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To Study the Effectiveness of H.Pylori Eradication in Indian Patients of Non-Ulcer Dyspepsia (Nud)

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ABSTRACT

Background: Dyspepsia can be defined as painful, difficult, or disturbed digestion, which may be accompanied by symptoms such as nausea and vomiting, heartburn, bloating and stomach discomfort. Helicobacter pylori is the main cause of duodenal and gastric ulcers. It is globally accepted that the organism has also been linked to gastric cancer. Most researchers believe that there is a relation, although an imperfect one, between non-ulcer dyspepsia and infection with H. pylori. Several well designed trials have been published in the past years,these have also given conflicting results suggesting that any effect of H.pylori eradication treatment on non-ulcer dyspepsia (NUD) is at best small and may not be an efficient use of resources.

Objectives: To find out the effectiveness of H.pylori eradication treatment in non-ulcer dyspepsia (NUD).

Materials and Methods: This study was hospital based prospective study on OPD patients of KPS Institute of Medicine and Associatd LLR hospital ,GSVM Medical College Kanpur (UP) India**.** Total 200 patients were screened on the basis of symptom of dyspepsia and inclusion and exclusion criteria. On upper G.I.endoscopy 122 patients were NUD and 78 were ulcerative dyspepsia**.** Three groups were made randomly A , B and C .Group A and B with H. pylori positive each group having (n=48) and Group C(n= 26) H.pylori negative. Group A with H.pylori positive (n=48) were given HP KIT (Clarithromycin 500 bid ,amoxicillin 1gm bid, pantoprazole 40 mg bid) for 14 days. In other two groups B and C having H.pylori positive and other H.pylori negative repectively given pantoprazole 40 mg bid for 14 days. Symptoms of dyspepsia were observed after 14 days and 30 days of treatment in follow up.

Results : The total 200 cases studied for dyspepsia, maximum 122 (61%) cases were non- ulcer and 78 (39%) cases were of ulcer type by esophagogastroduedenoscopic (EGD) evaluation.The maximum number of cases (97%) showing improved symptoms were of HP KIT group A (n=48). In the other two groups only 61% showed improvement in symptoms were of pantoprazole group B (n=48) while those H.pylori negative group C (n=26) on RUT showed complete recovery with pantoprazole.

Conclusions: Most of the NUD cases in our study (78.68%) were H.pylori positive by RUT kit method . This shows that majority of NUD cases had H.pylori infection. HP KIT treatment is effective in non-ulcer dyspepsia with H.pylori positive cases in symptom improvement and recurrence as compared to pantoprazole only (p<.001)

Keywords: Non-ulcer dyspepsia (NUD) , H.pylori , HP Kit, RUT, EGD.

INTRODUCTION

Non-ulcer dyspepsia (NUD) refers to dyspepsia with no organic cause. It may also be, referred to as functional, essential or idiopathic dyspepsia.

Helicobacter pylori is the main cause of duodenal ulcer, gastric ulcers, and gastric cancer. Many studies have shown a relationship between H.pylori and non-ulcer dyspepsia.

Symptoms of non-ulcer dyspepsia;

- Abdominal pain
- Bloating
- Indigestion
- Nausea

What causes non-ulcer dyspepsia :

The symptoms seem to come from the upper GI but the cause is not known. On investigations , nothing structural abnormalities were found inside the gut. The lining inside the gut looks normal and are not inflamed. The amount of acid in the stomach is normal the diagnosis is NUD.

The following are some theories as to possible causes:

1. Sensation in the stomach or the first part of the small intestine (the duodenum) may be altered in some way - an 'irritable stomach'. About one in three people with non-ulcer dyspepsia also have irritable bowel syndrome and have additional symptoms of lower abdominal pain, erratic bowel movements, etc. The cause of irritable bowel syndrome is not known.
2. A delay in emptying the stomach contents into the duodenum may be a factor in some cases. The muscles in the stomach wall may not work as well as they should.
3. Infection with a germ negative bacteria called Helicobacter pylori (commonly called as H. pylori) may be the causative agent in some cases.

