Concomitant Therapy versus Triple Therapy: Efficacy in H. Pylori Eradication and Predictors of Treatment Failure

Abdul Moeez Kaiser Butt, Shahid Sarwar and Muhammad Arif Nadeem

Department of Medicine, Services Institute of Medical Sciences, Lahore, Pakistan

ABSTRACT

Objective: To compare concomitant therapy (CT) and triple therapy (TRT) for success in *helicobacter (H.) pylori* eradication and identify factors associated with treatment failure.

Study Design: Quasi-experimental comparative study.

Place and Duration of Study: Department of Medicine and Gastroenterology, Services Institute of Medical Sciences from December 2018 till July 2019.

Methodology: Patients with *H. pylori* infection were randomly assigned to receive two weeks of either CT or TRT. *H. pylori* eradication was confirmed by repeat biopsy four weeks post-treatment. Treatment outcome was compared using Chi-square test, while binary logistic regression identified predictors of treatment failure.

Results: Two hundred and eleven patients with *H. pylori* infection, having mean age 40.15 (±13.04) and male/female ratio 0.9/1 (100/111) after randomisation, were treated with CT in 105 patients (49.8%) and TRT in 106 patients (50.2%). *H. pylori* was eradicated in 84.3% (150/178) patients with completed follow-up. *H. pylori* eradication was achieved in 91.9% of CT group as compared to 77.2% in TRT group (p = 0.007, OR 3.38: 95% CI 1.3-8.3). Age ≥40 years (p = 0.02), symptoms duration >6 months (p = 0.001), and prior proton pump inhibitor use for >4 weeks (p = 0.01), were identified as independent predictors of treatment failure.

Conclusion: CT achieves better *H. pylori* eradication than TRT. Older age, longer duration of illness, and previous proton pump inhibitor use were independent predictors of *H. pylori* treatment failure.

Key Words: *Concomitant therapy, Eradication, H. pylori, Triple therapy.*

How to cite this article: Butt AMK, Sarwar S, Nadeem MA. Concomitant Therapy versus Triple Therapy: Efficacy in H. Pylori Eradication and Predictors of Treatment Failure. *J Coll Physicians Surg Pak* 2021; **31(02)**:128-131.

INTRODUCTION

H. pylori infection is the most common chronic bacterial infection in humans. This infection is strongly associated with low socio-economic status, infected parents, and increasing number of siblings.[1-3] Predominant route of *H. pylori* transmission is feco-oral with evidence of its presence in food, water and even in oral cavity, explaining its high prevalence in areas with poor sanitation and hygiene.[4] It was identified in drinking water source in a study from Karachi.[5]

With improvement in hygienic conditions, better sanitation and awareness, *H. pylori* prevalence is declining in the developed countries.[6] In a study of US veterans with gastrointestinal symptoms, sero-prevalence of *H. pylori* was 73% among those born before 1920 as compared to 22% in those born after 1980.[7]

Correspondence to: Dr. Shahid Sarwar, Department of Medicine, Services Institute of Medical Sciences, Lahore, Pakistan
E-mail: shahidsarwardr@gmail.com

Received: August 03, 2020; Revised: January 02, 2021; Accepted: January 30, 2021
DOI: https://doi.org/10.29271/jcpsp.2021.02.128

However in developing world its prevalence is still high varying from 30.6% to 82% as noted in a meta-analysis of EMRO (Eastern Mediterranean regional office) countries.[8] In a study of 540 children from urban slum area of Karachi, sero-prevalence of *H. pylori* was 47.2%.[9]

Due to strong association of *H. pylori* infection with dyspepsia, peptic ulcer disease, gastric carcinoma and gastric mucosa-associated lymphoid tissue (MALT) lymphoma, every person diagnosed with *H. pylori* infection needs to be treated.[10] Eradication of *H. pylori* is only possible with treatment regimens comprising of multiple antibiotics. TRT, including proton pump inhibitor, macrolide and amoxicillin for 10-14 days, was considered first line therapy of *H. pylori* for many years with expected response rate of 80-85%.[10]

However, there is growing concern regarding efficacy of TRT, due to increasing clarithromycin resistance; 37% clarithromycin resistance was reported in 162 gastric biopsies tested in Karachi.[11] In the presence of resistant strain, response to TRT drops to 22% from 90% in patients with clarithromycin sensitive strain.[12] Due to increasing high clarithromycin resistance in the Pakistani population, there is a need to treat the patients with newer multi-drug combinations to achieve higher efficacy. One such promising combination is CT, which includes four drugs for

14 days which has shown promising results in number of studies with reported eradication rate as high as 93.4%.[13]

Due to diverse resistance patterns in different regions and variable treatment success rate, it is important to develop evidence-based regional eradication strategies with identification of factors effecting treatment outcome. Newer combinations should be tested in the local population for better response rate in *H. pylori* eradication.

