

THE EFFICACY OF CONCOMITANT VS CLARITHROMYCIN BASED TRIPLE THERAPY IN *HELICOBACTER PYLORI* INFECTED PEPTIC ULCER PATIENTS

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Helicobacter pylori (*H. pylori*) causes the most common chronic bacterial infection affecting over 50% of the world's population (more than 80% in developing country). Myanmar is high prevalence area of *H. pylori* with varying in different areas. It is responsible for the cause of 90% or more of duodenal ulcers and 60% or more of all gastric ulcer. Recently, Maastricht V Consensus Report recommended that concomitant therapy consisting of PPI, amoxicillin, clarithromycin and a nitroimidazole administered concurrently, should be the preferred first line non-bismuth quadruple therapy. Many researchers around the world have been being encouraged to work on the effectiveness of concomitant treatment nowadays. To compare the efficacy of concomitant and clarithromycin based triple therapy in *H.pylori* infected peptic ulcer patients. This was a hospital based randomized comparative trial conducted on the 120 study population with *H. pylori* positive peptic ulcers, comprising 62 patients in the concomitant therapy and 58 in the triple therapy. In the concomitant therapy group, 7 days regime of four drugs, clarithromycin, amoxicillin, tinidazole and rabeprazole was given and in the triple therapy group, 10 days regime of three drugs, clarithromycin, amoxicillin and rabeprazole was used. The result of the study showed that satisfactory eradication rates had been achieved in both groups, 93.5 % in the concomitant group comparing 87.9 % in the triple therapy group. The concomitant therapy led to a non-statistically significant advantage (6%) over triple therapy. Both therapies showed improvement in peptic ulcer healing with no statistically significant difference. The concomitant treatment regime had non-statistically significant superiority over triple therapy while the triple therapy can still be used as a first line treatment with the use of longer duration.

Keywords: *H.Pylori* infection, clarithromycin based triple therapy, concomitant therapy, peptic ulcer, eradication rate of *H.Pylori* infection, peptic ulcer healing.

INTRODUCTION

Helicobacter pylori (*H. pylori*) has been co-existing with humans for thousands of years, and infection with this bacterium is very common. It causes the most common chronic bacterial infection affecting over 50% of the world's population (more than 80% in developing country)¹. The prevalence of *H. pylori* in Myanmar varies in different areas and it was found out that in general population with dyspeptic symptoms the prevalence was 48%.²

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 Organization³. It is

responsible for the cause of 90% or more of duodenal ulcers and 60% or more of all gastric ulcer⁴.

Although *H. pylori* is susceptible to a number of antimicrobials, *H. pylori* infection has proven challenging to cure because the prevalence of bacterial strains resistant to the most commonly used antimicrobials, in particular clarithromycin (CLA), increases. Most Consensus Conferences and Clinical guidelines recommend the prescription of a triple therapy including a proton pump inhibitor (PPI) and clarithromycin with either amoxicillin or metronidazole, as a first-line treatment.⁵ However, the efficacy of current conventional clarithromycin-based triple therapy has decreased to an unacceptably low level worldwide (lower than 80%).⁶ In general, antibiotic resistance to clarithromycin

has been identified as one of the major factors affecting *H. pylori* eradication rate⁷. 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%⁸.

Therefore, researchers around the world have been working on the establishment of new eradication regime for a long time. Recently, Maastricht V Consensus Report recommended that concomitant therapy consisting of PPI, amoxicillin, clarithromycin and a nitroimidazole administered concurrently, should be the preferred non-bismuth quadruple therapy as it had been shown to be the most effective to overcome antibiotic resistance. Many researchers around the world have been being encouraged to work on the effectiveness of concomitant treatment nowadays and so, in this research, the efficacy of the concomitant therapy had been compared with that of the standard triple therapy in order to provide better eradication treatment to Myanmar people.

METHODS

It is a hospital based randomized comparative study conducted on the 120 study population with *H. pylori* positive peptic ulcers, comprising 62 patients in the concomitant therapy and 58 in the triple therapy and had been carried out from December 2015 to June 2017 at Department of Gastroenterology, Yangon General Hospital. **Inclusion Criteria** is proved *Helicobacter pylori* infected peptic ulcer patients who is >18 years of age. And **Exclusion Criteria** are (1) Patients who had previously received any treatment for *Helicobacter pylori* eradication (2) Patients with acute upper GI bleeding at the time of endoscopy. (3) Patients who had taken proton pump inhibitors, H₂ receptor blockers, any antibiotic in two weeks preceding the study (4) Concomitant anticoagulant usage of enzyme inhibitor (e.g. ketoconazole) (5) Previous gastric surgery (6) Pregnancy or lactation (7) Known allergy to the prescribed antibiotics (8) Patients with malignant ulcer. They were divided randomly into two treatment groups according to the random number table. The first group (A) had received a 7 days concomitant regimen

