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Efficacy of *Lactobacillus reuteri* Supplementation in Eradication of *H. pylori*: A Comparison Study with Triple Drug Therapy

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Helicobacter pylori (H. pylori) infections affect roughly one-half of the world's population. Although many standard regimens, including triple-drug therapy, eradicate *H. pylori*, the success rate and efficacy have been declining due to associated side effects and symptom severity. The addition of probiotics to a standard regimen can considerably increase eradication rates. The objective is to find the efficacy of a probiotic *Lactobacillus reuteri (L. reuteri)* in eradicating human *H. pylori* infection and effect on symptoms regression and side effects associated with triple therapy. This prospective interventional study was conducted in 90 *H. pylori*-positive patients. 45 patients

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received standard triple treatment (group-I) for 14 days. Another 45 patients received a combination of standard triple therapy and *L. reuteri* (group-II) for 14 days. After the completion of treatment, *H. pylori* status was evaluated using a 13-C Urea-Breath Test (UBT). Each subject is interviewed with a validated Gastrointestinal Symptoms Rating Scale (GSRS) questionnaire to record symptoms and symptom severity before and after the therapy. Group-II patients showed a significantly higher eradication rate (86.67%) than group-I patients (66.67%). The absolute values of 13C-UBT (group-I: 14.02± 5.4, group-II: 11.9±3.73) revealed that a more substantial reduction in *H. Pylori* load was observed in group II. Statistical analysis proved that group II patients had a significant reduction in GSRS mean scores (baseline score: 15.39±4.52 to end score: 5.33±2.34) compared to group-I patients (baseline score: 14.47±3.67 to end score: 9.86±4.78). Addition of *L. reuteri* has reduced side effects associated with triple drug therapy except bloating. In conclusion, supplementation of *L. reuteri* to standard triple drug therapy significantly improved the eradication rate of *H. pylori*, reduced intensity of gastrointestinal symptoms and also treatment related side effects.

Keywords: H. pylori; L. reuteri; pyloflush; triple drug therapy; eradication rate; 13-C urea-breath test.

ABBREVIATIONS

GSRS : Gastrointestinal Symptoms Rating Scale
H. pylori : Helicobacter pylori
L. reuteri : Lactobacillus reuteri
PPI : Proton Pump Inhibitor
PUD : Peptic Ulcer Disease
QoL : Quality of Life,
RUT : Rapid Urease Test
UBT : Urea Breath Test

1. INTRODUCTION

Helicobacter pylori (H. pylori) is a gram-negative bacterium that colonizes the stomach and causes an illness similar to peptic ulcer disease [1]. *H. pylori* infections roughly affect one-half of the world's population. They are more prevalent in developing countries than developed countries. In India, the prevalence of *H. pylori* infection is as high as 80 percent, with peptic ulcer disease being the most common manifestation [2]. *H. pylori* infections are mostly contracted as a consequence of direct human-to-human transmission or as a result of environmental contamination [3]. The person-to-person transmission may occur through three potential pathways: the gastro-oral, the oral-oral and the faecal-oral routes [4]. If left untreated, the colonization persists chronically. Chronic *H. pylori* infections are associated with chronic gastritis, gastric adenocarcinoma and gastric mucosa-associated lymphoid tissue lymphoma [5].

H. pylori infection can be diagnosed using either invasive method(s) or non-invasive method(s). Upper gastro-endoscopy is a frequently used invasive method in detecting *H. pylori* infection and its allied lesions. Other methods such as biopsy, culture, and histology are also used to detect and confirm the presence of *H. Pylori* infection. 13C Urea Breath Test (UBT), stool-antigen test and antibody-based serology tests are the non-invasive tests. Rapid Urease Test (RUT) is a relatively inexpensive test that has a diagnostic accuracy of >90% [6].

There are specific standard regimens for the eradication of *H. pylori* infection, which remain preferred based on regional bacterial resistance patterns, local recommendations, and drug availability. Some of the regimens used in the eradication of *H. pylori* infection contain triple-drug treatment, non-bismuth quadruple treatment, bismuth-based quadruple treatment, and levofloxacin-containing treatment [7].

