

The effects of probiotics on treatment of *Helicobacter pylori* eradication in children

Mustafa Akcam, MD, Tugba Koca, MD, Hakan Salman, MD, Nermin Karahan, MD.

ABSTRACT

الأهداف: للتحقق من معدلات القضاء والآثار الجانبية للبروبيوتيك المضاف للعلاج الثلاثي القياسي من أجل القضاء على جرثومة المعدة الملوية البوابية (*Helicobacter pylori*).

الطريقة: أجريت هذه الدراسة المفتوحة الاستطلاعية في العيادات الخارجية التابعة لقسم طب الأطفال، أمراض الجهاز الهضمي، كلية الطب، جامعة سليمان ديميريل، اسبرطة، تركيا وذلك خلال الفترة من مارس 2012م إلى مايو 2013م. شملت الدراسة 61 طفلاً مصاباً بجرثومة المعدة الملوية البوابية من تتراوح أعمارهم ما بين 7 إلى 18 عاماً. لقد قمنا بتقسيم الأطفال عشوائياً إلى مجموعتين: تلقت المجموعة الأولى العلاج الثلاثي المعياري (لأنزورازول، أموكسيسيلين، وكلاريثروميسين لمدة 14 يوماً)، بينما تلقت المجموعة الثانية العلاج المعياري القياسي بالإضافة إلى البروبيوتيك (المجينة اللبنية، اللبنية الحمضة، والشقاء اللبنية). وقد قمنا أيضاً بتسجيل الآثار الجانبية للعقاقير. وبعد ذلك أجرينا اختبار التنفس 14C-اليوريا لمدة 6 أسابيع وذلك بعد التوقف عن العلاج.

النتائج: أشارت نتائج الدراسة إلى ظهور جرثومة المعدة لدى 61 من 95 طفلاً (64.2%). ولقد استكمل الدراسة 56 مريضاً (38 أنثى، و 18 ذكر)، ولقد كان متوسط العمر 13.9 ± 2.7 عاماً. وكان معدل استئصال الجرثومة المجموعة لدى المجموعة الأولى 68.9%، فيما كان لدى المجموعة الثانية 66.6% ($p=0.78$). ولوحظ عدم وجود اختلافات واضحة من الناحية الإحصائية بين المجموعتين وذلك من ناحية الآثار الجانبية.

الخاتمة: أظهرت الدراسة بأنه لم يكن لإضافة علاج البروبيوتيك تأثير على معدل القضاء على جرثومة المعدة الملوية البوابية، كما لم يكن له أي آثار جانبية. لذلك فنحن بحاجة للمزيد من الدراسات الكبيرة العشوائية المتحكم بها وذلك من أجل التحقق من تأثير البروبيوتيك على جرثومة المعدة والقضاء عليها.

Objectives: To investigate the eradication rates and side effects of probiotics added in standard triple therapy for the treatment of *Helicobacter pylori* (*H. pylori*).

Methods: A prospective open study was performed in the outpatient clinics of the Department of Pediatric Gastroenterology, School of Medicine, Suleyman Demirel University, Isparta, Turkey between March 2012 and May 2013. Sixty-one symptomatic children (range 7-18 years) with *H. pylori* infection were randomized to 2 groups: group 1 received standard triple therapy (lansoprazole, amoxicillin, and clarithromycin for 14 days), group 2 received the standard triple therapy plus probiotics (*Lactobacillus casei*, *Lactobacillus acidophilus*, and *Bifidobacterium lactis*). Side effects of the drugs were recorded. The 14C-urea breath test was performed for 6 weeks after discontinuation of the therapy.

Results: *Helicobacter pylori* infection was detected in 61 of 95 (64.2%) children. Fifty-six patients (38 girls and 18 boys) completed the study. Their mean age was 13.9 ± 2.7 years. *Helicobacter pylori* eradication rate was 68.9% in group 1, and 66.6% in group 2 ($p=0.78$). No statistically significant difference was observed between the 2 groups in terms of side effects.

