Comparison of efficacy and pharmacoeconomics of two Helicobacter pylori eradication regimens in peptic ulcer disease

Syeda Zaineb Kubra Hussaini, Syeda Zaineb Humaira Hussaini, Ruheena Yasmeen, Bader Unnisa, Aamir Ali Asgar Syed1, Md Nematullah Khan1, Syed Ibrahim Hassan2

PharmD Intern, Deccan School of Pharmacy, 1Department of Pharmacy Practice, Deccan School of Pharmacy, 2Department of Gastroenterology, Princess Esra Hospital, Deccan College of Medical Sciences, Hyderabad, Telangana, India

**Abstract**

**Background:** Helicobacter pylori, the cause of most peptic ulcer diseases, infects approximately 50% of the population worldwide. Indian data on cost and effectiveness of the standard first-line therapies for H. pylori eradication are scarce. Thus, the present study was aimed at comparing the cost and efficacy of two standard first-line therapies: Regimen I comprising pantoprazole (40 mg) plus amoxicillin (750 mg) plus clarithromycin (500 mg) (PAC) and Regimen II comprising rabeprazole (20 mg) plus amoxicillin (625 mg) plus metronidazole (200 mg) (RAM).

**Methodology:** This prospective, observational, bottom-up study collected demographic, economic, diagnostic, and therapeutic data from 60 H. pylori-positive patients. The study was carried out for 6 months in the Gastroenterology Department of a Tertiary Care Hospital in Hyderabad, Telangana, India.

**Results:** Health-care system perspective was used to account for direct costs. Average cost per patient for complete H. pylori eradication was Rs. 10,221 and Rs. 8568 for Regimen I and Regimen II, respectively. Inpatient cost was considerably higher than the outpatient cost. Diagnostic costs ranked first in direct costs, followed by hospitalization costs, medication costs, and finally, physician’s office visit cost. Individual patient’s costs difference between two regimens was found to be statistically significant. Overall, Regimen I proved to be more efficacious than Regimen II, but Regimen II proved to be more cost-effective than Regimen I. Furthermore, incremental cost-effectiveness analysis revealed additional cost of Rs. 127 per patient if the patient was treated with Regimen I instead of Regimen II.

**Conclusion:** Our study showed that Regimen II (RAM) was more cost-effective than Regimen I (PAC), but PAC achieved faster H. pylori eradication than RAM. We assume that this study provides local clinical data as to which regimen may be useful in a particular patient. National Level Clinical Trials are required to further ascertain this conclusion.

**Keywords:** Cost-effectiveness analysis, Helicobacter pylori, peptic ulcer disease, perspective, pharmacoeconomics

Address for correspondence:
Assoc. Prof. Aamir Ali Asgar Syed, Deccan School of Pharmacy, Hyderabad, Telangana, India. E-mail: syed.aamir12@gmail.com

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INTRODUCTION

*Helicobacter pylori*, the cause of most peptic ulcer diseases, infects approximately 50% of the population worldwide.[1] *H. pylori* infection increases the risk of peptic ulcer disease, gastric cancer, mucosa-associated lymphoid tissue lymphoma, and uninvestigated dyspepsia.[2-4] Endoscopic tests for diagnosis of *H. pylori* include histology, rapid urease testing, culture, and polymerase chain reaction whereas nonendoscopic tests include antibody testing, urea breath test, and fecal antigen test. The American College of Gastroenterology recommends proton pump inhibitor (PPI) plus amoxicillin plus clarithromycin or metronidazole based triple drug therapy as the standard first-line therapy for the treatment of *H. pylori*-induced peptic ulcers. Quadruple therapy includes the first-line therapy drugs along with bismuth/quinolones/probiotics. Quadruple therapy may be initiated as second-line therapy in case of failure of the first-line therapy.[9]

Economic conditions, *H. pylori* eradication rates, and antibiotic resistance pattern may differ among countries. Local data must be considered before commencing on clarithromycin or metronidazole based triple regimens owing to the development of drug resistance.[6-8] Again, Indian data on cost and effectiveness of the standard first-line therapies are scarce. Thus, the present study was aimed at comparing the cost and effectiveness of two standard first-line therapies: pantoprazole (40 mg) plus amoxicillin (750 mg) plus clarithromycin (500 mg) (PAC) b.i.d (twice daily) and rabeprazole (20 mg) plus amoxicillin (625 mg) plus metronidazole (200 mg) (RAM) b.i.d (twice daily).