This study was planned to compare efficacy of 14 days clarithromycin-based TRT and non-bismuth CT in helicobacter pylori eradication; and to identify host-related factors responsible for treatment failure.

METHODOLOGY

This quasi-experimental comparative study was conducted at the Department of Medicine and Gastroenterology, Services Institute of Medical Sciences, from December 2018 till July 2019, following approval by Ethical Review Board. All consecutive patients diagnosed to have *H. pylori* infection on endoscopic biopsy, performed at the Endoscopy Unit, were included after informed consent. Patients with age under 18 years, severe comorbidities including cardiovascular, respiratory, endocrine, renal, haematological and hepatic disorders, those having received previous *H. pylori* eradication therapy, previous gastric surgery, allergy to the antibiotics used in study, pregnancy or lactation, alcohol abuse or drug addiction and intake of antibiotics, proton pump inhibitors, corticosteroids or nonsteroidal anti-inflammatory agents within last four weeks, were excluded from study.

Minimum sample size needed was 138, keeping margin of error 5%, confidence level 95% and expected response distribution 10%. To counter possible dropouts due to outpatient-based follow up and need for follow-up endoscopic biopsy, a sample size was determined in excess of 200. After detailed clinical history and physical examination, including indications for endoscopy, patients were randomly classified as group A and B, using simple random sampling, generated online at Stat Trek®. Diagnosis of *H. pylori* was based on positive evidence of bacteria with at least two different stains; while all histopathology samples were tested with hematoxylin and eosin (H&E), giemsa and warthin-starry silver stains.

Group A received TRT including esomeprazole 40mg twice a day (BID), amoxicillin 1g BID, and clarithromycin 500mg BID for 14 days. Group B received non-bismuth quadruple or CT, which included esomeprazole 40mg BID, amoxicillin 1g BID, clarithromycin 500mg BID and metronidazole 500mg BID for 14 days. Patients were explained possible side effects related to medications including metallic taste, diarrhea, abdominal pain, nausea and vomiting. Patients had weekly follow-up regarding compliance, adverse events and symptoms improvement. Compliance was defined as 100% intake of medication. Patients unable to complete therapy, due to side effects, non-compliance or failure to follow-up, were excluded from final analysis. All patients had follow-up endoscopy 4 weeks after treatment discontinuation; and repeat endoscopic biopsy was tested for *H. pylori* using three different stains, and bacterial identification on at least two stains was defined as treatment failure; whereas, no bacterial isolation in at least two stains was labelled as successful *H. pylori* eradication.

Data was analysed using SPSS version 22.® Quantitative variable like age was expressed as mean ± standard deviation (SD); whereas, qualitative variables like gender, endoscopic findings, prior use of PPI were given as percentage. Outcome of treatment between two groups was compared using Chi-square (x^2) test to determine Odd's ratio (OR) for successful *H. pylori* eradication.

Univariate analysis of variables like age, gender, duration of illness for its association with treatment outcome, was carried out using unpaired student's t test or chi square for quantitative and qualitative variables respectively. The magnitude of the effect is described with odds ratio (OR) and 95% confidence interval (CI). Multi-variate binary logistic regression analysis was performed, using successful *H. pylori* eradication as dependent variable and variables with significant association on univariate analysis (p-value <0.05) as independent variables. Predictive value of model was checked by determining 2 log likelihood and testing with Hosmer and Lemeshow test. A p-value of less than 0.05 was considered statistically significant.

RESULTS

A total of 211 patients were included in study after *H. pylori* detection on endoscopic biopsy. Mean age was 40.51(SD ± 13.04), 103 (48.8%) were below 40 years of age and 108 (51.2%) ≥40 years of age. Male to female ratio was 0.9/1 (100/111). The predominant presenting complaint was dyspepsia in 153 (72.5%) patients, 105 (49.8%) of them had epigastric pain syndrome, while 48 (22.7%) complained of post-parandial distress syndrome. Epigastric pain was noted in 50 (23.7%) patients, while eight (3.8%) patients had endoscopy for persistent vomiting. Duration of symptoms was less than six months in 102 (48.3%) patients, and 109 (51.7%) were symptomatic for more than six months. Majority of patients (n=162, 76.8%) had used proton pump inhibitors in the past for more than four weeks.

