, sequential, and concomitant therapies for *Helicobacter pylori* eradication in a randomized, double-blinded, comparative clinical trial in Palestine.

## MATERIALS AND METHODS

### Patients and medications

This study was a randomized, prospective double blind trial performed at the GI clinic in Specialized Arab Hospital, Nablus, Palestine between April 2010 and January 2012. Both the care giver and the patient were blind to treatment. The data analyst and the medical secretary who did randomization were not blind to treatment. Patients presenting with dyspepsia or epigastric pain, and underwent upper endoscopy, with 2 antral biopsies, and tested positive for *H. pylori* by RUT were included in this study. The exclusion criteria were as follows (1) patients younger than 18 years; (2) allergy to antibiotics; (3) Being on antibiotic or PPI 2 weeks before testing; (4) active upper GI bleeding.

After a positive (RUT), patients were randomly allocated into three groups: Group (A) received the standard Triple therapy; Esomeprazole 40 mg OD, Amoxicillin 1 g, and Clarithromycin 500 mg both given bid for 10 days. Group (B) received Sequential therapy; Esomeprazole 40 mg OD and Amoxicillin 1 g bid for 5 days then Esomeprazole 40 mg bid, Clarithromycin 500 mg, and Tinidazole 500 mg both given bid for another 5 days. Group (C) received concomitant therapy; Esomeprazole 40 mg OD, Amoxicillin 1 g, Tinidazole 500 mg, and Clarithromycin 500 mg, all given bid, for 10 days. Eradication of *H. pylori* was assessed; by stool antigen testing was done by Specialised Arab Hospital Lab. (ACON Labs, Foresight® *H. pylori* antigen EIA Test Kit) done four weeks after completion of treatment. Simple randomization was used in this study. Randomization was done by sealed opaque envelopes, with a given number for each patient, was done by our medical secretary.

The three groups were followed by regular telephone calls during treatment period and were asked about side effects. Compliance assessment was done by counting pills at the end of treatment period. Statistical analysis

Per protocol analysis was used to compare the eradication rates among the three treatment regimens. SPSS version 15 was used in data analysis. Continuous variables were presented using mean and standard deviation and frequency tables were used to describe categorical variables.  $\chi^2$  ( $P < 0.05$ ) was used. Intension to treat was used to have analysis of eradication rate for the three groups.

## RESULTS

The total number of unique patients who underwent upper endoscopy during the study period was 1122, of those 673 patients were tested by RUT. The total number of positive RUT was 242 (36%). 39 patients were excluded for different reasons listed in the methods. A total of 203 patients were included in the study. Of those, 163 patients completed the study (80% completion rate); 40 patients did not like

to continue the study despite repeated attempts and call phones. As shown in table 1 and 2, the three patient groups did not differ significantly in age, sex, gastroscopic diagnosis, or dropout rates.

The overall eradication rate was 73% (119/163). In an ITT the eradication rate was, 119/203 (59%). In per protocol analysis, the eradication rates were 70.2%, 70.9% and 77.2% in groups A, B and C respectively. As shown in table 3, the eradication rate achieved by the concomitant therapy was numerically higher than that by both sequential and triple therapy. However, No statistical significance was found among any of the three groups.

It was found that the overall eradication rate was 76.6% for female and 69.8% for males (Table 3) with no statistical significance between the two groups ( $p = 0.325$ ).

Patient compliance with the therapies was very good and not different among the three groups. The complete follow up rate was 80%. No serious side effects were reported by the patients

**Table 1** Demographic characteristics of patients at entry at each treatment group.

Patients characteristics (n)	Group A	Group B	Group C
Number of patients enrolled in the study (203)	62	64	77
Number of patients completed the study (163)	51	55	57
Age(year) mean +standard deviation	40.37+14.1	38.49+13.78	41.42+12.46
Sex(F\M)%	1	8	6
Dropout n (%)	(51\49)	(50.9\49.1)	(47.2\52.8)
	11 (18%)	9 (14%)	20 (26%)

**Table 2** Clinical characteristics of patients at entry at each treatment group.

Endoscopic diagnosis	Group A	Group B	Group C
	Number (%)	Number (%)	Number (%)
Gastritis	27 (52.9)	32 (58.2)	24 (42.9)
Duodenitis	8 (15.7)	8 (14.5)	10 (17.9)
Gastric ulcer	1 (2)	4 (7.3)	4 (7.1)
Duodenal ulcer	14 (27.5)	16 (29.1)	11 (25.6)
GERD	15 (29.4)	11 (20)	12 (21.4)
Gastric cancer	3 (5.9)	0 (0)	1 (1.8)
Candida esophagitis	1 (2)	3 (5.5)	1 (1.8)

