Gastroenterology and Hepatology From Bed to Bench.

ORIGINAL ARTICLE

The efficacy and safety of adding the probiotic *Saccharomyces boulardiito* standard triple therapy for eradication of *H.pylori*: a randomized controlled trial

Homayoun Zojaji, Mehdi Ghobakhlou, Hassan Rajabalinia, Elnaz Ataei, Somayeh Jahani Sherafat, Bijan Moghimi-Dehkordi, Rasoul Bahreiny

Gastroenterology and Liver Diseases Research Center, Shahid Beheshti University of Medical Science, Tehran, Iran

ABSTRACT

Aim: Evaluating the efficacy and safety of adding the probiotic *Saccharomyces boulardiito* standard triple therapy for eradication of *Helicobacter pylori*.

Background: Several probiotics such as *Saccharomyces boulardii* have been investigated for their clinical efficacy. This probiotic, inhibit *H. pylori* urease by lowering the gastric pH, adhesion of *H. pylori* to gastric epithelial cells, stabilize the gastric barrier function and reduce the side effects of antibiotics.

Patients and methods: In this randomized controlled trial we evaluated 160 adult patients with biopsy confirmed *H.Pylori* infection referred to gastroenterology ward of Taleghani hospital. The patients were randomized into two treatment regimens: patients in group A (n=80) were given amoxicillin (1000 mg, b.i.d), clarithromycin (500 mg, b.i.d), omeprazole (20 mg, b.i.d) and probiotic of *saccaromyces boularidi* (Yomogi) (250 mg, b.i.d) for 14 days, moreover patients in group B (n=80) were given amoxicillin (1000 mg, b.i.d), clarithromycin (500 mg b.i.d) and omeprazole (20 mg,b.i.d) for 14 days.

Results: 160 patients (66 male 41.25%, 94female 58.75%) with the mean age of 47.1±11.4 years were evaluated. The success rate for *H. pylori* eradication in group A was higher 75(87.5%) than group B 65 (81.2%), but the difference between two groups was not significant (p=0.350). Moreover, in case group side effects as nausea, diarrhea, abdominal discomfort and bloating were significantly lower than control group in first and second weeks.

Conclusion: This study showed that *saccaromyces boularidi* decreased the adverse effects associated with *H.pylori* therapy but did not significantly decrease the eradication rate of *H.pylori*.

Keywords: *Helicobacter pylori*, Probiotic, *Saccharomyces boulardii*, Anti-*helicobacter pylori* eradication therapy.

(Please cite as: **Zojaji H, Ghobakhlou M, Rajabalinia H, Ataei E, Jahani Sherafat S, Moghimi-Dehkordi B, et al. The efficacy and safety of adding the probiotic *Saccharomyces boulardiito* standard triple therapy for eradication of *Helicobacter pylori*; a randomized controlled trial. Gastroenterol Hepatol Bed Bench 2013;6(Suppl.1):S99-S104).**

Introduction

Helicobacter pylori (*H.pylori*) affects approximately 50% of the world's population and it is a leading cause of peptic ulcers and chronic gastritis. Moreover *H.pylori* was defined as a possible risk factor for gastric adenocarcinoma and mucosa-associated lymphoid tissue lymphoma (1). It was classified as a type 1 carcinogen by the World Health Organization (WHO) in 1994 (2).

Treatment with amoxicillin, clarithromycin and a proton pump inhibitor (PPI) is the first-line triple therapy to eradicate *H.Pylori*. However, due to high prevalence of treatment failure related to

Received: 8 March 2013 *Accepted*: 11 May 2013
Reprint or Correspondence: Homayoun Zojaji, MD. Gastroenterology and Liver Diseases Research Center, Shahid Beheshti University of Medical Science, Tehran, Iran
E-mail: zojajy@yahoo.com

antibiotic resistance, frequent and uncontrolled use of antibioticand severe and frequent antibiotic adverse effects (3,4) the clinicians have considered several alternatives therapies. These methods include: extended treatment duration, the use of new antibiotics, and quadruple therapy as the first option or recently the addition of probiotics to triple therapy (4-6). Probiotics are live microorganisms that may have a positive effect on gastrointestinal microorganism and recover health conditions (7). These agents have become progressively popular in the world to treat a diverse type of gastrointestinal disease (8-10). In this regard numerous probiotic strains have been investigated for their clinical efficacy, including multiple bacterial strains and fungal strains as *Saccharomyces boulardii* (*S. boulardii*) (11-13). The probiotics inhibit *H. pylori* urease by lowering the gastric pH, adhesion of *H. pylori* to gastric epithelial cells, stabilize the gastric barrier function (14) and reduce the side effects of antibiotics (15,16). However previous studies have provided conflicting information regarding the positive effect of probiotic on *H.pylori* eradication (17).

