

Comparison of 10 and 14 days of triple therapy versus 10 days of sequential therapy for *Helicobacter pylori* eradication: A prospective randomized study

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ABSTRACT

Background/Aims: The aim of the present study was to compare between the efficacy and tolerability of a sequential therapy (ST) as the first-line treatment for adults with *Helicobacter pylori* infection and that of standard triple therapy (TT).

Materials and Methods: This was a prospective, randomized open-label, single-center study. We enrolled 206 patients who were divided into the following three treatment groups: Group A (pantoprazole 40 mg bid (twice daily), amoxicillin 1 g bid, and clarithromycin 500 mg bid for 10 d), Group B (the same TT as Group A for 14 d), and Group C (pantoprazole 40 mg bid and amoxicillin 1 g bid for 5 d, followed by pantoprazole 40 mg bid, clarithromycin 500 mg bid, and metronidazole 500 mg bid for additional 5 d).

Results: Intention-to-treat (ITT) analysis revealed that 14 d of TT achieved a higher eradication rate than 10 d of ST (54.8% vs. 50.7%), but the difference was not statistically significant ($p=0.623$); further, 10 d of TT achieved 45% eradication rate. Per-protocol (PP) analysis revealed that the success rate for 10 d of ST was more than that for 10 d of TT (70.6% vs. 65%; $p=0.571$); however, the success rate for 10 d of TT was not statistically different from that for 14 d of TT. The eradication rates achieved in the ITT analysis were lower than those achieved in the PP analysis for 10 (45% vs. 65%) or 14 (54.7% vs. 69%) d of TT or for 10 d of ST (50.7% vs. 70.6%). No statistically significant difference was observed. Adverse effects and compliance were not significantly different among the three groups.

Conclusion: Neither 10 d of ST nor 14 d of TT achieved the optimum *H. pylori* eradication rate.

Keywords: *Helicobacter pylori*, proton-pump inhibitor, clarithromycin

INTRODUCTION

The eradication of *Helicobacter pylori* infection remains a great concern worldwide because it is strongly associated with peptic ulcer, gastric cancer, and gastric mucosa-associated lymphoid tissue lymphoma (1-3). The standard therapy for *H. pylori* infection comprises a proton-pump inhibitor (PPI) and clarithromycin with either amoxicillin or metronidazole, which remains the recommended regimen in Europe and the United States (2,3). It has been observed that the eradication of *H. pylori* is effective in preventing gastric cancer, and it is considered to be a predominant strategy for the prevention of gastric cancer (4,5). Despite the early successful results of this approach, *H. pylori* eradication rates have declined to below 75% (6). This is primarily related to the increase in the prevalence of clarithromycin and metronidazole-resis-

tant *H. pylori* strains, which are a cause of great concern worldwide (7). This resistance necessitates modifications in the therapeutic strategies that are currently needed to overcome antibiotic resistance (8). Several therapeutic designs have been suggested to increase the eradication rate. A proposed alternative therapeutic approach to standard triple therapy (TT) is sequential therapy (ST) (9). ST comprises a PPI bid and amoxicillin 1 g bid for 5 d followed by a TT comprising a PPI bid, clarithromycin 500 mg bid, and metronidazole bid for the next 5 d (2).

Initial trials of ST have shown an advantage over standard TT, which can be attributed to improvements in the eradication of clarithromycin-resistant strains (10,11). It was found that ST resulted in significantly superior cure rates than standard TT (12). Recent studies from Italy have con-

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firmed high success rates (90.6%-93%) of ST (12,13). The majority of trials using sequential regimens were conducted in Italy, South Korea, and Taiwan, whereas only a single study was conducted in the Middle East (14). A large study conducted in Latin America reported an eradication rate of 82.2% with TT and only 76.5% with 10 d of ST (15). It has been reported that sequential regimens still did not attain acceptable cure rates (grade A \geq 95% or grade B \geq 90%) by per-protocol (PP) analysis (16,17).

These variations may be linked to differences in the antibiotic resistance rates. In the present study, we compared the treatment outcomes of 10 d of ST with those of conventional TT for 10 and 14 d.

MATERIALS AND METHODS

This was a prospective, randomized single-center study with parallel group design conducted between August 2014 and November 2016. Individuals in the endoscopy unit presenting with dyspepsia who underwent an upper endoscopy and confirmed *H. pylori* infection using the rapid urease test were included after evaluation for inclusion and exclusion criteria. All patients provided a written informed consent. The exclusion criteria included individuals with esophageal reflux disease; previous eradication therapy for *H. pylori*; and the use of antibiotics, bismuth, or PPI during the last 4 weeks. Individuals allergic to medications, those who had previous gastric surgery, those with coexistence associated disorders (decompensated liver cirrhosis and uremia), and those with gestation or lactation were also excluded. The aim of this study was to compare between the efficacy of 10 d of sequential regimen as the first-line treatment for *H. pylori* infection and that of TT.

