

The Efficacy of Probiotics in Treatment of *Helicobacter*

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Abstract

Background: The standard triple therapy has lost a considerable proportion in its efficiency in treating *Helicobacter pylori* infection. As such several alternatives and adjuvants have been proposed. One of the most promising modulation is the supplementation of this therapy with probiotics.

Aims: This study aimed to investigate the efficiency of probiotic supplementation to traditional triple therapy in the eradication of *Helicobacter pylori* infection and alleviation of side effects.

Patients and Methods: This is a cross-sectional study included 310 consecutive patients newly diagnosed with gastritis or dyspepsia and infected with *H. pylori*. Patients were randomly divided into three groups based on treatment regimes. Group A: 100 patients received triple therapy consisting of omeprazole, amoxicillin and levofloxacin for two weeks. Group B: 100 patients received tinidazole, levofloxacin and omeprazole for two weeks. Group C: 110 patients received the second protocol plus the probiotic. All patients were reinvestigated four weeks after accomplished treatment by stool antigen test for *H. pylori*.

Results: The rate of successful *H. pylori* eradication was 77.74%. In multivariate analysis, each of age ≤ 35 years (OR=0.51, 95%CI=0.28-0.93), being married (OR= 0.37, 95%CI=0.21-0.71), never smoker (OR= 0.55, 95%CI=0.32-0.95) and treatment regime with triple therapy supplemented probiotics (OR= 3.36, 95%CI=2.5-21.7) were significantly associated with increased the eradication rate. The overall incidence of side effect in group C was (7.27%) was lower than that B (19%) with significant difference, and group A (15%) with no significant difference.

Conclusions: The use of probiotics as an additive for the standard triple therapy significantly increases the eradication of *H. pylori* and may reduce the incidence of side effect of the traditional therapy.

Keywords: *Helicobacter*, probiotics, treatment

1. Introduction

1.1 Definition

Helicobacter pylori is a common bacteria infecting about half of world's population, with higher prevalence in developing countries, where *H. pylori* could infect up to 80% of the population, than in developed ones. It is also associated with the development of gastrointestinal disorders as chronic gastritis, peptic ulcer, and gastric adenocarcinoma and involved in the development of other extra-gastric disorders such as mucosa-associated lymphoid tissue (MALT) lymphoma, idiopathic thrombocytopenic purpura, vitamin B12 deficiency, and iron

deficiency (Goderska, Pena, & Alarcon, 2018).

1.2 Treatment

1.2.1 Classical Treatment and Difficulties

In adults, the current standard eradication treatment for *H. pylori* infections comprises triple or quadruple combination therapies. Triple therapy involves a proton pump inhibitor (PPI) as pH-control pharmaceutical, and the concomitant or consecutive treatment with two antibiotics (clarithromycin, metronidazole or amoxicillin) for 1–2 weeks. The success of this therapy is unfortunately under pressure due to a rising antibiotic resistance (Gatta et al., 2013).

Antibiotic resistance stems from escape mutations, drug inactivation, drug efflux pumps and altered membrane permeability but also antibiotic tolerance due to the presence of biofilm-embedded or dormant, nonreplicating bacteria can cause recalcitrant and recurrent infection (Francesco et al., 2013).

A meta-analysis of 87 studies showed that average rates of *H. pylori* antibiotic resistance were 47.22% (30.5–75.02%) for metronidazole, 19.74% (5.46–30.8%) for clarithromycin, 18.94% (14.19–25.28%) for levofloxacin and 14.67% (2–40.87%) for amoxicillin, 11.70% (0–50%) for tetracycline, 11.5% (0–23%) for furazolidone and 6.75% (1–12.45%) for rifabutin (Thung et al., 2016).

For this reason, the Maastricht group in Europe reviews *H. pylori* eradication efficacies and optimal treatment regimens per region on a 2-year basis (Malfertheiner et al., 2017). Currently, treatment being prolonged to 2 weeks and quadruple therapy, which includes bismuth or a third antibiotic (tetracycline, levofloxacin or furazolidone), is becoming more strongly recommended as a first-line treatment (Malfertheiner et al., 2017; Fallone et al., 2016). The high dosage and longitude of these treatments places a heavy burden on the patient and a lack in patient compliance is, therefore, another main reason for treatment failure. When treatment fails, rescue therapy is considered, but is recommended only in patients who have failed to respond with three or more prior treatments (Fallone et al., 2016).

