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Research Article

The Efficacy of Paraprobiotic, Probiotic, and Mineral Supplementation on the Eradication Rate of Helicobacter pylori in Patients with Dyspepsia: A Randomized Clinical Trial

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Background. *Helicobacter pylori* (*H. pylori*) eradication regimens have been a concern, all along. Our study is aimed at assessing the effect of para- and probiotics plus minerals (Pyloshot) on *H. pylori* eradication rate. *Methods*. In this open-label randomized trial, 69 eligible adult patients with *naïve H. pylori infection*-related dyspepsia were randomly assigned into the group A, who received esomeprazole 40 mg BID, amoxicillin 1000 mg BID, and clarithromycin 500 mg BID, and group B with the same regimen plus one Pyloshot capsule BID for 10 days. Demographics and dyspepsia symptom severity scores (SSS), number needed to treat (NNT), dyspepsia SSS, and drug adverse effects were recorded at baseline and the end of treatment. *H. pylori* eradication was confirmed via ^{14}C UBT eight weeks later. *Results*. Sixty-six patients completed the study. The intention-to-treat (ITT) and per-protocol (PP) eradication rates were slightly better in group B (85.2% vs. 80%, $p = 0.562$, and 87.8% vs. 84.8%, $p = 0.720$, respectively). Adverse effects were significantly lower in group B (20.6% vs. 54.3%; $p = 0.004$). No significant differences in dyspepsia symptom improvement rates ($p = 0.255$) and mean difference of SSS ($p = 0.231$) were found between treatment groups. NNT for overall dyspepsia and epigastric pain syndrome (EPS) was 11 and 5 at the end of treatment, respectively. *Conclusion*. Adding Pyloshot to the *H. pylori* regimen could slightly improve the eradication rate and SSS of dyspepsia. NNT was considerably better among EPS patients. Adverse effects were significantly decreased by this regimen. Further trials with larger sample sizes should be thought out. This trial is registered with IRCT20141201020178N10.

1. Introduction

Helicobacter pylori (H. pylori) infects 50% of the population worldwide and up to 90% in developing countries. Chronic infection with H. pylori exacerbates several gastroduodenal and extragastric disorders, including nonulcer dyspepsia, chronic gastritis, peptic ulcer disease, gastric cancer, iron deficiency anemia, and primary immune-mediated thrombocytopenia [1–3]. The gastric microbiome is a challenging issue nowadays. *H. pylori* and other species (such as *non-pylori Helicobacter*) may exist in the stomach for a short or long time. It seems that several *non-pylori Helicobacter* species could be associated with some gastric disorders. Generally, *H. pylori* is the leading bacterial cause of gastric diseases and could conspicuously manipulate the conformation of other gastric microbiomes [3]. Hence, the necessity of proper *H. pylori* eradication therapy should be taken into consideration [1].

Standard triple therapy, consisting of proton-pump inhibitors (PPI), clarithromycin, and amoxicillin or metronidazole for 10-14 days, could be considered as first-line *H. pylori* eradication therapy, especially in low resistance areas (clarithromycin resistance rate < 15%) [3]. However, treatment efficacy has decreased due to the high antibiotic

resistance rate, host-related factors, variety in virulence of *H. pylori* species, poor adherence to treatment regimen, and medication adverse events [1, 2, 4]. Several therapeutic strategies have been reviewed to increase the efficacy of the treatment regimen, including extending the duration of treatment to 14 days, substituting the antibiotics by low resistance ones, administration of high-dose PPI, using esomeprazole and rabeprazole rather than the other PPIs, and adding probiotics or other supplementation to the treatment regimen [5, 6].

Adding the probiotics to the treatment regimen could be associated with modification of gastrointestinal (GI) microflora and lower medication adverse effects, which improves adherence to the treatment by patients and leads to higher H. pylori eradication rates [1, 3, 7–11], although some studies did not indicate so [12, 13]. A recent meta-analysis found that many probiotic strains, including *Lactobacillus* [7–11, 14], *Bifidobacterium* [7, 9, 14], *Saccharomyces* [9, 11, 14], and multistrain probiotics [8–11], are associated with significantly higher eradication rates compared with the control group. Probiotics may reduce *H. pylori* load in prevalent areas and could be utilized for treatment and/or short- and long-term prophylaxis [15].