In our knowledge not enough evidence are available on the beneficial effects of adding probiotics into the eradication regimen of *H. Pylori* in Iran. Therefore this study aimed to evaluate the efficacy and safety of adding the probiotic *Saccharomyces boulardiito* standard triple therapy for eradication of *H.pylori*.

Patients and Methods

In this randomized controlled trial we evaluated 160 adult patients with biopsy confirmed *H.Pylori* infection referred to gastroenterology ward in Taleghani hospital (a tertiary academic center in Tehran-Iran) during 2011-2012. All adult patients who came to our hospital and were candidate for upper GI endoscopy within 12 months were evaluated in this trial. Patients <15 years old, pregnant women or lactation patients with history of hepatic, cardio-respiratory, renal, neoplastic diseases or coagulopathy, patients receiving antibiotics, PPIs, H2 receptor blockers, bismuth salts, or probiotics within the previous four weeks, patients with previous gastric surgery and sensitivity to any of the drugs used in this study were excluded from this study. The study was approved by the Ethics Committee of Gastroenterology and Liver Diseases Research Center, Shahid Beheshti University of Medical Sciences and it was in agreement with the principles of the Helsinki II Declaration. Moreover the patients were informed about the study protocol and written consent was obtained from all patients. Patients with biopsy confirmed *H.pylori* were included. Then they were randomized into two treatment regimens: patients in Group A (n: 80) were given amoxicillin (1000 mg, b.i.d), clarithromycin (500 mg b.i.d), omeprazole 20 mg bid and *saccharomyces boulardii* probiotic (250 mg, b.i.d) for 14 days, andpatients in Group B (n:80) were given amoxicillin (1000 mg, b.i.d), clarithromycin (500 mg b.i.d) and omeprazole (20 mg b.i.d) for 14 days. Patient compliance was evaluated at the end of the treatment by pill count and was considered as good compliance if > 95% of the medication had been taken. Modest compliance > 70%, Poor compliance < 70% and dropped out.

Patients were asked to report any side effects of therapy during the treatment period (end of first, second, third and fourth weeks of treatment) and were given a possible side effect list, such as epigastric pain, diarrhea, taste disturbance, constipation, and stomatitis. Eight weeks after treatment, Urea Breath Test (UBT) was performed in all patients. Successful eradication was defined as a negative 13C-urea breath test result (UBT) eight weeks after discontinuation of the therapy.

Statistical analysis

The data were entered in SPSS version 17. Values were reported as mean ± standard deviation. Non-parametric t-test, chi-square test

were used to compare two independent groups. P<0.05 were considered to be significant.

Results

In this clinical trial, 160 patients (58.7% female) with mean age 47.1±11.4 years were evaluated. Regarding sex and age the difference between case and control groups was not significant (p>0.05).

The most frequent esophagogastroduodenoscopy (EGD) finding group A and B was antral gastritis (51% and 44% respectively). The difference between two groups was not significant (p>0.05) (figure 1).

The success rate for *H. pylori* eradication was higher in group A 75(87.5%) than in group B 65 (81.2%), but the difference between two groups was not significant (p=0.350) (Table 1).

Table 1. Distribution of *H.pylori* eradication and compliance in two groups

		Groups* (%)		
		A (n=80)	B (n=80)	P-value
Compliance				0.46
	Good	52(65)	46(58.2)	
	Moderate	23(28.8)	24(30.4)	
	Poor	5(6.3)	9(11.4)	
UBT results				0.27
	Negative	70(87.5)	65(81.2)	
	Positive	10(12.5)	15(18.8)	

*Group A (n: 80) were given amoxicillin (1000 mg, b.i.d), clarithromycin (500 mg b.i.d), omeprazole 20 mg bid and *saccharomyces boulardii* probiotic (250 mg, b.i.d) for 14 days; Group B (n:80) were given amoxicillin (1000 mg, b.i.d), clarithromycin (500 mg b.i.d) and omeprazole (20 mg b.i.d) for 14 days.