METHODOLOGY

The study was prospective, observational, pilot study comparing two different regimens, PAC versus RAM twice daily in inpatients and outpatients of the Gastroenterology Department of a Tertiary Care Hospital in Hyderabad. Patients were recruited by consecutive sampling method, according to the order in which they presented to the gastroenterologist for consultation. *H. pylori*-positive patients confirmed through rapid urease test (*Campylobacter*-like organism [CLO] test), above 18 years of age, and of both genders were included in the study. Patients having history of gastric surgery, allergy to antibiotics used in the study, previous nonsteroidal anti-inflammatory drug use, severe comorbid conditions, pregnant and lactating women, those not willing to give or not able to give verbal informed consent were excluded from the study. The study was carried out for 6 months from November 2014 to April 2015. The study was approved by the Institutional Ethics Committee of Owaisi Hospital and Research Centre.

Data collection

We collected demographic, clinical, and economic data from *H. pylori*-positive patients. The study required a minimum of two visits during the 6-month survey. Patients were recruited by consecutive sampling method, according to the order in which they presented to the Gastroenterologist for consultation. We included only those cases where we are able to get all data from beginning to end of therapy. The data were collected from patients’ treatment chart/case sheets, laboratory reports, medication bills, and patient’s attendees. All subjects gave informed consent to participate in the study and allowed the use of their personal data for research purposes. First endoscopy was performed at the beginning of the study for detection of gastrointestinal ulcers. Presence of *H. pylori* was confirmed by rapid urease test (CLO test). Second endoscopy was performed after every 10 days for 1 month after the completion of their treatments until the *H. pylori* status was found to be negative. Direct costs included costs of medical consumption (consultations, medication, diagnostic tests, and hospitalizations) related to diagnosis and treatment of disease.[9]

Statistical analysis

Descriptive statistics were used to analyze the demographic, clinical, and treatment characteristics of the study population. Outcome variables were represented as percentages. Continuous variables were compared using Student’s *t*-test whereas categorical variables were compared using Pearson’s Chi-square test.

RESULTS

In this cohort comparison study, the efficacy and pharmacoeconomics of two different regimens were evaluated and determined in sixty patients. Among thirty patients of Regimen-I (PAC), 43% patients were male and 57% patients were female. The most common age group was between 18 and 25 years [Table 1]. On the other hand, Regimen-II (RAM) comprised 37% male and 63% female patients. The most common age group was between 36 and 45 years [Table 1]. In general, majority of the people in both the groups were in the age group of 18–25 years, uneducated, with the monthly income of less than Rs. 10,000 [Table 2]. Major presenting complaints were burning epigastric pain, followed by nausea and vomiting [Table 2]. On evaluating the cause of chest pain through electrocardiogram, it was confirmed that all patients had noncardiac chest pain. Majority of the patients
were tobacco chewers, followed by smokers [Table 3]. The common diagnosis among Regimen-I was reflux esophagitis with pangastritis and duodenitis with duodenal ulcers whereas Regimen-II had reflux esophagitis with gastroduodenitis and duodenal ulcers [Table 4]. As the adverse effects associated with H. pylori regimens were minor,[10] the economic aspects of adverse effects were not taken into account.

**Efficacy and cost-effectiveness analysis**

Direct costs include costs of medical consumption (consultations, medication, diagnostic tests, and hospitalizations) related to diagnosis and treatment of disease.[9] Diagnostic tests ranked the top category followed by hospitalization cost, drugs costs, and finally, physician office visit costs [Table 5]. Efficacy was presented as eradication rates. Both the regimens achieved 100% eradication rates, but the duration of eradication of H. pylori differed among the two regimens. The cost was calculated till 100% success in treatment was achieved. While Regimen I (PAC) required only 20 days to achieve 100% H. pylori eradication, Regimen II (RAM) required 30 days to achieve 100% eradication [Table 5]. In contrast, Regimen II (RAM) required lesser cost (Rs. 8568) per patient whereas Regimen I (PAC) required more cost (Rs. 10,221) per patient [Table 5]. Majority of the patients in Regimen I (PAC) had an expense range between Rs. 10,000 and 15,000 whereas majority of the patients in Regimen II (RAM) had an expense range between Rs. 5000 and 10,000 [Table 5].

The cost-effectiveness ratio (CERs) and incremental cost-effectiveness ratio (ICER) were calculated. The regimen with the lowest CER was considered cost-effective than other. In our study, Regimen II (RAM) proved to be more cost effective than Regimen I (PAC). Furthermore, ICER indicated that extra cost per patient for obtaining eradication in one additional patient with PAC instead of RAM was Rs. 127 [Table 5]. Individual total patient costs of two regimens compared by paired t-test, yielded a $P = 0.043$. Thus, there was a statistically significant difference between the total costs of two regimens.