Nonviable microbial cell components known as paraprobiotics can promote the probiotic effects by modulating the host immune responses, reducing tumor necrosis factor (TNF), and barrier function enhancement. Information about paraprobiotics is limited, and some of the features related to their biological activities like the mechanism of promoting the host's health system remained incomprehensible [16]. The most plausible explanation is that structures on the cell surface of this selected strain are responsible for the therapeutic effect [15]. Lactic acid bacteria contain antimicrobial elements effective against H. pylori. *Lactobacillus reuteri*, as one of the *Lactobacillus species*, entitles broad-spectrum antimicrobial effects due to the secretion of *reuterin* which improves H. pylori eradication rate. As a paraprobiotic, the dead *Lactobacillus reuteri* impedes the attachment of H. pylori to the gastric mucosa by adhering to its surface and leads to the unharmed passing of H. pylori through the digestive tract and decreasing the bacterial load [15, 17, 18].

Pyloshot® contains the nonviable *Lactobacillus reuteri* with three other probiotic strains (*Lactobacillus acidophilus*, *Lactobacillus casei*, and *Bifidobacterium lactis*) plus mineral components, such as zinc gluconate, magnesium oxide, and calcium carbonate which have known effects on establishing an appropriate acid-base balance and the natural function of digestive enzymes and are well-advised in patients with dyspepsia in a dose of 200 mg of the dead cell of *Lactobacillus reuteri* [19, 20].

This trial is designed to assess the efficacy of adding paraprobiotic, probiotics, and mineral supplements to the standard triple therapy on the eradication rate of *H. pylori* in patients with dyspepsia.

2. Method and Materials

2.1. Study Design and Subjects. This study was a single-center open-label randomized controlled clinical trial. All adult patients (above 16 y/o) with a diagnosis of *H. pylori*-related dyspepsia [3, 21] who were referred to the gastroenterology clinic of Rasoul-e-Akram Hospital between March 2020 and October 2020 were enrolled in this trial. The diagnosis of *H. pylori* infection was confirmed by at least one of the following: C^{14}urea breathe test (UBT) and Giemsa staining and/or rapid urease test on the tissue samples taken via an upper endoscopy.

Exclusion criteria included all patients with concomitant systemic disease (uncontrolled hypertension/thyroid disease, diabetes mellitus, and liver, kidney, pulmonary, or heart disease), history of peptic ulcer disease, neurological disorders, major psychiatric disorders, malignancy, pregnancy, lactation, upper abdominal surgery, prior history of *H. pylori* eradication during the last one year, concomitant use of anticoagulants and corticosteroid, smoking, history of alcohol consumption, positive PCR result for COVID-19, any history of allergy to the medications, uncooperativeness, and participating in another clinical trial over the past three months. Moreover, patients were excluded from the trial if they had taken PPI/histamine 2-receptor antagonist within two weeks and any probiotics or antibiotics during the last two months before starting the study.

All the researchers deemed Helsinki's ethical principles. A written consent form was taken from eligible participants after a complete explanation of treatment strategies. The ethics committee of Iran University of Medical Sciences approved this trial by the ethical code of IR.IUMS.FMD.REC.1399.031. The trial has been registered in the Iranian Registry of Clinical Trials (IRCT20141201020178N10).

2.2. Interventions. Baseline demographic and clinical data were recorded. Sixty-nine eligible patients were randomly assigned to treatment groups. Randomization was done via a computer-generated simple randomization table.

Group A ($N = 35$) received esomeprazole 40 mg BID half an hour before breakfast and dinner, amoxicillin 1000 mg BID, and clarithromycin 500 mg BID for ten days.

Group B ($N = 34$) received the same treatment regimen plus a capsule of Pyloshot® BID, before a meal with a glass of water for ten days (for better modification of gastrointestinal (GI) microflora).

Pyloshot® capsule contains 100 mg dead *Lactobacillus reuteri* (*dried spray method*) and alive *Lactobacillus acidophilus*, *Lactobacillus casei*, and *Bifidobacterium lactis*. Each capsule contains not less than 8×10^{10} colony-forming units (CFU)/g for all strains. Other ingredients include zinc gluconate 5 mg, magnesium oxide 50 mg, and calcium carbonate 50 mg.