1.2.2 Probiotics

Probiotics are defined as living microorganisms that, when administered in adequate amounts, can improve microbial balance in the intestine and exert positive health effects on the host (FAO/WHO 2002), including beneficial effects on the prevention of intestinal infections, cardiovascular disease, cancer, and anti-allergic effects (Piano et al., 2006).

Probiotics can be microorganisms from the bacteria or yeasts group. However, most of probiotics are bacteria, among them lactic acid bacteria, typically associated with the human gastrointestinal tract, which are the most widely used (Rodes et al., 2013). They include Gram positive cocci and rods *Lactobacillus* and *Bifidobacterium*, which are the two most common species used as probiotics and are extensively investigated for their beneficial effects on the host, including promotion of gut maturation and integrity, antagonism against pathogens, and modulation of the immune system and tumor promoting agents (Goderska et al., 2018).

Non-immunological Mechanism

The first line of defense against pathogenic bacteria is acidity of the stomach and the gastric mucosa barrier. This first line of defense could be stronger due to the production of antimicrobial substances competing with *H. pylori* for adhesion receptors, stimulating mucin production and stabilizing the gut mucosal barrier (Goderska, Pena, & Alarcon, 2018).

Antimicrobial Substances

Probiotics may inhibit *H. pylori* growth by secreting short chain fatty acids and antibacterial substances (Cheng et al., 2008).

Immunologic Mechanisms

Probiotics could modify the immunologic response by the modulation of anti-inflammatory cytokines secretion, which would result in a reduction of gastric activity and inflammation (Boulangé et al., 2016).

1.3 Aims of the Study

This study aimed to investigate the efficiency of probiotic supplementation to traditional triple therapy in the eradication of *Helicobacter pylori* infection and alleviation of side effects.

2. Patients and Methods

2.1 Design and Settings

This is a cross-sectional study on a consecutive series of patients newly diagnosed with gastritis or dyspepsia and infected with *H. pylori* admitted to department of Gastroenterology / Baghdad Medical City and Gastro-Intestinal Tract (GIT) center with medical wards during the period from October 2018 to December 2019. Patients were entered consecutively into the study until an arbitrary sample size of 150 patients was reached after application of the inclusion and exclusion criteria.

2.2 Inclusion Criteria

Patients with the following criteria were included:

- age 18–60 years;
- Both sexes are involved
- presented with upper gastrointestinal symptoms,
- confirmed *H. pylori* infection;

2.3 Exclusion Criteria

Patients with the following conditions were excluded from the study:

- chronic diseases, e.g. renal failure and cirrhosis;
- malignancies;
- gall bladder disorders;
- History of gastrointestinal surgery.
- Pregnant and lactating women
- The use of antibiotics or probiotics in the past month
- Prior history of treatment of *H. pylori* infection
- known allergy to the used medications.

2.4 Ethical Consideration

A verbal consent from each participant was obtained prior to data collection after explaining the aim of study. Each patient was given the complete unconditioned choice to withdraw anytime. The confidentiality of data throughout the study was guaranteed and the patients were assured that data will be used for research purpose only.

2.5 Definitions

- *H. pylori* infection was defined as positivity to one or more of these tests: *H. pylori* antigen in stool; histopathological confirmation of *H. pylori* and/or and rapid urease test.
- *H. pylori* eradication is defined in this study as concomitant negativity to all previously positive tests 4 weeks after the end of therapy (6 weeks after the end of the standard triple therapy).

2.6 Patient Assessment

Eligible patients were underwent to the following evaluation.

- Full history-taking and full clinical examination.
- The infection with *H. pylori* was established by one of following criteria:

A positive serology test, culture or urea breath test.

- Detection of *H. pylori* antigen in a stool sample (On Site *H. pylori* Ag Rapid Test, USA). This is a qualitative detection of *H. pylori* antigens based on the monoclonal anti-*H. pylori* antibodies conjugated with colloid gold. According to the test, positive cases are characterized with two bands of color changes.
- After 4 weeks of therapy, the *H. pylori* antigen was re-examined in stool and urea breath test was also conducted.