**DISCUSSION**

*H. pylori* eradication drugs include bismuth salts (colloidal bismuth subcitrate, bismuth subsalicylate), metronidazole, tinidazole, secnidazole, tetracycline, amoxicillin, clarithromycin, azithromycin, omeprazole, lansoprazole, quinolones, and ranitidine.[11-16] However, chances of drug resistance and failure of therapy are more with single drug therapy. Hence, three-drug therapy (PPI + two antibacterials) or four-drug therapy (PPI + two antibacterials + bismuth salt) are indicated. Our study revealed that PAC regimen was more effective (more eradication rates in a short duration of time) but slightly more costly than RAM regimen. On average, RAM regimen proved to be more cost-effective than PAC because PAC regimen proved to be more

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**Table 1: Sociodemographic characteristics of the study population**

|                | Men  |    | Women |    |
|----------------|------|----|-------|----|
|                | PAC  | RAM| PAC   | RAM|
|                | (n=13)|   |
| Age (years)    |      |    |       |    |
| 18-25          | 30.7 | 27.2| 29.4  | 31.5|
| 26-35          | 23.0 | 27.2| 29.4  | 21.0|
| 36-45          | 23.0 | 18.1| 17.6  | 21.0|
| 46-55          | 15.3 | 9.0 | 17.6  | 15.7|
| 56-65          | 7.6  | 18.1| 5.8   | 10.5|
| Income (Rs.)   |      |    |       |    |
| <10,000        | 23.0 | 18.1| 29.4  | 21.0|
| 10,000-19,999  | 15.3 | 22.2| 23.5  | 21.0|
| 20,000-29,999  | 30.7 | 9.0 | 17.6  | 15.7|
| 30,000-39,999  | 15.3 | 27.2| 11.7  | 21.0|
| >40,000        | 15.3 | 18.1| 17.6  | 10.5|
| Occupation     |      |    |       |    |
| Unskilled      | 23.0 | 9.0 | 17.6  | 21.0|
| Semiskilled    | 15.3 | 9.0 | 5.8   | 10.5|
| Skilled        | 15.3 | 18.1| 11.7  | 15.7|
| Clerical       | 7.6  | 9.0 | 17.6  | 10.5|
| Administrators | 7.6  | 18.1| 11.7  | 5.2 |
| Managers       | 15.3 | 27.2| 5.8   | 5.2 |
| Executives     | 15.3 | 9.0 | 5.8   | 10.5|
| Homemakers     | 0    | 0  | 23.5  | 21.0|

Table includes homemakers, all of whom were women. **PCA** = Pantoprazole (40 mg) plus amoxicillin (750 mg) plus clarithromycin (500 mg), **RAM** = Rabeprazole (20 mg) plus amoxicillin (625 mg) plus metronidazole (200 mg)

**Table 2: Common complaints of the patients**

| Complaints               | Number of patients (PAC) | Number of patients (RAM) | $P$   |
|--------------------------|--------------------------|--------------------------|-------|
| Burning epigastric pain  | 9                        | 9                        | 0.7862|
| Bloating                 | 1                        | 0                        |       |
| Nausea/vomiting          | 7                        | 4                        |       |
| Loss of appetite and weight | 1                      | 3                        |       |
| Hematemesis              | 4                        | 5                        |       |
| Melena                   | 2                        | 4                        |       |
| Excessive burping        | 3                        | 5                        |       |

**Table 3: Social habits of the patients**

| Personal history          | Number of patients (PAC) | Number of patients (RAM) | $P$  |
|---------------------------|--------------------------|--------------------------|------|
| Tobacco chewer            | 5                        | 7                        | 0.24 |
| Smoker                    | 2                        | 4                        |      |
| Smoker + tobacco chewer   | 1                        | 2                        |      |
| Alcoholic + smoker        | 2                        | 1                        |      |
| Ex-smoker                 | 1                        | 1                        |      |

**Table 4: Social habits of the patients**

| Personal history          | Number of patients (PAC) | Number of patients (RAM) | $P$  |
|---------------------------|--------------------------|--------------------------|------|
| Tobacco chewer            | 5                        | 7                        | 0.24 |
| Smoker                    | 2                        | 4                        |      |
| Smoker + tobacco chewer   | 1                        | 2                        |      |
| Alcoholic + smoker        | 2                        | 1                        |      |
| Ex-smoker                 | 1                        | 1                        |      |
costly than RAM. Majority of our study population was uneducated, in the age group of 18–25 years, and belonging to a lower socioeconomic status. To the best of our knowledge, currently, there are no Indian studies focusing predominantly on sociodemographic parameters of _H. pylori_ patients.