2.3. Study Measurements

2.3.1. H. pylori-Related Dyspepsia. H. pylori-related dyspepsia diagnosed by the presence of at least one of the following complaints: post-prandial pain (at least 3 days per week), early satiety (at least 3 days per week), epigastric pain/burning (1 time per week) during the last 3 months beside the evidence of H. pylori infection [3, 21].

2.3.2. H. pylori Eradication Rate. H. pylori eradication was confirmed by C^{14}-UBT eight weeks after the end of treatment. All patients who participated in the trial were included in the intention-to-treat (ITT) analysis for eradication rates. The patients who completed the study with the 80/80 rule of adherence to the treatment regimens were included in the per-protocol (PP) analysis for eradication rates.

2.3.3. Medication Adverse Effects/Patients' Compliance. Medication adverse effects were recorded both by patients using a self-reported daily questionnaire and by the physician at the end of treatment. Patients were strongly advised not to discontinue the study medications when they experienced mild to moderate (tolerable) adverse events. The severity of adverse effects was scored on a Linkert scale of 0 to 3 as follows: 0 = no evidence of adverse reactions, 1 = mild (no restriction in daily activity), 2 = moderate (minor restriction in daily activity), and 3 = severe (significant restriction in daily activity). We assessed all participants for adherence to the study medication at the end of the treatment, categorized as excellent, good, and poor based on consuming more than 90%, 60%–90%, and less than 60% of total dispensed pills, respectively [6].

2.3.4. Modified Glasgow Dyspepsia Severity Score (GDSS). A questionnaire consists of the frequency of dyspepsia (being scored on 0-4 scales), the intensity of dyspepsia (0-2 points scale), and treatment required for dyspepsia that could be over the counter or prescribed medications (both being scored on a scale of 0-2) [22]. We used GDSS to assess the severity of symptoms right before and after the treatment and also 8 weeks after the end of treatment. The minimum and maximum achievable scores are 0 and 10, respectively, and at least 2-point reduction in the total score after treatment is considered an improvement. The number needed to treat (NNT) based on symptom severity improvement was calculated after the end of treatment and 8 weeks later.

2.3.5. Dyspepsia Subtypes. Dyspepsia subtypes categorized as post-prandial distress syndrome (PDS), epigastric pain syndrome (EPS), and overlap features.

2.4. Study Endpoints. Our primary endpoint was to compare eradication rates of *H. pylori* between treatment groups, 8 weeks after the end of treatment, through the intention-to-treat (ITT) and per-protocol (PP) analysis eradication rates. We also evaluated and recorded the incidence of the medication adverse events, improvements in symptom severity scores, and the NNT totally and across the subtypes of dyspepsia as our secondary endpoints.

2.5. Statistical Analysis. We estimated the total sample size of 70 patients (35 in each group), assuming at least 85% in group B (with Pyloshot®) and 50% in group A (without Pyloshot®) (35% difference) reach our primary endpoint (H. pylori eradication), by 85% power and at the significance level of 0.05, using G∗Power software [23]. Quantitative variables are reported as mean and standard deviation (SD), percentages, or absolute values. We performed an independent sample t-test or Mann–Whitney U test to compare means among the study groups. We used chi-square or Fisher's exact tests to compare proportions between treatment groups. Data were checked for normality using Q-Q plots and the Kolmogorov-Smirnov test. Analysis was done by SPSS version 20.0.

3. Results

A total number of 70 participants were recruited in this trial. One lady informed us in the first follow-up that she did not take any study medication due to the pregnancy, and finally, 69 patients were enrolled in the study.

The mean age was 44.05 ± 13.66 and 42.49 ± 14.17 years in group A ($N = 35$) and group B ($N = 34$), respectively. There was no significant difference in smoking, history of consuming nonsteroidal anti-inflammatory drugs (NSAIDs), and *H. pylori* treatment history at least one year prior to the recent presentation between the groups.