2.7 The Study Groups

According to treatment protocol, patients were randomly allocated to three groups

Group A: 100 patients treated with standard triple therapy comprising omeprazole 40 mg b.d., amoxicillin 1000 mg b.d., and levofloxacin 500 mg o.d. for two weeks

Group B: 100 patients received tinidazole 500 mg, levofloxacin 500 mg and omeprazole 40 mg, balance two capsule daily for two weeks.

Group C: 110 patients received the second protocol plus the probiotic (Protexin Balance/UK). This probiotic provides a complex blend of 7 strains of friendly bacteria and prebiotic in easy to swallow capsules. probiotics are *Lactobacillus casei*, *Lactobacillus rhamnosus*, *Streptococcus thermophilus*, *Bifidobacterium breve*, *Lactobacillus acidophilus*, *Bifidobacterium longum*, *Lactobacillus bulgaricus*, (TVC: 200 million colony forming unit (CFU) TVC: 2×10^8 CFU) and also FOS (fructooligosaccharide-prebiotic), magnesium stearate (source: mineral and vegetable), and vegetable capsule (hydroxypropyl methyl cellulose).

All patients were asked to have full and regular usage of the treatment protocol in order for effective eliminating *H. pylori*. They were also encouraged to maintain complete abstinence smoking, eating chocolate, cheese or eggs and not to use antidepressants.

All patients were re-examined 4 weeks after completion the treatment by stool antigen test for *H. pylori*. Accordingly, successful treatment was set as a negative stool antigen test for *H. pylori*.

2.8 Statistical Analysis

Student t test and analysis of variance (ANOVA) were used to compare means between two and three groups, respectively. Univariate and multivariate logistic regression were used to find out the independent predictors for successful *H. pylori* eradication after the treatment period. In these tests, the odds ratio (OR) and its corresponding 95% confidence interval (CI) were calculated.

3. Results

3.1 Demographic and Clinical Characteristics of the Patients

This study included a total of 310 patients with a confirmed infection with *H. pylori*. The mean age of the patients was 36.3 ± 10.7 years (range= 18-65 years). The male female ratio was almost 1:1. Most patients were overweight with a mean BMI of 29.39 ± 4.33 . About two-third of the patients were married, and one-third of them were smokers. The coexistence of another illness was reported in 54.19% of the patients with hypertension was the most frequent comorbidity reported in 21.29% of the patients followed by diabetes (17.1%). Three therapeutic regimes were used: Amoxicillin-levofloxacin –PPI in 100 patients (32.26%), Tinidazole-levofloxacin –PPI without probiotic in 100 patients (32.26%), and Tinidazole-levofloxacin –PPI with probiotic in 110 patients (35.48%) as shown in Table 1.

Table 1. Baseline Characteristics of the Patients (N=310)

Variables	Frequency (%)
Age, years	
18-29	78(25.16%)
30-41	160(51.61%)
42-53	39(12.58%)
54-65	33(10.65%)
Sex	
Male	157(50.65%)
Female	153(49.35%)
BMI, kg/m²	29.39±4.33
Marital status	
Married	199(64.19%)
Single	111(35.81%)

Smoking	
Never	206(66.45%)
Ex/current smokers	104(35.55%)
Comorbidities	
No comorbidity	142(45.81%)
Hypertension	66(21.29%)
Diabetes mellitus	53(17.1%)
Hypertension and diabetes	28(9.03%)
Others	21(6.77%)
Treatment Regime	
Amox-levof-PPI	100(32.26%)
Tinid-levof-PPI	100(32.26%)
Tinid-levof-PPI+Prob	110(35.48%)

3.2 *H. pylori* Eradication

After 4 week of treatment, out of 310 patients, 241(77.74%) had a successful eradication of *H. pylori* according to confirmatory tests. The other 69(22.26%) patients had no complete cure of the infection (Figure 1).