(Rabeprazole 20 mg BD, Amoxicillin 1 G BD, Clarithromycin 500 mg BD, and Tinidazole 500 mg BD)

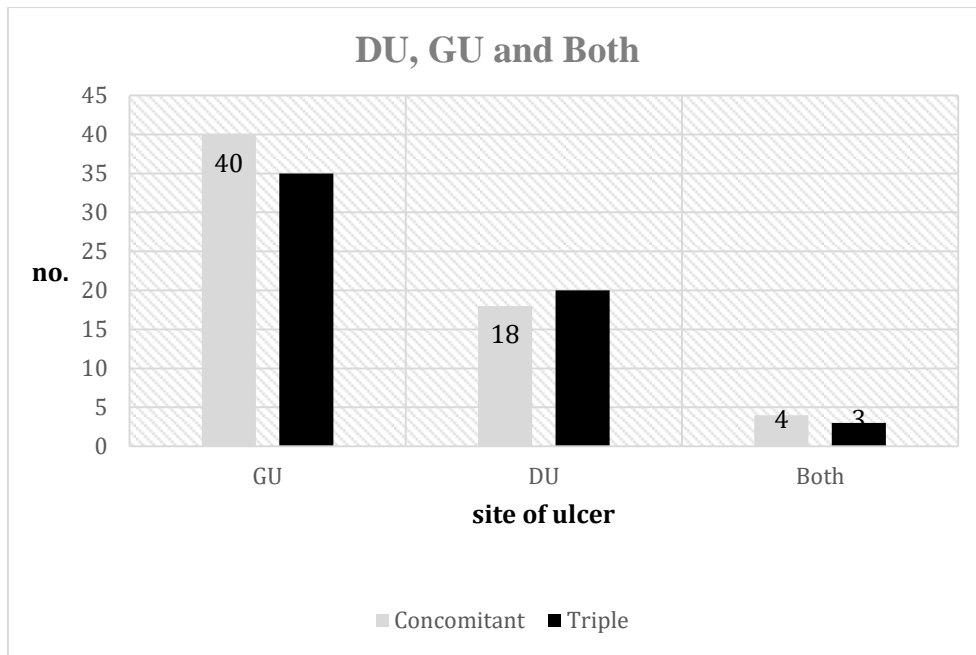
The second group (B) had received standard triple therapy for 10 days (Rabeprazole 20 mg BD, Amoxicillin 1G BD, and Clarithromycin 500 mg BD). Patients had been asked to return 8 weeks from the start of antibiotic treatment to undertake the upper GI endoscopy to determine the outcome of eradication therapy. At that time, the stage of the ulcer had been noted down again and compared with the pretreatment condition. The CLO test was repeated and the eradication of the infection had been determined.

RESULTS

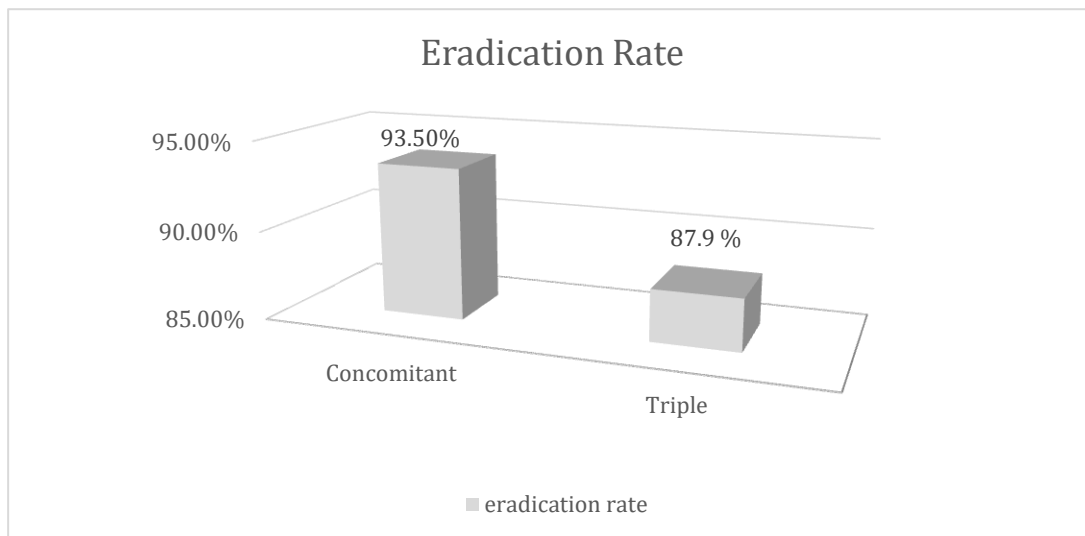
In this study, eleven patients had been lost in the follow up and so total 132 participants were recruited to meet the preset sample size for achieving the statistically strong conclusion. Most of the participants were above 40 years of age. The study included more male proportion comprising 82 out of 120 (68%) and only 31.7% was female. Regarding smoking status, 57 out of 120 patients (47.5%) were non-smokers. Twenty-five patients (20.8%) were current smokers, thirty-eight patients (31.7%) were ex-smokers.

