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A Prospective Study on Side Effect Profile in Helicobacter Pylori Positive Patients Taking Standard Triple Therapy

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Abstract

Helicobacter pylori eradication fails in 10% of patients particularly due to occurrence of drug resistance and side effects. **AIM:** The objective of the research is to monitor the side effect and on tolerability of standard triple therapy to eradicate *H. pylori*. **METHODOLOGY:** A prospective observational study was carried out in the gastroenterology department for which Rapid Urease test was carried out in patients with abdominal symptom as chief complaint and 90 *H.pylori* positive patients were recruited for this study. The side effects were assessed using *de Bore et al.* questionnaire, which was provided during first and second week. In order to evaluate the impact of side effects on treatment compliance, tolerability was assessed using a 5-point scale. **RESULT AND DISCUSSION:** The result was analyzed using paired T test. On analyzing the tolerability, no discomfort was observed in 32 patients (36.4%) during the first week which was increased to 38 (43.3%) at the second week. Slight discomfort has been reported in about 52.3% (46 patients) and 50% (44patients) in the first and second week. Moderate discomforts were seen in 11.3% (10patients) and 6.81% (6 patients) after completion. Among all these categories bitter taste was the most common side effect. The most severe side effect which may result in discontinuation of therapy was diarrhea, whose incidence was reduced by the addition of probiotics thrice daily. **CONCLUSION:** Thus, it was concluded as early identification of side effect can reduce the incidence of drug discontinuation and decrease drug resistance.

Keywords

Helicobacter Pylori, Standard Triple Therapy, Rapid Urease Test, Side effect.

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INTRODUCTION:

Helicobacter pylori (H.pylori) is a Gram-negative bacterium that selectively colonizes the gastric epithelium. *H. pylori* infection is closely associated with the incidence of gastrointestinal diseases [1, 2]. In some developing countries, the prevalence of *H. pylori* is about 80–90% [3]. If left untreated it may cause chronic gastritis, and extra gastric manifestations such as vitamin B12 deficiency, thrombocytopenia purpura. [4]

Current treatment guidelines recommend Standard Triple therapy, combining a proton-pump inhibitor (PPI) with Amoxicillin and Clarithromycin is the mainstay of treatment.[5] Clarithromycin is the most

effective single agent against H. pylori in vivo[6] has additive antibacterial activity with its metabolite as well as amoxicillin.[7] This action is due to decrease in pH gradient across the mucus layer and to change the pharmacokinetic properties of amoxycillin and clarithromycin in the stomach.[8,9]

But its eradication rate has been declined due to the antibiotic resistance and poor patient compliance caused by side effects of traditional regimen such as diarrhea, nausea, vomiting etc. [10, 11, 12]. Various other factors in the failure of H. pylori eradication are included poor diet, a high bacterial load of the gastric, internalization of bacteria, gastric acidity, gene polymorphisms, antimicrobial washout, and most importantly, antibiotic resistance.[13]

Antibiotic associated side effect is a major drawback involving complex regimens in H. pylori eradication [14]. About 20-25% of people experience side effect that can result in cessation of treatment and thus causing failure of eradication. Gastrointestinal side effects may be due to reduction in normal flora or overgrowth of potentially pathogenic antibiotic resistant strains. [15, 16] In regions with high resistance to clarithromycin, treatment with four drugs including bismuth subsalicylate, PPI, tetracycline, and metronidazole are recommended as primary therapies. [17]

Since medication compliance has been considered the most important factor in H. pylori eradication, a major goal is aimed at early identification of side effects so as improving the compliance thus indirectly decrease the eradication rate and antibiotic resistance.