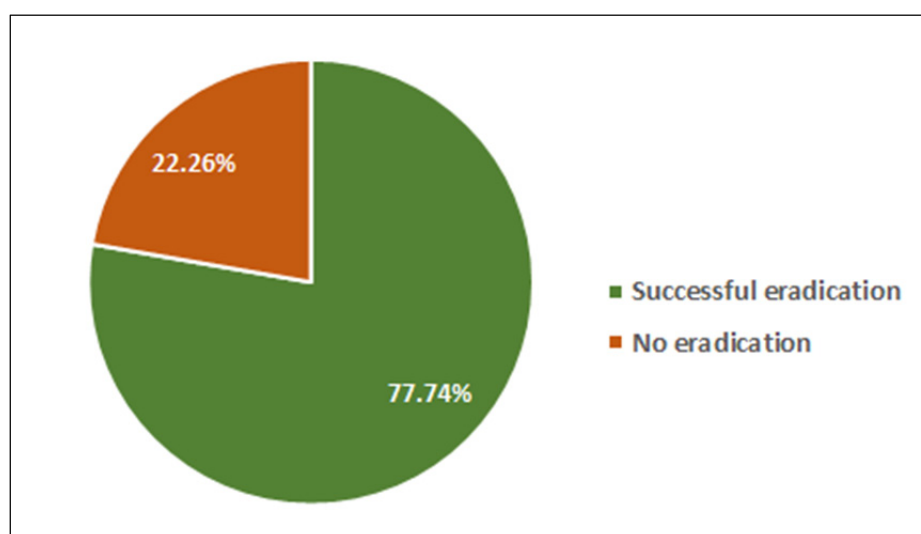


Figure 1. proportion of successful eradication

3.3 Factors Associated with Successful Eradication of *H. pylori*

Five factors were found to be significantly associated with successful eradication of *H. pylori*. Patients with successful eradication had significantly younger age than those with no eradication (34.79 ± 9.58 years vs. 38.98 ± 11.13 years). Furthermore, 68.57% of patients with successful eradication were married compared with 52.94% amongst no eradication with a significant difference. Ex/current smoking was more frequent among patients with persistence than eliminated cases (44.93% vs. 30.29%). The absence of comorbidities in general seems to facilitate *H. pylori* eradication as 50.21% of cured patients showed no comorbidity compared with 30.43% of non-cured patients who had such privilege. Finally, and most importantly, the addition of probiotic significantly increased the cure rate which was 84.55% in patients receiving probiotic additive compared to only 79% in Tinid-levof-PPI and 69% in Amox-levof-PPI group (Table 2).

Table 2. Factors associated with successful eradication of *H. pylori*

Variables	Successful eradication (n=241)	No eradication (n=69)	P-value
Age (years)	34.79±9.58	38.98±11.13	0.026
Sex			
Male	121(50.21%)	36(52.22%)	0.773
Female	120(49.79%)	33(47.83%)	
Marital status			
Married	162(68.57%)	37(52.94%)	0.038
Single	79(31.43%)	32(47.06%)	
Smoking			
Never	168(69.71%)	38(55.07%)	0.023
Ex/current smoker	73(30.29%)	31(44.93%)	
BMI (Kg/m ²)	29.45±4.61	29.34±3.6	0.692
Comorbidities			
No comorbidity	121(50.21%)	21(30.43%)	0.011
Hypertension	45(18.67%)	21(30.43%)	
Diabetes mellitus	35(14.52%)	18(26.09%)	
Hypertension and DM	22(9.13)	6(8.7%)	
Others	18(7.47%)	3(4.35%)	
Treatment Regime			
Amox-levof-PPI	69(69%)	31(31%)	0.024
Tinid-levof-PPI	79(79%)	21(21%)	
Tinid-levof-PPI+Prob	93(84.55%)	17(15.45%)	

3.4 Predictors of Successful Eradication of *H. pylori*

In order to find out whether probiotic is independent factor that interfere with *H. pylori* eradication, all factors that showed significant association with patient's outcome were entered with univariate and then multivariate models.

In univariate model, all the aforementioned factors demonstrated a significant association with the patient's outcome. Each of younger age (≤ 35 years), being married, never smoking, or present no comorbidity increases the eradication rate by almost double (odds ratio in most cases close to 0.5). On the other hand, the combination of Tinid-levof-PPI+Prob increase the eradication rate by about 4-time compared with Amox-levof-PPI protocol (OR= 4.22, 95%CI=1.63-10.9, p= 0.008). However, in multivariate analysis, comorbidity lost its significant effect, while age, marital status, smoking and treatment regime remained significant. In this regard, Tinid-levof-PPI+Prob was found to increase the eradication rate by 3.36-time compared with Amox-levof-PPI protocol (OR= 3.36, 95%CI=2.5-21.7, p= 0.012) as shown in Table 3.

