Modified Amoxicillin Triple Therapy vs Standard Triple Therapy for Eradication of *Helicobacter pylori* Infection

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Abstract

Significance: Eradication regimens for Helicobacter pylori (H. pylori) have undergone several modifications during the last 15-20 years due to diminishing eradication rates in concordance to increasing clarithromycin resistance. In addition to the standard triple therapy, novel H. pylori eradication regimens have emerged recently. In standard triple therapy, amoxicillin is reported to suffer the least from resistance and remains the standard of care in most countries for H. pylori infection achieving 70-85% eradication rates. However, the bactericidal effect of amoxicillin depends on the percent time above MIC (%T>MIC), not Cmax/MIC or AUC/MIC and hence a three to four times daily dosing may be considered to increase effectiveness. The study aimed to compare H. pylori eradication rates, adverse effect profiles and compliance rates of standard triple therapy (sTT2) versus a modified triple therapy dosing schedule (mTT4=amoxicillin 500mg QID). **Methodology:** A prospective, open label, randomized control study utilizing consecutive sampling with random allocation of 112 symptomatic adult patients (G-Power version 3.1), who underwent esophago-gastroduodenoscopy (EGD) and tested positive for H. pylori either by rapid urease test, stool antigen, or giemsa staining were included in the study. Patients with recent PPI and NSAID use, active gastrointestinal bleeding, malignancy and those who did not consent were excluded. A 2-week standard triple therapy (STT2: amoxicillin 1000mg BID, clarithromycin 500mg BID and PPI) was compared to a modified dosing schedule (MTT4: amoxicillin 500mg QID, clarithromycin 500mg BID and PPI) with measurement of H. pylori stool antigen at least 6 weeks post-treatment. Statistical differences in baseline characteristics, eradication and compliance rates between two different regimens were assessed by Chi-square test and were performed using SPSS (IBM® SPSS® Statistics ver. 22). P values < 0.05 were considered as statistically significant. **Results:** Based on a per-protocol analysis, mTT4 dosing scheme significantly increased the eradication rates of H. pylori compared to sTT2 dosing (90% versus 74.5%, p = 0.044). Likewise, mTT4 is associated with a statistically lower incidence of patients complaining adverse events compared to sTT2 (57.4% versus 75.9% p = 0.038). There was no significant difference in the eradication rates of H. pylori infection between sTT2 and mTT4 in an intention-to-treat analysis although a trend towards statistical significance was noted in favor of mTT4 (83.3% versus 69.0%, p = 0.076). **Conclusion:** The dosing scheme of amoxicillin affects the eradication rates of H. pylori. Modified (mTT4) dosing of amoxicillin in triple therapy resulted in a higher eradication rate of H. pylori in a per-protocol analysis. Although amoxicillin is empirically dosed 1 gram twice daily in H. pylori infection, amoxicillin taken at a dose of 500mg 4 times daily may achieve higher chance of eradication success and render lower incidence of adverse effects to patients.

Keywords: Randomized control trial, Helicobacter pylori eradication, amoxicillin

Introduction

In the Philippines, a recent retrospective study in a tertiary hospital reported local *Helicobacter pylori (H. pylori)* positivity rates of 9.94%[1]. *H. pylori* infection plays an important role in the pathogenesis of chronic gastritis, peptic ulcer disease, gastric adenocarcinoma, and mucosa-associated lymphoid tissue lymphoma[2]. In a local study by Gestura in 2004, sixty percent (60%) of the study population was positive for H. pylori infection (mean age of 44 years ± 13), 70% were males. H. pylori culture showed a sensitivity of 45% (95% CI [29.5–62.1]), specificity of 98% (95%CI [81.5–100%]), positive likelihood ratio of 19.93 (95% CI [1.254– 317.04]) and a negative likelihood ratio of 0.56 (95% CI [0.406–0.772])[3]. H. pylori strains isolated in the study were sensitive to metronidazole, clarithromycin, amoxicillin and tetracycline. Standard amoxicillin based triple therapy with either clarithromycin or metronidazole in combination plus a proton pump inhibitor has been recognized as the primary treatment for eradication of *H. pylori* since 1996[4]. Eradication regimens for Helicobacter pylori (H. pylori) have undergone several modifications during the last 15-20 years due to diminishing eradication rates in concordance to increasing clarithromycin resistance[5]. In addition to the standard triple therapy, novel H. pylori eradication regimens have emerged recently[6]. In standard triple therapy, amoxicillin is reported to suffer the least from resistance and remains the standard of care in most countries for H. pylori infection achieving 70-85% eradication rates. However, the bactericidal effect of amoxicillin depends on the percent time above MIC (%T>MIC), not Cmax/MIC or AUC/MIC and hence a three to four times daily dosing may be considered to increase effectiveness[7].

The objective of the study was to compare *H. pylori* eradication rates of standard triple therapy (sTT2) versus a modified triple therapy dosing schedule (mTT4=amoxicillin 500mg QID). Secondary objectives were to compare the adverse effect profiles and compliance rates among the two treatment groups.