The first-line regimen in eradicating the *H. pylori* infection is triple-drug treatment consisting of a proton-pump inhibitor (PPI) and two antibiotics. Triple drug regimen has an eradication rate of 70-80%. It is given for 14 days and consists of a PPI bid, clarithromycin 500 mg bid, amoxicillin 1 g bid, or metronidazole 500 mg tid [8]. The success rate with triple therapy is reducing due to associated side effects and symptom severity, particularly with clarithromycin or metronidazole, thus leading to treatment failure of *H.* pylori [9].

A meta-analysis recommends the practice of probiotics an adjuvant in the standard treatment to increase the *H. pylori* eradication rate [10]. Probiotic supplementation is often associated with reduced antibiotic-associated side effects like nausea, vomiting, diarrhoea, and epigastric pain, thus improving medication tolerance and

patient compliance [11]. When Probiotics are administered in an adequate quantities, they confer a health benefit on the host [12]. A majority of probiotics are of the genera *Lactobacillus* and *Bifidobacterium* [13]. *With regards to H. pylori eradication, Lactobacillus* species have proven to be more efficacious [14].

Of many Lactobacillus species, Lactobacillus reuteri (L. reuteri) produces a variety of antimicrobial substances like hydrogen peroxide, lactic acid, and reuteri and reutericyclin. These substances possess inhibitory activity against both gram-positive and negative bacteria, yeast, fungi, and parasites. For *H. pylori* eradication, *Lactobacillus reuteri* strain DSM17648 (Pyloflush) has a unique property of specifically aggregating *H. pylori* in the stomach. Pyloflush hinders the mobility of *H. pylori* by adhering to the gastric mucosa, thus, entangling the cells into aggregates and masking *H. pylori* surface sites [15]. Freeze-dried and spray dried preparation at a daily quantity of 2×10^{10} (non-viable lyophilized cells) considerably diminish the *H. pylori* load after a 14-day management period in *H. pylori*-positive patients. Pyloflush has also become a significant probiotic for combating antibiotic resistance in *H. pylori* infection and decreasing *H. pylori* load [16].

The objective of our study was to find out the efficacy of *Pyloflush* supplementation in *H. pylori* eradication and to compare the eradication rate of the standard triple-drug alone with standard triple therapy plus Pyloflush supplementation.

2. MATERIALS AND METHODS

Study design and settings: It was a double-centred, prospective and interventional study performed at the Department of Surgical Gastroenterology, Sagar Hospitals and Infinity Gastro Clinic, Bengaluru, India, from October 2019 to April 2020.

Inclusion criteria: Dyspepsia patients aged between 18 and 75 years of any sex and confirmed cases of gastric *H. pylori* infection with 13c urea breath test were eligible for this study.

Exclusion criteria: Patients with conditions such as severe gastritis (easy risk of bleeding), peptic ulcer disease, gall bladder disorders and other chronic diseases such as diabetes, renal failure, cirrhosis, etc., were excluded from the study as they affect the outcomes of this study. Moreover, patients with a previous history of *H. pylori* infection and medication history of proton pump inhibitors, H_2-receptor antagonists and antibiotics in the four weeks preceeding the study were excluded.

Sources of Data: Date sources were found to be OPD consultation notes, case sheets of the patients, endoscopy, RUT reports, patient interviews regarding symptoms and the result of the Urea-Breath Test (UBT).

Study procedure: A total of 90 patients with H. pylori infection were enrolled in the study after checking for eligibility by the physician. Permuted block randomisation (1:1) was followed in order to ensure same size of two treatment groups. All patients were not aware of treatment taken and Gastroenterologist was blinded from treatment regimen given to patient. This study involved the use of Triple Drug therapy and *Lactobacillus reuteri* (Strain: DSM17648, spray dried, available as 'Pyloflush' capsule manufactured by Lupin Pharmaceuticals, India). Status of *H. pylori* was determined using the Urea Breath Test (UBT) before and after the therapy. 90 patients were randomly assigned to one of the following parallel groups:

Group-I: 45 patients were randomly assigned to receive only triple-drug therapy for 14 days. Triple drug therapy involves using one Proton Pump Inhibitor (PPI) - Esomeprazole 40 mg bid before meals, two antibiotics, namely Clarithromycin 500 mg bid and Amoxicillin 1 g bid after meals.

