COMPARISON OF TRIPLE VS CONCOMITANT THERAPY FOR H. PYLORI INFECTION ERADICATION: A PROSPECTIVE RANDOMIZED CONTROLLED STUDY

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ABSTRACT

Significance: Eradication of *H. pylori* has become interest for research for the optimal regimen. This study aims to compare the efficacy of triple therapy versus concomitant therapy in eradicating *H. pylori* infection. **Methodology:** This is a prospective, open label, randomized controlled trial wherein 110 subjects with symptoms of dyspepsia and esophagogastroduodenoscopy findings of peptic ulcer disease or gastritis were enrolled. The diagnoses of h.pylori infection were confirmed using rapid urease test, histology or giemsa stain. Patients with (a) previous H. pylori eradication therapy, (b) allergic history to the medications used, (c) patients with previous gastric surgery, (d) presence of serious comorbidities and (e) pregnant women will be excluded from the study. 40 mg omeprazole twice daily, 500 mg clarithromycin twice daily, and 500 mg 2 capsule amoxicillin twice daily for 14 days) or concomitant therapy (40 mg omeprazole twice daily, 500 mg clarithromycin twice daily, 500 mg 2 capsule amoxicillin twice daily, and 500 mg metronidazole twice daily for 14 days). H.pylori infection eradication were determined using stool antigen testing after a month free of antibiotics and proton pump inhibitor. **Results:** Ninety (90) percent eradication rate of H. Pylori was achieved with CT (compared to 74.5% in TT, p 0.044). Higher adverse effect profile (34.5% vs 25.4% p-value 0.284) was seen. However, compliance rate (90% vs 83.6% p-value 0.073) was not significantly different. **Conclusion:** The eradication rate for the concomitant therapy was much higher than those of the standard triple therapy and can be used as first line therapy.

Keywords: H.pylori, eradication, concomitant therapy

INTRODUCTION

Helicobacter pylori (H. pylori) has long been globally recognized pathogen known to cause gastric ulcers or related dyspeptic symptoms in many infected patients. Eradication of *H. pylori* has become interest for research for the optimal regimen which are composed of both antibiotics and gastric acid-reducing agents as a standard of treatment. Challenges arise from bacterial antibiotic resistance, lack of follow-up to confirm treatment success/failure, as well as poor compliance due to adverse effect and high pill burden. This study aims to compare the efficacy of Triple therapy versus concomitant therapy in eradicating *H. pylori* infection

The general objective of this study is to determine the efficacy of clarithromycin-based triple therapy versus concomitant therapy among patients with *H.pylori* infection.

Specific objectives

1. To determine the local eradication rate of h. pylori infection.
2. To determine and compare the Helicobacter pylori (H. pylori) eradication rate of conventional clarithromycin-based triple therapy and concomitant therapy.
3. To determine and compare adverse drug events resulting from antibiotic therapy of conventional clarithromycin-based triple therapy and concomitant therapy.

MATERIALS AND METHODS

Study Design and Participants

This is a prospective randomized controlled trial to be conducted from June 2019- December 2019 at University of Santo Tomas Hospital in Manila, Philippines in accordance with the principles of good clinical practice from the Declaration of Helsinki.

All consecutive adult (18-85 years old) patients with symptoms of dyspepsia and esophago-gastro-duodenoscopy findings of peptic ulcer diseases (gastric and duodenal) or gastritis were recruited into this study. The diagnoses of h.pylori infection were confirmed using rapid urease test, histology or giemsa stain. Patients with (a) previous H. pylori eradication therapy, (b) allergic history to the medications used, (c) patients with previous gastric surgery, (d) presence of serious comorbidities and (e) pregnant women were excluded from the study.