MATERIALS AND METHODS:

A prospective observational study was carried out in the gastroenterology department of a territory care hospital. The duration of the study was six months. Upper GI endoscopy and Rapid Urease test was carried out in 90 patients with abdominal symptom as their chief complaint and *H.pylori* positive patients were recruited for this study. Written informed consent was obtained as per ICMR biomedical research guideline from patients diagnosed as Helicobacter pylori positive satisfying the inclusion and exclusion criteria. All information relevant for the study will be collected from case records and by directly interviewing the patients. The selected subjects were provided with Standard Triple therapy containing Amoxicillin, Proton pump inhibitor and Clarithromycin for a period of 14 days

Inclusion Criteria

- Patients on standard Triple therapy for Helicobacter pylori
- Patients of age 18-80 years.
- Patients with positive rapid urease test (RUT).

Exclusion Criteria

- Patients with previous history of Helicobacter pylori eradication.
- Patients with hepatic and renal impairment.
- Pregnant and lactating women.
- Patients on prolonged proton pump inhibitors, antibiotics therapy, anticoagulants and NSAIDS.
- Patients who have a history of allergy or hypersensitivity to any antibiotics in the regimen.

Side effect profile and treatment tolerability were assessed in each patient using de Boer et al. questionnaire. Often the uncertainty in defining a symptom as a side effect make it extremely difficult to compare side effect profile, to avoid this de Boer et al. questionnaire was administered twice during the study, after the first and second week of treatment course, respectively. In order to obtain the highest compliance patient were provided careful instructions and training. The questionnaire contains two parts in which the first one is tolerability which was assessed using a five-point scale. This consist of no side effect, slight discomfort, moderate discomfort, severe discomfort but continued the treatment and severe discomfort hence forced to discontinue. The second part involves assessing side effects like taste disturbance, loss of appetite, nausea, diarrhea headache etc. which was asked to justify based on severity

For data entry we had used the software Microsoft excel and all the analysis were carried out with the help of statistical software SPSS v.22 version for WINDOWS.

The side effects during and after the treatment was statistically assessed using paired T test. A calculated p-value less than 0.05 considered to be statistically significant.

RESULTS

Background characteristics of the patient were collected, and the results are demonstrated in Chart 1

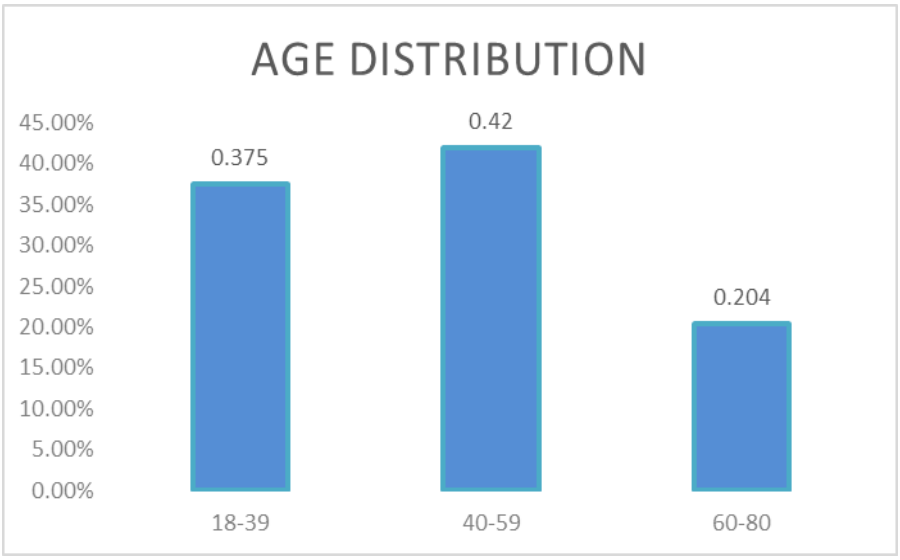

Chart 1 Age Distribution

The gender distribution is demonstrated in Chart 2. Out of the total patients enrolled in the study, the prevalence of *H.pylori* infection was higher in males i.e. 50/88 (56.8%) compared to females i.e. 38/88 (43.2%). It was estimated that majority of these male patients consumed food from outside on a regular basis.