PATHOPHYSIOLOGY:

The path-physiological mechanisms of H. pylori infection causing dyspepsia are unclear, but may include:

1. Changes in acid secretion,
2. Abnormal motility or altered visceral perception.
3. The prevalence of H pylori infection is higher in patients with non-ulcer dyspepsia than in healthy controls.

A pivotal question is whether curing the H. pylori infection leads to a sustained improvement in symptoms in patients with non-ulcer dyspepsia.

HELICOBACTER PYLORI:

Helicobacter pylori, previously known as Campylobacter pylori, are a Gram-negative, microaerophilic bacterium usually found in the stomach. It was identified in 1982 by Australian scientists *Barry Marshall and Robin Warren*, who found that it was present in a person with chronic gastritis and gastric ulcers, conditions not previously believed to have a microbial cause. It is also linked to the development of duodenal ulcers and gastric cancer. However, over 80% of individuals infected with the bacterium are asymptomatic, and it may play an important role in the natural stomach ecology.

H. pylori is found in the mucus, on the inner surface of the epithelium, and occasionally inside the epithelial cells themselves. It adheres to the epithelial cells by producing adhesins, which bind to lipids and carbohydrates in the epithelial cell membrane.

H. pylori colonized on the surface of regenerative epithelium **(Warthin-Starry silver stain)**

Colonization with H. pylori is not a disease in and of itself, but a condition associated with a number of disorders of the upper gastrointestinal tract.

Several methods of testing exist, including invasive and noninvasive testing methods.

1. Noninvasive tests for H. pylori infection :

- Blood antibody tests
- Stool antigen tests
- The carbon urea breath test (in which the patient drinks 14C—or 13C-labelled urea, which the bacterium metabolizes, producing labeled carbon dioxide that can be detected in the breath).

It is not known which non-invasive test is more accurate for diagnosing a H. pylori infection. The clinical significance of the levels obtained with these tests are also not clear. Some drugs can affect H. pylori urease activity and give false negative results with the urea-based tests.

2. Invasive tests for H. pylori infection: It is an endoscopic biopsy of gastric mucosa to test for H. pylori infection. Low-level infections can be missed by biopsy, so multiple samples are recommended**.**

The most accurate method for detecting H. pylori infection is with a histological examination from two sites after endoscopic biopsy of gastric mucosa, combined with either a rapid urease test or microbial culture.

Helicobacter pylori eradication protocols:

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It is a standard name for all treatment protocols for peptic ulcers and gastritis; the primary goal is not only temporary relief of symptoms, but also total elimination of Helicobacter pylori infection. Patients with active duodenal or gastric ulcers and those with a prior ulcer history should be tested for H. pylori. Appropriate therapy should be given for eradication. To date, it remains controversial whether to test and treat all patients with functional dyspepsia, gastro-esophageal reflux disease, or other non-GI disorders as well as asymptomatic individuals.

Regimens for *Helicobacter pylori* therapy:

Achieving optimal eradication of *H. pylori* has proven difficult. Combination regimens that use two or three antibiotics with a proton pump inhibitor and/or bismuth are required to achieve adequate rates of eradication and to reduce the number of failures due to antibiotic resistance. In the United States, up to 50% of strains are resistant to metronidazole and 13% are resistant to clarithromycin. At present, many gastroenterologist disagree on the optimal regimen.

First-line therapy: Triple therapy:

In areas of low clarithromycin resistance, including the United States, a 14-day course of "triple therapy" with an oral proton pump inhibitor, clarithromycin 500 mg, and amoxicillin 1 g (or, if penicillin allergic, metronidazole 500 mg), all given twice daily for 14 days, is still recommended for first-line therapy. This regimen only achieves rates of eradication in up to 70% of cases.