**Table 3** Eradication rates for each treatment group. Per protocol (pp).

Eradication per protocol	Group A	Group B	Group C
Eradication rate pp(%) <sup>1</sup>	(70.6%)	(70.9%)	(77.2%)
Eradication rate PP per sex % (M\F)	(68\73.1) <sup>2</sup>	(66.7\75) <sup>3</sup>	(73.5\82) <sup>4</sup>

<sup>1</sup>  $P$  value=0.435 ( $>0.05$ ) between A and C;  $P$ =0.449 ( $>0.05$ ) between B and C;  $P$ =0.0971 ( $>0.05$ ) between A and B; <sup>2</sup>  $p$  value=0.764 ( $>0.05$ ); <sup>3</sup>  $p$  value =0.562 ( $>0.05$ ); <sup>4</sup>  $p$  value=0.529 ( $>0.05$ ).

**Table 4** Antibiotic resistance in *H. pylori* isolates from selected countries in Middle East.

Country	Number tested	Antibiotics		
		Amoxicillin	Metronidazole	Clarithromycin
Middle East				
Bahrain	83	-	57	33
Egypt	42	0	100	3
Iran	112	-	42	-
Israel	138	0.8	40-60	10
Lebanon	54	0	30	2
Saudi	223	1.3	80	4
UAE	16	-	63	-

## DISCUSSION

The aim of this study was to compare the efficacy of triple, sequential and concomitant therapies to determine the best first line treatment in Palestine. Surprisingly, there was no statistical significance in the eradication rates between any of the treatment regimens.

The eradication rates achieved by the three protocols were relatively low between 70 and 77%. For triple therapy, the results were similar to other countries as the eradication rates with triple therapy have declined to unacceptable low rates in most countries by the early 2000s<sup>[14]</sup>. However, the eradication rates of sequential and concomitant therapies that were obtained in this study were lower than other countries<sup>[8,13,16-18]</sup>.

The sequential therapy had been evaluated in various randomized trials and therapeutic success was confirmed overall with respect to the standard triple therapy<sup>[19]</sup>. Moreover, several studies showed that concomitant therapy is equally effective as sequential therapy<sup>[12,13]</sup>. The rationale for the different eradication success rates in different areas of the world can be attributed mainly to *H. pylori* resistance, which shows great variety even within individual societies.

Despite its increasing resistance; the current standard triple therapy, as recommended for *H. pylori* eradication by different clinical societies and their guidelines based on a PPI combined with clarithromycin and amoxicillin and/or metronidazole, continues to be the first-line option indifferent countries around the globe<sup>[20-26]</sup>.

The combination of PPI-amoxicillin-levofloxacin is a good option as second-line therapy. In the case of failure of second-line therapy, the patients should be evaluated using a case-by-case approach. European guidelines recommend culture before the selection of a third-line treatment based on the microbial antibiotic sensitivity. *H. pylori* isolates after two eradication failures are often resistant to both metronidazole and clarithromycin. The alternative candidates for third-line therapy are quinolones, tetracycline, rifabutin and furazolidone<sup>[27-30]</sup>. None of the previous options is guaranteed to achieve high eradication rates. Thus, therapies based on new antibiotics should be introduced to overcome the problem of resistance.

We have an ethical question, is it ethical to use any of these therapies? And what would be the best alternative eradication therapy of this global microorganism<sup>[31]</sup>? There are no clear answers especially at a place of relatively limited resources.

## CONCLUSION

*H. pylori* is still a major health problem in our region (36% prevalence in this study) triple, sequential and concomitant use of different antibiotics may not add much to eradication rates, and an urgent new regimen with novel antibiotics is mandatory. The eradication rates were low with the three protocols, less than 80%, and were not significantly different as first line treatment of *H. pylori*. The sequential and concomitant therapies were not superior to standard triple therapy in our study.