Regarding the subtypes of dyspepsia in groups A and B, 15 (42.8%) and 15 (44.1%) patients were suffering from postprandial distress syndrome (PDS), 15 (42.8%) and 15 (44.1%) were suffering from epigastric pain syndrome (EPS), and five (14.4%) and 4 (11.8%) patients were suffering from overlap of both symptoms, respectively (Table 1).

3.1. Eradication Rate. Overall, 66 patients completed the study (2 patients in group A due to loss of follow-up and poor compliance and 1 patient in group B due to loss of follow-up were dropped out of the study). The ITT eradication rate was 80% (95% CI: 66.1%-93.9%) and 85.2% (95% CI: 72.7%-97.8%) in groups A and B, respectively (p value = 0.562). The PP analysis eradication rate was 84.8% (95% CI: 71.9%-97.7%) and 87.8% (95% CI: 76.1%-99.6%) in groups A and B, respectively (p value = 0.720). *H. pylori* eradication rates based on ITT and PP analyses were slightly better in group B (Table 2).

3.2. Side Effects. Among all participants, 26 patients (37.7%) reported transient and tolerable mild to moderate adverse events, 54.3% (19/33) in group A (without Pyloshot) and 20.6% (7/33) in group B (with Pyloshot) (p value = 0.004). Bitter taste was the most common side effect in group A (7/33, 20.6%), and dry mouth/unfavorite taste was the most common in group B (3/33, 8.8%). Compliance rates were excellent in both groups. The frequency of the adverse effects among treatment groups is summarized in Table 3.

3.3. Symptom Improvement. The average symptom severity score (SSS) at baseline, based on the GDSS, was 5.75 ± 1.72 and 5.06 ± 2.09 in groups with and without Pyloshot, respectively ($p = 0.139$). Before and after treatment overall SSS score differences were 2.21 ± 0.41 vs. 1.95 ± 0.35 in groups with and without Pyloshot, respectively ($p = 0.231$). Symptom improvement rate was slightly better in group B (with Pyloshot, 24/33; 72.7%) compared with group A (without Pyloshot, 22/33; 63.6%) at the end of treatment ($p = 0.255$) and eight weeks after the end of treatment (18/33 (54.5%) vs. 16/33 (48.4%); $p = 0.490$).

We calculated NNT for group B based on symptom improvements and subtypes of dyspepsia. Regarding the

Table 1: Demographic and clinical characteristics of the patients in both treatment groups.

	Group A (without Pyloshot) $N = 35$	Group B (with Pyloshot) $N = 34$	P value
Male/female, N	17/18	16/18	0.9
Age, mean (SD), years	44.05 (13.66)	42.49 (14.17)	0.64
Smokers, N (%)	6 (17.1%)	6 (17.6%)	0.95
History of NSAID consumption, N (%)	8 (22.8%)	7 (20.5%)	0.81
History of H. *pylori* treatment more than one year before recent presentation, N (%)	3 (8.5%)	4 (11.7%)	0.71
Mean ± SD of SSS of dyspepsia	5.06 ± 2.09	5.75 ± 1.72	0.13
Dyspepsia subtypes, N (%)			
PDS	15 (42.8%)	15 (44.1%)	0.91
EPS	15 (42.8%)	15 (44.1%)	0.91
Overlapping features	5 (14.4%)	4 (11.8%)	1

N: number; SD: standard deviation; NSAIDs; nonsteroidal anti-inflammatory drugs; PDS: postprandial distress syndrome; EPS: epigastric pain syndrome; SSS: symptom severity score.

Table 2: Eradication rates with ITT and PP analyses among treatment groups.

	Group A (without Pyloshot)		Group B (with Pyloshot)		p value
	Patients	Eradication rate (%)	Patients	Eradication rate (%)	
ITT analysis	28/35	80% (95% CI: 66.1%-93.9%)	29/34	85.2% (95% CI: 72.7%-97.8%)	0.562
PP analysis	28/33	84.8% (95% CI: 71.9%-97.7%)	29/33	87.8% (95% CI: 76.1%-99.6%)	0.720

ITT: intention-to-treat; PP: per-protocol; CI: confidence interval.

Table 3: Side effects in study treatment groups.