Regarding drug compliance 52(65.0%) in group A and 46(58.2%) in group B showed good compliance. The difference between case and control groups was not significant (p>0.05) (Table 1).

The frequency of side effects as nausea, diarrhea, abdominal discomfort and bloating in group A, were significantly lower than group B in first and second weeks (p<0.05), where as skin rash, insomnia in case group did not show remarkable difference compared to control group (Table 2).

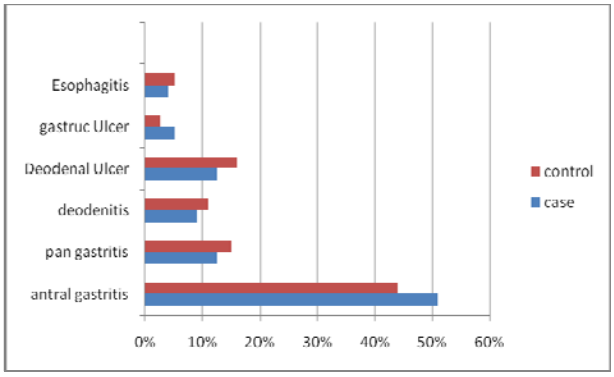

Figure 1. Esophagogastroduodenoscopy findings in cases (group A) and control (group B)

Discussion

Recently, the alternative anti-*H.pylori* treatments have been extended and more studies have been steered to describe components that may effect on *H.pylori* infection. In general, probiotics can strengthen host systems and assist in recovery from certain diseases and in particular *S. boulardii* induces morphologic changes in *H. pylori* cells consistent with cellular damage (18) and in one trial by Gottel et al. was shown *S. boulardii* reduce 12% of *H. pylori* colonization in infected children (19). Furthermore de Bortoli et al. indicated that the addition of probiotics to standard triple therapy (esomeprazole, clarithromycin, amoxicillin) could increase the eradication rate of *H. pylori* infection and reduce the side effects of antibiotic therapy (20).

To evaluate this hypothesis, we designed a comparative clinical trial study to assess any positive effect of *S.boulardii* on *H.pylori* infection and side effects of therapy. The success rate for *H.pylori* eradication was higher in probiotic group (87.5%) than control (81.2%), but the difference between two groups was not significant. However, side effects as nausea, diarrhea, abdominal discomfort and bloating were significantly lower in group A than group B during the first and second weeks. These findings were in accordance with Cremonini et al. study that indicated the efficacy of probiotics for eradication of *H. pylori*

Table 2. Frequency of side effects of probiotic in group A compare to group B

	Group A (n=80) (%)				Group B (n=80)			
	1st week	2st week	3st week	4st week	1st week	2st week	3st week	4st week
Nausea	12(15)*	14(17.5)*	5(6.3)	0	23(28.8)*	29(36.3)*	10(12.5)	1(1.3)
Diarrhea	11(13.)*	10(12.5)*	5(6.3)	1(1.3)	24(30)*	21(26.3)*	9(11.3)	4(5)
Abdominal discomfort	17(21.)*	18(22.5)*	6(7.5)*	3(3.8)	42(52.5)*	36(45)*	19(23.8)*	6(7.5)
Insomnia	4(5)	1(1.3)	1(1.3)	0	5(6.3)	0	1(1.3)	1(1.3)
Metal taste	9(11.3)	8(10)	0	0	9(11.3)	7(8.8)	0	0
Bloating	17(21.3)*	18(22.5*)	9(11.3)	4(5)	37(46.3)*	39(48.8)*	18(22.5)	11(13.8)
Rash	3(3.8)	1(1.3)	0	0	4(5)	2(2.5)	0	0

