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Sequential and concomitant non-bismuth quadruple therapies are ineffective for *H. pylori* eradication in Palestine. A randomized trial*

Yasser Abu-Safieh#, Hanin Yamin

Internal Medicine and GI Department, Specialized Arab Hospital, Affiliated with School of Medicine, An-Najah University, Nablus, Palestine
Email: #yaserasaf@hotmail.com

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ABSTRACT

Background: Increasing clarithromycin resistance has undermined the effectiveness of traditional clarithromycin-containing triple eradication therapy of *Helicobacter pylori* infections. Sequential and concomitant therapies show improved outcome with clarithromycin resistance. Aim: To evaluate the effectiveness of sequential and concomitant 4-drug non-bismuth therapies for eradication of *Helicobacter pylori* in a prospective, randomized, clinical trial conducted in Palestine. Patients and Methods: Patients who underwent upper endoscopy for a clinical indication and tested positive for rapid urease test were included. Subjects randomly allocated into two groups: One received a modified sequential therapy: esomeprazole 40 mg OD and amoxicillin 1 g BID for 5 days then esomeprazole 40 mg OD, clarithromycin 500 mg BID and tinidazole 500 mg BID for another 5 days. The other group received concomitant therapy in which the same 4 drugs and doses were all given daily for 10 days. Stool antigen was tested 4 weeks after completion of treatment. Results: Five hundred thirty three (533) patients were tested for *H. pylori* and 180 (34%) were positive; 141 patients were included in the study and 112 patients completed. The overall per protocol eradication rate was (74%; 95% CI = 65.9% - 82.1%). The eradication rates for sequential therapy was, (70.9%; 95% CI = 58.9% - 82.9%) and for concomitant therapy (77.2%; 95% CI = 66.3% - 88.1%). The results intention-to-treat were: sequential 61%, concomitant 57%. Conclusion: Neither sequential nor concomitant therapy achieved an acceptable *H. pylori* eradiation rate in Palestine.

Keywords: *Helicobacter pylori*; Eradication Therapies; Sequential Therapy; Concomitant Therapy

1. INTRODUCTION

Helicobacter pylori infection causes peptic ulcers, gastric mucosa—associated lymphoid tissue lymphoma (MALT lymphoma), and gastric cancer [1]. Standard treatments for *H. pylori* infection endorsed by US and European authorities contain clarithromycin or metronidazole in conjunction with other antibiotics and acid inhibitors [2,3]. The prevalence of clarithromycin and metronidazole resistance has increased substantially in recent years along with a corresponding decrease in the eradication rate for *H. pylori* infections [4]. Eradication rates in most Western countries have generally declined to unacceptable levels such that therapy fails in approximately 1 in 5 patients [5]. A simple treatment regimen that would return eradication levels to those seen at the advent of *H. pylori* treatment is urgently needed [5]. 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 approach to the problem of clarithromycin resistance has been to administer the drugs sequentially [6,7]. 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 [6-8]. The difference between the two approaches was related to improved results with clarithromycin resistant strains [6,7]. 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 [6,9]. It has been proposed that the same four drugs (a PPI, clarithromycin, metronidazole, and amoxicillin) can be given concomitantly as a non sequential four drug, three antibiotic non-bismuth containing quadruple therapy [10,11], and

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#Corresponding author.

clinical studies have shown that the efficacy of this regimen is equivalent to sequential therapy [12,13]. Palestine is a region where *H. pylori* infection and resistance to antimicrobial, among *H. pylori* strains, is thought to be high. These therapies have not formally been tested in Palestine. The aim of this study was to compare the efficacy of sequential and concomitant (non-bismuth) quadruple therapies for *H. pylori* eradication in a prospective, randomized, comparative clinical trial in Palestine.

2. MATERIALS AND METHODS

2.1. Patients and Medications

This study was a randomized trial performed at the GI clinic in Specialized Arab Hospital, Nablus, Palestine between April 2010 and January 2012. Patients presenting with dyspepsia or epigastric pain, and underwent upper endoscopy, with 2 antral biopsies. Those who tested positive for *H. pylori* by rapid urease testing (RUT) were included in this study. The exclusion criteria were: 1) patients younger than 18 years; 2) allergy to the antibiotics; 3) taking antibiotic or PPI within the 2 weeks before testing; and 4) active upper GI bleeding.

The study was approved by IRB, School of Medicine, An Najah University, and all subjects signed informed written consent after the study had been explained to them. Those with a positive RUT and meeting the entry criteria were randomly allocated into two groups: a group receiving sequential therapy consisting of esomeprazole 40 mg od and amoxicillin 1 g bid for 5 days then esomeprazole 40 mg OD, clarithromycin 500 mg, and tinidazole 500 mg both given bid for another 5 days. The other group received concomitant therapy consisting of esomeprazole 40 mg OD (once daily), 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 Specialized Arab Hospital Lab. (ACON Labs, *Foresight*® *H. pylori* Antigen EIA Test Kit) done four weeks after completion of treatment. Randomization was done by sealed opaque envelopes, with a given number for each patient, was done by our medical secretary.

2.2. Statistical Analysis

Per protocol analysis was used as the primary comparison of the eradication rates among the treatment regimens. Intention-to-treat included all subjects who received at least one dose of medication. 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. X^2 ($P < 0.05$) was used. With confidence interval (CI = 95%).

