ISSN NO. 2320-5407

Journal homepage: http://www.journalijar.com

INTERNATIONAL JOURNAL OF ADVANCED RESEARCH

RESEARCH ARTICLE

MODIFIED SEQUENTIAL THERAPY REGIMEN VERSUS CONVENTIONAL TRIPLE THERAPY FOR HELICOBACTER PYLORI ERADICATION

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Manuscript Info

Manuscript History:

Received: 17 March 2015
Final Accepted: 22 April 2015
Published Online: May 2015

Key words:

H. pylori, Clarithromycin, Levofloxacin, Amoxicillin, pantoprazole, Eradication.

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Abstract

Background: The eradication rates using a conventional triple therapy for Helicobacter pylori (H. pylori) have declined due to increasing antibiotic resistance worldwide.

Aims: To compare the eradication rate of the 10-day sequential therapy for H. pylori infection with that of the 10-day standard triple therapy (PPI based).

Material Methods: This was a prospective, randomized hospital based study. A total of 300 patients were randomized into three groups of 100 each. Group A received triple therapy consisting of pantoprazole 40mg twice daily, clarithromycin 500mg twice and amoxicillin 1gm twice daily for 10 days. Group B, received Pantoprazole 40mg twice daily, amoxicillin 1gm twice daily from day 1-5 and pantoprazole 40mg twice daily, clarithromycin 500mg twice daily and Tinidazole 500mg twice daily from day 6 to 10. Group C received same regimen as Group B except Levofloxacin 250mg twice daily replaced clarithromycin for day 6-10 in this group. The pre and post treatment H. pylori status was assessed by rapid urease test (RUT). Successful eradication was confirmed at 4 weeks after completion of treatment.

Results: The all 300 patients completed the therapy schemes and the examination result indicated that the H. pylori eradication rate of each group was as follows – 86% Levofloxacin based regimen group, 81% with clarithromycin based sequential therapy and 68% with standard triple therapy. So the overall comparison across the groups predicted significant difference with $p < 0.05$.

Conclusion: The sequential therapy is better than standard triple therapy for eradication of H. pylori infection, especially the therapy scheme used in Group C.

INTRODUCTION

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[1] and recently have been associated with some non-gastrointestinal diseases.[2]

H. pylori treatment is not easy and requires combination of antibiotics often with additional non-antibiotic agents. The finding that the elimination of H. pylori infection changes the natural history of peptic ulcer disease[3] and gastric mucosa associated lymphoid tissue lymphoma[4] has lead to the development of successful strategies to clear the organism from persons with these disorders, keeping in view the prevalence of peptic ulcer disease.[5] The

standard triple therapy for H.pylori containing a proton pump inhibitor and clarithromycin with either amoxicillin and imidazole,[6] has lost its sheen because of disappointingly low eradication rates in some countries (with values < 45%-60%)[7] due to increasing antibiotic resistance.[8] De Francisco et al[9] discovered a novel program to eradicated H. pylori (sequential therapy) consisting of 5-day dual therapy (PPI + Amoxicillin) followed by 5-day triple therapy (PPI, Clarithromycin and Tinidazole).[10,11] Our study compared 2 kinds of modified sequential therapy and a standard triple therapy to explore difference in H. pylori eradication.

MATERIAL AND METHODS

Our study was a prospective, open labeled, hospital based randomized study conducted in SMHS Hospital – a tertiary care teaching hospital of Kashmir valley from 2009 October – 2011 October. It included both in-patients and out-patients between 18-70 years of age presented to hospital with symptoms of dyspepsia and GI bleed. The patients were endoscoped by expert gastroenterologists and rapid urease test was done on them for which single biopsy sample was taken from antrum and patients were asked to look for change in colour of urea containing medium within 24 hours after putting biopsy specimen in it (RUT KIT), change to red colour (phenol red used as indicator) indicated that test was positive for H. pylori and subject henceforth was included in the study. Rapid urease test was supplied to us by Allied Marketing Company.