Group-II: 45 patients received the same above triple therapy along with *Lactobacillus reuteri* (Pyloflush) 100mg bid after meals for 14-days. Each 100 mg of a Pyloflush capsule contains 1 x 10^{10} spray-dried cells of *Lactobacillus reuteri.*

Urea-Breath Test procedure: It is a non-invasive test that examines the breath to detect the presence of *H. pylori*. 30 ml liquid containing a small amount of urea (non-radioactive substance) was consumed on an empty stomach. After 5 min, the patient was asked to blow into the balloon.

GSRS scoring: Gastrointestinal Symptom Rating Scale (GSRS) was used to assess the symptomatic improvement in group-I and group-II patients. Each patient was asked to fill a standard GSRS questionnaire which includes 15

questions about symptoms to determine the severity of symptoms.

The GSRS is a disease-specific instrument of 15 items. All 15 questions were clinically divided into 5 categories: abdominal pain, reflux, indigestion, diarrhoea and constipation. The severity of symptoms was assessed before and after the treatment course for both group-I and group-II patients. The symptom severity was rated using scores ranging from 0 to 3. Score 0: no symptomatic discomfort; score 1: Mild to moderate discomfort; score 2: moderately severe discomfort and score 3: severe to very severe discomfort. For each symptom in group-I and group-II patients, a mean score was taken.

2.1 Statistical Analysis

Data was extracted using a pre-designed proforma and an Excel spreadsheet from Microsoft Office. The data were displayed in percentage and mean ± standard deviation whenever applicable. The Z-test was used to investigate the relationship between gender, age, and treatment regimen and eradication rate. The parametric t-test with Graph Pad prism-8 statistical software was used to determine the differences in GSRS rating and side effect profile. P <0.05 was used to determine statistical significance.

3. RESULTS

***H. pylori* eradication rate:** Table 1 showed that 66.67% (30/45) of group-I patients and 86.67% (39/45) of group-II patients tested negative for UBT, indicating that the eradication rate in group-II patients was significantly higher than that of group-I patients (*P*= 0.024). Male and female eradication rates were not significantly different (82.69% vs 68.42%; *P*= 1.88). Age also did not have significant impact on eradication of H.pylori as there was no significant difference between adults and elderly (82.53% vs 62.96%; *P*=1.95). The absolute values of 13C-UBT (group-I: 14.02± 5.4, group-II: 11.9±3.73) revealed that greater reduction in *H. Pylori* load was observed in group II (Fig. 1).

Table 1. Association of age, gender and treatment regimen with H. pylori eradication rate

S.no	Variable	H. pylori eradication rate	*P*-value
1	**Gender**		
	Male (52)	43(82.69%)	
	Female (38)	26(68.42%)	1.88
2	**Age**		
	Adults (63)	52(82.53%)	1.95
	Elderly (27)	17(62.96%)	
3	**Treatment groups**		
	Group-I (45)	30(66.67%)	
	Group-II (45)	39(86.67%)	**0.024**

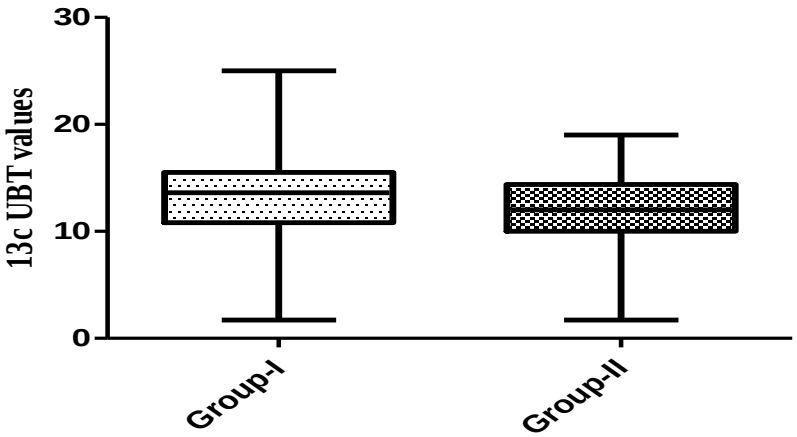

Fig. 1. 13C- UBT values in Group I and Group II patients

GSRS scores: Using a standard gastrointestinal symptoms rating scale (GSRS) questionnaire, the severity of symptoms associated with gastric *H. pylori* infection was investigated and scored before and after the treatment in both groups. The gastrointestinal symptoms recorded in group-I and group-II patients were represented in Table 2 and Table 3 respectively.

