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A Prospective study of role of triple therapy in control of Helicobacter Pylori infection in peptic ulcer disease

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Abstract
Background*: The use of triple therapy regimen for Helicobacter pylori (H. pylori) eradication is a highly efficacious, gold standard regimen. In the current study we have evaluated the H. pylori eradication rate following a triple therapy regimen that include pantoprazole, clarithromycin, amoxycillin.*
Objectives: *To evaluate the efficacy, safety and compliance of a triple therapy regimen with a PPI, amoxicillin and clarithromycin for the eradication of H. pylori .*
Materials and methods*: A total of 140 patients diagnosed with dyspepsia and H. pylori infection as documented by the rapid urease test (RUT) were treated with the following triple therapy regimen: pantoprazole (40mg ,12h), amoxycillin (1000 mg/12h),clarithromycin (500mg/12h) for a two-week period.Our primary expected outcome was H. pylori eradication as established by a negative rapid urease test at least six weeks after the end of treatment.*
Results*: 122 patients could complete the treatment and follow-up protocol. H. Pylori eradication rate was 83.6%. Triple therapy regimen had a similar effect in women (82.9%) and men (83.8%) for the eradication of H. pylori, which was not statistically significant. H. pylori eradication rates according to age groups were: 18-30 years (96%), 31-40 years (85.7%), 41-50 years (81.8%) and 51-60 years(76.7%) with metallic taste being the most common side effect.*
Conclusion*s:Two week triple therapy regimen consisting of pantoprazole, clarithromycin and amoxycillin is a simple and effective approach to the cure of H. pylori infection in patients with peptic ulcer disease. In those patients who took the drugs as prescribed the H. pylori cure rate was 83.6 %,.*
Key words: *Helicobacter pylori, eradication, rapid urease test , triple therapy regimen.*

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I. Introduction

Helicobacter Pylori invariably induces chronic gastritis of variable activity forming basis for peptic ulcer disease. Eradication of Helicobacter pylori (H. pylori) infection is a clinically important issue because of its association with benign and malignant diseases of the upper gastrointestinal tract as well as presence of an increasing antibiotic resistance.1-3 Despite different regimens for its eradication, complete H. pylori eradication is difficult because the bacterium lives beneath the gastric mucus, adhering to the gastric epithelium, where antimicrobial drugs have restricted access to this area.3Additionally, H. pylori is resistant to commonly used antimicrobial agents.4 This high resistance has required the development of a new mode of treatment protocols. The ideal therapy for H. pylori eradication has not yet been clearly defined, but it should be simple, safe, and free from side effects, with 100% efficacy and low cost.

Some studies have shown a decline in the success rate of common therapies, in particular triple regimens whose success rate has plummeted to 25%–60%.5-7 The numerous causes of this decline are varied, but include poor compliance, high antibiotic resistance, high gastric acidity, high bacterial loading, and polymorphism. Cure of the infection heals the ulcer8 and prevent relapse and ulcer complications as well.9,10Treating the infection successfully restores the quality of life of peptic ulcer patient and is most cost effective approach to the longterm management of this chronic relapsing disorder. 11

In1993, Bazzoli et al. reported a 100 % cure of the infection by a 1-week low-dose triple therapy regimen consisting of omeprazole 20 mg once daily, clarithromycin 250 mg b.d. and tinidazole 500 mg b.d.[12]This encouraging result has meanwhile been confirmed by many other authors.[13,14] Since resistance to metronidazole has rapidly increased in some countries[15]combination therapy with a proton pump inhibitor, amoxycillin, and clarithromycin seems to be more attractive. Such a regimen has proved to be as effective as the so called Italian triple therapy regimen.

It has been shown that omeprazole considerably enhances the potency of antibiotics to cure H. pylori infection Pantoprazole is as effective as omeprazole in the treatment of peptic lesions, suggesting a comparable control of gastric pH and this drug also exerts antibacterial activity against H. pylori in vitro.[16]The present study was designed to evaluate the efficacy and tolerability of a standard triple therapy consisting of pantoprazole 40 mg b.d, clarithromycin 500 mg b.d. and amoxycillin 1 g b.d for 2 weeks.