	Group A (without Pyloshot) $N = 35$	Group B (with Pyloshot) $N = 34$	Total ($N = 69$)	p value
Bitter taste	7 (20%)	3 (8.8%)	10 (14.5%)	—
Dry mouth	0	3 (8.8%)	3 (4.3%)	—
Anorexia	2 (5.7%)	0	2 (2.9%)	—
Nausea	4 (11.4%)	1 (2.9%)	5 (7.2%)	—
Diarrhea	2 (5.7%)	0	2 (2.9%)	—
Abdominal pain	1 (2.9%)	0	1 (1.4%)	—
Headache	1 (2.9%)	0	1 (1.4%)	—
Weakness	2 (5.7%)	0	2 (2.9%)	—
Overall side effects	19 (54.3%)	7 (20.6%)	26 (37.7%)	0.004

N: number.

overall symptom improvement, NNT was 11 and 16 at the end of the treatment and eight weeks later, respectively. Calculated NNT for PDS was 53 and 30 at the end of the treatment and eight weeks later, respectively. The NNT for EPS was 5 and 9 at the end of the treatment and eight weeks later, respectively, which is considered desirable (Table 4).

The study design, methods of follow-up, and treatment efficacy have been demonstrated at the flowchart (Figure 1).

4. Discussion

The *H. pylori* treatment regimens have been a concern, all along. Hereupon, developing treatments with antibiotics with lower resistance rates, extending the treatment duration, and adding probiotics has come to attention. The suggested mechanisms involved in the efficacy of probiotics, as live microbe, against H. pylori, include mucosal production, bactericidal elements, modifying the immune system, and direct competition and impeding bacterial invasion [24]. Probiotics could be utilized separately or in combination with each other for therapeutic and short- or long-time prophylaxis goals. [15]. As the pathogenicity of *H. pylori* varies based on bacterial, environmental, and host factors across the world, it is well-advised to assess the *H. pylori* treatment regimens regionally [6].

Table 4: Comparison of symptom improvement rates between treatment groups at the end of the treatment and eight weeks after the treatment completion.

	At the end of treatment		NNT	p value	At 8th week		NNT	p value
	Group A	Group B			Group A	Group B		
Overall N (%)	22/33 (63.6%)	24/33 (72.7%)	11	0.255	16/33 (48.4%)	18/33 (54.5%)	16	0.490
Dyspepsia subtypes N (%)								
PDS	10/14 (71.4%)	11/15 (73.3%)	53	1.000	7/14 (50%)	8/15 (53.3%)	30	0.816
EPS	9/15 (60%)	11/14 (78.6%)	5	0.427	8/15 (53.3%)	9/14 (64.3%)	9	0.425
Overlapping features	2/4 (50%)	2/4 (50%)	—	1.000	1/4 (25%)	1/4 (25%)	—	1.000

NNT: number needed to treat; N: number; PDS: postprandial distress syndrome; EPS: epigastric pain syndrome.

A previous meta-analysis was conducted on 30 randomized control trials including any treatment duration and combination in Asian or non-Asian patients of any age who were diagnosed with H. pylori infection. Totally 4302 patients regarding PP analysis and 4515 patients based on ITT analysis were enrolled. The PP and ITT eradication rate analyses for patients who received triple therapy plus probiotic compared to those who received just triple therapy were 83.5% and 78.5% and 74.1% and 68.2%, respectively. They indicated that the *H. pylori* eradication rate is significantly improved when probiotic supplementation is added to the triple therapy, compared to the triple therapy regimen alone (relative risk (RR) = 1.22, 95% confidence interval (CI): 1.091-1.153, PP; RR = 1.141, 95% CI: 1.106-1.176, ITT) [9]. One study showed that adding the probiotics to the standard therapy could significantly improve PP analysis (RR = 1.11; 95% CI: 1.08-1.15; $p < 0.001$) and ITT analysis (RR = 1.13; 95% CI: 1.10-1.16; $p < 0.001$) eradication rates. Overall, *H. pylori* eradication rates were 82.31% and 72.08% in the probiotic and the control group, respectively [14].