Even though the severity of all symptoms was improved in group-I and group-II patients between baseline and after 2 weeks, a noteworthy decline in severity and presentation of symptoms perceived in group-II patients. Group-I patients reported burping (mean score 2.3) as the most suffered symptom followed by abdominal pain, nausea and diarrhea, whereas group-II patients reported diarrhoea as a recurrent complaint (mean score 1.18) followed by hard stools and nausea. Table 4 showed that group II patients had a significant improvement in GSRS mean scores (baseline score: 15.39±4.52 to end score: 5.33±2.34) compared to group-I patients (baseline score: 14.47±3.67 to end score: 9.86±4.78).

Table 2. Gastrointestinal Symptoms Rating Scale (GSRS) - mean scores in Group-I patients

S.no	Symptoms	Day 1 (Before Therapy) Mean score	Day 15 (After Triple Therapy) Mean score
1	Abdominal Pain	2.83	2.19
2	Heart Burn	2.5	1.92
3	Acid Reflux	2.64	1.95
4	Hunger Pain	1.88	1.07
5	Nausea	2.63	2.16
6	Rumbling	2.0	1.63
7	Bloating	2.43	1.50
8	Burping	2.73	2.3
9	Flatus	2.60	1.8
10	Constipation	2.50	2.0
11	Diarrhea	2.48	2.04
12	Loose stools	2.2	1.4
13	Hard stools	1.9	1.63
14	Urgent need to empty the bowel	1.6	1.4
15	The sensation of not completely emptying the bowel	1.96	1.73

Table 3. Gastrointestinal Symptoms Rating Scale (GSRS) -mean scores in Group-II patients

S.no	Symptoms	Day 1 (Before Therapy) Mean score	Day 15 (After Triple Therapy) Mean score
1	Abdominal Pain	2.46	0.81
2	Heart Burn	2.89	1.0
3	Acid Reflux	2.55	0.46
4	Hunger Pain	1.89	0.84
5	Nausea	2.42	1.04
6	Rumbling	2.24	0.42
7	Bloating	2.38	0.36
8	Burping	2.68	0.56
9	Flatus	2.63	0.50
10	Constipation	2.44	0.98
11	Diarrhoea	2.70	1.18
12	Loose stools	2.33	0.48
13	Hard stools	2.22	1.16
14	Urgent need to empty the bowel	1.90	0.72
15	The sensation of not completely emptying the bowel	1.88	1.0

Table 4. Statistical analysis of GSRS scores

S.no	Treatment group	Before therapy	After therapy	*P*-value
1	Group-I	14.47±3.67	9.86±4.78	0.233
2	Group-II	15.39±4.52	5.33±2.34	**0.035**

Table 5. Side effect profile in group-I and group-II patients

S. No	Side effect	Group-I N (%)	Group-II N (%)	P-value
1	Abdominal pain	24(80)	21(70)	0.455
2	Nausea	26(86.67)	18(60)	**0.033**
3	Vomiting	13(43.3)	11(36.6)	0.352
4	Diarrhoea	15(50)	11(36.6)	**0.035**
5	Constipation	10(33.3)	6(20)	**0.026**
6	Epigastric pain	3(10)	4(13.3)	0.783
7	Taste disturbance	18(60)	13(43.3)	**0.047**
8	Skin Rashes	2(6.66)	2(6.66)	1.000
9	Bloating	4(13.3)	12(40)	**<0.001**

Side effect profile: Our study had also reported side effects associated with therapy. Univariate analysis was done to assess the significant difference between group-I and group-II patients in the existence of side effects (Table 5). Among all side effects, nausea (60% vs 86.67%, p= 0.033), diarrhoea (36.6% vs 50%, p= 0.035), constipation (20% vs 33.3%, p= 0.026) and taste disturbance (43.3% vs 60%, p= 0.047) were significatly less frequently reported in group-II patients while bloating (40% vs 13.3%, p<0.001) was triggered in the same group. Addition of *L. reuteri* has reduced all side effects associated with triple drug therapy except bloating.