Materials and methods

Using a prospective, open label, randomized control study design, the study was conducted in the endoscopy unit of tertiary teaching referral center in Manila Philippines. The study was approved by the ethics committee of the institute and has been performed in accordance with the ethical standards laid down in an appropriate version of the Declaration of Helsinki.

Utilizing consecutive sampling with random allocation, symptomatic adult patients who underwent esophago-gastroduodenoscopy (EGD) from September 2017 until October 2018 and tested positive for H. pylori either by rapid urease test, stool antigen, or giemsa staining were invited to participate in the study.

Patients with active and recent PPI and NSAID use, active gastrointestinal bleeding, malignancy and those who did not consent were excluded in the study.

After recruitment, patients were interviewed for baseline data, and were allocated to their respective treatment group. Subjects were asked to take a total 2000mg dose of amoxicillin divided in 4 times daily for the mTT4 group and 2 times daily for sTT2 in combination with standard doses of clarithromcycin and a PPI. Patients were tested for eradiaction of H. pylori by stool antigen testing at least 6 weeks after treatment and data on compliance and adverse reactions were collected on follow-up.

Esophagogastroduodenoscopy (EGD)

An EGD was performed without or without premedication after a 6-hour fast. Endoscopic diagnosis was made at the discretion of the endoscopist. Endoscopic findings were evaluated by one attending gastroenterologist and at least 1 assisting gastroenterology fellow. Disagreement was resolved by discussion.

Rapid Urease Test (RUT)

Biopsy samples(ranging from 1-2), approximately 2–3 mm each were taken from the antral and gastric body mucosa and placed on the yellow colored well containing urea and a pH indicator. The production of the urease enzyme by H. pylori results in the decomposition of urea into bicarbonate and ammonia which causes the pH to rise and the colour of the dot to change from yellow to red or pink. Positive results were read within 5 to 30 min. Samples that were weakly positive took up to 1 h to develop and no colour change at 1 h was regarded negative.

Stool Antigen Test (SAT)

Diluted faecal samples and a peroxidase-conjugated polyclonal antibody were added to the wells and incubated for 1 h at room temperature, then the wells were washed to remove unbound material. Substrate was added and incubated for 10 min at room temperature. In the presence of bound H pylori antigens, a colour develops. A stop solution was added and the results were read by spectrophotometry (450 nm)[8].

Histology

At least three (3) biopsy specimens (one each from antrum, the greater curvature and incisura) were taken from the gastric mucosa during endoscopic examination and were fixed in formalin to be used for the evaluation of *H. pylori* infection by Giemsa staining.

Statistical Analysis

All data retrieved from patient interview, follow-up, chart and endoscopic report review were transferred to an electronic spreadsheet (Microsoft Excel 2010) and were encoded. Data from electronic spreadsheets were imported into the IBM Statistical software package or SPSS™ version 22.0 was used for analyses of data. Data were summarized as frequencies and proportions. With an alpha (level of confidence) of 0.05 and beta (predicted relationship or power) 0.8 with medium effect size, ninety-two (92) subjects were needed in the study to meet minimum requirements using G-Power software(version3.1).

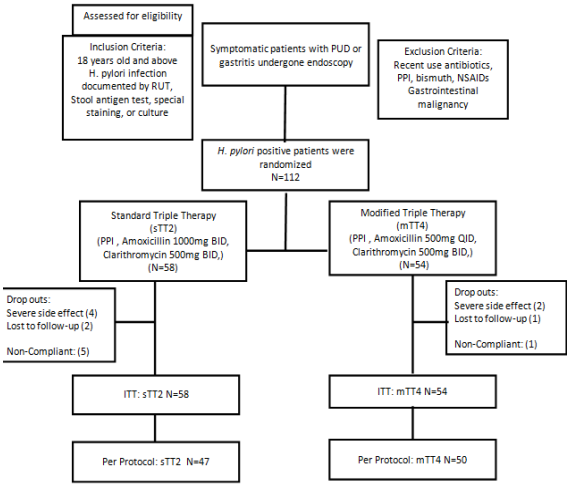

Figure 1. Study Design

Results and Discussion

One hundred and twelve (112) subjects were included in the study. Mean ages for sTT2 patients were 49.03 (+ 15.634) and 52.63(+13.184) for mTT4 patients. Gender (p = 0.575), BMI (p = 0.796, and smoking history (p = 0.147) were similar in both groups. Endoscopic findings such as the presence of gastric ulcer (p= 0.967), duodenal ulcer (p =0.897), chronic atrophic gastritis (p = 0.546), erosive gastroduodenitis (p = 0.341), and erosive esophagitis (p = 0.488) were analysed and were not statistically different in between the 2 treatment groups.