3. RESULTS

The total number of unique patients who underwent upper endoscopy during the study period was 1122 and 533 were tested by RUT. The total number of positive RUTs was 180 (34%); 39 patients were excluded for reasons listed in the methods. A total of 141 patients were included in the study and 112 patients (79%) completed the study. As shown in **Tables 1** and **2**, the two groups did not differ significantly in age, sex, endoscopic findings, or dropout rates.

The overall PP eradication rate was 83/112 (74%; 95% CI = 65.88% - 82.12%). In per protocol analysis, the eradication rates were 39/55 (70.9%; 95% CI = 58.9% - 82.9%) and 44/57 (77.2%; 95% CI = 66.3% - 88.1%) in those receiving sequential or concomitant therapies (p value = 0.45). The ITT eradication rates were 39/64 (61%), 44/77 (57%) for sequential or concomitant therapies, respectively.

It was found that the overall eradication rate was 76.6% for female and 69.8% for males (p = 0.325).

Patient compliance with the therapies was very good (the patients were seen 10 days after starting the regimen for 2 main reasons, 1-side effects of therapy, and 2-compliance, we count how many tablets left, it was writ-

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

Patients characteristics (n)	Sequential	Concomitant
Number of patients enrolled in the study (141)	64	77
Number of patients completed the study (112)	55	57
Age (yr) mean ± standard deviation	38.4 ± 13	41.412
Sex (F/M) %	(50.9/49.1)	(47.2/52.8)
Dropout, n (%)	9 (14%)	20 (26%)

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

Endoscopic diagnosis	Sequential	Concomitant
	Number (%)	Number (%)
Gastritis	32 (58.2)	24 (42.9)
Duodenitis	8 (14.5)	10 (17.9)
Gastric ulcer	4 (7.3)	4 (7.1)
Duodenal ulcer	16 (29.1)	11 (25.6)
GERD	11 (20)	12 (21.4)
Gastric cancer	0 (0)	1 (1.8)
Candida esophagitis	3 (5.5)	1 (1.8)

Table 3. Antibiotic resistance in *H. pylori* isolates from selected countries in Middle East.

Country	Number tested	Antibiotics		
Middle East		Amoxicillin	Metronidazole	Clarithromycin
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	-

ten on each prescription, the total number of tablets of each drug) and not different among the two groups. The complete follow up rate was 79%. No serious side effects were reported by the patients.

4. DISCUSSION

The aim of this study was to compare the efficacy of sequential and concomitant therapies to determine if either was suitable for use in Palestine. Somewhat surprisingly, neither proved effective as the eradication rates achieved by the two protocols were unacceptably low. For triple therapy the eradication rate declined to unacceptable lower rates in most countries by the early 2000s [14]. The eradication rates of sequential and concomitant therapies obtained in this study were lower than most other countries [8,13,15-18]. The rationale for the different eradication success rates in different areas of the world can most likely be attributed to differences in the prevalence of resistance.

In regard to clarithromycin resistance in the Middle East; resistance in Bahrain was 33% [19], in Egypt 3% [19], in Israel 10% [19], in Lebanon 2% [19], in Saudi Arabia 4% [19] and in Iran 23% [20]. See **Table 3**.

Studies evaluating concomitant regimen from Europe, Asia, and North America from 19 studies (2070 patients) revealed a mean cure rate (intension-to-treat) of 88% [21]. However, a recent study from Latin America by Greenberg *et al.*, had disappointing results with a 74% eradication rate for a 5 day concomitant regimen [22]. Another negative study was in Turkey showed a 75% eradication rate with a higher dose of metronidazole and 14 days duration of treatment [23]. And another study performed in Korea by Choi *et al.* achieved only a 63% cure rate in (38) patients [24].

In Palestine clarithromycin-containing therapies provide ineffective results for *H. pylori* eradication. We have an ethical question, is it ethical to use any of these therapies? Susceptibility testing is currently not available and trial and error are required to identify locally effective regimens.

5. CONCLUSION

H. pylori is still a major health problem in our region (34% prevalence in this study) and neither sequential nor concomitant (non-bismuth quadruple therapies) proved useful here. Additional studies with different antibiotics will be needed to identify any regimen that provides an acceptable eradication rate.

6. THE AUTHORS' CONTRIBUTION

1) Dr. Abu-Safieh, all patient were seen and evaluated by me and endoscopy and RUT, biopsy was done by me and interpretation of the test, inclusion and exclusion of the cases, and follow up of symptoms after treatment,

2) Dr. Yamin, my resident, she collected and reviewed the literature put up the references and shared in writing the proposal and doing most of the statistical analysis. Follow up the stool Ag results.

Randomization was done by our medical secretary, she was given equal number of 2 prescriptions, A, B, (Sequential, and concomitant respectively), sealed opaque envelop. No one of the authors knew the treatment which was given when the patient is coming for follow up. We got to know it after stool Ag results.

The Institutional Research Board (IRB) of school of medicine in An-Najah University, approved the study before starting. (I am teaching GI and internal Medicine in the same university).

The procedure and the research were explained to the patients and a written consent signed.

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