

Comparison of the Efficacy of Conventional Versus Sequential Regimen in Patients of Gastritis Presenting with Helicobacter Pylori

AHMAD ZAKA SUBHANI¹, ISRAR-UL-HAQUE², GHIAS-UL-HASSAN³, MUHAMMAD YASIR YOUNIS⁴, MUHAMMAD ASIM HAMEED⁵, GHIAS-UN-NABI-TAYYAB⁶

¹Senior Registrar Gastroenterology, Lahore General Hospital, Lahore

²Associate Professor Medicine, Medical Unit-1, Lahore General Hospital, Lahore

³Assistant Professor Gastroenterology, Medical Unit-1, Lahore General Hospital, Lahore

⁴Senior Registrar Gastroenterology, Lahore General Hospital, Lahore

⁵Assistant Professor Medicine, AMC/PGMI/Lahore General Hospital, Lahore

⁶Professor/HOD of Medicine and Gastroenterology Division, Medical Unit-1, Lahore General Hospital, Lahore

Corresponding author: Muhammad Yasir Younis

ABSTRACT

Objective: To compare the efficacy of conventional versus sequential regimen in patients of gastritis presenting with Helicobacter pylori.

Study Design: Randomized Controlled Trial

Setting: Unit I, Department of Gastroenterology, Lahore General Hospital, Lahore

Duration of Study: Six months after the approval of synopsis i.e. 30th November 2017 to 30th May 2018.

Methodology: 232 patients fulfilled inclusion criteria were enrolled in the study. Patients were randomly divided in two equal groups. In group A, conventional triple treatment was given. In group B, sequential therapy was given. After 30 days, urea breath test was done. Reports were assessed and if there will be no bacterium, and then efficacy was labeled. All this information was recorded through proforma. Data analysis was done using SPSS version 21.

Results: The mean age of patients was 38.63±13.11year in conventional group and 36.46±12.16years in sequential group. In conventional group, there were 88 (75.9%) male and 28 (24.1%) females. In sequential group, there were 74 (63.8%) male and 42 (36.2%) females. With conventional therapy, efficacy was achieved in 82 (70.7%) patients while with sequential therapy, efficacy was achieved in 100 (86.2%) patients. The difference was significant ($p < 0.05$).

Conclusion: Thus the sequential therapy is more effective than conventional therapy for eradication of H. pylori in patients of gastritis.

Keywords: Gastritis, H. pylori, conventional therapy, sequential regimen

INTRODUCTION

Gastritis is inflammation of the stomach lining caused by medication, NSAIDs, aspirin, ibuprofen, H. Pylori, anemia and autoimmune disorders [1, 2]. Helicobacter pylori (H. pylori) infection is responsible for the majority of duodenal and gastric ulcers, and there is strong evidence that this infection also increases the risk of gastric cancer, and gastric mucosa associated lymphoid tissue lymphoma and recently has been associated with some non-gastrointestinal diseases [3].

In a study, it was reported that gastritis was found in 75.3% cases, of whom 54.4% were found to be infected with H. pylori. Gastritis and H. pylori were noted in both the antrum and corpus in 75% of those infected cases [2].

H. pylori treatment still remains a challenge for physicians, and no current first-line therapies are able to cure the infection in all treated patients [4]. Two very large meta-analysis studies showed that standard 7-14 days triple therapies fail to eradicate H. pylori infection in up to 20-25% of patients [5]. As per 2017 guidelines H. pylori treatment guidelines, the consensus was also that a 14-day rather than a seven-day treatment including Clarithromycin triple therapy consisting of a proton pump inhibitor, clarithromycin, and amoxicillin or metronidazole [6].

In addition, the efficacy of these regimens is even decreasing worldwide. Indeed, during the last few years, different studies have found that the success rate following such regimens is disappointingly low, with values less than 45-60% in some countries. This phenomenon most likely depends on an increased bacterial resistance to antibiotics, particularly against clarithromycin - the key antibiotic in H. pylori treatment [7].

Eradication rates of standard triple therapy for Helicobacter pylori infections have decreased in recent years due to a worldwide increase in bacterial resistance. Sequential therapy has the advantage of a two-phase treatment regimen and achieves a superior result for H. pylori eradication in peptic ulcer disease [8].

