The efficacy of sequential treatment for *Helicobacter Pylori* eradication in dyspeptic patients

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Abstract

Myanmar is a high prevalence area of *H pylori* infection with sero-prevalence rate of 69%. The clarithromycin-based triple therapy is commonly used as empiric first line treatment for *H pylori* infection in Myanmar. However, the efficacy of sequential treatment for Myanmar patients with *H pylori* infection has not been investigated. The objective of the present study is to determine the efficacy and safety of sequential treatment for *Helicobacter pylori* eradication in dyspeptic patients. A total of 100 dyspeptic patients aged > 18 years with proved *Helicobacter pylori* infection were randomly assigned to receive either 10 day sequential therapy or 10 day triple therapy. After completion of treatment, compliance and side effects were assessed. The outcomes of the eradication therapy were assessed 4 weeks after treatment by the 13C urea breath test. The success rate of *H pylori* eradication between the sequential therapy and the triple therapy was not significant (85.7% Vs 95.1%, p = 0.147). The triple therapy had 66.7% relative risk reduction (RRR), 9.4% absolute risk reduction (ARR) and 11 number need to treat (NNT). The adverse events between two study groups did not differ significantly (23.8% Vs 31.7%, P = 0.422). Good compliance was achieved in all patients of two study population. The result of this study could not prove that the efficacy of sequential treatment was superior to that of triple treatment for *H pylori* eradication in Myanmar dyspeptic patients.

Introduction

Helicobacter pylori is a major cause of chronic gastritis, peptic ulcer disease, gastric carcinomas and gastric mucosa-associated lymphoid tissue (MALT) lymphoma and has been recognized as a class I gastric carcinogen in 1994 by the International Agency for Research on Cancer of the World Health Organization[1]. Estimates suggest that more than 50% of the world's population is infected with the bacterium. Among Southeast Asian countries, the reported seroprevalence rate was 35.9% in Malaysia, 31% in Singapore and 57% in Thailand[2]. In Myanmar, the overall seroprevalence of *H pylori* is 69%[3].

The triple drug treatment including a proton pump inhibitor, clarithromycin and amoxicillin or metronidazole to treat *H pylori* infection, proposed at the first Maastricht conference, has become

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universal since all the consensus conferences and guidelines around the world recommended it[4]. However, the most recent data show that this combination has lost efficacy, with an eradication rate ranging from 71% in the United States to 60% in Western Europe[5]. The eradication rate is uniformly less than the 80% target set at the beginning and well below what should be expected for treatment of an infectious disease[6]. One of the main reasons for this poor performance is the increasing number of strains of *H pylori* that are resistant to antibiotics. In Myanmar, a population-based endoscopic survey of *Helicobacter pylori* infection 2011 showed that metronidazole resistance was 37.3%, clarithromycin and amoxicillin resistance were 0%[7].

Investigators in different parts of the world have made several attempts to find new regimens as a more effective alternative to traditional triple therapies. One of these is sequential therapy. The sequential therapy (ST), consisting of 5 days of dual therapy (PPI plus amoxicillin) followed by 5 days of triple therapy (PPI plus clarithromycin plus tinidazole) has recently attracted widespread attention. However, controversial results regarding the sequential treatment have emerged in various studies worldwide. Analysis of the earlier studies showed promising results, where eradication rates with sequential therapy were 93.4% compared with 76.9% for standard triple therapy[8]. The number of studies were small and most of them were done in Italy. Recently Gatta et al (2013) analyzed 14 studies comparing sequential therapy with a triple therapy regimen in 2746 patients. The eradication rate reported was 84.3% (79.8% to 88.4%) for the sequential therapy and 75.3% (69.6% to 77.9%) for the triple therapy lasting 10 days[9].

Since then, several randomised controlled trials have been carried out in different parts of the world comparing sequential therapy with triple therapy providing a glimpse into current eradication rates with new and old treatments. Hence, we need to clarify whether it is time to adopt sequential therapy as a standard first line therapy for *H pylori* infection in our country.