Table 3. Predictors of successful eradication of *H. pylori*

Variables	No eradication (n=69)	Successful eradication (n=241)	Univariate analysis		Multivariate analysis		
			P-value	OR(95%CI)	P-value	OR(95%CI)	
Age (years)							
≤35	32(46.38%)	146(60.58%)	0.037	1.0 Reference	0.029	1.0 Reference	
>35	37(53.23%)	95(39.42%)		0.56(0.33-0.97)		0.51(0.28-0.93)	
Marital status							
Married	37(52.94%)	162(68.57%)	0.038	1.0 Reference	0.022	1.0 Reference	
Single	32(47.06%)	79(31.43%)		0.54(0.31-0.96)		0.37(0.21-0.71)	
Smoking							
Never	38(55.07%)	168(69.71%)	0.023	1.0 Reference	0.026	1.0 Reference	
Ex/current smoker	31(44.93%)	73(30.29%)		0.55(0.32-0.95)		0.55(0.32-0.95)	
Comorbidities							
No comorbidity	21(30.43%)	121(50.21%)	0.014	1.0 Reference	0.063	1.0 Reference	
Hypertension	21(30.43%)	45(18.67%)	0.952	1.04(0.28-3.85)	0.561	0.66(0.61-2.7)	
Diabetes mellitus	18(26.09%)	35(14.52%)	0.128	2.8(0.74-10.56)	0.501	1.37(0.39-6.87)	
HTN and DM	6(8.7%)	22(9.13)	0.101	3.1(0.8-11.88)	0.425	1.82(0.42-7.95)	
Others	3(4.35%)	18(7.47%)	0.525	1.64(0.36-7.45)	0.814	0.82(0.16-4.17)	
Treatment Regime							
Amox-levof-PPI	31(31%)	69(69%)	0.027	1.0 Reference	0.036	1.0 Reference	
Tinid-levof-PPI	21(21%)	79(79%)	0.109	2.64(0.78-4.72)	0.142	1.41(0.66-6.58)	
Tinid-levof-PPI+Prob	17(15.45%)	93(84.55%)	0.008	4.22(1.63-10.9)	0.012	3.36(2.5-21.7)	

3.5 Side Effects

A total of five side effects were reported in treated patients. The frequency of these side effects ranged from 0 to 6 cases in the different groups. Amox-levof-PPI group showed slightly higher rate of some of these effect, than other groups with no significant differences. However, the overall incidence of side effect in Tinid-levof-PPI+Prob was (7.27%) was lower than that of Amox-levof-PPI group (19%) with significant difference, and Tinid-levof-PPI group (15%) with no significant difference (Table 4).

Table 4. Side Effects

Side effect	Amox-Levof-PPI (n=100)	Tinid-levof-PPI (n= 100)	Tinid-levof-PPI+Prob (n=110)	P-value
Dyspepsia	3(3%)	1(1%)	1(0.91%)	0.408
Nausea/ vomiting	2(2%)	3(3%)	2(1.82%)	0.829
Dry mouth	4(0%)	2(0%)	0(0%)	0.110
Diarrhea	6(6%)	5(5%)	1(0.91%)	0.125
Abdominal Pain	4(4%)	4(4%)	2(1.82%)	0.582
Total	19(19%)	15(15%)	8(7.27%)	0.04

4. Discussion

In the early years of *H. pylori* treatment, the results of the standard triple therapy were satisfactorily successful, yielding eradication rates of 95-96% (Lind et al., 1996). However, during the recent decades, several reports had

indicated a serious decline in the eradication rate with this therapy (Chey & Wong, 2007). This has alarmed investigators to find an alternative treatment either by changing the antibiotics, adopting new systems and schedules of therapy, or adding adjuvants that may help enhancing the response to the standard treatment.

According to the result of the present study, the overall eradication of *H. pylori* after different treatment protocols was 77.74%. The effectiveness of eradication therapy regimens has been stratified as excellent (>95%), good (91%-95%), borderline (85%-89%), and unacceptable (<85%) (Graham, Lee, & Wu, 2014). In view of this suggestion, the present eradication rate unacceptable.

Studies worldwide used different protocols and demonstrated different eradication rates. In a Tanzanian study, Jaka et al. (2019) recruited 210 patients positive for *H. pylori*. First line treatment failure with clarithromycin-based triple therapy was observed 31% of patients (only 69% eradication). In Egypt, Abd-Elsalam et al. (Abd-Elsalam et al., 2016) used the standard triple therapy to treat 1090 patients infected with *H. pylori*. Six weeks after completion the treatment, the eradication rate was 59.36% in intention-to-treat population and 62.03% in per-protocol. However, a retrospective analysis performed on 156 American patients treated with similar therapy demonstrated that the cumulative eradication rate for the intent-to-treat population was 84%, while the per-protocol rate was 86% (Nayar, 2018).