One randomized trial showed that the efficacy (complete eradication of H. pylori) was achieved in 75.9% with sequential therapy and 58.7% with conventional triple therapy in gastritis patients. The difference was significant ($P < 0.05$) [9]. One more trial

showed that the sequential therapy showed more eradication rate than conventional therapy (83.9% versus 60.6%) that was statistically significant ($P < 0.039$) [10]. But one study showed that the efficacy was achieved in 75.6% with sequential therapy and 74.7% with conventional triple therapy in gastritis patients. The difference was insignificant ($P > 0.05$) [11].

Rationale of this study is to compare the efficacy of conventional versus sequential regimen in patients of gastritis presenting with H. pylori. Literature showed that sequential therapy is more effective than conventional triple regimen therapy. But controversial data have been extracted from literature which showed that there is no difference between both type of regimens. Moreover, there is no local evidence found in literature, which could help us in implementing the use of sequential therapy instead of conventional triple regimen. So we want to conduct this study to get local evidence with larger sample size. Then we will be able to implement the results of this study in local setting and will be able to implement the practice of prescribing sequential therapy for H. pylori eradication instead of conventional triple regimen which is current practice. So this will help us to get the evidence and will also help to reduce burden of gastroenterologists as well as burden of hospital.

MATERIALS AND METHODS

This randomized controlled trial was conducted at Unit I, Department of Gastroenterology, Lahore General Hospital, Lahore. Duration was six months from 30th November 2017 to 30th May 2018. The sample size of 232 cases (116 in each group) is calculated with 80% power of test, 5% level of significance and taking expected percentage of efficacy i.e. 75.9% with sequential therapy and 58.7% with conventional triple therapy in gastritis patients. Patients ages were ranging between 16-60 years. Patients with recurrent H. pylori attack previous treatment with antibiotics within the past 4 weeks (medical record), proton pump inhibitor treatment during the previous 8 week (on medical record), patient having esophageal strictures (on medical record), patients esophageal variceal (on endoscopy), patients with hepatitis B or C (on medical record), pregnant females, patients allergic to any

content of trial drugs (on history), patients with chronic kidney disease (creatinine>1.2mg/dl), and patients taking corticosteroids (on medical record) were excluded.

Informed-consent were taken. Demographic information like name, age, gender, duration of gastritis and treatment taking for gastritis were also obtained from. Then patients were randomly divided in two equal groups by using lottery method. In group A, patients were prescribed conventional triple treatment including omeprazole 1mg/kg/day for 14 days including amoxicillin 50mg/kg/day and metronidazole 20mg/kg/day. In group B, patients were prescribed sequential therapy including omeprazole 1mg/kg/day for 7 days including amoxicillin 50mg/kg/day followed by a second course for 7 days of claritromycin 15mg/kg/day and metronidazole 20mg/kg/day. Patients were advised to take therapy two times a day. All patients were followed-up in OPD for 30 days. After 30 days patients were advised to take stool with them in the early morning. All samples were sent to the pathology laboratory of the hospital for stool antigen test for H. pylori eradication. Reports were assessed and if there will be no bacterium, then efficacy was labeled. All this information was recorded through proforma.

Data analysis was done using SPSS version 21. Mean and standard deviation was calculated for continuous variables like age and duration of gastritis. Frequency and percentage was calculated for categorical variables like gender and efficacy. Both groups were compared for efficacy by using chi-square test taking p-values≤0.05 as significant. Data was stratified for age, gender and duration of gastritis. Post-stratification, chi-square test was applied taking p-values≤0.05 as significant.

RESULTS

The mean age of patients was 38.63±13.11year in conventional group and 36.46±12.16years in sequential group. Table 1

In conventional group, there were 88 (75.9%) male and 28 (24.1%) females. In sequential group, there were 74 (63.8%) male and 42 (36.2%) females. Table 2

The mean duration of gastritis was 16.48±7.65days in conventional group and 18.01±6.88days in sequential group. Table 3

With conventional therapy, efficacy was achieved in 82 (70.7%) patients while with sequential therapy, efficacy was achieved in 100 (86.2%) patients. The difference was significant (p<0.05). Table 4