The primary outcome measure of this trial was the *H. pylori* eradication rate and a comparison of the efficacy and tolerability of ST as the first-line treatment against those of standard TT.

This study was approved by joint institutional review board of medical research center Hamad Medical Corporation, Doha, Qatar, under IRB Number 14-00087, protocol Number 14074/14.

Sample Size

Sample size and power calculation were performed on the basis of published data by Zullo et al. (eradication rate: 93% vs. 73% among patients treated with ST and TT, respectively) (18). A total sample of 200 patients was needed to detect an effect size of 0.22 with 80% power and 5% level of significance.

Sampling Method

Patients were randomized into three treatment groups using simple random sampling (Figure 1), Group A: pantoprazole 40 mg bid, amoxicillin 1 g bid, and clarithromycin 500 mg bid for 10 d; Group B: the same TT as Group A but for 14 d; and Group C: ST, 5 d of pantoprazole 40 mg bid and amoxicillin 1 g bid, followed by 5 d of pantoprazole 40 mg bid, clarithromycin 500 mg bid, and metronidazole 500 mg bid.

Randomization was performed by computer-generated random numbers, and an allocation concealment technique was used to prevent selection bias (concealing the allocation sequence from those assigning participants to the three groups until the moment of assignment). The post-treatment of *H. pylori* infection status was evaluated by conducting a stool antigen test after 4 weeks.

Statistical analysis

Descriptive and inferential statistics were used to characterize the study sample and test the hypothesis. Descriptive results for age were expressed as mean \pm standard deviation for normally distributed data. Numbers (percentage) were reported for all qualitative variables (sex, ethnicity, *H. pylori* status, and adverse effects). The dependent variable was the treatment groups, and the independent variables were sex (male vs. female), ethnicity (Qatari vs. non-Qatari), *H. pylori* status (positive vs. negative), and adverse effects (positive vs. negative). Intention-to-treat (ITT) and PP analyses were performed to calculate the eradication rate. The ITT analysis included all randomized patients, whereas the PP analysis excluded

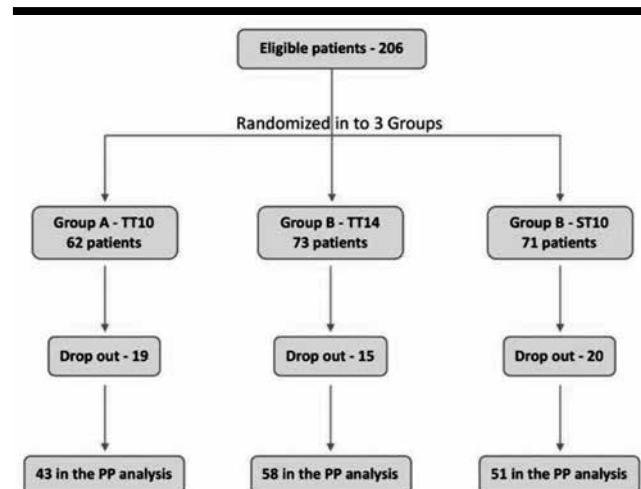


Figure 1. TT10: triple therapy for 10 d; TT14: triple therapy for 14 d; ST10: sequential therapy for 10 d; PP: per-protocol analysis

patients with unknown *H. pylori* status post-treatment or patients who were not in compliance with drug administration. Pearson's chi-square test was used to determine the difference among and between the three treatment groups. One-way ANOVA test was applied to compare the mean age among the three treatment groups, and Pearson's chi-square test was employed to compare the proportion for all qualitative variables (sex, ethnicity, and side effects). A two-sided p -value < 0.05 was considered statistically significant. All statistical analyses were performed using the Statistical Package for Social Sciences (SPSS), version 22.0 (IBM Corp.; Armonk, NY, USA).