This variation between different studies can be attributed to several factors, the most important of which is the massive use of antibiotic in developing countries compared with the strict legislations for antibiotic use in the developed countries. Furthermore, the compliance to the treatment seems to be better in developed countries. Both factors (massive use of antibiotic and incompliance) play a vital role in the development of antibiotic resistance by *H. pylori*, and eventually reduce the eradication rate.

Based on the results of the current study, four factors other than treatment regime were found to be significantly associated with successful eradication of *H. pylori*. These were younger age, married individuals, never smokers, and the absence of comorbidities. In a Japanese study including 369 patients, Yokota et al. (2019). reported that failed eradication was significantly associated only with older age. In another study in Ethiopia, patients living in rural area were 2.7-time more likely to achieve eradication compared to urban residents (Gebeyehu, Nigatu, Engidawork, 2019). In Taiwan, Yao et al. (2019) investigate the impact of T2DM on the eradication rate in 719 patients positive for *H. pylori* and previously treated with 7-day standard first-line triple therapy. The study revealed that *H. Pylori* was completely eradicated in 74.1% of the T2DM group and 85.3% of the T2DM-free group ($p=0.005$). Sarg  n et al. (2003) reported eradication rate of 50% of patients with T2DM compared to 85% in the non-diabetic group when a standard triple therapy was used for 10-day treatment ($p<0.001$). In another study by Vafaeimanesh et al. (2013), it was found that the 14-day protocol resulted in an eradication rate of 63% in the DM group and 87.7% in the control group ($p=0.017$). Camargo et al. (2007) evaluated the eradication rate of *H. pylori* in 264 patients. The eradication rate was only 41.3% for active smokers compared with 57.1% in non-smokers. Multivariate logistic regression analysis showed that smokers had a 2-fold higher probability of failure in *H. pylori* eradication than non-smokers.

These factors in general influence the patient's general health. Elderly patients generally use many medications, often experience some cognitive decline, and many of them have physical limitations. All these factors can affect medication compliance and possibly associated with unsuccessful outcome of therapies (Yokota et al., 2019). DM can impair the immune system to a variable extent. Furthermore, those patients are more susceptible to infections (especially bacterial and mycotic), causing frequent use of antibiotics, which may in turn contribute to the development of resistance. Moreover, DM can cause a damage for microvasculature of gastric mucosa associated to some reduction in the absorption of antibiotics (Jaap, Shore, & Tooke, 1997). Smoking on the other hand, can decrease the blood flow in the gastric mucosa with the eventual lower delivery rate of antibiotics to the this mucosa. Furthermore, smoking induces acid gastric secretion, which reduces the efficiency of several acid labile antibiotics, like clarithromycin and amoxicillin (Camargo et al., 2007). No available previous studies indicated the significant role of marital status in *H. pylori* eradication. The significant association in the present study may be attributed to the improvement in the general hygiene of married individuals and the regular taking of medication under the influence of his/her spouse. Elderly patients generally have many medications prescribed, often suffer from cognitive decline, and frequently have physical limitations, which would affect their medication compliance and possibly result in unsuccessful outcome of therapies.

In the present study, Tinid-levof-PPI+Prob was found to increase the eradication rate by 3.36-time compared with Amox-levof-PPI protocol (OR= 3.36, 95%CI=2.5-21.7, $p= 0.012$) which implies that patients using Tinid-levof-PPI+Prob had 3.36-time more like to cure than those using Amox-levof-PPI protocol. The eradication rate for Tinid-levof-PPI+Prob, Tinid-levof-PPI and Amox-levof-PPI was 84.55%, 79% and 69%,