Data was stratified for age. In patients aged 16-30years, efficacy was achieved in 30 (69.8%) with conventional therapy and 37 (84.1%) with sequential therapy. The difference was insignificant (p>0.05). In patients aged 31-45years, efficacy was achieved in 19 (70.4%) with conventional therapy and 39 (90.7%) with sequential therapy. The difference was significant (p<0.05). In patients aged 46-60years, efficacy was achieved in 33 (71.7%) with conventional therapy and 24 (82.8%) with sequential therapy. The difference was insignificant (p>0.05). Table 5

Data was stratified for gender. In male patients, efficacy was achieved in 61 (69.3%) with conventional therapy and 63 (85.1%) with sequential therapy. The difference was significant (p<0.05). In female patients, efficacy was achieved in 21 (75.0%) with conventional therapy and 37 (88.1%) with sequential therapy. The difference was insignificant (p>0.05). Table 6

Table 1: Descriptive statistics of age of patients

	n	Group	
		Conventional	Sequential
Age (years)	116	116	
	Mean	38.63	36.46
	Standard Deviation	13.11	12.16
	Minimum	19	16
	Maximum	60	60

Data was stratified for duration of gastritis. In patients having gastritis from 5-10days, efficacy was achieved in 23 (63.9%) with conventional therapy and 14 (82.4%) with sequential therapy. The

difference was insignificant (p>0.05). In patients having gastritis from 11-20days, efficacy was achieved in 27 (73.0%) with conventional therapy and 49 (90.7%) with sequential therapy. The difference was significant (p<0.05). In patients having gastritis from 21-30days, efficacy was achieved in 32 (74.4%) with conventional therapy and 37 (82.2%) with sequential therapy. The difference was insignificant (p>0.05). Table 7

Table 2: Distribution of gender of patients

	Sex	Group		Total
		Conventional	Sequential	
	Male	88 75.9%	74 63.8%	162 69.8%
	Female	28 24.1%	42 36.2%	70 30.2%
Total		116 100%	116 100%	232 100%

Table 3: Descriptive statistics of duration of gastritis

	n	Group	
		Conventional	Sequential
Duration (days)	116	116	116
	Mean	16.48	18.01
	Standard Deviation	7.65	6.88
	Minimum	5	7
	Maximum	30	30

Table 4: Comparison of efficacy in both group

	Efficacy	Group		Total
		Conventional	Sequential	
	Yes	82 70.7%	100 86.2%	182 78.4%
	No	34 29.3%	16 13.8%	50 21.6%
Total		116 100%	116 100%	232 100%

Chi-Square Test = 8.260, p-value = 0.004 (Significant)

Table 5: Comparison of efficacy in both group stratified for age

Age	Efficacy	Group		Total	p-value
		Conventional	Sequential		
16-30	Yes	30 69.8%	37 84.1%	67 77.0%	0.112
	No	13 30.2%	7 15.9%	20 23.0%	
	Total	43	44	87	
31-45	Yes	19 70.4%	39 90.7%	58 82.9%	0.028
	No	8 29.6%	4 9.3%	12 17.1%	
	Total	27	43	70	
46-60	Yes	33 71.7%	24 82.8%	57 76.0%	0.277
	No	13 28.3%	5 17.2%	18 24.0%	
	Total	46	29	75	

Table 6: Comparison of efficacy in both group stratified for gender

Sex	Efficacy	Group		Total	p-value
		Conventional	Sequential		
Male	Yes	61 69.3%	63 85.1%	124 76.5%	0.018
	No	27 30.7%	11 14.9%	38 23.5%	
	Total	88	74	162	
Female	Yes	21 75.0%	37 88.1%	58 82.9%	0.154
	No	7 25.0%	5 11.9%	12 17.1%	
	Total	28	42	70	

Table 7: Comparison of efficacy in both group stratified for duration

Duration	Efficacy	Group		Total	p-value
		Conventional	Sequential		

5-10	Yes	23 63.9%	14 82.4%	37 69.8%	0.172
	No	13 36.1%	3 17.6%	16 30.2%	
	Total	36	17	53	
11-20	Yes	27 73.0%	49 90.7%	76 83.5%	0.025
	No	10 27.0%	5 9.3%	15 16.5%	
	Total	37	54	91	
21-30	Yes	32 74.4%	37 82.2%	69 78.4%	0.374
	No	11 25.6%	8 17.8%	19 21.6%	
	Total	43	45	88	

