

## COMPARISON OF EFFECTIVENESS OF STANDARD TRIPLE THERAPY VERSUS BISMUTH-BASED THERAPY FOR THE MANAGEMENT OF PEPTIC ULCER DISEASE DUE TO *HELICOBACTER PYLORI*

MIRZA MISBA ALI BAIG<sup>1</sup>, UZMA PARVEEN<sup>1\*</sup>, RUQAIHA FAROOQ<sup>1</sup>, MAIMUNA TABASSUM<sup>1</sup>, FATIMA NAAZ<sup>1</sup>, SYED IBRAHIM HASSAN<sup>2</sup>

<sup>1</sup>Department of Pharmacy Practice, Deccan School of Pharmacy, Hyderabad, Telangana, India. <sup>2</sup>Department of Gastroenterology, Deccan College of Medical Sciences, Princess Esra Hospital, Shalibanda, Telangana, India.

Corresponding author: Uzma Parveen. Email: uzmaparveen78641@gmail.com

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### ABSTRACT

**Objective:** *Helicobacter pylori* is the primary agent causing peptic ulcer, therefore imposing a significant impact on health related quality of life, consequently affecting nearly 50% of global population. The objective of this study is to determine and assess the effectiveness of triple therapy versus bismuth containing quadruple therapy for eradication of peptic ulcer disease due to *H. pylori*.

**Methods:** A prospective randomized observational study was conducted at Princess Esra Hospital, Department of Gastroenterology for a period of 6 months. A total of 100 patients were randomly allocated in two groups. The data were assessed using various parameters. *H. pylori* eradication was validated using rapid urease test done at the start treatment 4 weeks after the completion.

**Results:** A total of 100 patients were recruited in the study. In triple therapy group medication adherence rate was found to be 82% in triple and 92% in quadruple therapy. The eradication rate was assessed using Chi-square test it was 82% and 97% in triple and quadruple therapy group, respectively. Hence, the difference was found to be statistically significant value <0.005. In addition, increased recurrence rate has been observed in triple therapy (17%) in contrast with quadruple therapy (2%).

**Conclusion:** Addition of bismuth to significant triple therapy improves cure rates with minimal side effects. Interestingly, we observed that when bismuth was added, it produced a significant higher eradication rate (97%) when compared with standard triple therapy (82%). According to our study, bismuth is highly effective treatment of peptic ulcer disease.

**Keywords:** *Helicobacter pylori*, Peptic ulcer disease, Eradication rate, Recurrence rate.

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### INTRODUCTION

*Helicobacter pylori* is one of the most prevalent pathogens which affects nearly 50% of population across the world [1,2]. Besides, the prevalence of pylori infection in India is nearly around 80% mostly occurring in rural population [3]. *H. pylori* primarily infects gastrointestinal (GI) tract, thereby provoking various GI diseases such as peptic ulcer disease and chronic gastritis and is also intricate in progression of cancer [4,5]. As soon as pylori resides in the stomach causing infection, it can constantly live for more than a decade in the acidic pH where they distort gastric mucosa, transform the secretion pattern of hormones, consequently inducing peptic ulcer disease [6].

Almost all consensus and clinical guidelines approved the use of standard triple therapy regimen consisting of proton-pump inhibitor and two antimicrobial agents as first-line therapy for eradication of pylori [7-9]. Recent research from the previous studies has concluded that the resistance to metronidazole and clarithromycin is being proliferating constantly, thereby reducing the eradication rate to <80%. Hence, the standard triple therapy is no longer effective in areas with higher antibiotic resistance. Hence, a unique antibiotic regimen is essential to further enhance eradication rate with least possible resistance.

Bismuth is a bactericidal antibiotic which causes lysis of bacteria, it is used to treat peptic ulcers and gastritis, remarkably antibiotic resistance does not occur with the usage of bismuth. Henceforth, bismuth therapy can be used as first-line therapy for successful eradication of pylori,

thus improving cure rates [10]. According to Maastricht V/Florence Consensus Report 2016, PBMT therapy is recommended as first-line therapy in region where there is higher rate of clarithromycin resistance [11].

*H. pylori* resistance and eradication rate were assessed by Sasaki *et al.* from 1995 to 2008, they observed that there is a rise in resistance rate from 8.7% to 54.5% and reduction rate was reduced from 90.6% to 74.8% [12].

*H. pylori* infection is a typical concern among Indian population, due to rise in antibiotic resistance with triple therapy, consequently decreasing the eradication rates. We evaluated whether addition of bismuth to the standard triple therapy could be effective in terms of treatment and eradication rates. Our aim was to determine which regimen is successful for eradication of pylori.