respectively. Such a result was frequently reported by many previous studies worldwide. In one study, 120 patients positive for *H. pylori* were randomized to receive triple therapy, either with or without a lyophilized and inactivated culture of *L. acidophilus* twice daily. A significantly more eradication rate was perceived in the augmented group (88 %), than non-probiotic treated control group (72 %) (Moodley et al., 2012). Almost similar results were stated by Bekar et al. (2011) from Turkey, who examined the impact of conjoining standard triple anti *H. pylori* therapy with kefir, a fermented milk derived product containing probiotics. The eradication rate was 78.2% versus 50% in favor of supplemented therapy. Ojetti et al. (Ojetti et al., 2012) used a single strain of *Lactobacillus* for 14 days also associated with a triple regimen of eradication (PPI + Levofloxacin + Amoxicillin) with 7 days in duration and obtained both increasing eradication and a reduction in adverse effects. Ahmed et al. (2013) investigated the effect of probiotic on eradication rate in 66 Iranian patients positive for *H. pylori*. The study revealed that 90% of supplanted group achieved eradication compared to 69.7% in control group (OR= 4.37, 95%CI= 1.07–17.62, p=0.04). In Saudi Arabia, Dajani et al. (2013) conducted an open randomized observational study to test three different regimes of *H. pylori* eradication treatment. The eradication rate for the traditional standard therapy was 68.9%, and adding the probiotic “*Bifidus infantis*” to triple therapy, led to a successful rate of eradication of 83% (P < 0.001). Pre-treatment with 2 weeks of *B. infantis* before adding it to standard triple therapy increased the success rate of eradication to 90.5%.

The wide variety and controversial results in previous studies may be attributed to the differences in study design, patient groups, different therapeutic regimens, probiotic dose, and probiotic species.

On the other hand, some studies did not verify significant benefits in probiotic use (Yoon et al., 2011) (Kindermann, 2009). Yoon et al. (2011) prepared a compound of 4 probiotics and used them for 4 weeks, to a treatment for *H. pylori* with PPI + amoxicillin + moxifloxacin. The study revealed neither increase eradication nor a reduction in the adverse effects. The different results are probably due to the different products used, their different concentrations, probiotic strain, dose and duration of use and also the strain of *H. pylori* in question, as suggested by Vitor and Vale (Wilhelm, Johnson, & Kale-Pradhan, 2011) and Wilhelm (Vitor & Vale, 2011).

In the current study, the overall incidence of side effect in Tinid-levof-PPI+Prob was (7.27%) which was lower than that of Amox-levof-PPI group (19%) with significant difference. In accordance with this result is the study of Park et al. (2007) who established that conjoining of first line anti *H. pylori* therapy with probiotic bacteria, comprising *Bacillus subtilis* and *Streptococcus faecium* decreased the side effects, enhanced patient's tolerance and improved the eradication rate of *H. pylori*. Also in line with this result is the study of Lakovenko et al. (2006) in which the authors reported that *H. pylori* eradication rate was 89.1 % in the group of probiotics supplementation to standard triple therapy and 63.5 % in the group of standard triple therapy. In a meta-analysis, Szajewska et al. (2015) demonstrated that *Saccharomyces boulardii* supplementation to standard triple therapy could increase the *H. pylori* eradication rate and markedly reduce the side effects, especially the diarrhea. Another meta-analysis showed that multi-strain probiotics improved *H. pylori* eradication rates, prevented any adverse reactions, and reduced antibiotic-associated diarrhea, especially probiotics including *Lactobacillus* and *Bifidobacterium* (McFarland et al., 2006). Many other studies have obtained similar results when *L. reuteri* was used as adjuvant to the triple therapy in *H. pylori* eradication (Ojetti et al., 2006; Francavilla et al., 2008; Efrati et al., 2012).

One of most important effect of probiotics in alleviation of side effects is creating an appropriate environment for the growth of normal intestinal anaerobic microbiota, and inhibiting the growth of harmful bacteria such as *Escherichia coli*, dysentery bacilli, *Staphylococcus aureus*. As such, probiotics can reduce the side effects associated with these pathogenic bacteria (Tompkins et al., 2008).

5. Conclusions and Recommendations

- 1) The overall eradication of *H. pylori* after different treatment protocols was 77.74%, which is globally unacceptable.
- 2) Each of younger age, married individuals and never smoking are independent factors that can increase the eradication rate of *H. pylori*.
- 3) Supplementation of the standard triple protocol with probiotic increased the eradication rate from 79% to 84.55%.
- 4) Using of probiotic as additives with standard treatment can reduce the incidence of antibiotic side effects

Competing Interests Statement

The authors declare that there are no competing or potential conflicts of interest.

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