Second-line therapy: Quadruple therapy

A 14-day course of "quadruple therapy" with a proton pump inhibitor, bismuth, tetracycline, and metronidazole or tinidazole is a more complicated but also more effective regimen. In 2011 randomized, controlled trial, the eradication rates were 93% with quadruple therapy and 70% with triple therapy. Bismuth-based quadruple therapy is recommended as first line therapy for patients in areas with high clarithromycin resistance (> 20%), in patients who have previously been treated with a macrolide antibiotic, or as second-line therapy for patients whose infection persists after an initial course of triple therapy.

Sequential therapy:

Sequential therapy is a newer approach that combines a 5-day course of a "dual therapy" using a proton pump inhibitor in combination with amoxicillin, with a sequential second 5-day course of the standard "triple therapy.

Other proposed regimes:

A number of other eradication regimens have been proposed in the table below as they are compared with standard regimes.

Table 1 : Comparison of *Helicobacter pylori* eradication regimens

Regimen	Duration, days	Drugs used	Notes
Triple therapy	7–14	PPI (standard dose) bid, amoxicillin 1 g bid and clarithromycin 0.5 g bid	First line therapy in areas with low clarithromycin resistance
Sequential therapy	10	1st 5 days: PPI (standard dose) bid and amoxicillin 1 g bid 2^{nd}5days: metronidazole 0.5 g bid and clarithromycin0.5 g bid	First line therapy

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Concomitant therapy	7–10	PPI (standard dose bid), amoxicillin 1 g bid, metronidazole 0.5 g bid and clarithromycin 0.5 g bid	First line therapy
Hybrid therapy	14	1st week: PPI (standard dose) and amoxicillin 1 g bid 2nd week: PPI (standard dose), amoxicillin 1 g, metronidazole 0.5 g and clarithromycin 0.5 g bid	First line therapy
Bismuth-containing quadruple therapy	10–14	PPI (standard dose) bid, tetracycline 0.5 g qid, metronidazole 0.25 g qid and bismuth standard dose qid	First line or second line therapy
Levofloxacin-based triple therapy	10	PPI (standard dose) bid, levofloxacin 0.5 g qid and amoxicillin 1 g bid	Second line therapy if there is no fluoroquinolone resistance
Levofloxacin-based quadruple therapy	10	PPI (standard dose) bid, bismuth standard dose qid and two antibiotics selected by sensitivity tests	Third line therapy if there is no fluoroquinolone resistance
Culture-guided therapy	10	PPI (standard dose) bid, bismuth standard dose qid, levofloxacin 0.5 g qid and amoxicillin 1 g bid	Third line therapy
High-dose dual PPI therapy	14	PPI (high dose) qid and amoxicillin 0.5 g qid	Third line therapy
Rifabutin triple therapy	14	PPI (standard dose) bid, rifabutin 0.15 g bid and amoxicillin 1 g bid	Third line therapy

Aims And Objectives: "Evaluation of upper gastroduedenoscopy in patients of dyspepsia with special reference to H. pylori in non- ulcer dyspepsia" and to evaluate effectiveness of H.pylori

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eradication treatment in H.pylori positive NUD patients in Indian patients.

Material and Methods:

This study was hospital based prospective study 200 patients with symptoms of dyspepsia were taken randomly irrespective of sex in the age group 18-64 year. An informed consent was obtained from all study subjects before their interview and examination. The enrolled patients were subjected to a protocol which included detailed history regarding mode of onset, presentation , duration of illness, personal antecedents including history of alcohol intake .

All patients (200) were subjected to general and systemic examination and those patient who fulfil the ROME CRITERIA of dyspepsia were advised following investigation-

Rome III Diagnostic criteria for functional dyspepsia:

Diagnostic criteria must include:

1. One or more of the following:
   a. Bothersome postprandial fullness
   b. Early satitation
   c. Epigastric pain
   d. Epigastric burning

   AND

2. No evidence of structural disease (including at upper endoscopy) that is likely to explain the symptoms.

* Criteria fulfilled for the last 3 months with symptoms onset at least 6 months prior to diagnosis.