In our randomized clinical trial, we noticed that patients who received triple therapy plus Pyloshot® had higher rates of *H. pylori* eradication (87.8% PP and 85.2% ITT) compared to the patients who received triple therapy alone (84.8% PP and 80% ITT), even though the differences were not statistically significant ($p = 0.720$ and 0.562, respectively). It might be related to the short duration and/or different probiotic component in our study regimen.

It seems that the maximum effect of adding probiotics is achieved when the eradication rate of a regimen is less than 80% [7]. Our results were in concordance with these findings regarding the higher eradication rates (>80%) in our study by using esomeprazole 40 mg BID in triple therapy [6].

Furthermore, in the subgroup analysis of probiotic type, they have shown that adding *Lactobacillus*-containing probiotics to the triple therapy substantially improves eradication rates (RR = 1.142, 95% CI: 1.084-1.203, PP; RR = 1.153, 95% CI: 1.092-1.217, ITT) [9].

We found that the eradication rate was slightly improved by adding the para- and probiotic supplementation to the triple therapy.

It has been noted that probiotic supplementation significantly decreases treatment-related adverse events, including taste disturbance [11, 14], nausea/vomiting, diarrhea, abdominal/epigastric pain [9–11, 14], and constipation [10, 11, 14]. This effect is probably related to the duration of probiotic consumption, particularly when it is prescribed for more than two weeks.

One study on 200 naive H. pylori-infected patients showed that in comparison with placebo, adding *Lactobacillus reuteri* to 14-day triple therapy and continuing for the next 2 weeks could not meaningfully improve *H. pylori* eradication (81.8% and 83.7% in ITT analysis ($p = 0.730$) and 86.2% and 87.2% in PP analysis ($p = 0.830$), respectively) but led to a significant reduction in adverse effects, specifically abdominal discomfort (abdominal distention (16.3% vs. 5.1%, respectively; $p = 0.010$) and diarrhea (23.5% vs. 11.1%; $p = 0.022$)) and GSRS score (1.9 ± 0.2 vs. 2.7 ± 0.3, respectively; $p = 0.030$) [25]. Significant beneficiary alteration of gastric microbiome media was reported in patients who received *Lactobacillus reuteri* [25].

This outcome might be attributed to the rapid gastrointestinal microbiota recuperation [3]. Our results were in concordance with this study. We found that the adverse events were overall significantly lower in the probiotic-supplemented group than in the control group (20.6% vs. 54.3%, respectively, $p = 0.004$).

In a study by Scaccianoce et al., the regimen containing 7-day standard triple therapy with *Lactobacillus reuteri* and the regimen containing 14-day standard triple therapy with a probiotic mixture had the lowest (6%) and highest (33%) rates of adverse effects, respectively, and none of the regimens achieved acceptable *H. pylori* eradication rate (>80% eradication rate at both ITT and PP analyses) [26]. The result of our study in regard to drug adverse effects was in concordance with this study.

However, McNicholl et al. could not reveal any significant difference in the medication adverse events and eradication rates between the intervention group (1×109 colony-forming units each strain, Lactobacillus plantarum and Pediococcus acidilactici) and placebo groups in combination with the 10-day triple or nonbismuth quadruple concomitant therapy [27]. Our results were not in the same line by their study. It seems that applying both patient- and physician-reported data gathering sheets, the same as in our study, could more precisely provide adverse event evaluation. On the other side, Pyloshot has a mineral components, such as zinc gluconate, magnesium oxide, and calcium carbonate which have known effects on establishing an appropriate acid-base balance and the natural function of digestive enzymes and are well-

