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Full Length Research Paper

Treatment of Helicobacter Pylori, comparison of three regimens, a double blind randomized trial

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Helicobacter pylori **infection is a common and serious bacterial infection but therapies are often prescribed empirically, increasingly compromised by antimicrobial resistance, and provide inferior results compared with antimicrobial therapies for other common infectious diseases. The aim of this study is to compare the effectiveness of standard triple, sequential, and concomitant therapies for eradication of *H. pylori* in a randomized, double-blinded, comparative clinical trial conducted in Palestine. 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 40mg 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 40mg OD, Clarithromycin 500 mg BID and Tinidazole 500mg BID for another 5 days, and Group C received concomitant therapy; Esomeprazole 40 mg OD, Amoxicillin 1g, Tinidazole 500mg 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 appropriately used to compare the eradication rates. 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 an intention to treat 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 rates achieved by the concomitant therapy was higher than both sequential and triple therapy, these differences were not statistically significant. 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.**

Key words: Helicobacter pylori, eradication therapies, ulcers, concomitant therapies

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 that have been endorsed by U.S. and European authorities rely on 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, and there has been a corresponding decrease in the eradication rate for H. pylori infection [(4)]. Eradication rates in most Western countries have declined to unacceptable levels. Eradication therapy fails in approximately 1 in 5 patients [(5)]. A simple and short 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 successful 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

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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 was therefore proposed that the same four drugs (a PPI, clarithromycin, metronidazole, and amoxicillin) can be given concomitantly as a nonsequential 4-drug, 3-antibiotic non-bismuth containing quadruple therapy to overcome this problem [10,11]. Interestingly, the efficacy of this therapy regimen was equivalent to sequential therapy in some studies[12,13]. Several studies in various countries have proven its efficacy with eradication rates above 90%[14,15]. With application of this regimen the treatment could even be shortened to 5 days[15]. 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 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 , 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 40mg 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 40mg bid , Clarithromycin 500 mg, and Tinidazole 500mg both given bid for another 5 days. Group (C) received concomitant therapy; Esomeprazole 40 mg OD, Amoxicillin 1g, Tinidazole 500mg , and Clarithromycin 500 mg, all given bid, for 10days. Eradication of H. pylori was assessed, stool antigen was done four weeks after completion of treatment.

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. X^2 ($P < 0.05$) was used.

RESULTS

The total number of unique patients who underwent upper endoscopy during the study period was 1,122, 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 drop out rates. Table 1.

The overall eradication rate was 73% (xx/yy). In an ITT the eradication rates were xxx. 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.

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 between70 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[14]. However, the eradication rates of sequential and concomitant therapies that were obtained in this study were lower than other countries[8,13,16-18].

The sequential therapy had been evaluated in various randomized trials and therapeutic success was confirmed overall with respect to the standard triple therapy[19]. Moreover, several studies showed that concomitant

Table1. 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(yr) mean +standard deviation	40.37+14.1	38.49+13.78	41.42+12.46
Sex(F\M)%	(51\49)	(50.9\49.1)	(47.2\52.8)
Drop out			

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

Endoscopic diagnosis	Group A Number (%)	Group B Number (%)	Group C 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(%)[a]	70.6	70.9	77.2
Eradication rate PP per sex %(M\F)	(68\73.1)[b]	(66.7\75)[c]	(73.5\82)[d]

[a] P value=.435(>.05) between A&C. P=.449(>.05) between B&C.P=.971(>.05) between A&B

[b] p value =.764(>.05), [c] p value =.562(>.05) , [d] p value=.529(>.05)

therapy is equally effective as sequential therapy[12,13]. 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[20-26].

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[27-30].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[31] ? 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.

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