Investigations:

Routine

1. Complete hemogram.
2. Blood sugar.level
3. Serum creatinine and electrolyte.
4. Liver function tests (serum bilirubin ,SGOT, SGPT,PT ,serum albumin)
5. Urinary pregnancy test (UPT)
6. Serological – (Hbs Ag, anti HCV, HIV)

Special investigations:

1. Upper gastro intestinal endoscopy (esophagogastroduodenoscopy)
2. Rapid urease test (RUT) by kit method.

Study Design: Hospital based prospective study

Place of study: Outpatients of KPS Postgraduate Department of Medicine and Associated LLR Hospital, GSVM Medical College, Kanpur. (UP) India.

Period of study: May 2017 to September 2018.

Selection of Cases: - All the patients came to the selected day of OPD with symptom of dyspepsia from last three months, fulfil the ROME criteria.

Ethical clearance: Ethical clearance was obtained from the ethics committee, GSVM Medical College, Kanpur (UP) India.

Inclusion Criteria:

- Individual 18-64 yrs

- Dyspepsia symptoms

- Child bearing age group who are sexually active and agree to use contraception throughout the treatment.

Exclusion Criteria:

- Patients with structural erosion, ulcer, reflux esophagitis ,hiatus hernia,
- Bleeding disorders.
- IBS
- Diabetes mellitus requiring treatment
- Anxiety disorder
- Seizure disorder
- Sleep disorder
- Malignant disease
- Alcohol and drug addict

Statistical analysis: The master table was prepared using MS excel software .The collected data was analysed using appropriate statistical tools like

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percentages, chi square test ,z score ,p value and conclusions were drawn accordingly.

Study pattern (Table 2):

Visit	Day
1st	0 Registration
2nd	1 EGD and biopsy ,treatment started
3rd	14 treatment end and follow up
4th	30 follow up

Grouping of Cases:

Patients after screening, were selected for the study and NUD patients (n=122) were alternatively grouped as follows–

Group A- (HP KIT group/ cases)-

Patients with established NUD, who gave consent and were willing to take HP KIT in the dosage of (Clarithromycin 500 bid ,amoxicillin 1gm bid, pantoprazole 40 mg bid) for 14 days .

Group B- (Non-HP KIT group/controls)-

Patients with established NUD who were not given HP KIT for the same duration of time in addition to Pantoprazole 40 mg bid for 14 days.

Group C (NUD with RUT KIT NEGATIVE)-

Were given Pantoprazole 40 mg bid for 14 days

All the patients were interviewed at 14 days and at 30 days for their symptoms improvement and recurrence. During study 4 patients of group B lost the follow up in between the treatment due to some personnel reason.

Results:

The total 200 cases studied of dyspepsia, maximum 122 (61%) cases were non- ulcer and 78 (39%) cases were of ulcer type by esophagogastroduedenoscopic (EGD) evaluation. (Table 3, Figure 1)

Table 3: DISTRIBUTION OF CASES ACCORDING TO EGD

Upper EGD finding	No. of Patients	%age
Non ulcer dyspepsia	122	61%
Ulcer dyspepsia	78	39%
Total	200	100%