### METHODS

A prospective randomized observational study was conducted in a tertiary care hospital for a period of 6 months from November 2018 to April 2019. A total of 100 patients were randomly allocated in two groups. The demographic data, therapeutic data, laboratory data endoscopic findings, side effects, and patient compliance were collected.

The study was authorized by the Institutional Ethics Committee of Owaisi Hospital and Research Centre. This study correlates the efficacy of two different regimens, triple therapy versus bismuth containing

quadruple therapy, administered twice daily in inpatient and outpatient of the gastroenterology department of a tertiary care hospital.

#### Inclusion and exclusion criteria

*H. pylori* positive patients were randomly allocated into two groups. Each group comprising 50 individuals.

The duration of treatment for both the groups was 14 days. The patients were entitled if they were above 18 years of age, *H. pylori* infection confirmed by rapid urease test and immunoglobulin (Ig)G and IgM antibodies test, and patients of both genders were incorporated in the study.

Patients <18 years of age previous surgery of GI tract, previous use of nonsteroidal anti-inflammatory drugs, known allergy to prescribed antibiotics, pregnant lactating women, history of malignancy, pediatric patients, ulcer complications, and severe comorbid conditions such as hepatic renal or cardiac disease were excluded from the study.

#### Drug therapy used for eradication of *H. pylori*

The treatment included in the study consists of Regimen I - amoxicillin (750 mg) bid, clarithromycin (500 mg) bid, esomeprazole (40 mg) Regimen II - bismuth (colloidal bismuth subcitrate, 120 mg), esomeprazole (40 mg), clarithromycin (500 mg), amoxicillin (750 mg) bid. All drugs have been administered for a period of 14 days. Bismuth and esomeprazole were taken before meals and other antibiotics were taken after meals. Four weeks after completion of the treatment, pylori eradication rate was confirmed using rapid urease test. Negative rapid urease test indicated positive cure rates.

#### Ethical approval

The study was approved by the Institutional Ethics Committee of Owaisi Hospital and Research Centre. Informed consent was obtained from all subjects who participated in the study and they permitted the use of their personal information for research design.

#### Data collection

Patients were enrolled randomly into two groups by consecutive sampling method. We have assembled the demographic information, clinical data, side effects, compliance to treatment, rapid urease test, and endoscopic findings from all the patients who were *H. pylori* positive.

The data were collected from patient treatment chart, case sheets, laboratory reports, and patient attenders. The study required a minimum of two visits during the 6-month survey, for diagnosis of GI ulcers such as duodenal ulcer and gastric ulcer, upper endoscopy was conducted before the treatment was commenced. Rapid urease test has been used for confirmation of pylori infection. Endoscopy and rapid urease test were repeated after 14 days up to month after the termination of treatment until the status of pylori was found to be negative.

#### Statistical analysis

Statistical analysis was performed using SPSS software version 20.0 for Windows. For evaluation of demographic, clinical, therapeutic data

in the study population, descriptive statistics were used. Outcome variables were illustrated as percentages. To determine the categorical data between two groups, Chi-square test was used. For comparison of continuous data between two groups, Student's t-test was used.  $p < 0.05$  is statistically significant.

#### RESULTS

A total of 100 patients satisfying the inclusion criteria were recruited in the study. Among 50 patients in triple therapy group, 36% were male and 64% were female, furthermore, the most prevailing age was around 29–38 years. On the contrary, quadruple therapy group consists of 29% of male and 21% of female, the most prevailing age was around 29–38 years (Table 1).

Risk factors associated with peptic ulcer disease are smoking (30%, 45%), alcohol (18%, 14%), and tobacco (26%, 22%), respectively, in both the groups (Table 2). The difference between the groups regarding risk factors is statistically insignificant.

A total of 34 patients completed the study in triple therapy group, 9 patients lost to follow up, and 7 patients discontinued the treatment after 6 days, henceforth, there is increased risk of recurrence of infection among these seven patients. In quadruple therapy group, 47 patients completed the treatment due to severe dyspeptic symptoms and other risk factors, 3 patients lost to follow up, and 1 patient discontinued the treatment because of side effect such as black stools (Table 3).

#### Medication adherence

Interestingly, in our study, we observed that medication adherence was higher in quadruple therapy as the patient consumed tablets at appropriate time due to its ability to reduce symptoms and improve prognosis of disease. Further, this prominent factor paves way for better adherence in quadruple therapy group. Even though the adherence is arithmetically higher in quadruple therapy group (92%) when compared to triple therapy group (82%), the results were statistically insignificant.