Objectives

The objectives of the study was to compare the success rate of the sequential treatment with standard triple therapy in *Helicobacter pylori* eradication and to compare the frequency of adverse events of the two different eradication regimens.

Materials and Method

A hospital based randomized controlled trial was used to study 100 dyspeptic patients with *H pylori* infection undergoing OGDS at Department of Gastroenterology in Yangon General Hospital from December 2012 to June 2014. Patients were randomly assigned into two groups, A (sequential treatment) and B (triple treatment) according to Random Number Table. SPSS 15.0 Statistical Software was used for data analysis. Descriptive statistics (age, sex, alcohol, smoking, BMI, adverse events, compliance) were shown with frequency and percentage. The mean age and BMI were expressed as a mean and standard deviation (SD) expressed as count and percent. Associa-

tions between eradication rates of sequential treatment and triple treatment were tested by Chi-square tests. The effectiveness of triple therapy was expressed as absolute risk reduction, relative risk reduction and number need to treat. Statistical significant level was demarcated at $P < 0.05$.

Results

Seventeen patients (8 patients from sequential and 9 patients from triple therapy) were lost to follow up. The anticipated drop-out rate was 12 patients. Hence, the outcome comparison between two study groups was done on the remaining 83 patients. (42 in sequential group & 41 in triple group). By evaluating the demographic aspects of the affected individuals, the present study demonstrated that the two study groups did not differ significantly in age, smoking, alcohol drinking, BMI and endoscopic diagnosis. However, the present study showed that female gender is significantly higher in sequential therapy than triple therapy. Among 83 patients, the eradication rates according to groups were as follows: 85.7% (95% CI 71.5% - 94.6%) for sequential therapy group and 95.1% (95% CI 83.5% - 99.4%) for triple therapy group. Although eradication rate of triple therapy was greater than that of sequential therapy, there was no statistical difference (P = 0.147) (Figure 1). The triple therapy had 66.7% of relative risk reduction (RRR), 9.4% of absolute risk reduction (ARR) with 11 number need to treat (NNT) (Table 1). In total, 10 (23.9%) patients in sequential treatment group and 13 (31.7%) patients in triple treatment group complained of mild self-limiting side effects. None of the side effects resulted in discontinuation of therapy. There was no statistically significant association between the study groups. (p = 0.422) (Table 2). Good compliance was achieved in 42 (100%) patients in sequential treatment group and in 41 (100%) patients in triple treatment group (Table 3).

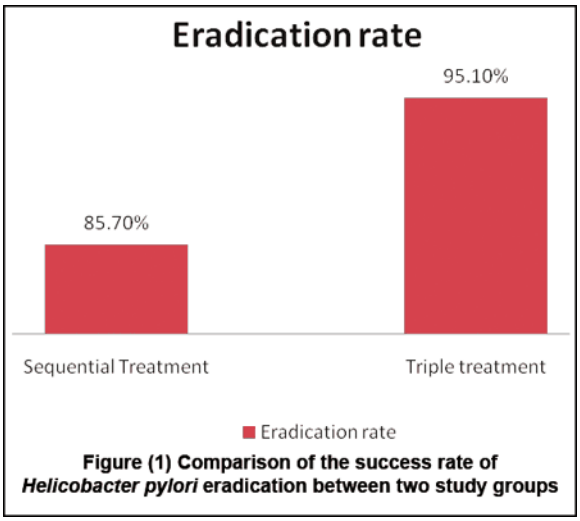

Figure (1) Comparison of the success rate of *Helicobacter pylori* eradication between two study groups

Table (1) Effectiveness of Triple therapy on *Helicobacter pylori* eradication

	Failure rate		RRR (CER-EER) / CER	ARR (CER-EER)	NNT (1/ARR) 95% CI
	Sequential (CER)	Triple (EER)			
In study	0.143	0.049	66.7%	9.4%	11 (8 - 29)

CER = Control event rate, EER = Experimental event rate, RRR = Relative risk reduction, ARR = Absolute risk reduction, NNT = Number need to be treated to prevent one more event