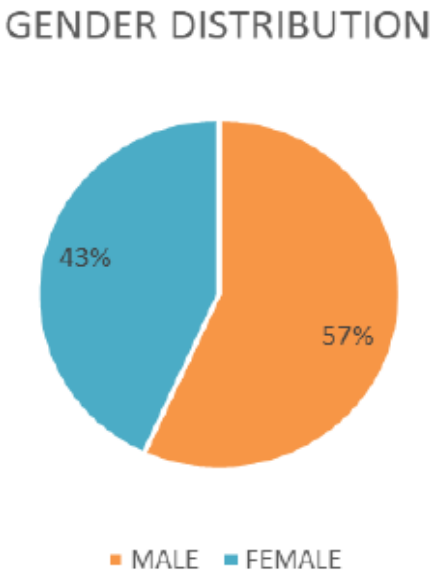

Chart 2 Gender Distribution

The tolerability of standard triple therapy is demonstrated in Chart 3. The side effects were categorized as mild, moderate, and severe based on the interference, with the daily activities.

Out of the total patients 32 (36.4%) can well tolerate the regimen at the first week and 38(43.3%) were at second week. Slight discomfort of side effects being reported about 52.3% (46 patients) in the first week and 50% (44/88) in the second week (Chart 3).

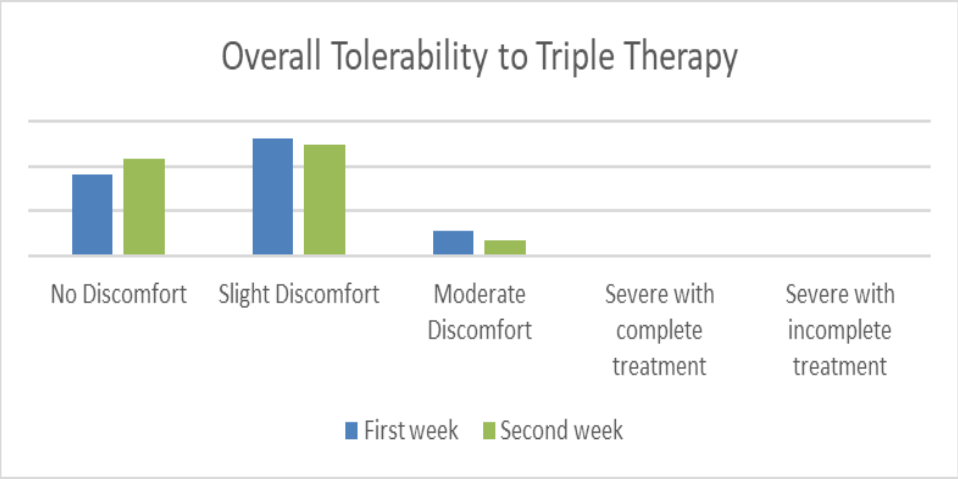

Chart 3 Tolerability to Standard Triple Therapy

After completion of regimen moderate discomfort of side effects seen in 10 patients at the first week and 6 patients at the second week

Side effects of Triple therapy is demonstrated in Table 1. Most reported side effect is bitter taste (41.1%) in both first and second week followed by nausea (15.5%), Loss of appetite and diarrhea (8.9%). The incidence of adverse effects like nausea, diarrhea, epigastric pain was mitigated through the addition of probiotics mainly Saccharomyces boulardii thrice daily for patients with moderate to severe side effect. (figure1 & 2)

Table 1. Side effect profile of Standard triple therapy

Side effects	First week				Second week			
	None	Mild	Moderate	Severe	None	Mild	Moderate	Severe
Bitter taste	38	13	25	12	38	21	20	9
Nausea	74	9	4	1	76	10	1	1
Diarrhoea	82	2	2	2	87	1	0	0
Vomiting	87	1	0	0	88	0	0	0
Headache	84	3	1	0	87	1	0	0
LOA	81	4	3	0	83	3	2	0
Stomach pain	85	2	1	0	87	1	0	0

