Tropical Gastroenterology 2018;39(4):182-187

Original Article

A Randomised Trial Comparing 10-Day Sequential and 14-Day Triple Drug Therapy in Eradication of *Helicobacter pylori* in Patients with RUT Positive Antral Gastritis

Shivi Gupta, Sandeep Thareja, Manish Manrai, Atul Abhishek Jha

Department of Medicine, Department of Gastroenterology, Army Hospital Research and Referral, New Delhi.

Corresponding Author: *Dr Manish Manrai*
Email: manishmanrai@outlook.com

ABSTRACT

***Background*:** For eradication of Helicobacter pylori in antral gastritis, the conventional triple drug therapy comprising of amoxicillin, clarithromycin, and a proton pump inhibitor (PPI) is the most widely used first line therapy. A novel first line regimen the sequential therapy comprising of amoxicillin followed by clarithromycin and a nitroimidazole (tinidazole or metronidazole) along with a PPI was shown to have higher eradication rates and was projected as a viable alternative to failing triple drug therapy.

***Aim*:** To compare the efficacy and side effect profile of sequential and triple drug therapy in eradication of *H pylori* infection in Indian population.

***Methods*:** A randomized controlled trial (RCT) was conducted in a tertiary care centre of North India. A total of 350 patients with rapid urease test (RUT) positive antral gastritis were randomized in the ratio of 1:1 to receive either 10 days of sequential or 14 days of triple drug therapy. Successful eradication was defined as RUT negativity by repeat endoscopy done 04 weeks after treatment completion. Side effect profile was assessed by patient interview at the time of repeat endoscopy.

***Results*:** The eradication rates were 93.14 % (163/175) and 91.4 % (160/175) in sequential and triple drug therapy group respectively which were similar (p-value 0.547). In terms of side effect profile, there was no significant difference between the two regimens.

***Conclusion*:** Both the 10 day sequential and 14-day triple drug therapies are equally efficacious in eradication of *H pylori* in Indian population with similar side effect profile.

KEYWORDS: *Helicobacter pylori*, Rapid urease test, Antral gastritis, Sequential therapy, Triple drug therapy.

Introduction

Helicobacter pylori is a microaerophilic, gram negative, common human bacterial pathogen, acquired in childhood with a prevalence of around 80% in developing countries like ours[1]. The organism resides in the stomach and has been clearly implicated in the causation of several gastrointestinal pathologies like antral gastritis, peptic ulcer, gastric mucosa associated lymphoid tissue (MALT) lymphoma and gastric cancer[2]. The recent American College of Gastroenterology guidelines strongly recommend eradication of *H pylori* in all patients diagnosed with the infection using either non-invasive or endoscopic investigative modalities[3]. Several eradication regimens are available presently, mostly involving two or more antibiotics along with a proton pump inhibitor (PPI). Of the multitude of regimens available, the conventional triple drug therapy comprising of amoxicillin, a βlactam antibiotic, clarithromycin, a macrolide, and a PPI all given twice daily for 10 to 14 days is the most widely used first line therapy for *H pylori* eradication. However due to ever increasing drug resistant strains of H pylori, the efficacy of this regimen is declining[4]. A novel first line regimen- the sequential therapy discovered in Italy in 2000 comprising of amoxicillin twice a day for first five days followed by clarithromycin and a nitroimidazole (tinidazole or metronidazole) both given twice daily for the next five days along with a PPI given twice daily throughout the 10 day therapy duration was shown to have higher eradication rates as compared to triple drug therapy in studies carried out in Italy and China (in both the studies both treatment regimen were given for 10 days each) and was projected as a viable alternative to the failing triple drug therapy[5,6]. There are two major randomized controlled trials conducted in India. One by Nasa M *et al* in 2013 at a government hospital in Mumbai which randomized a total of 231 patients to receive a 10-day sequential therapy or a 14-day triple drug therapy achieving eradication rates of 92.4% with sequential and 81.8% with triple drug therapy (p value 0.027)[7]. Second was by Javid G *et al* in 2013 in Kashmir. This trial randomized 272 patients to receive a 10-day sequential or 10-day triple drug therapy, achieving eradication rates of 76.0% vs 61.9% with sequential and triple drug therapy respectively (p value 0.005)[8]. Both these trials showed sequential therapy to be superior to triple drug therapy which was also statistically significant.