The duration of the regimens varies among different countries. Seven-day therapy was found to be cost-effective in most studies;[2,17-19] 10–14 days of therapy is being practiced in the US, but the duration of therapy is still controversial in Europe and other parts of the world.[20] Again, no single therapy can be used for all of India owing to variations in drug resistance patterns.[21] In our study, duration of both the regimens was 7 days but had to be continued for about a month to achieve complete _H. pylori_ eradication. Overall effectiveness of both the regimens was found to be equal because after 30 days of treatment both the regimens achieved 100% eradication rate.

Treatment failure has been attributed to clarithromycin and metronidazole resistance. Clarithromycin resistance has been particularly found in people with previous macrolide use, particularly for respiratory infections.[22] Metronidazole can be used in allergic or clarithromycin resistant patients. A randomized double-blind clinical trial reported almost no difference between clarithromycin and metronidazole based triple regimens for _H. pylori_ eradication, but metronidazole-based regimen offered low cost, good compliance, and milder side effects, in confirmation with our study.[23] Alcohol must be avoided while on metronidazole treatment to prevent the interaction between metronidazole and alcohol and the resultant disulfiram-like effect.

There are several limitations to our study. The study sample used was small. Due to time constraints, the study was performed as a pilot study containing a smaller number of patients. Hence, sample size and power estimation calculations were not done. There was a lack of retrospective data for this study. We did not stratify the sample based on the age, gender, and socioeconomic status. The adjusting factor to account for the influence of comorbidities on peptic ulcer disease has not been included. In addition, we did not have data on pharmacy dispensing or medication compliance in case of outpatients. In both cases, there is a risk of overestimation of drug use.

**CONCLUSION**

Our study showed that Regimen II (RAM) was more cost-effective than Regimen I (PAC), but PAC achieved faster _H. pylori_ eradication than RAM. We assume that this

| Table 4: Endoscopic findings of the patients |
|--------------------------------------------|
| Endoscopic findings                       | Number of patients (PAC) | Number of patients (RAM) | P |
|--------------------------------------------|--------------------------|--------------------------|---|
| Reflux esophagitis with erosive gastricoduodenitis and esophageal ulcer | 5                         | 5                         | 1.00 |
| Reflux esophagitis with pangastriitis and duodeniitis with duodenal ulcer | 11                        | 7                         | |
| Reflux esophagitis with gastroduodenitis and duodenal ulcer | 8                         | 11                        | |
| Reflux esophagitis with pangastriitis | 6                         | 7                         | |

PCA=Pantoprazole (40 mg) plus amoxicillin (750 mg) plus clarithromycin (500 mg), RAM=Rabeprazole (20 mg) plus amoxicillin (625 mg) plus metronidazole (200 mg)

| Table 5: Efficacy and cost-effectiveness ratio of two regimens for 30 days treatment |
|-----------------------------------------------------------------------------------|
| Direct cost | Total cost of regimen-I (PAC) for 30 patients | Total cost of regimen-II (RAM) for 30 patients |
|------------|-----------------------------------------------|-----------------------------------------------|
| Direct cost (inpatient and outpatient) of two regimens | | |
| Diagnostic test and procedure cost (%) | 144,148 (47) | 153,341 (60) |
| Drugs cost (%) | 48,750 (16) | 29,610 (11) |
| Physician office visits cost (%) | 15,970 (5) | 15,570 (6) |
| Hospitalization cost (%) | 97,770 (32) | 58,505 (23) |
| Total (Rs.) | 306,638 | 257,026 |
| Total average cost per patient (Rs.) | 10,221 | 8568 |

Comparative cost of two regimens

| Cost (Rs.) | 1000-5000 | 5001-10,000 | 10,001-15,000 | 15,001-20,000 |
|------------|-----------|-------------|---------------|---------------|
| Number of patients (RAM) | 10 | 15 | 5 | 0 |
| Number of patients (PAC) | 7 | 8 | 11 | 4 |

Regimen | Average cost per patient (Rs.) | Efficacy (eradication rate) | CER | ICER (additional cost of PAC over RAM (Rs.)) |
|---------|------------------------------|-----------------------------|-----|----------------------------------------|
| Regimen I (PAC) | 10,221 | 90% | 113.5 | 127 |
| Regimen II (RAM) | 8568 | 77% | 111,27 | |

CER = Cost-effectiveness ratio, ICER = Incremental cost-effectiveness ratio, PCA=Pantoprazole (40 mg) plus amoxicillin (750 mg) plus clarithromycin (500 mg), RAM=Rabeprazole (20 mg) plus amoxicillin (625 mg) plus metronidazole (200 mg)
study provides local clinical data as to which regimen may be useful in a particular patient. National Level Clinical Trials are required to further ascertain this conclusion.

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Nil.

**Conflicts of interest**

There are no conflicts of interest.

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