II. Materials And Methods

This prospective study was carried out on patients of Department of GENERAL SURGERY, Sri Venkateswara Ramanarain Ruia Government General Hospital (SVRRGGH), Tirupati , Andhra Pradesh for a period of 12months from September 2018 to October 2019.A total 140 adult patients (both male and females) of aged ≥ 18 with dyspepsia who were positive for rapid urease test were included in the study.

Study Design:Prospective study.

Study Location*:* Department of GENERAL SURGERY, Sri Venkateswara Ramanarain Ruia Government General Hospital (SVRRGGH), Tirupati.

Study Duration*:*September 2018 to October 2019.

Sample size: 140 patients.

Subjects & selection method: A total of 140 patients with symptoms of peptic ulcer disease who were positive for Helicobacter Pylori by rapid urease test.Written informed consent was obtained from all patients before enrolment.

***Inclusion criteria*:**

- ➢ Patients presenting with symptoms of peptic ulcer disease.
- ➢ Patients above 18 years of age.
- ➢ Patients positive for Helicobacter Pylori on rapid urease test.

***Exclusion criteria*:**

- ➢ Patients who had received Anti Helicobacter pylori treatment, within last 6 months.
- ➢ Patients suffering from bleeding disorders, on aspirin or anti platelet agents
- ➢ Patients unfit for gastroscopy.
- ➢ Patients who use PPI or H2 receptor blockers.
- ➢ Patients who had not consented to participate in the study.

***Procedure methodology*:**

Patients presenting with symptoms of peptic ulcer disease who were positive for *H. pylori* by the rapid urease test (RUT) received the triple therapy regimen consisting of pantoprazole 40mg, Amoxycillin-1000mg BD and Clarithromycin- 500mg BD for 14 days i.e., for a two-week period. Patient compliance was evaluated at the end of treatment, by pill count, and was considered good if more than 80% of the medication had been taken. No PPI or H_2-receptor blockers, only antacids on demand, were permitted prior to follow-up endoscopy, which was performed six weeks after the end of eradication treatment to determine *H. pylori* status. Successful eradication of bacteria was defined as negative rapid urease test at the follow-up examination.

STATISTICAL ANALYSIS:

Quantitative data was presented as proportion and analyzed using chi-square test. All analyses were carried out by using SPSS software. The data were entered into Microsoft Excel datasheet. p-value (probability that the result is true) of <0.05 was considered as statistically significant after assuming all the rules of statistical tests.

III. Results

Out of total 140 patients enrolled for the study 122 patients could complete the treatment and follow-up protocol. .

Table 1: Eradication rate H. pylori after completion of treatment

No of patients Positive for Hpylori	Patient negative for Hpylori	% of Eradication
122	102	83.6

After completion of the *H. pylori* eradication regimen, all patients underwent a rapid urease test at 6 weeks after the end of treatment. The eradication rate was 83.6% .

Table 2: Distribution of Study Population Based on Eradication rate of H. pylori in Age groups

Age group	Total cases	Patient negative for Hpylori	% of Eradication
18-30	25	24	96.0
31-40	21	18	85.7
41-50	33	27	81.8
51-60	43	33	76.7
Total	122	102	

(p=0.001)

H. pylori eradication rates with triple therapy were better in the younger age group. The eradication rates according to age category were: 18 to 30 years (96%), 31 to 40 years (85.7%), 41 to 50 years (81.8%) and 51-60 years (76.7%).

Table 3: **Distribution of Study Population Based on Eradication rate of H. pylori in Gender groups**

Gender	Total cases	Patient negative for Hpylori	% of Eradication
Males	75	63	83.8
Females	47	39	82.5
	122	102	

H. pylori eradication rates were similar between women (83.8%) and men (82.5%) after triple therapy regimen usage for 2weeks.This difference was statistically in- significant .

Table 4: Adverse effects of triple therapy with a PPI, ciprofloxacin and amoxycillin for 14 days

Adverse effect	Number of cases	Percentages
Nausea	5	4.1
Metallic taste	11	9.0
Abdominal pain	5	4.1
Diarrhea	2	1.6
Vomiting	7	5.7
Myalgia	9	7.3
	33	

The most frequent adverse event was metallic taste (*n=11*), followed by myalgia (*n=9*), vomiting (*n=7*). A total of 33 patients had noted side effects during active treatment (weeks 1 and 2).