The sequential approach was based on the premise that amoxicillin given for first five days increases the bacterial cell wall permeability by destroying ion efflux channels and improves the efficacy of antibiotics given over subsequent five days[9]. However, efficacy of sequential therapy is subject to significant geographic variations, as shown in a multicentre trial in six Latin American countries showing higher eradication rates with 14-day triple drug therapy as compared to 10-day sequential therapy[10]. Another study carried out in Taiwan showed no statistically significant difference between 10-day sequential and 14-day triple drug therapy[11]. Two other randomized controlled trials conducted in Canada and the USA also failed to show significant difference between the two regimens[12,13].

The reason for conducting the present study was to compare the eradication rates of the two regimens in Indian population as country-wise as well as within country variations in resistance pattern have been observed and results of other countries may not be applicable on Indian population where most oral antibiotics are available over the counter[14,15]. With this premise, the study was carried out to compare the *H pylori* eradication rates of a 10-day sequential therapy and 14-day triple drug therapy.

Methods

The study was conducted at the Department of Gastroenterology, Army Hospital (Research and Referral), New Delhi. It was a randomized, prospective study, conducted over a period of one and a half year from October 2015 to March 2017. The study was approved by the institutional ethics committee and a written informed consent was taken from all the patients participating in the study.

Sample size

For calculation of Sample size, the assumptions taken into account were minimum 80% power and 5% significance level (significant at 95% confidence level) and at most 5%

allowable risk. We assumed at 95% confidence level, 0.5 probability of success, and a margin of error (confidence interval) of +/- 8%, the sample size of 150 patients was required in each group. To be on safer side of normality of the data, a sample of 175 was considered in each group for the study.A total of 470 patients were screened till requisite sample size of 175 patients per group was achieved after excluding 120 patients. Division of patients in two groups was done by using simple random sampling 'Chit method'. We had prepared chit of 350 numbers and asked to draw a chit from the well shuffled lot. First 175 numbers were allotted to first group and 176 to 350 were allotted to second group. After each draw lot was again reshuffled for draw.

Inclusion criteria

Patients with symptoms of dyspepsia who had endoscopic evidence of antral gastritis and were RUT positive.

Exclusion Criteria

1. Patients less than 18 years or more than 60 years of age.
2. Patients with coagulopathy: INR> 1.4 or Platelet counts< 10,000/cumm.
3. Patients with normal upper GI endoscopy.

Study design (**Figure 1**)

Patients referred to the Gastroenterology OPD for dyspeptic symptoms which is defined as one or more of the following - post prandial fullness, early satiety, epigastric pain or burning as per Rome IV criteria, were taken up for upper gastrointestinal endoscopy. Olympus EvisExera III - GIF HQ 160 and 190 upper GI endoscopes were used for the study. Patients with endoscopic findings of antral gastritis (**Figure 2**), described as inflamed antral mucosa in the form of erythema or erosions over the greater curvature of antrum, were subjected to on the spot rapid urease test (RUT) which has sensitivity of 90-95% and specificity of 95-100%[16].

To perform the RUT, endoscopically guided antral mucosa sample was taken through the biopsy port and the tissue bit placed on the RUT kit (Pylo Dry kit, manufactured by Halifex Research Laboratory, Kolkata) and the test was read after one hour.

Patients were given regimen as per group they were randomized into, and were called after 04 weeks of completion of therapy for interview and repeat endoscopy and biopsy. Eradication was defined as RUT negativity on repeat endoscopic biopsy done 04 weeks after completion of therapy. Eradication rate was defined as percentage of patients showing eradication post therapy.

$$\text{Eradication rate (\%)} = \frac{\text{No. of RUT negative patients post therapy}}{\textit{Total no.of patients } (175)} \text{ X } 100$$

Statistical methods

Categorical variables were presented in number and percentage (%) and continuous variables were presented as mean ± SD. Normality of data was tested by Kolmogorov-Smirnov test.

Statistical tests were applied as follows-

1. Qualitative variables were compared using Chi-Square test /Fisher's exact test.

2. Student's unpaired t-test was applied to test the difference between mean values of two groups.

Statistical software SPSS version 17.0 was used to analyse the data. Alpha value (p-value) less than 0.05 was considered as significant at 95% confidence level. Alpha value (p-value) less than 0.01 was considered as significant at 99% confidence level.

Results

The study included 350 patients which were randomized into two study groups in a 1:1 ratio. Patients in the two groups were comparable in terms of age distribution, gender, risk factors like smoking, alcohol, NSAID intake and previous history of dyspeptic symptoms with no statistically significant difference between the two groups (**Table 1**).

The eradication rates obtained in sequential and triple drug therapy groups were 93.14 % and 91.4% respectively (**Table 2**), showing superior efficacy of sequential therapy group, however the difference was not statistically significant (p-value 0.547) (**Figure 3**).