## REFERENCES

- 1 Suerbaum S, Michetti P. *Helicobacter pylori* infection. *N Eng J Med* 2002; **347**: 1175-1186
- 2 European *Helicobacter Pylori* Study Group (EHPG). Current concepts in the management of *Helicobacter pylori* infection—the Maastricht 2-2000 Consensus Report. *Aliment Pharmacol Ther* 2002; **16**: 167-180
- 3 Howden CW, Hunt RH. Guidelines for the management of *Helicobacter pylori* infection. Ad Hoc Committee on Practice Parameters of the American College of Gastroenterology. *Am J Gastroenterol* 1998; **93**: 2330-2338
- 4 Me'graud F. *H. pylori* antibiotic resistance: prevalence, importance, and advances in testing. *Gut* 2004; **53**: 1374-1384
- 5 Vakil N. *Helicobacter pylori* treatment: a practical approach. *Am J Gastroenterol* 2006; **101**: 497-499
- 6 Moayyedi P. Sequential regimens for *Helicobacter pylori* eradication. *Lancet* 2007; **370**: 1010-1012
- 7 Zullo A, De FV, Hassan C, Morini S, Vaira D. The sequential therapy regimen for *Helicobacter pylori* eradication: a pooled-data analysis. *Gut* 2007; **56**: 1353-1357
- 8 Jafri NS, Hornung CA, Howden CW. Meta-analysis: sequential therapy appears superior to standard therapy for *Helicobacter pylori* infection in patients naive to treatment. *Ann Intern Med* 2008; **148**: 923-931
- 9 Graham DY, Lu H, Yamaoka Y. Therapy for *Helicobacter pylori* infection can be improved: sequential therapy and beyond. *Drugs* 2008; **68**: 725-736
- 10 Treiber G, Ammon S, Schneider E, Klotz U. Amoxicillin/metronidazole/omeprazole/clarithromycin: a new, short quadruple therapy for *Helicobacter pylori* eradication. *Helicobacter* 1998; **3**: 54-58
- 11 Okada M, Oki K, Shirota T, Seo M, Okabe N, Maeda K, Nishimura H, Ohkuma K, Oda K. A new quadruple therapy for the eradication of *Helicobacter pylori*. Effect of pretreatment with omeprazole on the cure rate. *J Gastroenterol* 1998; **33**: 640-645
- 12 Wu DC, Hsu PI, Wu JY, Opekun AR, Kuo CH, Wu IC, Wang SS, Chen A, Hung WC, Graham DY. Sequential and concomitant therapy with four drugs is equally effective for eradication of *H. pylori* infection. *Clin Gastroenterol Hepatol* 2010; **8**: 36-41
- 13 Yanai A, sakamoto K, Akanuma M, Ogura K, Maeda S. Non Bismuth quadruple therapy for first line *Helicobacter pylori* eradication: a randomized study in Japan. *World J Gastrointest Pharmacol Ther* 2012; **3**: 1-6
- 14 Graham DY, Fischbach L. *Helicobacter pylori* treatment in the era of increasing antibiotic resistance. *Gut* 2010; **59**: 1143-1153
- 15 Okada M, Nishimura H, Kawashima M, Okabe N, Maeda K, Seo M, Ohkuma K, Takata T. A new quadruple therapy for *Helicobacter pylori*: influence of resistant strains on treatment outcome. *Aliment Pharmacol Ther* 1999; **13**: 769-774
- 16 Essa AS, Kramer JR, Graham DY, Treiber G. Meta-analysis: four-drug, three-antibiotic, non-bismuth-containing "concomitant therapy" versus triple therapy for *Helicobacter pylori* eradication. *Helicobacter* 2009; **14**: 109-118
- 17 Sánchez-Delgado J, Calvet X, Bujanda L, Gisbert JP, Titó L, Castro M. Ten-day sequential treatment for *Helicobacter pylori* eradication in clinical practice. *Am J Gastroenterol* 2008; **103**: 2220-2223
- 18 Gao XZ, Qiao XL, Song WC, Wang XF, Liu F. Standard triple, bismuth pectin quadruple and sequential therapies for *Helicobacter pylori* eradication. *World J Gastroenterol* 2010; **16**: 4357-4362
- 19 Gatta L, Vakil N, Leandro G, Di MF, Vaira D. Sequential therapy or triple therapy for *Helicobacter pylori* infection: systematic review and meta-analysis of randomized controlled trials in adults and children. *Am J Gastroenterol* 2009; **104**: 3069-3079
- 20 Malfertheiner P, Megraud F, O'Morain C et al. Current concepts in the management of *Helicobacter pylori* infection: the Maastricht III Consensus Report. *Gut* 2007; **56**: 772-781
- 21 Asaka M, Kato M, Takahashi S, Fukuda Y, Sugiyama T, Ota H, Uemura N, Murakami K, Satoh K, Sugano K; Japanese Society for *Helicobacter* Research. Guidelines for the management of *Helicobacter pylori* infection in Japan: 2009 revised edition. *Helicobacter* 2010; **15**: 1-20
- 22 Bourke B, Ceponis P, Chiba N, Czinn S, Ferraro R, Fischbach L, Gold B, Hyunh H, Jacobson K, Jones NL, Koletzko S, Lebel S, Moayyedi P, Ridell R, Sherman P, van Zanten S, Beck I, Best L, Boland M, Bursey F, Chaun H, Cooper G, Craig B, Creuzenet C, Critch J, Govender K, Hassall E,