In this study, 73 (60.8%) of 120 patients had never been exposed to alcohol, twenty-six patients (21.7%) were currently drinking alcohol, twenty-one patients (17.5%) were ex-drinkers. The most presenting clinical feature is both haematemesis and melaena which was found in 29 of 120 patients (24%), comprising 11 in the concomitant group and 18 in the triple therapy group.

In figure 1, endoscopic diagnosis, 75 (62, 5%) of 120 patients had gastric ulcer alone and 38 (31.7%) had duodenal ulcer. Only 7 patients had both gastric and duodenal ulcer. In figure 2, after taking eradication treatment, 109 patients (90.8%) showed negative for *H. pylori* test. Eleven patients still showed positive result. In the concomitant group, the eradication rate was 93.5 % and that of the triple therapy group was 87.9%. The difference in eradication rates for the two groups was statistically not significant (p value 0.27).



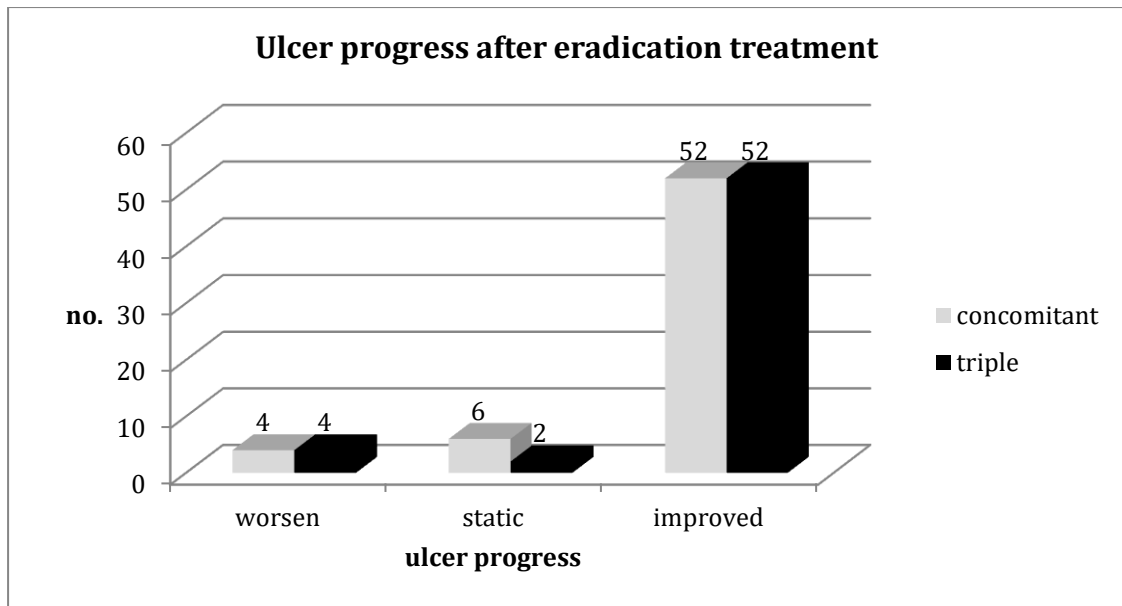
Chi-square = 0.449 p value = 0.79
 Figure (1) Comparison of endoscopic diagnosis between two study groups



Chi-square = 1.203 p value = 0.273
 Figure (2) Eradication rates of the two regimens

As shown in figure 3, after the eradication treatment, ulcer healing was seen in 104 patients (86.7%), 83.9 % in the concomitant group and 89.7 % in the triple therapy group. Unfortunately 8 patients (6.7%) were found to have worse ulcer, 6.5 % of the concomitant group and 6.9 % in the triple therapy group.