The two therapy groups showed similar incidence of nausea and vomiting but sequential therapy

was associated with higher incidence of metallic taste whereas triple drug therapy was associated with higher incidence of diarrhoea, none of which was statistically significant (**Table 3**). Overall nausea and vomiting were the commonest side effects.

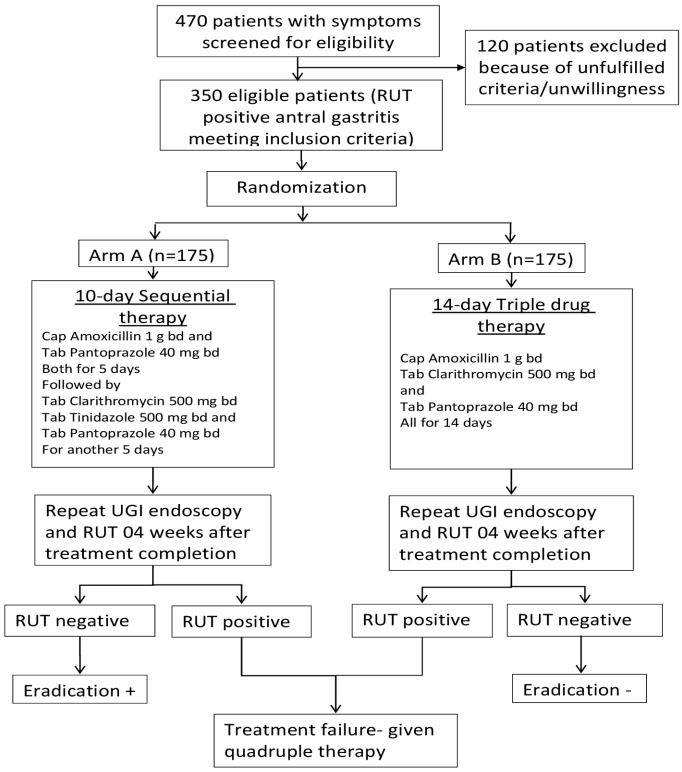

Figure 1: Study design.

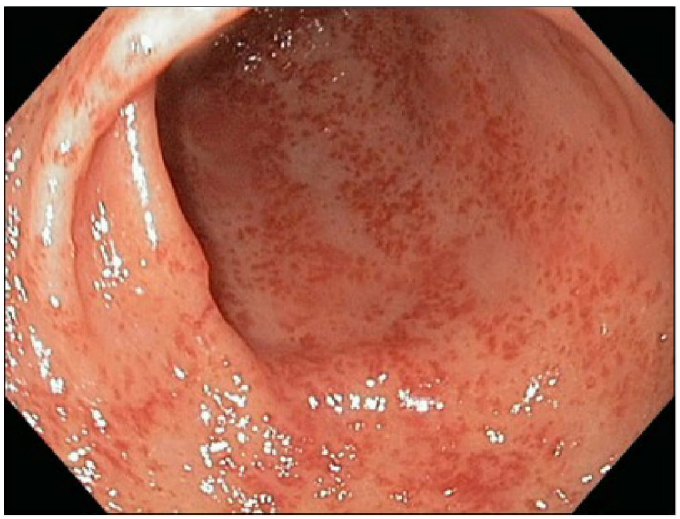

Figure 2: Endoscopic view of antrum showing inflamed mucosa.

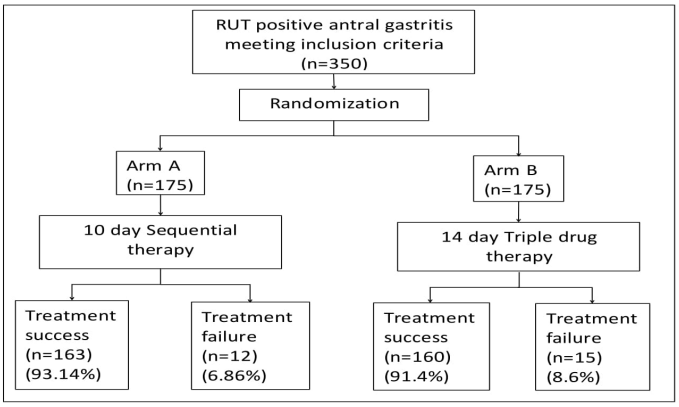

Figure 3: Result.

Table 1: Demographic profile.

	Sequential therapy (n)	Triple drug therapy (n)	p-value
Age	43.11±10.64	45.06±11.34	0.097
Gender Female / Male	84 / 91	92 / 83	0.392
Previous history of dyspepsia	23	24	0.857
Cigarette smoking	36	22	0.199
Alcohol drinking	21	18	0.259
NSAID intake	16	19	0.593

Table 2: Eradication rates with sequential and triple drug therapy.