Conclusion: We found no evidence in terms of eradication of *H. pylori*, or impact on adverse effects obtained after the addition of probiotics to standard treatment. Larger randomized controlled investigations are needed to clearly understand the effects of probiotics on *H. pylori* eradication.

Saudi Med J 2015; Vol. 36 (3): 286-290
doi: 10.15537/smj.2015.3.10124

From the Department of Pediatrics (Akcam, Koca, Salman), Division of Pediatric Gastroenterology, Hepatology and Nutrition, and the Department of Pathology (Karahan), School of Medicine, Süleyman Demirel University, Isparta, Turkey.

Received 6th October 2014. Accepted 19th January 2015.

Address correspondence and reprint request to: Dr. Tugba Koca, Department of Pediatrics, School of Medicine, Süleyman Demirel University, Isparta 32200, Turkey. Tel. +90 (246) 2119303. Fax. +90 (246) 2112830. E-mail: tgkoca@gmail.com

Helicobacter pylori (*H. pylori*) causes infection in around half of the world's population, and is implicated in the etiology of various diseases other than peptic disease.¹ The bacterium is considered to have carcinogenic effects in the long-term, and the agent is reported to be acquired in childhood, particularly in developing countries.^{2,3} The eradication of *H. pylori* in childhood is important not only to relieve peptic symptoms, but also to prevent late-term complications, such as cancer.⁴ To date, numerous treatment regimens have been attempted to eradicate the organism; however, the success rates are far from ideal. The most widely accepted first line treatment regimen includes the combination of a proton pump inhibitor and 2 antibiotics (amoxicillin and clarithromycin). The treatments initially yielded more successful results, but the rate of success has gradually declined due to resistance problems.⁵⁻¹¹ For this purpose, many different antibiotic combinations and treatment options have been attempted; however, all failed to achieve the desired level of success. In recent years, the clinical benefits of probiotics have been better recognized in various areas, and they have found a place in the eradication of *H. pylori* as an adjuvant, particularly in adults. The studies have utilized different strains and doses, and yielded conflicting results.¹²⁻¹⁵ There have been limited studies performed in children on the effect of supplementation of probiotics to triple therapy for eradicating *H. pylori* infection. In a study in pediatric patients, standard *H. pylori* eradication treatment has been added to *Lactobacillus acidophilus* (*L. acidophilus*) and *Bifidobacterium lactis* (*B. bifidum*), and a significantly higher eradication rate was achieved compared with the control group (83.7% versus 64.4%); additionally, there was no significant difference in terms of side effects.¹⁶ On literature review, there was a scarcity of studies carried out with the combination of probiotic strains of *Lactobacillus casei* (*L. casei*) 2401, *L. acidophilus* 2027, and *B. lactis* 2211. Therefore, we aimed to investigate the supplementation of this combination to standard triple therapy on *H. pylori* eradication rates and the side effects in children.

Methods. The study population consisted of 95 consecutive children (61 females, 34 males, mean

age 13.2 years, range 7-18 years) with uninvestigated dyspepsia, with predominantly chronic or recurrent upper abdominal pain, suggesting organic disease requiring an endoscopic evaluation. This study was conducted over a one-year period (between March 2012 and May 2013). All endoscopies were performed by the same gastroenterologist, using a fiber endoscope. *Helicobacter pylori* infection was detected in 61 of 95 (64.2%) children. The patients were divided into 2 groups according to the order of admission: i) group one (n=31) was administered with the standard triple therapy; and ii) group 2 (n=30) was administered with standard triple therapy plus probiotics.

Exclusion criteria. Patients who received antibiotics up to 10 days prior to inclusion, anti-acids, H2 receptor blockers, probiotics, and proton pump inhibitors, or who suffered from gastrointestinal disease, acute diarrhea, kidney, and/or liver failure, or marked neuropsychiatric disease were excluded from the study.