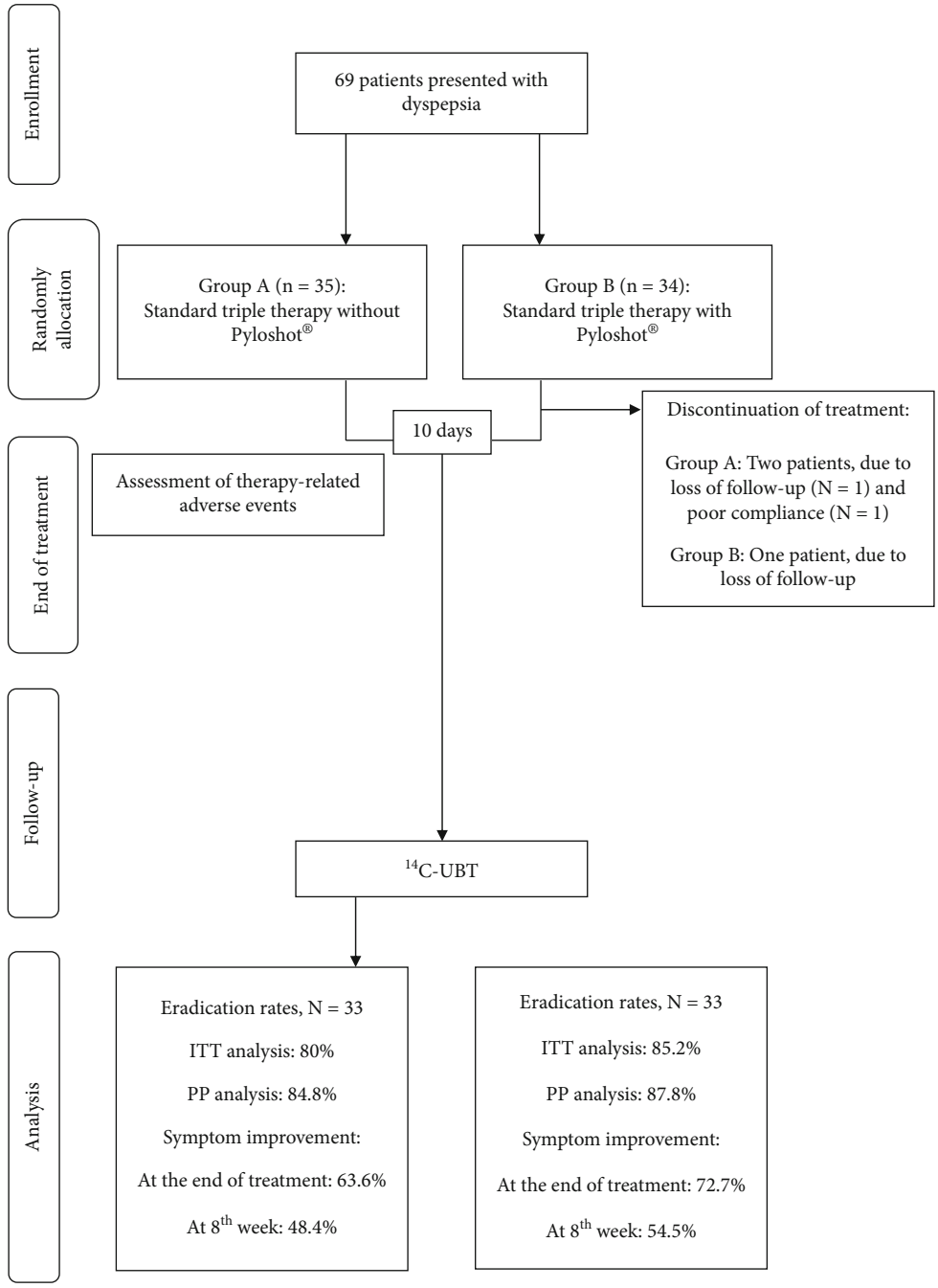

Figure 1: Flowchart of the study design, methods of follow-up, and treatment efficacy.

advised in patients with dyspepsia. It seems that by adding Pyloshot to the eradication regimens, a lower rate of adverse effects, better gastric media for treatment regimens, and lower symptom severity could be expected. [19, 20].

In a nutshell, several factors, including combination therapy, altering the duration of eradication regimen/probiotic therapy, diet, and the dose and species of the received probiotic supplement, have had different impacts on adverse effects and *H. pylori* eradication rates [3]. Paraprobiotics, as dead microbial cells such as the ones used in our study, have several benefits compared to living probiotic cells, like easier packing and carriage route, extended shelf life, and fewer production expenses. These criteria could make them to be a new therapeutic way for H. pylori eradication [15].

According to the recently updated guidelines of the American College of Gastroenterology (ACG), the Canadian Association of Gastroenterology (CAG), and the Maastricht VI guideline, the eradication of *H. pylori* leads to the durable relief of dyspepsia symptoms compared to placebo and PPI, although might not significantly [3, 28].