DISCUSSION

Helicobacter pylori infection is the main cause of peptic ulcer disease, mucosa associated lymphoid tissue lymphoma, and gastric cancer. Eradication of H. pylori has been shown to prevent the recurrence of peptic ulcer disease, including gastric and duodenal ulcers [12]. The first-line choice of treatment for H. pylori eradication has consisted of conventional triple therapy, which includes a proton pump inhibitor, clarithromycin and amoxicillin for 7–14 days in the United States and Europe [13, 14]. In a second Asian-Pacific consensus, conventional triple therapy is also recommended as a first-line therapy [15].

During the past few years, however, the efficacy of conventional triple therapy has decreased, with eradication rates of less than 80%. Decreased eradication rates are due primarily to increased bacterial resistance to clarithromycin, indicating the need for new first-line treatments [16, 17].

There is a discrepancy might be related to the regional antibiotics resistance rate. However, few studies have analyzed culture-based results [18-20]. So we compared the eradication rates of conventional therapy and sequential therapy for H. pylori eradication.

With conventional therapy, efficacy was achieved in 82 (70.7%) patients while with sequential therapy, efficacy was achieved in 100 (86.2%) patients. The difference was significant ($p < 0.05$). Thus conventional therapy has high rate of H. pylori eradication and is more effective than conventional regimen.

Chung et al. conducted a randomized trial and found that the efficacy (complete eradication of H. pylori) was achieved in 75.9% with sequential therapy and 58.7% with conventional triple therapy in gastritis patients. The difference was significant ($P < 0.05$). They concluded that although 10-day sequential therapy yielded a higher H. pylori eradication rate than 10-day conventional triple therapy, the sequential therapy protocol did not result in a sufficiently satisfactory eradication rate. This might be related to the higher antibiotics resistance rate especially to dual resistance. More effective regimens are needed to overcome antibiotic resistance [9].

In another trial, Khodadad et al., found that the sequential therapy showed more eradication rate than conventional therapy (83.9% versus 60.6%) that was statistically significant ($P < 0.039$). Qayoom et al., reported that H. pylori eradication rate was as 81% with clarithromycin based sequential therapy and 68% with standard triple therapy. So the overall comparison across the groups predicted significant difference with $p < 0.05$. The sequential therapy is better than standard triple therapy for eradication of H. pylori infection [3].

Among the first-line treatment options under development are sequential therapy regimens, which have shown higher eradication rates than conventional triple therapy in several recent meta-analyses [21-23]. Most clinical trials of sequential regimens, however, were performed in Italy, and there have been few reports from Asia. In contrast to this result, a recent large scale trial in Latin America shows 14-day conventional triple therapy has a 5.6% higher eradication rate than 10-day sequential therapy [24].

In recent prospective studies in Korea, sequential therapy showed higher eradication rates than conventional triple therapy, although most of these regimens still did not achieve satisfactory eradication rates [24-27].

But Choi et al., has found that the efficacy was achieved in 75.6% with sequential therapy and 74.7% with conventional triple therapy in gastritis patients. The difference was insignificant ($P > 0.05$) [11].

The mean age of patients was 38.63 ± 13.11 year in conventional group and 36.46 ± 12.16 years in sequential group. Data was stratified for age. In patients aged 16-30 years, efficacy was achieved in 30 (69.8%) with conventional therapy and 37 (84.1%) with sequential therapy. The difference was insignificant ($p > 0.05$). In patients aged 31-45 years, efficacy was achieved in 19 (70.4%) with conventional therapy and 39 (90.7%) with sequential therapy. The difference was significant ($p < 0.05$). In patients aged 46-60 years, efficacy was achieved in 33 (71.7%) with conventional therapy and 24 (82.8%) with sequential therapy. The difference was insignificant ($p > 0.05$).

In conventional group, there were 88 (75.9%) male and 28 (24.1%) females. In sequential group, there were 74 (63.8%) male and 42 (36.2%) females. Data was stratified for gender. In male patients, efficacy was achieved in 61 (69.3%) with conventional therapy and 63 (85.1%) with sequential therapy. The difference was significant ($p < 0.05$). In female patients, efficacy was achieved in 21 (75.0%) with conventional therapy and 37 (88.1%) with sequential therapy. The difference was insignificant ($p > 0.05$).