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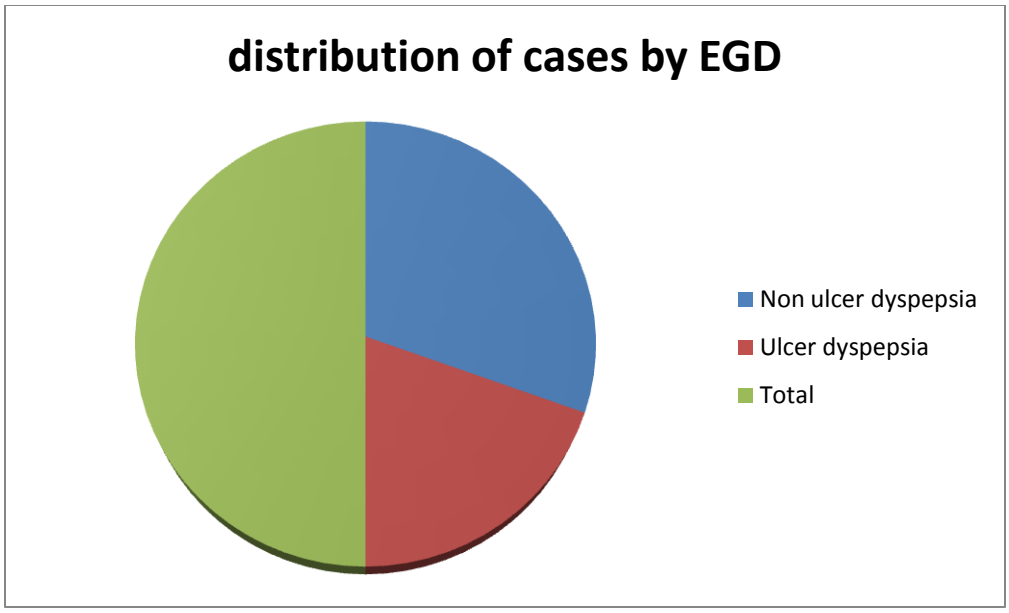

FIGURE 1: Case distribution according to EGD

Z=2.55, p=0.0108

Maximum number of cases 97% showing improved symptoms were of HP kit group.

Majority of cases 61% showing improved symptoms were of pantoprazole group.

While those who were negative by RUT improved completely with pantoprazole only. (Table 4, Figure 2

Table 4: Distribution showing treatment effect in non- ulcer dyspepsia (NUD)

Treatment	RUT STATUS	Symptoms Improved	Symptoms not improved	Dropout	Percentage
HP Kit (GROUP A) (n=48)	POSITIVE	47	1	0	97.91
Pantoprazole (GROUP B)(n=48)	POSITIVE	32	12	4	66.66
Pantoprazole (GROUP A) GROUP C(n=26)	NEGATIVE	26	0	0	100

Figure 2: Treatment effect in NUD

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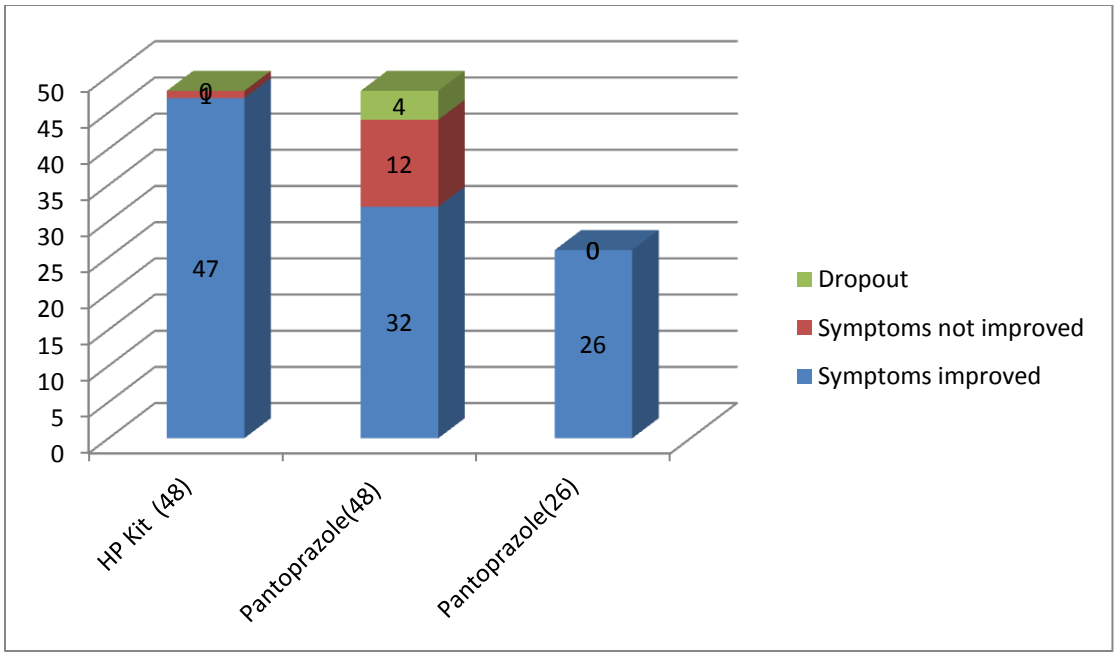