In our study, we have evaluated both the eradication rate and improvements in dyspepsia symptoms and have observed higher symptom improvement in the probiotic group compared to the standard triple therapy. The NNT

for overall symptom improvement was 11 at the end of the treatment and 16 at 8 weeks later for the probiotic-added group. Previously published studies reported an NNT of 12.5 (95% CI: 10-20) [3], 10 regarding ITT analysis for *Lactobacillus*-containing probiotics [13] and 15 [29] for *H. pylori* eradication therapy, which is in line with the findings of the present trial. Furthermore, it seems that the EPS subtype was more improved compared to the other subtypes, and it may be related to the acid-lowering agents such as zinc, magnesium, and calcium in this product (NNT = 5 and NNT = 9 at the end and 8 weeks after completion of the treatment; p value = 0.427 and p value = 0.425, respectively). Insignificant differences may relate to the small sample size. NNT for overall symptom and EPS subtype of dyspepsia in our study is similar to previous studies.

A recent meta-analysis on 9,004 H. *pylori*-infected patients who randomly received 10 different treatment regimens determined that probiotic combined regimes were superior to the standard triple therapy. They showed that *Bifidobacterium-Lactobacillus* and *Bifidobacterium-Lactobacillus-Saccharomyces* combinations had more superiority among probiotic regimens and provide higher eradication rates (78.3% and 88.2%, respectively) and lower adverse events. Combining *Bifidobacterium-Lactobacillus-Saccharomyces* with standard triple therapy could improve the eradication rate up to 88.2% (95% CI, 83.1-93.4; SUCRA value 34.5%). Comparatively, triple therapy had a lesser amount of efficacy than most of the treatment regimens (eradication rate 72.8%, 95% CI, 71.4-74.2; SUCRA value 17.2%). Mixture of various probiotics, starting probiotics afore or next triple therapy, and probiotic prescription for extended period can increase therapeutic beneficiary outcome in these patients [30].

The main strength of our study was assessing the efficacy of adding dead *Lactobacillus reuteri* combined with 3 probiotics and mineral supplements to the triple therapy on eradication rate improvement, symptom relief, and lowering adverse effects in *H. pylori*-infected patients with dyspepsia. However, we faced some limitations. The first one was the small sample size of this study. The second one was the nonblinded design of our study with the missing placebo effect. The third one was the inability to eliminate the role of diet as a confounding factor. The fourth one was lack of gastric microbiome medium assessment and any beneficiary effect due adding probiotics to *H. pylori* eradication regimens. Finally, the last one was the inability to attribute the results to the probiotic alone because Pyloshot® contains some mineral components with acid-lowering effects.

5. Conclusion

Collectively, findings of the present trial showed that adding (dead *Lactobacillus reuteri*) paraprobiotic, minerals, and probiotics to the standard clarithromycin-based triple therapy could slightly improve *H. pylori* eradication and symptom improvement rates and, less significantly but considerably, could alleviate the medication adverse events and improve the NNT among patients, especially with EPS type of dyspepsia. Further studies with larger sample sizes, longer duration of probiotic consumption, and adding probiotics to the other H. pylori treatment regimens should be thought out.

Data Availability

The authors authorized the data available on request through corresponding/first author: Marjan Mokhtare (marjanmokhtare@yahoo.com, mokhtaredr@gmail.com, and mokhtare.m@iums.ac.ir).

Additional Points

Significance Statement. Our study assesses the role of adding dead *Lactobacillus reuteri* as a paraprobiotic, minerals, and probiotics to *Helicobacter pylori* standard triple therapy on the improvement of eradication rates. The findings of the present trial differentiate it from similar studies, including the use of a paraprobiotic supplement, assessment of dyspepsia symptom improvement rates across the dyspepsia subtypes, and determining the number needed to treat (NNT) for symptom improvements. *Helicobacter pylori* eradication and symptom severity rates were slightly improved, and the medication's adverse events were significantly reduced.

Consent

Informed consent was obtained from all individual participants included in the study.

Conflicts of Interest

There are no conflicts of interest.

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