The mean duration of gastritis was 16.48 ± 7.65 days in conventional group and 18.01 ± 6.88 days in sequential group. Data was stratified for duration of gastritis. In patients having gastritis from 5-10 days, efficacy was achieved in 23 (63.9%) with conventional therapy and 14 (82.4%) with sequential therapy. The difference was insignificant ($p > 0.05$). In patients having gastritis from 11-20 days, efficacy was achieved in 27 (73.0%) with conventional therapy and 49 (90.7%) with sequential therapy. The difference was significant ($p < 0.05$). In patients having gastritis from 21-30 days, efficacy was achieved in 32 (74.4%) with conventional therapy and 37 (82.2%) with sequential therapy. The difference was insignificant ($p > 0.05$).

CONCLUSION

Thus the sequential therapy is more effective than conventional therapy for eradication of H. pylori in patients of gastritis. Now, we have resolved the controversy and found local data in favor of sequential regimen as it is more effective than conventional regimen. Now, we will implement the results of this study in local setting and implement the practice of prescribing sequential therapy for H. pylori eradication instead of conventional triple regimen.

REFERENCES

- Rasheed F, Ahmad T, Bilal R. Frequency of Helicobacter pylori infection using 13C-UBT in asymptomatic individuals of Barakaho, Islamabad, Pakistan. J Coll Physicians Surg Pak 2011;21(6):379-81.
- Shahid S. Frequency of H. pylori causing gastritis and peptic ulcer disease in pediatric population. J Gastrointest Dig Syst 2016;6(5 Suppl):41.
- Qayoom A, Hakim M, Tanvir M, Khan B, Malik S. Modified sequential therapy regimen versus conventional triple therapy for helicobacter pylori eradication. Int J Adv Res 2015;3(5):1207-11.
- Malferteiner P, Selgrad M, Bornschein J. Helicobacter pylori: clinical management. Curr Opin Gastroenterol 2012;28(6):608-14.
- Zullo A, Hassan C, Ridola L, De Francesco V, Vaira D. Standard triple and sequential therapies for Helicobacter pylori eradication: an update. Eur J Intern Med 2013;24(1):16-9.
- Chey WD, Leontiadis GI, Howden CW, Moss SF. ACG Clinical Guideline: Treatment of Helicobacter pylori Infection. Am J Gastroenterol 2017;112:212-39.
- Molina-Infante J, Romano M, Fernandez-Bermejo M, Federico A, Gravina AG, Pozzati L, et al. Optimized nonbismuth quadruple therapies cure most patients with Helicobacter pylori infection in