On endoscopy, 90 (42.6%) patients had nodular antral hyperemia, 51 (24.2%) had gastric erosions, eight (3.8%) depicted duodenal ulcer, six (2.9%) patients had hypertrophic gastric folds, and three (1.4%) had gastric ulcer. Endoscopic examination was normal in 53 (25.1%) patients. After randomisation for *H. pylori* eradication, 106 (50.2%) patients received TRT and 105 (49.8%) were treated with CT. Patients in both groups had no significant difference in baseline variables as shown in Table I.

Complete follow-up with repeat endoscopic biopsy for confirmation of *H. pylori* eradication was achieved in 178 patients (84.3%), 92 (86.7%) in CT group and 86 (81.9%) in CT, while 33 (15.7%) patients were lost to follow-up. *H. pylori* eradication was achieved in 150 (84.3%) patients; 71 (77.2%) patients in TRT group and 79 (91.9%) patients of CT group had bacterial clearance. This difference in *H. pylori* eradication among two treatment arms was significant (p = 0.007) with odds ratio (OR)

of 3.38 (95% CI 1.33-8.32) in favour of CT, for *H. pylori* eradication. Interestingly, improvement of symptoms was not different between two treatment regimens, 75 (81.5%) in TRT group and 73 (84.9%) in CT group had relief in symptoms (p = 0.54, OR 0.78, 95% CI: 0.35-1.73).

Table I: Comparison of patients in triple therapy and concomitant therapy groups.

	Triple therapy (n-106)	Concomitant therapy (n-105)	p-value
Age (mean ± sd)	40.1 (±12.8)	40.89 (±13.2)	0.69
Age (<40 / ≥40 years)	54/52	49/56	0.53
Male / female (No. of patients)	53/53	47/58	0.44
Symptoms duration ≥6 months	53	56	0.65
POI intake ≥4 weeks	81	81	0.9

Table II: Correlation between patient's variable and outcome of eradication therapy.

	Successful *H. pylori* eradication n- 150	Failed *H. pylori* eradication n-28	p-value
Age (<40 / ≥40 years)	78/72	8/20	0.02
Male / Female (No. of patients)	73/77	15/13	0.63
Duration of symptoms (<6 / ≥6 months)	76/74	5/23	0.001
PPI intake more than 4 weeks	114	27	0.01

Variables compared between patients with and without successful *H. pylori* eradication are shown in Table II. Age more than 40 years (p = 0.02), symptoms duration more than six months (p = 0.001) and more than four weeks intake of PPI before eradication therapy (p = 0.014) were significantly associated with unsuccessful *H. pylori* therapy. For independent association with failure of *H. pylori* eradication, odds ratio (OR) for age ≥40 years was 2.70 (95% CI: 1.12-6.57), for symptoms duration ≥6 months, OR was 4.72 (95% CI: 1.70-13.0) and for PPI intake >4 weeks OR was 8.52 (95% CI: 1.11-64.9). Model comprising of these three variables had 2 log likelihood of 139.18 for predicting outcome of treatment with 84.3% accuracy. Contingency Table drawn, using Hosmer and Lemeshow test, showed no significant difference in observed and predicted outcome in multi-step analysis (p = 0.718) favouring excellent correlation between model-based expected outcome and observed outcome of *H. pylori* treatment.

DISCUSSION

Increasing resistance to antibiotics has adversely affected treatment outcome in *H. pylori* eradication. New and more effective therapeutic options are now needed to overcome treatment failures. In newer guidelines, clarithromycin containing triple therapy is no more recommended as first line therapy.[14] Among newer combinations of drugs for *H. pylori* therapy, non-bismuth quadruple (CT) has shown promising results in a number of studies.

In a study of 246 patients by Georgopoulos *et al*., per protocol cure rate was 93.3% (95% CI, 87.2%-97.1%) for CT as compared to 78.5% (95% CI 70.3%-84.9%) for 10 days of TRT with p-value of 0.0014.[15] In another study of 510 patients, CT had higher efficacy than TRT in both intention-to-treat (84.8% *vs*. 65.7% p=0.001) and per protocol (86.9% *vs*. 67.2%, p=0.001) analysis.[16]

In a study of 770 patients by Molina-Infante *et al*., more adverse events were noted with CT than TRT (47% *vs*. 39%, p = 0.016) but compliance was equal; and response was much superior in concomitant therapy group (93.8% *vs.* 82.3%, p = <0.001).[17] In a meta-analysis published in American Journal of Gastroenterology comparing the outcome in 3,305 patients in CT group and 3,327 in TRT group, CT was superior in terms of eradication rate relative risk 1.15;95% CI:1.09-1.21; p<0.001).[18] CT has even shown superior efficacy than newer combinations like sequential therapy (93.4% *vs.* 84.8%, p = 0.004).[13] Per-protocol analysis in this study has shown marked superiority of CT as compared to TRT in this population (91.9% *vs.* 77.2%, p = 0.007), just like the trend being observed all over the world. In light of evolving evidence, CT is being regarded as first line therapy for *H. pylori* eradication.