DISCUSSION:

It is controversial whether H.pylori eradication treatment is effective in NUD or not. In our study three groups was made randomly A,B and C ,two groups A and B consists of 48 patients in each with H.pylori positivity third group C had 26 patients with H.pylori negative by RUT.

Group A with H.pylori positive was given HP KIT (clarithromycin 500mg bid ,amoxicillin 1gm bid, pantoprazole 40 mg bid) for 14 days and other two groups B and C was given only pantoprazole 40 mg bid for 14 days and symptoms of dyspepsia were observed after 14 days and 30 days of treatment in follow up.

Most of the H.pylori positive patients symptom improved (97%) after HP kit given for 14 days as shown in **Table- 4.** While those on pantoprazole only improved less (66%) as compared to HP kit ($p<.010$). $Z=2.55$, this shows that H.pylori eradication is effective in H.pylori positive cases of NUD.

Similar observation was observed in study of **Paul Moayyedi et al (2000)**[1] in which H. pylori eradication treatment was significantly superior to placebo in treating non-ulcer dyspepsia.

Similarly **Sander J O Veldhuyzen van Zanten (2000)**[2] found that H.pylori eradication therapy has a small but statistically significant effect in H pylori positive non-ulcer dyspepsia.

LORI M. DICKERSON, PHARM.D., and DANA E. (2004)[3] stated the benefits of eradicating H. pylori infection in patients with non-ulcer dyspepsia.

Moayyedi P et al (2006)[4] suggested H. pylori eradication was more effective than either H2 receptor antagonists or sucralfate alone in treating non-ulcer dyspepsia.

Brian J. Lanier,et al (2011)[5] study also support as that treating *H. pylori* in patients with non-ulcer dyspepsia reduces symptoms, but doesn't improve quality of life in the short term , but may alleviate symptoms in the long term

CONCLUSIONS:

➢ The study was conducted in K.P.S. Institute of Medicine, GSVM Medical College and associated LLR hospital , Kanpur (UP) India. The study groups which include cases of non –ulcer dyspepsia was taken from outdoor clinic. Total 200 patients of non-ulcer dyspepsia were randomly selected after satisfying the various inclusion and exclusion criteria .The relevant history had been collected by a series of questionnaire .The selected subjects underwent detailed clinical examination (age, sex ,family history, general and systemic examination), biochemical investigations and esophagogastroduedenoscopy with biopsy and RUT. The subjects who were positive by RUT kit underwent HP Kit treatment for 14 days. All the data were studied and statistically analyzed. The following conclusions were made after the study:

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- Most of the NUD cases in our study(78.68%) were H.pylori positive by RUT kit method . This shows that majority of NUD cases had H.pylori infection .

- HP KIT treatment is effective in non –ulcer dyspepsia with H.pylori positive cases in symptom improvement and recurrence as compared to pantoprazole (ppi) only (p<.010) .

Limitation of study: In our study sample size is small and duration of follow up is also less so the causation of NUD by H. pylori is a subject of further study with large sample size and long duration of follow up.

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