*P<0.05

in 85 asymptomatic carriers. They randomized patients in three probiotic therapy groups (*S. boulardii*, *L.rhamnosus* GG or a mixture of *L. acidophius* and *Bifidobacterium lactis*) and placebo for 14 days. After second week, the eradication rates were similar for all groups (81% for *S. boulardiivs* 80% *forplacebo*). But antibiotic-associated diarrhea in all the probiotic groups was significantly lower (5%) than placebo group (30%)(21). Moreover, the other study by Cindoruk et al. in 2007 in turkey evaluated *S. boulardii* for both eradication of *H. pylori* and the reduction of side-effects of the standard triple treatment. They studied 124 carriers with dyspepsia who were receiving the triple therapy and randomized to either *S.boulardii* (1g) or placebo group for two weeks. Then patients were followed up for six weeks regarding side-effects and *H. pylori* eradication rate. The patients showed no significant difference in *H.pylori* eradication (71% in *S. boulardiivs;* 60% in placebo), however epigastric distress and global dyspepsia symptom scores in *S. boulardii* group were significantly lower than control group (16).

In addition, Yasar et al. in another survey in turkey in 2010, studied the efficacy of probiotics in *H.pylori* eradication therapy and specified that the addition of probiotic-containing yogurt to the triple therapy did not significantly increase the *H. pylori* eradication rates, however, they informed that probiotics decreased the frequency of stomatitis and constipation (22).

Our results and these mentioned studies indicate that *S. boulardii* did not decrease eradication rate of H. pylori where as it is significantly reduce the side effects of the standard triple therapy. On the other hands, Lesbros-Pantoflickova reported that probiotics reduce the risk of developing disorders associated with high degrees of gastric inflammation (23).

Moreover Wilhelm et al. reported probiotics reduce adverse effects and increase tolerability of *H. pylori* eradication regimens. They may especially be useful in patients with recurrent *H. pylori* infection and a history of gastrointestinal adverse effects with antibiotics (24). In addition Kotowska signified that *S. boulardii* effectively reduces the risk of antibiotic-associated diarrhea in children (25).

The most of reviewed studies signified treatment with probiotics is relatively safe (22,23, 26), however it is not risk free and are potentially pathogenic (27) moreover a study described 3 patients with fungaemia after intake of *S. Boulardii* (28). In contrast to these findings, we did not detect any remarkable adverse effect related to *S. Boulardiiin* in group A of our study.

In conclusion, we showed *S. boulardii* decreased the adverse effects associated triple therapy but did not significantly decrease the eradication rate of *H.pylori*. We suggest further trials with higher dose of *S. boulardiior* other types of probiotics in combination with standard therapy which may provide significant results.

Acknowledgements

We would like to thanks all patients who participated in this study. The project is supported by Research Center for Gastroenterology and Liver Diseases. This article is taken from the Mehdi Ghobakhlou Fellowship thesis project.

References

1. Go MF, Crowe SE. Virulence and pathogenicity of *Helicobacter pylori*. Gastroenterol Clin North Am 2000; 29: 649-70.

2. Eslick GD, Lim LL, Byles JE, Xia HH, Talley NJ. Association of *Helicobacter pylori* infection with gastric carcinoma: a meta-analysis. Am J Gastroenterol 1999; 94: 2373-79.

3. Kearney DJ. Retreatment of *Helicobacter pylori* infection after initial treatment failure. Am J Gastroenterol 2001; 96: 1335–39.

4. Suerbaum S, Michetti P. Medical progress: *Helicobacter pylori* infection. N Engl J Med 2002; 347: 1175-86.

5. Malfertheiner P, Megraud F, O'Morain C, Bazzoli F, El-Omar E, Graham D, et al. Current concepts in the management of *Helicobacter pylori* infection: the Maastricht III Consensus Report. Gut 2007; 56: 772-81.

6. Lessbros-Pantoflickova D, Corthesy-Theulaz I, Blum AL. *Helicobacter pylori* and probiotics. J Nutr 2007; 137: 812-18.

7. Hoffman FA, Heimbach JT, Sanders ME, Hibberd PL. Executive summary: scientific and regulatory challenges of development of probiotics as foods and drugs. Clin Infect Dis 2008; 46: S53-S57.

8.Vanderhoof JA, Young R. Probiotics in the United States. Clin Infect Dis 2008; 46: S67-S72.

9. Amagase H. Current marketplace for probiotics: a Japanese perspective. Clin Infect Dis 2008; 46: S73-S75.

10.Saxelin M. Probiotic formulations and applications, the current probiotics market, and changes in the marketplace: a European perspective. Clin Infect Dis 2008; 46: S76-S79.