In this study, age ≥40 years, duration of symptoms more than six months and prior PPI use for more than four weeks were identified as predictors of treatment failure in this study population. Patients with older age, more PPI exposure, and longer duration of illness are more likely to have prior exposure to antibiotics, which may be one reason for higher chances of treatment failure.

Jaka *et al*. in a study of 210 patients from Tanzania, noted 31% failure of *H. pylori* eradication with TRT and identified poor drug compliance (OR 7.39, 95% CI 3.25-16.7) and clarithromycin-resistance mutations (OR 23.12, 95% CI 9.38-56.9) as predictors of treatment failure.[19] Age more than 45 years (OR 2.35 CI 1.36-4.25), smoking (OR 1.37, CI 1.01-1.87), and high pre-treatment urea breath test (UBT) results (OR 1.36 CI 1.08-1.72), were predictors of treatment failure in another study by Perri *et al*.[20] With increasing resistance of *H. pylori* to different combinations of antibiotics, it is essential to identify host factors posing risk of treatment failure. It will help individualise *H. pylori* therapy for each patient, increasing chances of successful outcome.

There was a high dropout of patients from study, which was expected due to mild nature of symptoms in majority of patients, resulting in complacency as well as reluctance to undergo follow-up endoscopy. Endoscopic biopsy was used for confirmation of *H. pylori* eradication instead of urea breath test or fecal antigen test, which are standard of care as these are expensive tests as compared to free endoscopic service for poor patients of a tertiary care centre. Resistance testing before treatment in this study patients could have identified antibiotics responsible for treatment failure, thus enabling further in-depth analysis; however, it is not available in majority of laboratories, and is expensive as well so is not done in clinical practice. Despite these limitations, this study with a larger patient cohort will serve as a milestone in formulating *H. pylori* treatment protocols for the patients.

CONCLUSION

Concomitant therapy (CT) achieves better *H. pylori* eradication than triple therapy (TRT), when given for two weeks. Patients with older age, longer duration of illness and previous proton pump inhibitor use are at higher risk of *H. pylori* treatment failure.

ETHICAL APPROVAL:
This study was conducted with the approval from the Ethics Committee of the Services Institute of Medical Sciences

PATIENTS' CONSENT:
Informed consents were obtained from all patients.

CONFLICT OF INTEREST:
The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:
AMKB: Conception and design, acquisition of data, revising the manuscript, approval of the version, agreement to be accountable for all aspect.
SS: Conception and design, analysis and interpretation, drafting of article, approval of the version, agreement to be accountable for all aspects.
MAN: Conception and design, revising manuscript critically, final approval of the version and agreement to be accountable.