Six patients (9.7%) of the concomitant group had ulcers in the static stage comparing with 2 patients (3.4%) of the triple therapy group. Most of the patients did not experience any adverse effects from their respective treatment. However, 38 out of 120 patients (32%) suffered from minor side effects.



Chi-square = 1.869 p value = 0.393
 Figure (3) Ulcer Progress after eradication treatment

DISCUSSION

Most of the socio-demographic characteristics (age, sex, occupation, smoking and alcohol drinking) were similar in both groups and there was no statistically significant difference. In contrary to currently accepted pathology, endoscopic diagnosis in this study showed that gastric ulcer was nearly twice in common than duodenal ulcer. Seventy five (62.5%) of 120 patients had gastric ulcer alone and 38 (31.7%) had duodenal ulcer only. But 7 patients had both gastric and duodenal ulcer. However, there was not statistically significant in the comparing groups concerning the occurrence of GU and DU.

In this study, eradication rate of the 10 days triple therapy group was 87.9%. This finding was quite higher than that in findings of some recent studies and consensus reports from developed countries. The Toronto

Prolonging treatment duration, from 7 to 10 days or from 10 to 14 days, was associated with a significantly higher eradication rate¹¹. In this study, 10 days triple therapy was resulted in 87.9 % eradication rate. Therefore, the eradication rate might be more than 87.9% if duration would be extended to 14 days as recommended.

The eradication rate of 7 days concomitant therapy, twice a day, was 93.5%.

Consensus, a meta-analysis of 12 studies, found that the efficacy of clarithromycin - based triple therapy was decreased from 80% in studies from 2000 to 2005 to only 62% in more recent studies (2006-2011)⁹. However, it was consistent with the result in a recent Myanmar study, in which the eradication rate of 10 day triple therapy in dyspeptic patients was found to be 95%¹⁰. Moreover, *Maastricht V Consensus* reported that rabeprazole and esomeprazole were less effected by CYP2C19 genotype. In this study, rabeprazole 20 mg twice a day had been used as PPI in eradication regime, which might lead to a higher eradication rate than other developed countries. In addition, one of the key factors to influence the eradication rate was duration of regime. One review article concluded that increasing the duration of PPI-based triple therapy raised the *H. pylori* eradication rate.

The efficacy of concomitant therapy was highly depended on clarithromycin and metronidazole resistance. In Myanmar, a population-based endoscopic survey of *Helicobacter pylori* infection 2011 showed that metronidazole resistance was 37.3%.⁸. There had been irrational use of metronidazole which could be available as an over the counter drug without a doctor's prescription.

But, unlike clarithromycin, metronidazole resistance can be overcome to some extent by increasing dose, frequency, and duration of the prescription.

In this study, the eradication rates of two groups were 93.5% for the concomitant group and 87.9% for the triple therapy group respectively. Although 7 days concomitant group yielded a higher eradication rate than 10 days triple therapy group, the difference was not significant statistically. The study had clearly showed that the 10 days triple therapy regime was still effective in eradication treatment. The reason might be due to the fact that the resistance to the main drug, clarithromycin, was still low in Myanmar¹². In this study, improvement of ulcer was seen in 86.7% of cases, but there was no statistically significant between concomitant and triple therapy groups (p value=0.393).

CONCLUSION

This was a hospital based randomized comparative trial conducted on the 120 study population with *H. pylori* positive peptic ulcers, comprising 62 patients in the concomitant therapy and 58 in the triple therapy. In the concomitant therapy group, 7 days regime of four drugs, clarithromycin, amoxicillin, tinidazole and rabeprazole was given and in the triple therapy group, 10 days regime of three drugs, clarithromycin, amoxicillin and rabeprazole was used. The baseline characteristics of the participants were not much different.

The drug compliance was seen to be satisfactory in both regimes with little untoward effects. The result of the study showed that satisfactory eradication rates had been achieved in both groups, 93.5 % in the concomitant group comparing 87.9 % in the triple therapy group. The concomitant therapy led to a non-statistically significant advantage (6%) over triple therapy. Both therapies showed improvement in peptic ulcer healing with no statistically significant difference.

According to the results obtained in this study, it could be concluded that the concomitant treatment regime had non-statistically significant superiority over triple therapy while the triple therapy can still be

used as a first line treatment with the use of longer duration.

CONFLICT OF INTEREST

There is no conflict of interest.

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