A total of 654 patients participated in our study, out of which rapid urease test was positive in 463. 163 subjects dropped out of study, the rest 300 were randomized into three groups (A, B, C) of 100 patients each by using method of simple random sampling to avoid selection bias. Group A received standard triple therapy, Group B clarithromycin based sequential therapy and Group C received Levofloxacin based sequential therapy.

Exclusion Criteria

1. Patients < 18 of > 70 years of age.
2. Pregnant or lactating mothers.
3. Patients on prolonged PPI therapy, anticoagulants, steroids, NSAIDs.
4. Malignancy of esophagus or stomach.
5. Comorbid conditions like severe cardiovascular, pulmonary or endocrine disease or hepatic or renal dysfunction.

Patients or guardians signed consent before participation in the study. A detailed clinical history, relevant physical examination and abdominal examination were carried out. Routine laboratory studies were performed, including USG abdomen.

Therapy Regimens: Group A patients received standard triple therapy for 10 days consisting of Pantoprazole 40mg twice daily, clarithromycin 500mg (twice daily), amoxicillin 1gm twice daily, Group B and Group C received modified sequential therapy in which both groups initially received pantaprazle 40mg twice daily, amoxicillin 1g twice daily for day 1-5 followed by pantoprazole 40mg twice daily, clarithromycin 500mg twice daily and tinidazole 500mg twice daily for 6 – 10 days in group B and pantoprazole 40mg twice daily, levofloxacin (250mg twice daily) and tinidazole for day 6-10 in group C. Each subject was re-endoscoped at 4 weeks after completion of treatment and single biopsy specimen taken from antrum for H. pylori eradication and test used was rapid urease test.

Statistical Analysis: The difference between the proportions of eradicated infections of three treatments was calculated by using the method recommended by Newcombe and Altman.[12] The level of significance was assessed by using Mannwhitney 'U' test and Krushkall Wallace test for non-metric variables. Students 't' test and ANOVA was used for metric variables. Intergroup variance was checked at 95% CI. MS Excel, Minitab and Statistical Package for Social Science (SPSS) were used for data analysis.

RESULTS

General Data:

A total of 654 patients participated in study of which rapid urease test was positive in 463 and among those 163 (35.20%) dropped out of the study. Details of group divisions were as follows: Group A, 100 patients, 50 male and 50 females with mean$\pm$SD age of 43.3$\pm$14.7 years. Group B, 59 patients male and 41 patients were females with a mean$\pm$SD of 45.4$\pm$14.4 years and in Group C 56 patients were males and 44 females with a mean$\pm$SD of 44.1$\pm$16.1. The inter-group difference between groups A and groups B, group A and group C and between group B and group C was not statistically significant, besides ANOVA did not suggest any significant difference (p value > 0.05).

Table 1: Characteristics of patients in various groups					
		Group A (n=100)	**Group B (n=100)**	**Group C (n=100)**	**ANOVA**
Age Mean±SD Years		43.3±14.7	45.4±14.4	44.1±16.1	0.6576
Sex	Male	50	59	56	0.429
	Female	50	41	44	

Presenting Symptoms and Endoscopic Findings

Most of the patients in studied groups presented with dyspepsia, which was seen in 59% in group A, 66% in group B and 66% in group C. Malena was seen in 29, 29 and 26% subjects in three different groups. Haematemesis was seen in 15, 12 and 13 patients in group A, B and C respectively. The inter-group difference was not statistically significant. Endoscopically most subjects had gastritis across all groups. It was 69% in group A, 53% in group B and 57% in group C. Duodenal ulcer was seen in 13%, 19% and 21% of patients in groups A, B and C respectively. This was followed by normal i.e. patients labeled as non-ulcer dyspepsia (12%, 17% and 18%) and least common findings seen endoscopically was gastric ulcer (6%, 11%, and 4%) respectively. The inter-group difference was not significant.