Diagnosis of *H. pylori* infection. All patients underwent upper gastrointestinal tract endoscopy. A nodular appearance in the gastric mucosa was considered to support *H. pylori* infection. Biopsy specimens were obtained, 2 from the antrum, and 2 from the corpus. In the patients with endoscopically suspected gastric inflammation, biopsy specimens were taken from areas with abnormal appearing mucosa. A rapid urease test (Helident, RTA, Kocaeli, Turkey) was performed on one of the biopsy specimens, and the other specimens were fixed in 10% formalin solution. The slides were then stained with hematoxylin-eosin and Giemsa, and a histopathological examination was performed to determine *H. pylori* infection. The diagnosis of *H. pylori* infection was established on the basis of the detection of a nodular appearance in the upper gastrointestinal tract endoscopy, positive rapid urease test, and the detection of *H. pylori* in the histopathological examination. Patients meeting at least 2 of these criteria were included in the study.

14C-urea breath test. Patients swallowed a capsule containing 14C-labeled urea. After 20 minutes, the patient breathed into a breath cartridge. The cartridges were read by a Heliprobe analyzer. All breath tests were conducted in the same laboratory. The 14C- urea breath test was performed to diagnose the *H. pylori* eradication rate at 6 weeks after discontinuation of therapy.

Patient compliance and side effects. The patients were questioned for the presence of side effects at days 0, 7, 14, and 28. The presence of any intolerance such as abdominal pain, nausea, vomiting, constipation,

Disclosure. Authors have no conflict of interests, and the work was not supported or funded by any drug company.

belching, taste problems, lack of appetite, and diarrhea that would mandate the discontinuation of therapy were recorded. The questionnaires were analyzed by the same author who was blinded to the treatment allocation.

Treatment. Group 1 received standard triple therapy (50 mg/kg/day amoxicillin [Largopen® tablet, Bilim Pharmaceuticals, Tekirdag, Turkey] in divided doses every 12 hours, 15 mg/kg/day clarithromycin [Klacid®, Abbott laboratories, Dublin, Ireland] in divided doses every 12 hours, and 30 mg lansoprazole [Lansor® pellet capsule, Sanovel Pharmaceuticals, Istanbul, Turkey] twice daily before breakfast, and 30 minutes before dinner for 14 days). Group 2 received standard triple therapy plus capsules containing 7×10^9 CFU *L. casei* 2401, *L. acidophilus* 2027, and *B. lactis* 2211 (Maflor® plus capsule, Mamsel Pharmaceuticals Inc, Cidex, France) twice daily for 14 days. The success of the therapy was evaluated by performing 14C-urea breath test for 6 weeks after the completion of therapy. Before participation in the study, an informed consent was obtained from at least one parent, and the study was carried out with the approval of the Ethics Committee of Suleyman Demirel University, School of Medicine. We followed the principles outlined in the Helsinki Declaration.

Statistical analysis. The IBM SPSS Statistics for Windows version 20.0 (IBM Corp, Armonk, NY, USA) was used in the statistical analysis, and the data were analyzed using chi-square test and the independent-sample t-test. *P* values <0.05 were considered significant.

Results. *Helicobacter pylori* infection was detected in 61 of 95 (64.2%) children. The study design and characteristics of enrolled children are shown in Figure 1. Of the 56 patients who completed the study, 38 were girls and 18 were boys, and the mean age was 13.9 ± 2.7 years. There was no significant difference between the groups in terms of age ($p=0.33$), and gender ($p=0.85$). The demographic characteristics and eradication rates of each group are presented in Table 1. The eradication rates were 68.9% in group 1, and 66.6% in group 2 (Table 1). There was no significant difference between the 2 groups ($p=0.78$). There were no significant differences between the 2 groups in terms of abdominal pain, nausea, vomiting, constipation, belching, taste problems, lack of appetite, diarrhea, or any other intolerance that would mandate the discontinuation of therapy at baseline, and days 7, 14, and 28 (Table 2). None of the patients developed serious side effects mandating discontinuation of therapy.