Table (2) adverse events between two groups

Side effects	Sequential therapy (N = 42) n (%)	Triple therapy (N = 41) n (%)	P value
Yes	10 (23.8)	13 (31.7)	0.422
No	32 (76.2)	28 (68.3)	

Table (3) compliance between two groups

Compliance	Sequential therapy (N = 42) n (%)	Triple therapy (N = 41) n (%)
Good (> 80% of pills)	42 (100%)	41 (100%)
Poor (< 80% of pills)	0	0

Discussion

Among 83 patients, the eradication rate for 10 day triple therapy group was 95.1% (95% CI 83.5% - 99.4%). This finding was not in compatible with results from developed countries. Two meta-analyses including more than 53,000 patients showed that the cure rate is, at present, below 80%[10]. Clarithromycin resistance is the major cause of eradication failure for standard triple therapy. In areas with clarithromycin resistance of < 10% [i.e., The Netherlands, Sweden, Ireland, Germany, Malaysia and Taiwan (South)], it is still possible to employ a standard triple therapy to achieve a per-protocol (PP) eradication rate > 90%[11]. In Myanmar, a population-based endoscopic survey of *Helicobacter pylori* infection 2011 showed that metronidazole resistance was 37.3%, clarithromycin and amoxicillin resistance were 0%[7]. So, it can be concluded that low clarithromycin and amoxicillin resistance in our country might lead to the high eradication rate for triple therapy. The new-generation PPIs' efficacy was not affected by CYP2C19 polymorphisms, and they obtained higher eradication rates than first-generation PPIs in extensive metabolizer patients. In this study, we used new generation PPI (rabeprazole) instead of first generation PPI (omeprazole). This might lead to higher eradication rate in triple therapy. The meta-analysis done by Hyuk Yoon et al, 2013 pointed out that extending the duration of Triple treatment (TT) from 7 to 10 days improves the eradication rate of triple therapy[12]. In the present study, we chose 10 days triple treatment and it might be one reason that led to high eradication rate of TT in our population.

In the present study, the eradication rate of sequential therapy was quite similar to that of Aminian K et al (2010) study[13] and Hyuk Soon Choi[14] et al (2012) i.e. (85.7% vs. 80.4% vs. 82.0%). Moreover, it was also proved comparable with a very large and comprehensive meta analysis done by Gatta L15 et al, (2013) which concluded that the overall eradication rate of sequential therapy was suboptimal at 84.3%. The failure of sequential therapy might be expected in settings with high rates of clarithromycin and metronidazole resistance. Clarithromycin containing sequential therapy loses efficacy in the face of clarithromycin resistance between 15% and 20%, and when metronidazole

resistance approaches 40%, thus increasing the likelihood of dual (i.e., clarithromycin + metronidazole) resistance[16]. Hyuk Yoon[12]et al (2013) concluded that the sequential treatment might be able to overcome clarithromycin resistance in the *H pylori* eradication. They concluded that Sequential treatment is mainly suitable for high isolated Clarithromycin resistance (CLA-R) and the efficacy of Sequential treatment (ST) appears to be inadequate when Metronidazole resistance (MET-R), CLA-R and MET-R coexist. This suboptimal efficacy of sequential treatment in area with high metronidazole resistance was well suggested in a recent large RCT from Latin America[12]. In our country the use of metronidazole is common because it is easily available with low cost. It is commonly used as over-the-counter drug in parasitic diseases, gynecological infections and dental infections. Thus, this suboptimal efficacy of ST could be due to high resistance of metronidazole (37.3%) in our country[7].

The overall adverse effects rates were similar in sequential and triple therapy groups (31.7% Vs 23.9%, P value = 0.422). Both treatments were well tolerated. None of side effects resulted in discontinuation of therapy. Most common side effects were diarrhoea and bitter taste. Good compliance (> 80% of prescribed medications) was achieved in 42 (100%) patients in sequential treatment group and in 41 (100%) patients in triple treatment group.

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