Out of 140 patients ,122 patients completed the study without contravening the protocol; three patients were lost to follow up, five took medication that was not permitted, and four did not follow the time schedule of the study, six patient dropped out to other adverse reactions.

IV. Discussion

Helicobacter pylori infection is an important risk factor of peptic ulcer, chronic gastritis, maltoma and gastric adenocarcinoma and its eradication can be effective in the treatment and prevention of these diseases.[17,18] Several treatment regimens were suggested but none of them was ideal. Also, several studies were done on the type of drugs, dosage and duration of treatment that had contradictory results[19].

Several factors were considered in the treatment regimens such as cost of drugs, effectiveness, side effects and duration of drug needed to be used.[20] Rate of H.pylori eradication has been estimated to more than 95% during 1995[21] by using the triple therapy regimen of PPI, amoxycillin and clarithromycin. Triple therapy combining a PPI with two antibiotics, preferably amoxicillin and clarithromycin (PPI-CA), for H. pylori infection is widely accepted in Europe and the United States. During the Second Spanish Consensus Conference (2005) it was recommended as standard first choice regimen, the use of a PPI together with 1 g of amoxicillin and 500 mg of clarithromycin every 12 hours. In case of allergy to amoxicillin, metronidazole 500 mg every 12 h should be chosen.

During the Third Conference of Consensus at Maastricht (2007) this triple therapy regimen was recommended as first-line treatment. The same guideline is also present in other consensus documents produced in Italy by the "Cervia II Working Group" (2007) and in the United States by the American College of Gastroenterology (2007). [21,22,23]

Consensus at Maastricht (1997), only treatments with an efficiency higher than 80% (intention to treat) should be recommended for clinical practice.[24]Graham et al., in a recent review, assess and confirm that treatment to eradicate H. pylori infection should have an efficiency above 80 or 85%, in intention to treat or per protocol, respectively.[25]

Gisbert et al., (2000), published a meta-analysis on the effectiveness of triple therapy with a PPI, clarithromycin and amoxicillin or metronidazole/tinidazole, reviewing 22 previously reported studies (1996-1999). They found similar efficacy in the intention to treat and per protocol analyses (81 and 84%).[26] In this meta-analysis, the observed efficiency of the eradicating treatment was very close to or exceeded 90%.[26]

Boixeda et al., (2003) found the same trend in a study of 890 patients, and detected an eradication rate of 77%.[27] Calvet et al., (2005) reported an eradication rate of triple therapy regimen (intention to treat) of 73 and 79% for 7 and 10 days of treatment, respectively.[28]

Kadayıfçı et al. were the first in Turkey to systematically analyze the efficiency of the triple treatment in first-line H.pylori eradication.They evaluated 94 studies involving patients who underwent an Standard triple therapy regimen during the 10-year period between 1996 and 2005.[29,30] In the present meta-analysis, the eradication rate was found to be 68.8% .[31]

Gisbert et al. published two studies where a high multisite effectiveness of triple therapy with PPI, Levofloxacin, Amoxycillin for 10 days was found as second and third-line treatment in the eradication of H. pylori.[32]The loss of effectiveness of triple therapy with PPI, Clarithromycin and Amoxycillin motivates the use of triple therapy with levofloxacin replacing Clarithromycin as first-line treatment for the eradication of H. pylori.

In our study, we noted that the eradication rate was associated with some baseline variables such as patients age and gender. The eradication rate gradually decreased with increasing patients age.While there was no significant variation in eradication rate among both genders. In a study by Cai et al.,occupation, gender and protocol compliance were positively associated with eradication rate.[33] In another study by Silva[34] no significant difference was observed regarding sex, tobacco use, alcohol consumption, and NSAID use for H. pylori eradication. However for elderly patients the difference was meaningful. According to our findings, it appeared that older men compared with other sex-age groups had a lower H. pylori eradication rate. Factors that affect this rate such as poor compliance, high antibiotic resistance, high gastric acidity, high bacterial loading, and some polymorphisms might be highlighted more in older males. This should be studied further.

V. Conclusion

2-week triple therapy regimen consisting of pantoprazole, clarithromycin and amoxycillin had effectively attained eradication of H. pylori infection in 83.6% of patients who took the drugs as prescribed. Also, the treatment regimen was sufficient for relief from dyspeptic symptoms.

Limitations

1.Is is a large group study.
2.A large group multivariate analytic study has to be conducted.

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