RESULT

Between August 2014 and November 2016, 206 patients were enrolled in the study and their data were analyzed (Figure 1). A total of 54 participants were excluded from the study. This high drop-out rate was attributed to multinational participants, and it was difficult to ensure that they completed the study. Only two patients did not undergo any treatment, one patient stopped treatment because of adverse effects, and 152 patients completed the study, of which 43 were in the TT Group A, 58 were in the TT Group B, and 51 were in the ST Group C (Table 1, 2). Clinical characteristics of all patients were compa-

table among the three therapeutic arms receiving *H. pylori* eradication. Using ITT analysis, 14 d of TT achieved a higher eradication rate than 10 d of ST (54.8% vs. 50.7%; $p=0.623$), whereas 10 d of TT achieved 45% eradication rate. Using PP analysis, the eradication rate was greater for 10 d of ST than for 10 d of TT (70.6% vs. 65%; $p=0.571$), whereas 14 d of TT had no significant differ-

Table 2. *Helicobacter pylori* eradication rates in intention-to-treat and per-protocol analysis among 3 groups.

| | Eradication rate n/N (%) | 95% Confidence Interval | p |
|-----------------------------|-----------------------------|-------------------------|-------|
| Intention-to-treat (n=206) | | | 0.536 |
| • 10 day triple therapy | 28/62 (45.0) | 32.6-57.4 | |
| • 14 day triple therapy | 40/73 (54.8) | 43.6-66.4 | |
| • 10 day sequential therapy | 36/71 (50.7) | 39.1-62.3 | |
| Per-protocol (n=152) | | | 0.845 |
| • 10 day triple therapy | 28/43 (65.1) | 50.7-79.3 | |
| • 14 day triple therapy | 40/58 (69.0) | 57.1-80.9 | |
| • 10 day sequential therapy | 36/51 (70.6) | 58.1-83.1 | |

Table 1. Demographic and clinical characteristics of enrolled patients randomized in the 3 groups

| | Overall n=206 | Group A: 10 days triple Therapy | Group B: 14 days triple therapy | Group C: 10 days Sequential therapy | p |
|---|------------------|---------------------------------------|---------------------------------------|--|-------|
| Number of patients enrolled in the study | 206 | 62 (30.1) | 73 (34.4) | 71 (34.5) | |
| Age in years | 38.85±11.78 | 36.42±10.67 | 39.78±11.93 | 40.01±11.78 | 0.150 |
| Gender | | | | | |
| • Female | 95 (46.1) | 35 (56.5) | 31 (42.5) | 29 (40.8) | 0.146 |
| • Male | 111 (53.9) | 27 (43.5) | 42 (57.5) | 42 (59.2) | |
| Ethnicity | | | | | 0.988 |
| • Qatari | 51 (24.8) | 15 (24.2) | 18 (24.7) | 18 (25.4) | |
| • Non-Qatari | 155 (75.2) | 47 (75.8) | 55 (75.3) | 53 (74.6) | |
| Adverse effects | 83 (40.3) | 23 (37.1) | 29 (39.7) | 31 (43.7) | 0.738 |
| • Abdominal Pain | 47 (22.8) | 10 (16.1) | 16 (21.9) | 21 (29.6) | |
| • Diarrhea | 14 (6.8) | 5 (8.0) | 6 (8.2) | 3 (4.2) | |
| • Bloating | 12 (5.8) | 5 (8.0) | 4 (9.5) | 3 (4.2) | |
| • Constipation | 3 (1.4) | 1 (1.6) | 2 (2.7) | 0 (0.0) | |
| • Taste alteration | 7 (3.4) | 2 (3.2) | 1 (1.4) | 4 (5.6) | |

Results are expressed as mean ± standard deviation, and number (percentage)

ence. The eradication rates observed in the ITT analysis were lower than those observed in the PP analysis for 10 d of TT (45% vs. 65%), 14 d of TT (54.7% vs. 69%), and 10 d of ST (50.7% vs. 70.6%). No significant difference was observed in adverse effects and compliance of patients among the three groups.

Helicobacter pylori eradication rate

Of the patients, 197 were diagnosed with gastritis and nine with peptic ulcer disease (seven with duodenal ulcer and two with gastric ulcer); the overall eradication rates by ITT and PP analyses are shown in Table 2. The ITT analysis revealed the eradication rate of 45% (28/62) in the 10 d TT group, 54.8% (40/73) in the 14 d TT group, and 50.7% (36/71) in the 10 d ST group, with $p=0.536$, and the PP analysis revealed the eradication rate of 65.1% (28/43), 69% (40/58), and 70.6% (36/51), respectively (Figure 2), with $p=0.845$. The success rate in the ST group was nearly equal to that in the conventional TT group by the PP analysis, but it was inferior by the ITT analysis.

Adverse effects

Patients were evaluated for both compliance and possible side effects. The overall adverse effects occurred in 37%, 39.7%, and 43.7% of patients after treatment with 10 d of TT, 14 d of TT, and 10 d of ST, respectively; however, they were mild and well tolerated in most patients (Table 1). Abdominal pain and diarrhea were the most frequent adverse events. Only one patient discontinued treatment because of adverse events (abdominal pain). All regimens were well tolerated with comparable drop-out rates.