Table 2: Presenting symptoms of studied subjects			
	Standard therapy group Group A	**Clarithromycin based Group B**	**Levofloxacin based Group C**
Dyspepsia	59 (59%)	66 (66%)	66 (66%)
Malena	29 (29%)	29 (29%)	26 (26%)
Hematemesis	15 (15%)	12 (12%)	13 (13%)

H. Pylori Eradication Rate

Rapid urease test (RUT) determined major eradication of H. pylori in patients receiving Levofloxacin based sequential therapy (80%), whereas the subsequent reduction in clarithromycin based sequential therapy (81%) and 68% in standard therapy group. The inter-group difference of A and C was significant ($p < 0.05$) besides A and B was also significant ($p < 0.05$), whereas group B and C was insignificant. The overall comparison across three groups predicted significant difference ($p < 0.05$).

Table 3: H. pylori eradication rates in various groups						
Standard therapy group Group A	**Clarithromycin based Group B**	**Levofloxacin based Group C**	**RESULTS**			
			AC	**AB**	**BC**	**Overall**
68/100 (68%)	81/100 (81%)	86/100 (86%)	<0.05	<0.05	0.000	<0.05

DISCUSSION

The belief that no organism can survive in the acidic environment of the stomach was shattered by Barry Marshall and Robbin Warren in 1982 when they identified the organism H. pylori.[13] H. pylori affects 80% of the

population in developing countries and 20-50% in industrialized countries.[1] H. pylori is the main cause of gastritis, peptic ulcer disease, gastric adenocarcinoma and mucosa associated lymphoid tissue lymphoma.[1] Between 80-90% of peptic ulcer is caused by or associated with H. pylori infection.

The aim of treatment of H. pylori infection in any clinical situation is eradication of bacterium from foregut which is presently defined as negative test for H. pylori at least 28 days after the end of antimicrobial therapy. Maastricht III initial consensus report on H. pylori recommended that a triple therapy consisting of PPI, clarithromycin and amoxicillin for 7 days is the first choice of treatment for H. pylori infection,[14] which subsequently evolved into 14 days standard triple therapy. But there are worldwide reports of declining eradication rates with standard triple therapy ($\leq$ 80%) with some European countries reporting 25-60% success rate only.[15,16] The main reasons attributed to eradication failure with standard triple therapy include antibiotic resistance particularly resistance to clarithromycin and metranidazole, with prevalence to the tone of 12.9% in the United States and around 24% in some European countries, poor compliance and rapid metabolism of PPIs.[17,18,19] As a general rule for the treatment of infectious diseases, clinicians should use regimens that have an eradication rate of $\geq$ 90%.[20] To achieve this, many newer regimens have been devised which include sequential therapy (De-Francisco et al)[9], concomitant quadruple therapy,[21] hybrid therapy[22] and bismuth containing quadruple therapy.[23]

Sequential therapy a novel approach for H. pylori infection with reported eradication rates of $\geq$ 93.5%[24,25] refers to the idea of adding more antibiotics to the regimen, but in sequence rather than giving all 4 drugs together. In this connection, Jafri and colleagues[26] performed a meta-analysis of clinical trials of sequential therapy, and showed that staggering the treatment with multiple antibiotics, does not increase side effects, but still eradicates almost all H. pylori isolates. Thus sequential therapy combines the initial and the repeated therapy in one treatment sequence, for the same cost and with the same side effect profile as those of the present standard therapy. The mechanism proposed for the success of sequential therapy is that bacterial develop efflux channels for clarithromycin which rapidly transfers the drug out of the bacterial cell, preventing the antibiotic from binding to the ribosome.[27] Because amoxicillin acts on bacterial cell wall and weakens it, the initial phase of treatment prevents the development of efflux channels by weakening cell wall of bacterium.[27]

Sequential therapy is currently suggested as first line therapy in curing H. pylori infection, but results coming from the use in clinical practice are scarce.[28] We evaluated the efficacy of this regimen compared to standard triple therapy in our current study, and the results of this study showed that modified sequential therapy is superior to triple therapy for the eradication of the H. pylori infection.

CONCLUSION

In conclusion, our large, prospective, randomised controlled study shows the superiority of sequential therapy for eradicating H. pylori infection compared to standard triple therapy and so modified sequential therapy seems to be a valid therapeutic strategy for management of H. pylori infection in clinical practice.

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