	Sequential therapy	Triple drug therapy
Treatment success	163 (93.14%)	160 (91.4%)
Treatment failure	12 (6.86%)	15 (8.6%)
		p-value 0.547

Table 3: Side effect profile.

	Sequential therapy (n)	Triple drug therapy (n)	p-value
Nausea	8	8	1.000
Vomiting	7	7	1.000
Diarrhea	1	3	0.622
Metallic taste	3	0	0.247

Discussion

This study was a randomized trial aimed at comparing the *H pylori* eradication rates of 10day sequential and 14-day triple drug therapy in Indian population. All these patients were treatment naive and had never received any anti-*H pylori* treatment before. The study population belonged to middle income groups comprising serving and veteran Armed forces personnel, and their family members, mainly coming from northern states of India.

Our study showed no statistically significant difference in the eradication rates between the two groups, the rates being 93.14% (163/175) in sequential drug therapy group and 91.4% (160/175) in the triple therapy group (p-value of 0.547). The results of this study concur with the previous studies of Liou JM *et al* (Taiwan), Greenberg ER *et al* (Latin American countries), Van Zanten SV *et al* (Canada) and Coss E *et al* (USA)[3]. Also, the eradication rates achieved in the two study groups in our study were similar to those achieved in the RCT by Liou JM *et al* showing eradication rates of 91.6% (556/607) and 91.0% (548/602) in sequential and triple drug therapy respectively in per protocol analysis (p value 0.726)[17]. Studies conducted by Thyagarajan *et al*[18], Mhaskar *et al*[19] and Abraham *et al*[20] described variable resistance patterns to clarithromycin a decade back. Resistance to clarithromycin and nitroimidazole are the most important factors, adversely affecting the eradication rates of triple drug and sequential therapy respectively, we however did not include study of resistance pattern of *H pylori* to different drugs used.

Our results are different from other Indian studies in terms of comparable eradication rates, exceeding 90% in both sequential and triple drug regimen which can be attributed to good compliance to therapy, good quality of generic drugs provided free of cost to all patients, early stages of infection (patients with only antral gastritis were included in the study) and infection with probably sensitive strains of *H pylori*.

Analysis of the side effect profile

When we compared the side effect profile of the two regimens we found minor differences between the two regimens none of which were statistically significant. Overall, both the regimens were well tolerated with 100% compliance which was assessed via questionnaire and individual checking of empty blister packs on follow-up visit. Our study showed almost similar minor side effects which is similar to results of the trial conducted in Italy by Vaira Dino *et al* showing similar frequency of minor side effects - 17.5% (25/143) and 17.1% (25/146) in sequential and triple drug therapy groups respectively although the duration of triple drug therapy in their study was 10 days only[5].

Conclusion

The variable eradication rates seen in various RCTs comparing sequential and triple drug therapy can be attributed to regional resistance patterns of *H pylori* to various antibiotics[21,22]. The comparable eradication rates of the two regimens seen in our study, both exceeding 90% can be attributed to good compliance and follow-up, good quality drugs provided free of cost to all patients and initiation of treatment at early stages of infection with probably sensitive strains of *H pylori* (exact latest resistance patterns of *H pylori* to clarithromycin and tinidazole are not available in Indian population). Hence there is a lot of scope for further studies on *H pylori* in Indian population. The strengths of our study include a large sample size, use of highly sensitive and specific RUT for demonstrating both infection and eradication of *H pylori* and close follow-up and monitoring of response to therapy.

The limitations of our study include exclusion of elderly patients (age more than 60 years) and those with peptic ulcer disease and gastric cancer which are known complications of *H pylori* infection and use of a single modality (RUT) for documentation of eradication. Other limitations being that biopsy was only taken from antrum and we also did not study the resistance pattern of *H pylori* strains. Nevertheless, our study does show that triple drug therapy is as efficacious as sequential therapy in eradication of *H pylori* infection in Indian population although more studies are required to be carried out in our setup to study efficacy of a 10-day vs 14-day sequential

therapy and also vs triple drug therapy besides studying the resistance pattern of H pylori.

To conclude, in Indian population both sequential and triple drug therapy are equally efficacious with eradication rates exceeding 90% and having similar side effect profile and tolerability.