#### Side effects

The most common side effect in triple therapy group is abdominal pain, whereas in quadruple therapy group, the most common side effect is black stools.

Among 100 patients, the most common diagnosis was reflux esophagitis with erosive gastroduodenitis, erosive pangastritis and duodenitis, gastroduodenitis with duodenal ulcer, and gastroduodenitis with gastric ulcer. There was no significant difference observed between endoscopic findings in both the groups ( $p > 0.05$ ) (Table 4).

#### Eradication rates

Rapid urease test is a non-invasive test used for distinguishing the presence of *H. pylori*. In developing countries such as India, where there is increase economic burden, these tests are needed which are cheap and accurate. The eradication rates are confirmed using rapid urease test

**Table 1: Association between drug effect and clinical variables**

Variable	Triple therapy	Quadruple therapy	t-value	p-value
Age (Mean±SD)	40.0±13.82	37.41±10.41	1.06	0.12
Male	18 (36.00)	29 (58.00%)		
Female	32 (64.00)	21 (42.00)		
Risk factors			Odd Ratio	
Smoking	15 (30)	21 (45)	0.75 (1.70–1.18)	0.04
Alcohol	4 (18)	7 (14)	1.11 (1.70–1.18)	0.14
Tobacco	13 (26)	11 (22)	1.23 (1.14–1.52)	0.20
Adherence	41 (82)	46 (92)	1.11 (1.18–2.94)	0.18
Dropout	9 (18)	3 (6)	0.76 (0.33–1.17)	0.73
Eradication rate	34 (82.93)	46 (97.87)	2.18 (1.17–1.18)	0.05
Recurrence rate	7 (17.00)	1 (2.00)	1.41 (1.18–2.94)	0.04
Negative rapid urease test	34 (82.9)	46 (97.7)	1.22 (1.00–1.28)	0.21

Table 2: Treatment side effects

Side effects	Triple therapy group	Quadruple therapy group	Odds ratio	p-value
Headache	3	3	3.84	0.04
Constipation	4	5	(1.14–3.47)	
Abdominal pain	5	3		
Pruritus	1	1		
Black colored stools	0	8		

Table 3: Frequency response to treatment in triple and quadruple groups

Rapid urease test post-treatment	Triple therapy	Quadruple therapy	p-value
Positive	7	1	0.21
Negative	34	46	

Table 4: Endoscopic findings of the patients

Endoscopic findings	Triple therapy group	Quadruple therapy group	p-value
Reflux esophagitis with erosive duodenitis	8	5	0.13
Reflux esophagitis with erosive gastroduodenitis	22	13	
Reflux esophagitis with erosive pangastritis and duodenitis	4	10	
Gastroduodenitis	3	01	
Reflux esophagitis with gastroduodenitis and duodenal ulcer	5	7	
Reflux esophagitis with gastric and duodenal ulcer	1	0	
Reflux esophagitis with erosive gastritis and duodenitis	3	5	
Reflux esophagitis with gastritis and gastric ulcer	3	5	

both before and after the treatment. In our study, we observed that the eradication rates are higher in quadruple group (97%) in comparison with triple therapy group (82%) (Figs. 1 and 2). Henceforth, there was a significant difference in both the groups in terms of eradication rate.

#### Recurrence rates

This study found that after the screening of rapid urease test after 4 weeks, infection recurred in 7 patients in triple therapy group. However, we observed that there was a statistically significant difference in both the groups. p value was found to be <0.05 (Fig. 3).

#### DISCUSSION

*H. pylori* is the primary agent causing peptic ulcer, notably imposing a significant impact on quality of life, consequently affecting nearly 50% of global population. According to the American College of Gastroenterology regulations 2007, wherein triple therapy is proposed as the first-line agent for the management of pylori [13]. Substantial evidence from previous literature reported that the standard triple therapy does not produce acceptable eradication rates, because of rise in antibiotic resistance worldwide. Hence, other therapies such as sequential therapy, concomitant therapy, and bismuth-based quadruple therapy can be used as alternatives.