- Kaplan A, Keelan M, Noad G, Robertson M, Smith L, Stein M, Taylor D, Walters T, Persaud R, Whitaker S, Woodland R; Canadian Helicobacter Study Group. Canadian Helicobacter Study Group Consensus Conference: update on the approach to Helicobacter pylori infection in children and adolescents – an evidence-based evaluation. *Can J Gastroenterol* 2005; **19**: 399–408
- 23 Caselli M, Zullo A, Maconi G, Parente F, Alvisi V, Casetti T, Sorrentino D, Gasbarrini G; Working Group of the Cervia II Meeting. "Cervia II Working Group Report 2006": guidelines on diagnosis and treatment of Helicobacter pylori infection in Italy. *Dig Liver Dis* 2007; **39**: 782–789
- 24 Chey WD, Wong BC. American College of Gastroenterology guideline on the management of Helicobacter pylori infection. *Am J Gastroenterol* 2007; **102**: 1808–1825
- 25 Fischbach W, Malfertheiner P, Hoffmann JC, Bolten W, Bornschein J, Götze O, Höhne W, Kist M, Koletzko S, Labenz J, Layer P, Miehle S, Morgner A, Peitz U, Preiss J, Prinz C, Rosien U, Schmidt W, Schwarzer A, Suerbaum S, Timmer A, Treiber G, Vieth M; German society for hygiene and microbiology; German society for pediatric gastroenterology and nutrition e. V; German society for rheumatology. S3-guideline "Helicobacter pylori and gastroduodenal ulcer disease" of the German society for digestive and metabolic diseases (DGVS) in cooperation with the German society for hygiene and microbiology, society for pediatric gastroenterology and nutrition e. V., German society for rheumatology, AWMF-registration-no. 021/001. *Z Gastroenterol* 2009; **47**: 1230–1263
- 26 Fock KM, Katelaris P, Sugano K, Ang TL, Hunt R, Talley NJ, Lam SK, Xiao SD, Tan HJ, Wu CY, Jung HC, Hoang BH, Kachintorn U, Goh KL, Chiba T, Rani AA; Second Asia-Pacific Conference. Second Asia-Pacific Consensus Guidelines for Helicobacter pylori infection. *J Gastroenterol Hepatol* 2009 **24**: 1587–1600
- 27 Gisbert JP, Morena F. Systematic review and meta-analysis: levofloxacin-based rescue regimens after Helicobacter pylori treatment failure. *Aliment Pharmacol Ther*, 2006, **23**(8): 35–44
- 28 Saad RJ, Schoenfeld P, Kim HM, Chey WD. Levofloxacin-based triple therapy versus bismuth-based quadruple therapy for persistent Helicobacter pylori infection: a meta-analysis. *Am J Gastroenterol* 2006, **101**: 488–496
- 29 Qasim A, Sebastian S, Thornton O, Dobson M, McLoughlin R, Buckley M, O'Connor H, O'Morain C. Rifabutin- and furazolidone-based Helicobacter pylori eradication therapies after failure on standard first- and second-line eradication attempts in dyspepsia patients. *Aliment Pharmacol Ther* 2005, **21**: 91–96
- 30 Zullo A, Ierardi E, Hassan C, De Francesco V. Furazolidone-based therapies for Helicobacter pylori infection: A pooled-data analysis. *Saudi J Gastroenterol* 2012; **18**: 11–17
- 31 Graham DY, Fischbach LA. Letter: The ethics of using inferior regimens in H. pylori randomized trials. *Aliment Pharmacol Ther* 8 MAR 2012.

**Peer reviewers:** Claudio Chiesa, MD, Institute of Translational Pharmacology, National Research Council, Via del Fosso del Cavaliere, 100, 00133-Rome, Italy; Orhan Sezgin, Professor Dr., Gastroenterology Department, Faculty of Medicine, Mersin University, Mersin, 33100, Turkey.