11. McFarland LV. Evidence-based review of probiotics for antibiotic-associated diarrhea and Clostridium difficile infections. Anaerobe 2009; 15: 274-80.

12.Czerucka D, Piche T, Rampal P. Review article: yeast as probiotics-Saccharomyces boulardii. Aliment Pharmacol Ther 2007; 26: 767-78.

13. Elmer GW, Surawicz CM, McFarland LV. Biotherapeutic agents. A neglected modality for the treatment and prevention of selected intestinal and vaginal infections. JAMA 1996; 275: 870-76.

14. Kim MN, Kim N, Lee SH, Park YS, Hwang JH, Kim JW, et al. The effects of probiotics on PPI-triple therapy for *Helicobacter pylori* eradication. Helicobacter 2008; 13: 261-68.

15. Nista EC, Candelli M, Cremonini F, Cazzato IA, Zocco MA, Franceschi F, et al. Bacillus clausiitherapy to reduce side-effects of anti-*Helicobacter pylori* treatment: randomized, double-blind, placebo controlledtrial. Aliment Pharmacol Ther 2004; 20: 1181-88.

16. Cindoruk M, Erkan G, Karakan T, Dursun A, Unal S. Efficacy and safety of Saccharomyces boulardii in the 14-day triple anti-*Helicobacter pylori* therapy: a prospective randomized placebocontrolleddouble-blind study. Helicobacter 2007; 12: 309-16.

17. Sheu BS, Wu JJ, Lo CY, Wu HW, Chen JH, Lin YS, et al. Impact of supplement with Lactobacillus- and Bifidobacterium-containing yogurt on triple therapy for *Helicobacter pylori* eradication. Aliment Pharmacol Ther 2002;16:1669–75.

18.Vandenplas Y, Brunser O, Szajewska H. *Saccharomyces boulardii* in childhood. Eur J Pediatr 2009; 168: 253-65.

19.Gotteland M, Poliak L, Cruchet S, Brunser O. Effect of regular ingestion of *Saccharomyces boulardii* plus inulin or Lactobacillus acidophilus LB in children colonized by *Helicobacter pylori*. Acta Paediatr 2005; 94: 1747-51.

20. de Bortoli N, Leonardi G, Ciancia E, Merlo A, Bellini M, Costa F, et al. *Helicobacter pylori* eradication: a randomized prospective study of triple therapy versus triple therapy plus lactoferrin and probiotics. *Am J Gastroenterol* 2007; 102:951-56.

21. Cremonini F, Di Caro S, Covino M, Armuzzi A, Gabrielli M, Santarelli L, et al. Effect of different probiotic preparations on anti-*helicobacter pylori* therapy-related side effects: a parallel group, triple blind, placebo-controlled study. Am J Gastroenterol 2002; 97: 2744-49.

22. Yaşar B, Abut E, Kayadıbı H, Toros B, Sezıklı M, Akkan Z, et al. Efficacy of probiotics in *Helicobacter pylori* eradication therapy. Turk J Gastroenterol 2010; 21: 212-17.

23. Lesbros-Pantoflickova D, Corthésy-Theulaz I, Blum AL. *Helicobacter pylori* and Probiotics. J Nutr 2007;137: S812-18.

24. Wilhelm SM, Johnson JL and Kale-Pradhan PB. Treating bugs with bugs: the role of probiotics as adjunctive therapy for *Helicobacter pylori*. Ann Pharmacother 2011;45:960-66.

25. KotowskaM, Albrecht P, Szajewska H. *Saccharomyces boulardii* in the prevention of antibiotic-associated diarrhoea in children: A randomized double-blind placebo-controlled trial. Aliment Pharmacol Ther 2005; 21:583-90.

26. Saavedra JM, Abi-Hanna A, Moore N, Yolken RH. Long-term consumption of infant formulas containing live probiotic bacteria: tolerance and safety. Am J Clin Nutr 2004; 79:261-67.

27. Ishibashi N, Yamazaki S. Probiotics and safety. Am J Clin Nutr 2001; 73: S465-70.

28. Muñoz P, Bouza E, Cuenca-Estrella M, Eiros JM, Pérez MJ, Sánchez-Somolinos M, et al. Saccharomyces cerevisiaefungemia: an emerging infectious disease. Clin Infect Dis 2005; 40: 1625-34.