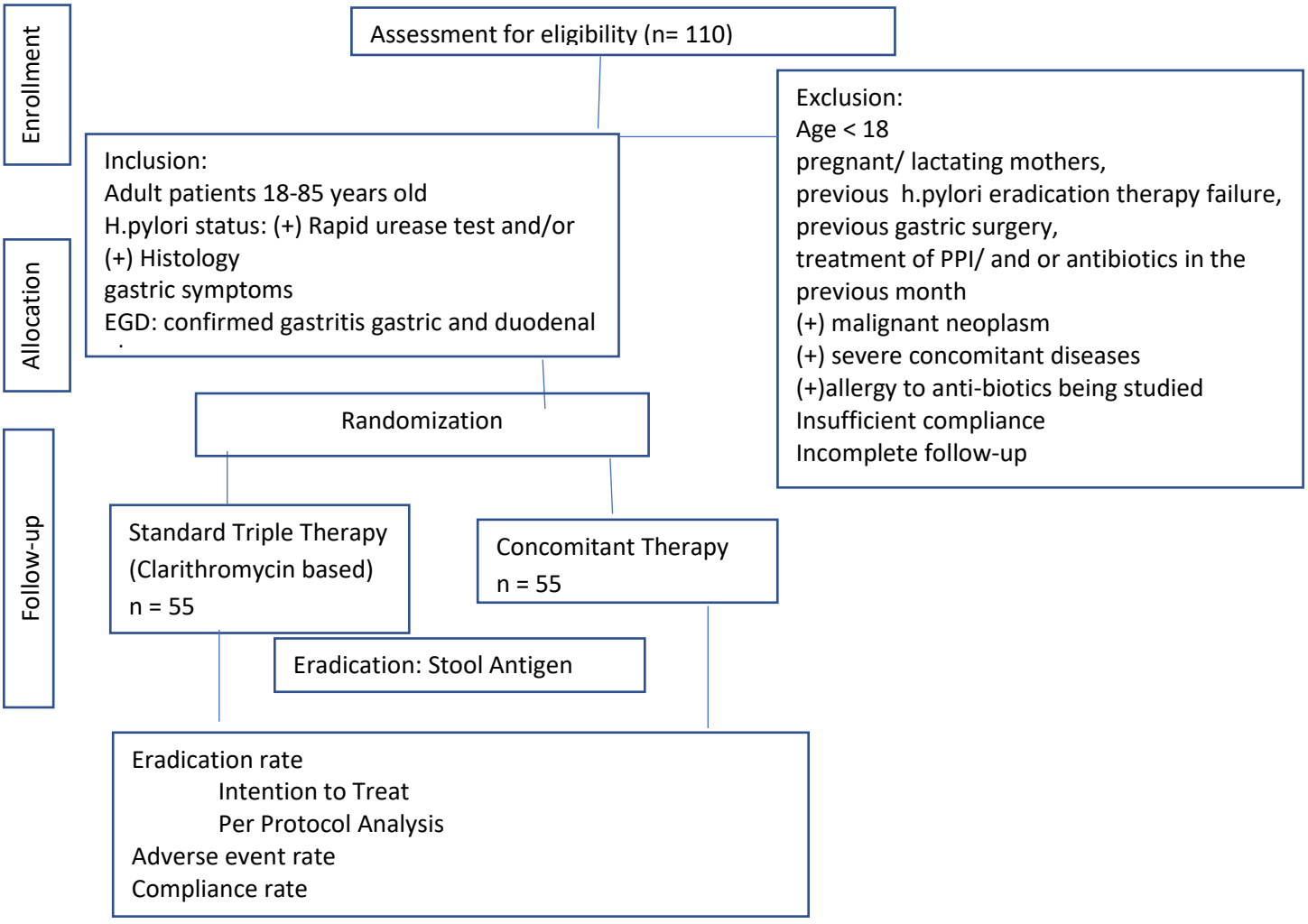
Randomization and Intervention

Patients who met the inclusion criteria were randomized using a computer-generated number sequence, participants were randomly assigned to triple therapy group (40 mg omeprazole twice daily, 500 mg clarithromycin twice daily, and 500 mg 2 capsule amoxicillin twice daily for 14 days) or concomitant therapy (40 mg omeprazole twice daily, 500 mg clarithromycin twice daily, 500 mg 2 capsule amoxicillin twice daily, and 500 mg metronidazole twice daily for 14 days). All drugs will be taken 1 hour before a meal (breakfast or dinner)

An independent research assistant generates the computerized random number sequence. The sequence was concealed in a sealed opaque envelope until the intervention was assigned. After the written informed consents were obtained from the participants, an independent research assistant assigned the therapies according to the treatment allocations which were kept in the opaque envelopes.

Patients were asked to follow up at the 2nd week to assess drug compliance and adverse events. The patients with peptic ulcers found on the initial endoscopy received an additional 4 to 6 weeks monotherapy with 40 mg omeprazole orally once daily after 2 weeks treatment of anti-biotics, while patients with esophagitis and gastritis took 4 weeks of proton pump inhibitor following eradication therapy. H. pylori infection eradication were determined using stool antigen testing after a month free of antibiotics and proton pump inhibitor.

Flowchart of the patients in the study.



Outcome measures

At the start of the study, demographics, indication and result of esophagogastroduodenoscopy. smoking and drinking history, NSAID use as well as comorbidities were recorded. The primary outcome for this study was eradication rate analyzed as intention to treat and per protocol analysis. Secondary outcome were frequency of adverse events and compliance rate.