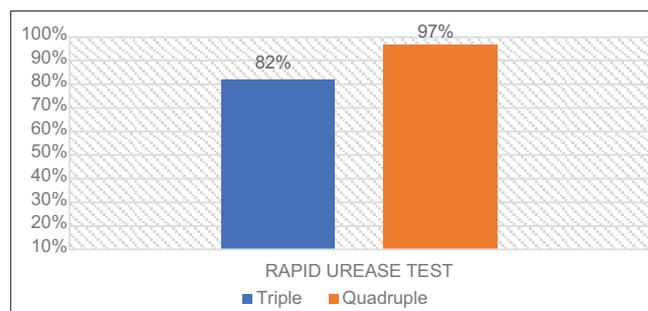


Fig. 1: Negative rapid urease test after treatment between both the groups

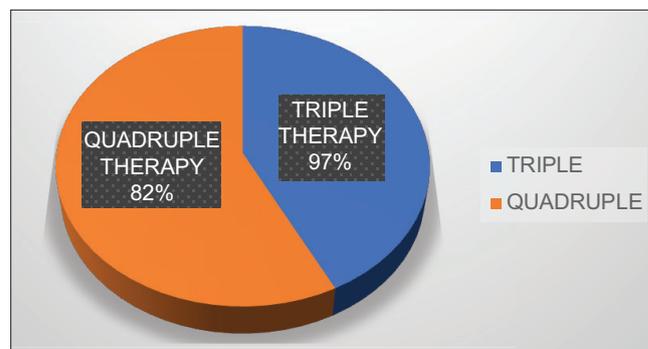


Fig. 2: Comparison of eradication rates in triple and quadruple therapy

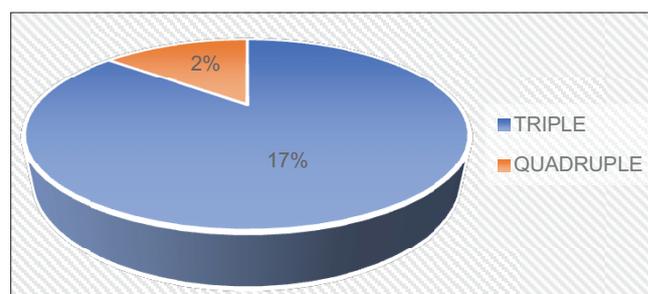


Fig. 3: Recurrence rate in both triple and quadruple therapy

Even though various studies have demonstrated the eradication rates for triple and quadruple therapy, our study particularly validates the effectiveness of bismuth use in Indian population. Notably, our study validates the effectiveness of bismuth use in Indian population, further according to this study, bismuth was effective in the management of peptic ulcer disease caused by *H. pylori* pathogen in country like India where there is rise in antibiotic resistance. In our study, we added bismuth to standard triple therapy and compared with standard triple therapy alone which includes amoxicillin, clarithromycin, and esomeprazole. Hence, we found that on addition of bismuth, there is a significant difference in eradication rate between the two groups. We observed that bismuth produces adverse effect such as black stools in some patients, the discoloration is not permanent and is non-dangerous. The compliance to triple and quadruple regimen was found to be 82% and 92%, respectively.

In Asia, the resistance to metronidazole and clarithromycin was found to be 18.9% and 37.1%, respectively, and tetracycline resistance was found to be 24% [14]. Bismuth is an antimicrobial agent when used in combination with other antibiotics, it increases the eradication rate by decreasing bacterial load [15-17]. Bismuth relatively overpowers the resistance against clarithromycin [18,19], metronidazole [20,21], and levofloxacin [22,23].

### Limitations

The time period of the study was limited. There was a lack of retrospective data for this study. In addition, we do not have data on antibiotic resistance which may influence results. The patients were randomly allocated irrespective of age, gender, and socioeconomic status.

### CONCLUSION

Antibiotic resistance is a major intimidating problem in India which is contributing to rise in various *H. pylori*-related diseases, imposing a significant impact on quality of life. Hence, our study observed that on addition of bismuth to the standard triple therapy resulted in improvement of cure rates with minimal side effects. Interestingly, we observed that when bismuth was added, it produces a significant higher eradication rate (97%) when compared with standard triple therapy (82%). Furthermore, we achieved an acceptable medication adherence rate in both the groups; however, the medication compliance was more in quadruple therapy in comparison with triple therapy. Hence, according to our study, bismuth is highly effective in the treatment of peptic ulcer disease and can be used as first-line therapy. However, further clinical investigations are essential to determine this interpretation.

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### AUTHORS' CONTRIBUTIONS

Dr. Ibrahim Hassan was the principal clinical guide and treating physician for *H. pylori* patients, Mirza Ali Baig was the pharmacy guide and overall supervisor who contributed to research design, and Uzma Parveen and Ruqaiyah Farooq were active in preparing the manuscript, data compilation, manuscript review, manuscript editing, and data analysis, and Maimuna Tabassum and Fatima Naaz contributed in preparing tables and references. All authors scrutinized and validated the final manuscript.

### CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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