4. DISCUSSION

The study was conducted on 90 patients who were selected based on inclusion and exclusion criteria. The following observations were made from this study:

In this interventional study, *H. pylori* infection was more prevalent in male patients and eradication rate was also higher in males. Similar results were seen in previous gender-specific analyses conducted by Ibrahim A et al. [17] and De Martel C et al. [18]. However, the gender difference in *H. pylori* infection is controversial and hence it is not significant.

In our study, the age group above 60 years showed a lower eradication rate of *H. pylori* infection than the adult age group. NSAIDs use, concomitant diseases, medications causing gastro-mucosal membrane damage were considered important risk factors for delayed onset of symptoms and more severe forms of H.pylori infections [19]. Therefore, percentage of eradication rate in elderly depends upon how faster Peptic Ulcer Disease (PUD) heals and it is recommended to have Proton Pump Inhibitors (PPIs) for NSAID or low dose aspirin users [20].

The main objective of our study was to evaluate the benefit of adding *L. reuteri* to the treatment regimen. Our secondary objective was to compare the eradication rate between two groups of patients; one group taking *L. reuteri* as an adjuvant during triple therapy and the other group on triple treatment only.

L. reuteri (Strain: DSM17648) was used in our study. Supplementation of lactobacillus was significantly associated with higher rates of eradication. Studies conducted previously also suggest the addition of *L. reuteri* to standard eradication therapies [21–23]. The stain DSM17648 acts as highly specific anatagonist to different strains of *H.pylori* as well as *H. heilmanii* and decrease the *H.pylori* load from the stomach by selective bacterial–bacterial cell interaction thereby increasing the rate of eradication.

For evaluating the symptomatic changes before and after the therapy, our study used a standard GSRS questionnaire, and we found only a slight change in presentation of GI symptoms in group-I patients with a slight reduction in symptom severity, i.e., symptomatic regression was not significantly achieved with triple-drug therapy alone whereas, group-II patients showed a drastic decrease in presentation and severity of symptoms. These findings were similar to the previous study conducted by Veronica ojetti et al. [24]. Our study is similar to the previous survey

(Suzuki H et al., [25], which used GSRS to analyze symptomatic changes before and after treatment and found that the quality of life (QOL) improves significantly after the successful eradication of *H. pylori* infection.

Esomeprazole's most common side effects are headache, diarrhoea, and abdominal pain [26]. In our study, when pantoprazole was given in combination with *L. reuteri* (group-II), the frequency and severity of these side effects were less reported.

Abnormal taste, *diarrhoea, rash, nausea, vomiting* and abdominal pain are commonly reported side effects of clarithromycin and amoxicillin [27]. These side effects were reported less frequently in group-II patients. Our study confirms that the use of probiotics during *H. pylori* eradication reduces the treatment-associated side effects [28]. However, bloating was reported frequently with the use of probiotics. This may be because the changes in gut microbiota can result in bacterial species producing more gas than usual, which can lead to bloating [29].

5. CONCLUSION

In conclusion, addition of *L. reuteri* to standard triple drug therapy significantly improves the eradication rate of *H. pylori*, reduces intensity of gastrointestinal symptoms and also treatment related side effects. Future research should focus on the appropriate dose and duration of lactobacillus supplementation, as well as how to boost eradication rates to the highest level possible.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT AND ETHICS APPROVAL

All the patients gave written informed consent to participate in the study. Institutional Human Ethical Committee of College of Pharmaceutical Sciences, Dayananda Sagar University, Bengaluru, had approved and issued a certificate of clearance (DSCP/P- D/IHEC/2019-20/0003) for the same.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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