References

1. Perez-Perez, G. I., D. Rothenbacher, and H. Brenner. 2004. Epidemiology of *Helicobacter pylori* infection. Helicobacter 9(Suppl. 1):1-6.
2. Suerbaum S, Michetti P. *Helicobacter pylori* infection. N Engl J Med. 2002; 347:1175-86. [PMID: 12374879]
3. Chey W.D, Wong Benjamin C Y. ACG Clinical Guideline: Treatment of *Helicobacter pylori* infection. Am J Gastroenterol. 2007; 112:212-238
4. Yoon K, Kim N, Nam R H, Suh J H, Lee S, Kim J M *et al*. Ultimate Eradication rate of *Helicobacter pylori* after first, second or third line therapy in Korea. J Gastroenterol Hepatol. 2015; 30:490-495
5. 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.Ann Intern Med. 2007; 146:556-563.
6. Ying-Qun Zhou, Ling Xu, Bing-Fang Wang, Xiao-Ming Fan, Jian-Ye Wu, Chun-Yan Wang *et al*. "Modified Sequential Therapy Regimen versus Conventional Triple Therapy for *Helicobacter pylori* Eradication in Duodenal Ulcer Patients in China: A Multicenter Clinical Comparative Study," Gastroenterology Research and Practice, vol. 2012, Article ID 405425, 8 pages, 2012.
7. Nasa M, Choksey A, Phadkey A, Sawant P. Sequential therapy vs Standard triple drug therapy for *Helicobacter pylori* eradication: a randomized study. Indian J Gasteroenterol. 2013 Nov;32(6):392-6.
8. Javid G, Zargar S A, Bhat K, Khan B A, Yatoo G N, Gulzar G M *et al*. Efficacy and safety of Sequential therapy vs Standard triple therapy in *Helicobacter pylori* eradication in Kashmir, India: a randomized comparative trial. Indian J Gasteroenterol. 2013 May;32(3):190-4.
9. Douglas R. Morgan and Sheila E. Crowe. *Helicobacter pylori* infection. Sleisenger and Fordtrans gastrointestinal and liver disease. 2015; 51: 856-867.
10. Greenberg ER, Anderson GL, Morgan DR, Torres J, Chey W D, Bravo L E *et al*. 14-day triple, 5-day concomitant, and 10-day sequential therapies for Helicobacterpylori infection in seven Latin American sites: a randomised trial. Lancet. 2011; 378:507–14.
11. Ji Young Chang, Ki-Nam Shim, Chung Hyun Tae, Ko Eun Lee, Jihyun Lee, Kang HoonLee *et al*. Sequential versus triple therapy for the first-line treatment of *Helicobacter pylori*: a multicentre, open-label, randomised trial. Lancet 2013; 381: 205–13.
12. Van ZantenS V, Aplin L, Chang H-J, Morse A L, Lazarescu A, Girgis S *et al*. Su1198 Community *H. pylori* Project Treatment Trial results from the Canadian Arctic. Gastroenterology. 2014;146: S-400.
13. CossE,GetaR M and Dunbar K B. Sequential therapy is not better at eradication of primary Helicobacterpylori infection when compared to standard triple therapy in the United States-a prospective, randomized evaluation in a United States population. Gastroenterology. 2014;146: S-399.
14. Vakil N, Megraud F. Eradication therapy for *Helicobacter pylori*. Gastroenterology. 2007; 133:985-1001.
15. Megraud F, Coenen S, Versporten A, Kist M, Lopez-Brea M, HirschlAM *et al*. *Helicobacter pylori* resistance to antibiotics in Europe and its relationship to antibiotic consumption. Gut 2013; 62:34-42
16. Chey WD, Wong BC. Practice Parameters Committee of the American College of Gastroenterology. American College of Gastroenterology guideline on the management of *Helicobacter pylori* infection. Am J Gastroenterol. 2007; 102:1808.
17. Jyh-Ming Liou, Chieh-Chang Chen, Chi-Yang Chang, Mei-Jyh Chen, Chien-Chuan Chen, Yu-Jen Fang *et al*. Gut. 2016;65:1784–1792.
18. Laine L, Estrada R, Trujillo M, Knigge K, Fennerty MB *et al*. Effect of proton-pump inhibitor therapy on diagnostic testing for *Helicobacter pylori*. Ann Intern Med. 1998; 129:547.
19. Chey WD, Spybrook M, Carpenter S, Nostrant TT, Elta GH, Scheiman JM. Prolonged effect of omeprazole on the 14C-urea breath test. Am J Gastroenterol. 1996; 91:89.
20. 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; 56:772.
21. Graham DY, Lee YC, Wu MS. Rational *Helicobacter pylori* therapy: evidence-based medicine rather than medicine-based evidence. Clin Gastroenterol Hepatol2014; 12:177–86. e3.
22. Wu JY, Liou JM, Graham DY. Evidence-based recommendations for successful *Helicobacter pylori* treatment. Expert Rev Gastroenterol Hepatol. 2014; 8:21–8.