Definition of Terms:

Compliance is defined as consumption of more 80% assigned treatment regimen, More specifically 12 pieces of amoxicillin, 6 pieces of Clarithromycin and 6 pieces of metronidazole.

Dropout is defined as those patient wherein outcome cannot be assessed at the end of the study.

Statistical Analysis

A sample size of 110 respondents yielded a power of 80.00% at a significance level of 5.00% (two-tailed). This is evenly divided into triple therapy and concomitant therapy respectively, thus, 55 cases and 55 controls are needed. G Power version 3.1.7 sample size calculator was used to calculate the sample size.

All statistical analysis were analyzed using Stata Statistical Software, Version 25. Categorical variables will be analyzed using chi-square and presented as mean and standard deviation, while qualitative or continuous variables will be evaluated using Independent sample t-test and presented as frequency and percent distribution. Comparative analysis, for both intention-to-treat (ITT) and per-protocol analysis (PPA), were` analyzed using z-test for two independent proportions. A p-value of 0.05 will be considered statistically significant.

RESULTS AND DISCUSSION

One hundred and twelve (110) subjects were included in the study. Mean ages for triple therapy (TT) patients were 49.03 (+ 15.634) and 52.63 (+13.184) for concomitant (CT) patients. Endoscopic findings such as the presence of gastric ulcer (p= 0.967), duodenal ulcer (p =0.897) and chronic atrophic gastritis (p = 0.546) were not statistically different in between the 2 treatment groups.

Major outcome of treatment was the eradication of H. pylori infection with concomitant (CT) versus standard triple therapy (TT). There was no significant difference in the eradication rates of H. pylori infection between CT and TT in an intention-to-treat analysis although a trend towards statistical significance was noted in favor of CT (81.8% versus 72.9%, p = 0.076). CT was associated with higher incidence of patients of adverse events compared to TT (76.36% versus 58.2% p = 0.038). However, difference on compliance to both regimens were statistically not significant. Based on a per-protocol analysis, CT significantly increased the eradication rates of H. pylori compared to TT (90% versus 74.5%, p = 0.044).

Adverse effect profiles of patients involved and participated in the study were collected during follow-up. Among the reported adverse effects taste disturbances were the most commonly reported in both TT and CT (25.4% and 34.5% p = 0.284). Other adverse effects reported were abdominal pain (p = 0.632), diarrhea (p = 0.417), bloatedness (p = 0.494), constipation (p = 0.407), anorexia (p = 0.631), dizziness and nausea (p = 0.928), headache (p = 0.589) and vomiting (p = 0.431) were likewise analyzed and were not also statistically different between the two groups.

Table 1. Demographic and clinical characteristics of the enrolled patients

	Triple therapy group (N 55)	Concomitant group (N 55)	P value
Age (years)	49 .03 + 15.634	52.63 + 13.184	0.065
Gender			0.575
Male	21 (38.2%)	28 (50.9%)	
Female	34 (61.8%)	27 (49.1%)	
Endoscopic Diagnosis			
Gastric ulcer	30 (54.5%)	32 (58.2%)	0.967
Duodenal ulcer	20 (36.3%)	13 (23.6%)	0.897

Gastritis	8 (14.5%)	7 (12.7%)	0.546

Table 2. Outcomes of Treatment

	Conventional group	Concomitant group	P value
Eradication Rate			
Intention to Treat	40/55 (72.7%)	45/55 (81.8%)	0.076
Per Protocol	35/47 (74.5%)	45/50 (90.0%)	0.044
Adverse events	32/55 (58.2%)	42/55 (76.36%)	0.038
Compliance	46/55 (83.6%)	50/55 (90%)	0.073

Table 3. Adverse Events

Characteristic	Triple Therapy (n=55)	Concomitant Therapy (n=55)	p-value
Taste Disturbance	14 (25.4%)	19 (34.5%)	0.284
Abdominal Pain	13 (23.6%)	11 (20.0%)	0.632
Diarrhea	12 (21.8%)	8 (14.5%)	0.417
Bloatedness	9 (15.50%)	6 (10.9%)	0.494
Constipation	7 (16.4%)	4 (7.2%)	0.407
Anorexia	7(16.4%)	5 (9.0%)	0.631
Dizziness/Nausea	3 (5.4%)	3 (5.6%)	0.928
Headache	2(3.6%)	3 (5.6%)	0.589
Vomiting	3 (5.4%)	5 (9.0%)	0.401

CONCLUSION

Concomitant therapy achieved a significantly higher eradication rate than the standard triple therapy. However, adverse effects were higher. These adverse effects were mild and were not able to affect compliance to the regimen. Therefore, it can be used as a first line treatment for H. pylori eradication.

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