Table 1. Demographic profile of the subjects (N = 112)

Characteristic	Standard Triple Therapy (n = 58)	Modified Triple Therapy (n = 54)	p-value (Two-tailed)
Age (years)	49.03 (SD ± 15.634)	52.63(SD ± 13.184)	0.065
Sex			
Male	27 (46.3%)	28 (51.9%)	0.575
Female	31 (53.4%)	26 (48.1%)	
Body Mass Index	23.61 (SD ± 3.4)	24.1 (SD ± 3.6)	0.796
Smoking status			
Non-smoker	36 (62.1%)	35 (64.8)	0.147
Previous/Occasional smoker	17 (29.3%)	11 (20.4%)	
Daily Smoker	5 (8.6%)	8 (14.8%)	
Endoscopic findings			
Gastric ulcer	12 (20.7%)	11 (20.4%)	0.967
Duodenal ulcer	8 (13.8%)	7 (13.0%)	0.897
Chronic atrophic gastritis	30 (51.7%)	31 (57.4%)	0.546
Erosive gastroduodenitis	31 (53.4%)	24 (44.4%)	0.341
Erosive esophagitis	23 (39.7%)	18 (33.3%)	0.488

Table 1. Demographic Profile

Major outcomes of treatment was the eradication of H. pylori infection with a modified (500mg four times daily) dosing of amoxicillin compared to amoxicillin given 2 times daily in 1000mg doses. There was no significant difference in the eradication rates of H. pylori infection between sTT2 and mTT4 in an intention-to-treat analysis although a trend towards statistical significance was noted in favor of mTT4 (83.3% versus 69.0%, p = 0.076). Likewise, mTT4 is associated with a statistically lower incidence of patients complaining adverse events compared to sTT2 (57.4% versus 75.9% p = 0.038). Based on a per-protocol analysis, mTT4 dosing scheme significantly increased the eradication rates of H. pylori compared to sTT2 dosing (90% versus 74.5%, p = 0.044).

Table 2. Major outcomes of triple therapy for *H. pylori* eradication

	Standard Triple Therapy f (%)	Modified Triple Therapy f (%)	p-value (Two-tailed)
Eradication Rate			
Intention-to-Treat	40/58 (69.0%)	45/54 (83.3%)	0.076
Per-Protocol	35/47 (74.5%)	45/50 (90.0%)	0.044*
Patients reporting adverse events	44/58 (75.9%%)	31/54 (57.4%)	0.038*
adverse events leading to discontinuation	4/44 (9.1%)	2/31 (6.5%)	0.678
adverse events leading to non-compliance	5/44 (11.4%)	1/31 (3.2%)	0.201
Compliance	47/58 (81.0%)	50/54 (92.6%)	0.073

Table 2. Major outcomes of triple therapy for H. pylori eradication

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 sTT2 and mTT4 (25.9% and 35.2% 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 3. Adverse events (N = 112)

Characteristic	Standard Triple Therapy (n=58)	Modified Triple Therapy (n=54)	p-value (Two-Tailed)
Taste Disturbance	15(25.9%)	19(35.2%)	0.284
Abdominal Pain	14 (24.1%)	11 (20.4%)	0.632
Diarrhea	12 (20.7%)	8 (14. 8%)	0.417
Bloatedness	9 (15.50%)	6 (11.1%)	0.494
Constipation	7 (12.1%)	4 (7.4%)	0.407
Anorexia	7/46 (12.1%)	5/44 (9.3%)	0.631
Dizziness/Nausea	3 (5.2%)	3 (5.6%)	0.928
Headache	2(3.4%)	3 (5.6%)	0.589
Vomiting	3 (5.2%)	5 (9.3%)	0.401

Table 3. Adverse effect profile of the treatment regimen

Protocol violations were reported in table 2. Modified triple therapy (mTT4) showed at trend towards a higher compliance(p = 0.073) rate than sTT2 (81%). Reasons of violations of the protocol were identified and it was noted that non-compliance (less than 90% of treatment drug was taken) loss to follow-up, and a severe side effects were listed as the causes of the violations.

Table 4. Description of protocol violations according to therapy

Violation	Standard Triple Therapy (n=58)	Modified Triple Therapy (n=54)	p-value (Two-Tailed)
Overall	11(19%)	4(7.4%)	0.73
Non-compliance(<90%of medications taken)	5(8.6%)	1(1.9%)	0.112
Lost to follow-up	2(3.4%)	1(1.9%)	0.601
Severe side effect profile	4(6.9%)	2(3.7%)	0.453
For Per Protocol Analysis	47	50	
Total ITT Sample	58	54	

Table 4. Description of protocol violations according to therapy

Conclusion

The dosing scheme of amoxicillin affects the eradication rates of H. pylori. Modified (mTT4) dosing of amoxicillin in triple therapy resulted in a higher eradication rate of H. pylori in a per-protocol analysis. Although amoxicillin is empirically dosed 1 gram twice daily in H. pylori infection, amoxicillin taken at a dose of 500mg 4 times daily may achieve higher chance of eradication success and render lower incidence of adverse effects to patients.

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