- populations with high rates of antibiotic resistance. *Gastroenterology* 2013;145(1):121-8. e1.
8. Chan C-C, Chien N-H, Lee C-L, Yang Y-C, Hung C-S, Tu T-C, et al. Comparison of 10-day sequential therapy with 7-day standard triple therapy for *Helicobacter pylori* eradication in inactive peptic ulcer disease and the efficiency of sequential therapy in inactive peptic ulcer disease and non-ulcer dyspepsia. *BMC gastroenterol* 2015;15(1):170.
 9. Chung JW, Jung YK, Kim YJ, Kwon KA, Kim JH, Lee JJ, et al. Ten-day sequential versus triple therapy for *Helicobacter pylori* eradication: A prospective, open-label, randomized trial. *J Gastroenterol Hepatol* 2012;27(11):1675-80.
 10. Khodadad A, Farahmand F, Rashtian P. Comparison of sequential and standard triple therapy for eradication of *helicobacter pylori* in children. *Iran j Pediatr* 2014;24(2):14.
 11. Choi HS, Chun HJ, Park SH, Keum B, Seo YS, Kim YS, et al. Comparison of sequential and 7-, 10-, 14-d triple therapy for *Helicobacter pylori* infection. *World J Gastroenterol* 2012;18(19):2377-82.
 12. Hentschel E, Brandstatter G, Dragosics B, Hirschl AM, Nemeč H, Schutze K, et al. Effect of ranitidine and amoxicillin plus metronidazole on the eradication of *Helicobacter pylori* and the recurrence of duodenal ulcer. *N Engl J Med* 1993;328(5):308-12.
 13. Chey WD, Wong BC. American College of Gastroenterology guideline on the management of *Helicobacter pylori* infection. *Am J Gastroenterol* 2007;102(8):1808.
 14. Malfertheiner P, Megraud F, O'Morain C, Bazzoli F, El-Omar E, Graham D, et al. Current concepts in the management of *Helicobacter pylori* infection: the Maastricht III Consensus Report. *Gut* 2007;56(6):772-81.
 15. Fock KM, Katelaris P, Sugano K, Ang TL, Hunt R, Talley NJ, et al. Second Asia-Pacific consensus guidelines for *helicobacter pylori* infection. *J Gastroenterol Hepatol* 2009;24(10):1587-600.
 16. Chung J-W, Lee GH, Han JH, Jeong J-Y, Choi K-S, Kim DH, et al. The trends of one-week first-line and second-line eradication therapy for *Helicobacter pylori* infection in Korea. *Hepato-gastroenterology* 2011;58(105):246-50.
 17. Kim BG, Lee DH, Ye BD, Lee KH, Kim BW, Kim SG, et al. Comparison of 7-day and 14-day proton pump inhibitor-containing triple therapy for *Helicobacter pylori* eradication: neither treatment duration provides acceptable eradication rate in Korea. *Helicobacter* 2007;12(1):31-5.
 18. Vaira D, Zullo A, Vakil N, Gatta L, Ricci C, Perna F, et al. Sequential therapy versus standard triple-drug therapy for *Helicobacter pylori* eradication: a randomized trial. *Ann Intern Med* 2007;146(8):556-63.
 19. Zullo A, Vaira D, Vakil N, Hassan C, Gatta L, Ricci C, et al. High eradication rates of *Helicobacter pylori* with a new sequential treatment. *Aliment Pharmacol Therap* 2003;17(5):719-26.
 20. Sirimontaporn N, Thong-Ngam D, Tumwasorn S, Mahachai V. Ten-day sequential therapy of *Helicobacter pylori* infection in Thailand. *Am J Gastroenterol* 2010;105(5):1071.
 21. Zullo A, De Francesco V, Hassan C, Morini S, Vaira D. The sequential therapy regimen for *Helicobacter pylori* eradication: a pooled-data analysis. *Gut* 2007;56(10):1353-7.
 22. Jafri NS, Hornung CA, Howden CW. Meta-analysis: sequential therapy appears superior to standard therapy for *Helicobacter pylori* infection in patients naive to treatment. *Ann Intern Med* 2008;148(12):923-31.
 23. Gatta L, Vakil N, Leandro G, Di Mario F, Vaira D. Sequential therapy or triple therapy for *Helicobacter pylori* infection: systematic review and meta-analysis of randomized controlled trials in adults and children. *Am J Gastroenterol* 2009;104(12):3069.
 24. Greenberg ER, Anderson GL, Morgan DR, Torres J, Chey WD, Bravo LE, et al. 14-day triple, 5-day concomitant, and 10-day sequential therapies for *Helicobacter pylori* infection in seven Latin American sites: a randomised trial. *The Lancet* 2011;378(9790):507-14.
 25. Kim Y, Kim S, Yoon J, Suk K, Kim J, Kim D, et al. Randomised clinical trial: the efficacy of a 10-day sequential therapy vs. a 14-day standard proton pump inhibitor-based triple therapy for *Helicobacter pylori* in Korea. *Aliment Pharmacol Therap* 2011;34(9):1098-105.
 26. Park H, Jung M, Jung J, Kwon J, Kim E, Seo H, et al. Randomised clinical trial: comparative study of 10-day sequential therapy with 7-day standard triple therapy for *Helicobacter pylori* infection in naïve patients. *Aliment Pharmacol Therap* 2012;35(1):56-65.
 27. Choi WH, Park DI, Oh SJ, Baek YH, Hong CH, Hong EJ, et al. Effectiveness of 10 day-sequential therapy for *Helicobacter pylori* eradication in Korea. *Korean J Gastroenterol* 2008;51(5):280-4.