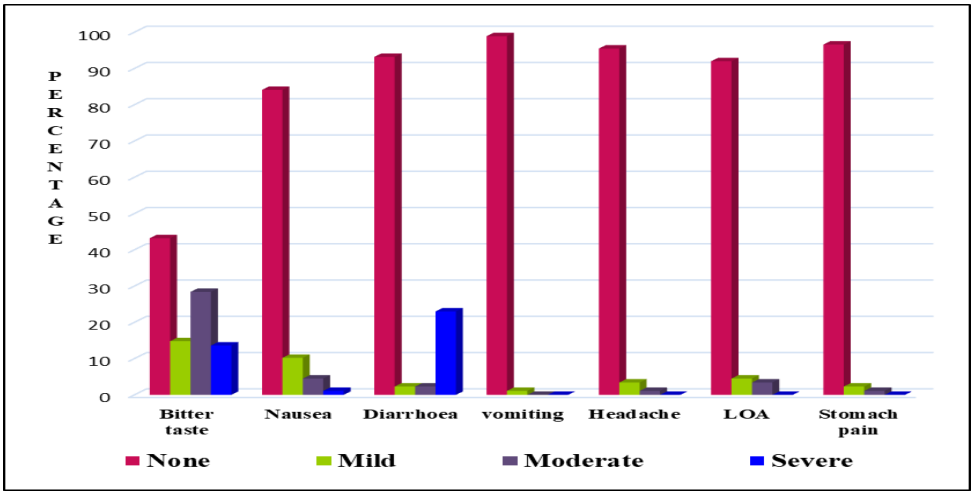

Figure 1: Diagrammatic representation of distribution of side effects in first week

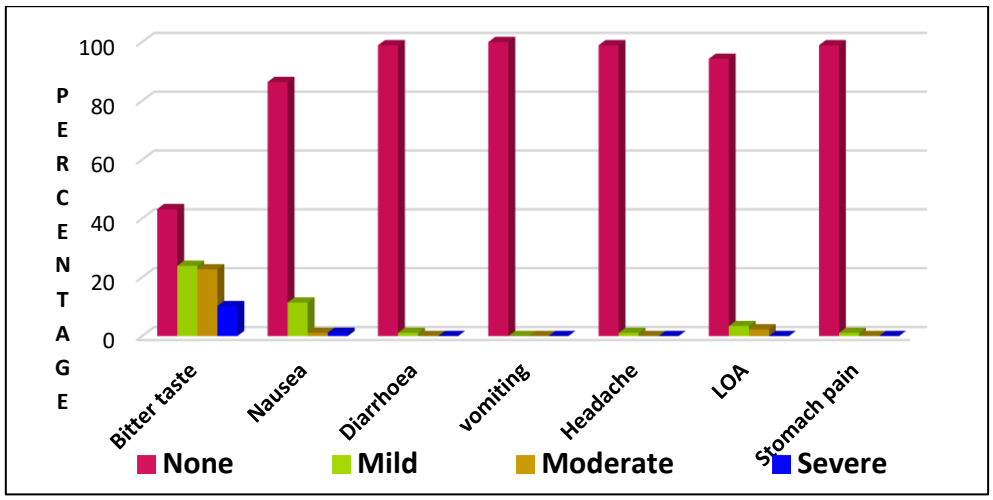

Figure 2: Diagrammatic representation of distribution of side effects in second week

The incidence of adverse effects such as bitter taste (p-value ≤0.011), nausea (p-value ≤0.041), diarrhea (p-value ≤0.027), vomiting (p-value ≤0.032), headache (p-value ≤0.01), loss of appetite (p-value ≤0.038), and abdominal pain (p-value ≤0.018) was reduced significantly in the second week

DISCUSSION:

The study describes the tolerability and side effects of standard triple therapy in H. Pylori patients.