DISCUSSION

We believe that there is a fundamental need for the effective and efficient treatment of *H. pylori* infection in medicine; therefore, we need to determine whether 10 d of ST eradicates *H. pylori* infection better than the

standard TT for adults with dyspepsia. This would have a sizable cost-effective implication and would provide patients with a better standard of care. Our study revealed that 10 d of ST and 10 or 14 d of TT did not meet the expected *H. pylori* eradication rate, as is clearly shown in the ITT and PP eradication rates of 70.6% and 69% or 65%, respectively. The main reason for these sub-optimal results is the resistance to clarithromycin and metronidazole that has been reported to be 21.2% for clarithromycin, 78.1% for metronidazole, and 20% for dual resistance (19). ST was first introduced in Italy in 2000 (10). According to three meta-analyses based on randomized controlled trials (RCTs) conducted in Italy before 2008, the eradication rate with ST was >90%, which was higher than that with TT (75.7%-79.2%), and this was attributed to the low dual resistance rate to clarithromycin and metronidazole in Italy, which was 3.5%-4.3% (11,13,20,21). Recent systematic reviews and meta-analyses have reported a statistically significant effect in favor of ST vs. TT lasting 10 d in trials conducted in China, Greece, India, Italy, and Spain (9). In addition, several studies conducted in different countries have compared 10 d of ST with 7 d of TT and have demonstrated some favorable results for ST; a trial from Ireland found a superior result for ST (68% vs. 55%) (22). A study from Taiwan also showed a favorable result for ST, whereas a study from Brazil found equal eradication rates (86%) for both regimens (21,23).

However, this has not been observed in other parts of the world because of the difference in antibiotic resistance that has reduced such results to below the expected rate. In a recently published meta-analysis of RCTs, the authors found that 10 d of ST is more successful than 7 or 10 d of TT but not 14 d of TT (9). A multicenter randomized trial conducted in six Latin American countries concluded that 14 d of TT resulted in 82.2% success rates, which was 5.6% higher than 10 d of ST (15). This has also been observed in systematic reviews and meta-analyses conducted in Taiwan, which have shown that 10 or 14 d of ST is not significantly superior to 14 d of TT (24). Another meta-analysis conducted last year showed that 14 d of ST, but not 10 d of ST, was more effective than 14 d of TT as the first-line treatment (24). Only two RCTs in the USA and Canada have compared 10 d of ST with 14 d of TT, and both studies have shown no significant change in the eradication rates between both regimens (25,26).

One of the limitations of our study was the lack of antibiotic sensitivity data because we did not conduct susceptibility tests; even the study that tested the antibiotic

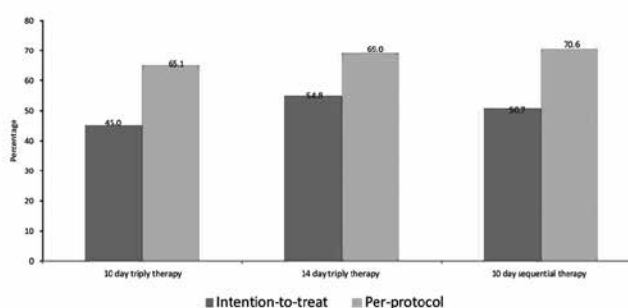


Figure 2. *Helicobacter pylori* eradication rate in per-protocol and intention-to-treat analyses among the three groups

resistance pattern in all samples had to send the samples to a specialized laboratory in Germany. This would explain the influence of antibiotic sensitivity on the eradication rates, particularly that of clarithromycin resistance that is considered to be the major contributing factor regulating the efficacy of *H. pylori* eradication with ST or TT (27). Further, this study was conducted in a single center. Therefore, it is difficult to generalize the study result to another area. However, the study had a reasonably good sample size, and the number of patients was sufficient for statistical analysis.

Thus, 10 d of ST resulted in a higher *H. pylori* eradication rate than 10 d of conventional TT. However, neither ST nor TT achieved satisfactory eradication rates in an area with high clarithromycin and metronidazole resistance.

Ethics Committee Approval: Ethics committee approval was received for this study from the Institutional Review Board of Medical Research Center of Hamad Medical Corporation (IRB NO: 14-00087; Protocol No: 14074/14).

Informed Consent: Written informed consent was obtained from the patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - A.E., N.S.; Design - A.E., N.S.; Supervision - R.M.; Data Collection and/or Processing - A.E.; Analysis and/or Interpretation - A.S.; Literature Search - A.E.; Writing Manuscript - A.E.; Critical Review - A.E.

Conflict of Interest: The authors have no conflict of interest to declare.

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