REFERENCES

1. Eusebi LH, Zagari RM, Bazzoli F. Epidemiology *H. Pylori* infection. *Helicobacter* 2014; **19 (Suppl 1)**:1-5. doi:10.1111/hel.12165.
2. Weyermann M, Rothenbacker D, Brenner H. Acquisition of *helicobacter pylori* infection in early childhood: independent contributions of infected mothers, fathers, and siblings. *Am J Gastroenterol* 2009; **104(1)**:182-9. doi: 10.1038/ajg. 2008.61.
3. Ford AC, Forman D, Bailey AG, Goodman KJ, Axon AT, Moayyedi P. Effect of sibling number in the household and birth order on prevalence of Helicobacter Pylori: A cross-sectional study. *Int J Epidemiol* 2007; **36(6)**:1327-33. doi: 10.1093/ije/dym201.
4. Burucoa C, Axon A. Epidemiology of helicobacter pylori infection. *Helicobacter* 2017; **22 (suppl 1)**. doi: 10.111/hel.12403.
5. Khan A, Farooqui A, Kazmi SU. Presence of helicobacter pylori in drinking water of Karachi, Pakistan. *J Infect Dev Ctries* 2012; **6(3)**:251-5. doi: 10.3855/jidc.2312.
6. Leja M, Axon A, Brenner H. Epidemiology of Helicobacter pylori infection. *Helicobacter* 2016; **21(suppl 1)**:3-7. doi: 10.1111/hel.12332.
7. Nguyen T, Ramsey D, Graham D, Shaib Y, Shiota S, Velez M, *et al*. The prevalence of helicobacter pylori remains high in African, American and Hispanic veterans. *Helicobacter* 2015; **20(4)**:305-15. doi: 10.1111/hel.12199.
8. Eshraghian A. Epidemiology of *helicobacter pylori* infection among the healthy population in Iran and countries of the Eastern Mediterranean region: A systematic review of prevalence and risk factors. *World J Gastroenterol* 2014; **20(46)**:17618-25. doi:10.3748/wjg.v20.i46.17618.
9. Jafri W, Yakoob J, Abid S, Awan S, Siddiqui S, Jafri F, *et al*. Seroprevalence of hepatitis E and helicobacter pylori in a low socio-economic area of a metropolitan city in a developing country. *Br J Biomed Sci* 2013; **70(1)**:27-30. doi: 10.1080/09674845.2013.11669926.
10. Chey WD, Leontiadis GI, Howden CW, Moss SF. ACG clinical guidelines: Treatment of helicobacter pylori infection. *Am J Gastroenterol* 2017; **112**:212-238. doi:10.1038/ajg. 2016.563.
11. Rajper S, Khan E, Ahmad Z, Alam SM, Akbar A, Hasan R. Macrolide and fluoroquinolone resistance in helicobacter pylori isolates: an experience at a tertiary care center in Pakistan. *J Pak Med Assoc* 2012; **62(11)**:1140-4.
12. Luther J, Higgins PD, Schoenfeld PS, Moayyedi P, Vakil N, Chey WD. Empiric quadruple vs triple therapy for primary treatment of *helicobacter pylori* infection: Systematic review and meta-analysis of efficacy and tolerability. *Am J Gastroenterol* 2010; **105**:65-73. doi:10.1038/ajg.2009.508.
13. Kim SY, Lee SW, Choe JW, Jung SW, Hyun JJ, Jung YK, *et al*. Helicobacter pylori eradication rates of concomitant and sequential therapies in Korea. *Helicobacter* 2017; **22(6)**. doi:10.1111/hel.12441.
14. Fallone CA, Moss SF, Malfertheiner P. Reconciliation of recent helicobacter pylori treatment guidelines in a time of increasing resistance to antibiotics. *Gastroenterol* 2019; **157(1)**:44-53. doi:10.1053/j.gastro.2019.04.011.
15. Georgopoulos S, Papastergiou V, Xirouchakis E, Laudi F, Lisgos P, Spiliadi C, *et al*. Nonbismuth quadruple concomitant therapy versus standard triple therapy, both for the duration of 10 days, for first line H pylori eradication: A randomised trial. *J Clin Gastroenterol* 2013; **47(3)**:228-32. doi:10.1097/MCG.0b013e31826015b0.
16. Campillo A, Ostiz M, Amorena E, Kutz M, Lalglesia M. Quadruple concomitant non-bismuth therapy *vs*. classical triple therapy as first line therapy for *helicobacter pylori* infection. *Med Clin (Barc)* 2016; **147(5)**:199-201. doi:10.1016/j.medcli.2016.05.017.
17. Molina-Infante J, Lucendo AJ, Angueira T, Rodriguez-Tellez M, Perez-Asia A, Balboa A, *et al*. Optimised empiric triple and concomitant therapy for *helicobacter pylori* eradication in clinical practice: The OPTRICON study. *Aliment Pharmacol The* 2015; **41(6)**:581-9. doi:10.1111/apt.13069.
18. Chen MJ, Chen CC, Chen YN, Chen CC, Fang YJ, Lin JT *et al*. Systematic review with meta-analysis: Concomitant therapy *vs*. triple therapy for the first line treatment of helicobacter pylori infection. *Am J Gastroenterol* 2018; **113(10)**: 1444-1457. doi:10.1038/s41395-018-0217-2.
19. Jaka H, Mueller A, Kasang C, Mshana SE. Predictors of triple therapy treatment failure among H. pylori infected patients attending at a tertiary hospital in North-West Tanzania: A prospective study. *BMC Infect Dis* 2019; **19(1)**:447. doi:10.1186/s12879-019-4085-1.
20. Perri F, Villani MR, Festa V, Quitadamo M, Andriulli A. Predictors of failure of helicobacter pylori eradication with standard maastricht triple therapy. *Aliment Pharmacol Ther* 2001; **15(7)**:1023-9. doi: 10.1046/j.1365-2036.2001. 01006.x.