For the cure of any disease the appropriate medications must be provided to obtain effective outcomes. H. pylori infection is one among the most common gastrointestinal infections. Because of the increasing rate of drug resistance and lack of absolute superior antibiotics, eradication research focuses on all kind of regimes.[18,19] Several therapies are available for H. pylori eradication.[20] The standard triple therapy is the first line treatment for H. pylori which consists of proton pump inhibitors (PPI), clarithromycin and amoxicillin. The treatment course ranges from 10days to 2 weeks. [21, 22]

Since the therapy include combination regimen the occurrence of side effects is higher. Moreover, macrolide antibiotics, such as clarithromycin, have been related to increased contractility of gastrointestinal smooth muscle, which may lead to increased motility and accelerated transit with diarrhea.[23] However, there is difficulty in differentiating a symptom from a side effect. Additionally, because of such discrepancies, the frequencies of side-effects in many triple therapy studies have a broad range, but the severity of manifestations is described as `mild' to `moderate'. [24-27]

There were some relevant gastrointestinal side effects observed during the eradication. Side effect profile and treatment tolerability were assessed in each patient using de Boer et al. questionnaire. [28] This is regarded as the most accurate proposed, because it planned as a mix of previously adopted questionnaires. [28-30]

In most studies frequency and severity of side effects of the treatment are poorly described for standard first-line triple therapy the overall rate of adverse events was 53.3% in a multicenter study by Misiewics et al. and these were rarely serious with only one patient experiencing pseudomembranous colitis.[31]

The most frequently reported adverse events in their study was diarrhea, headache, and taste disturbance which was similar to our study in which the most common were taste disturbance, nausea and diarrhea.

However, J. C. Thijs et al. found only acceptable incidence of side effects may be since patients were already about possible side effects before starting treatment could have influenced the results negatively. [32] Although the incidence of the individual side effects was rather high, they were generally very mild. Practically all patients completed the prescribed treatment, and more than 80% had no or just minor side effects.

In contrast another study by Lind T et al found that high incidence of adverse effects with triple therapy (33%) when compared with other regimens and among them the most common adverse effect was loose stools and taste perversion. [33] He also concluded that incidence of gastrointestinal side effects were more with addition of amoxicillin which will be the reason for highest rate of side effects with triple therapy when compared with other regimens containing metronidazole. He also specifies that taste disturbance is more with regimens containing clarithromycin that could be the result of highest prevalence of taste disturbance and diarrhea in this study. [34]

The data regarding the side effects of Standard Triple Therapy shows that 43.2% of patients were able to tolerate the therapy without any side effects. The most common side effects experienced were mild nausea, bitter taste and diarrhea. In this study the most common reported side effect was bitter taste which has the potential to cause discontinuation of therapy. This study aims to identify the side effects early and provide appropriate measure to avoid discontinuation that may increase the risk of drug resistance and disease reappearance.

For those patients with moderate to severe side effect that can even lead to stoppage of therapy supplementation of probiotic was useful. A probiotic is defined as a `live microbial organism which, when ingested, beneficially affects human health, including amelioration or prevention of a specific disease state'. [35] Most probiotics are deemed to colonize the human gut, and certain species, such as *Lactobacillus* spp., can colonize the human stomach, directly or indirectly antagonizing *H. pylori*. [36-40]. This effect can prevent or decrease the incidence of antibiotic associated side effects

CONCLUSION:

The study was conducted to assess the tolerability and side effect of Standard Triple Therapy. The study was conducted using 90 patients who were RUT positive. The patients after being recruited were provided with regimen containing Amoxicillin (1000mg), Clarithromycin (500mg), and Proton Pump Inhibitor twice daily. 36.4% and 43.2% patients were able to tolerate the therapy without any side effects during the first and second week and out of the 88 patients 52.3% and 50% patients' experienced mild side effects like bitter taste, nausea, and diarrhea.

Mostly reported side effect is bitter taste (41.1%) in both first and second week followed by nausea (15.5%), Loss of appetite and diarrhoea (8.9%). The incidence of adverse effects like nausea, diarrhoea, epigastric pain was mitigated through the addition of probiotics.

Early identification of side effects can reduce the incidence of drug discontinuation and decrease drug resistance. Furthermore, the reduction in antibiotic-associated side effects such as nausea, vomiting, diarrhea, and epigastric pain improves medication tolerance and patient compliance.

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CONFLICT OF INTEREST:

Conflict of interest declared none.

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