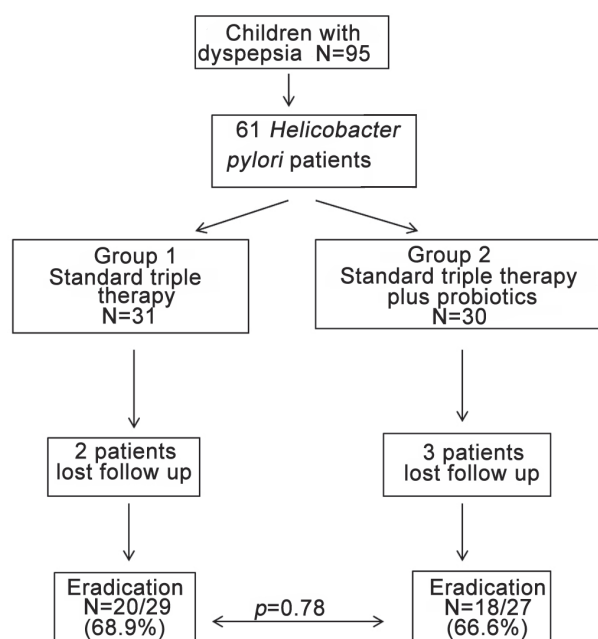


Figure 1 - Study design and characteristics of enrolled children in a study on *Helicobacter pylori* eradication in Turkey.

Table 1 - *Helicobacter pylori* eradication rates with 14C-urea breath test (UBT) among 56 patients.

Variables	Group 1	Group 2	<i>P</i> -value
Number of patients	29	27	
Gender, female/male	20/9	18/9	0.85
Age (years)	13.49 ± 3.2	14.45 ± 2.3	0.33
UBT (-)	20	18	0.78
Eradication rate (%)	(68.9)	(66.6)	

Discussion. Despite intensive efforts to eradicate *H. pylori*, success rates are around 50% in developing countries.^{17,18} This rate is as high as 75% in developed countries.^{19,20} The eradication rate remains low in developing countries such as in Turkey, where the disease is highly prevalent and there is uncontrolled use of antibiotics. Therefore, it is important to conduct studies with the purpose of increasing eradication rates in such countries. This has prompted studies on probiotics administered in addition to standard therapy protocols. The strain and the dose of probiotics and the duration of use have appeared as new concerns in previous studies. The results of these studies are not comparable due to the fact that each study has utilized different strains and different methods.

The studies in children suggested an eradication rate of 90% using *L. acidophilus*, *L. rhamnosus*, *L. bulgaricus*, *L. casei*, and *B. infantis* strains,²¹ and Wang et al¹⁶

Table 2 - Complaints of patients during treatment as found in a study on *Helicobacter pylori* eradication in Turkey.

Variables	Group 1				Group 2			
	Days, n (%)							
	0	7th	14th	28th	0	7th	14th	28th
Abdominal pain	86 (25.0)	38 (11.0)	24 (7.0)	17 (5.0)	77 (21.0)	44 (12.0)	40 (10.0)	18 (5.0)
Nausea	51 (15.0)	20 (6.0)	20 (6.0)	10 (3.0)	48 (12.0)	18 (5.0)	18 (5.0)	7 (2.0)
Vomiting	24 (7.0)	3 (1.0)	3 (1.0)	0 (0.0)	3 (8.0)	2 (2.0)	7 (2.0)	0 (0.0)
Constipation	24 (7.0)	20 (6.0)	6 (2.0)	13 (4.0)	25 (7.0)	11 (3.0)	11 (3.0)	2 (2.0)
Belching	44 (13.0)	24 (7.0)	24 (7.0)	13 (4.0)	62 (14.0)	33 (9.0)	33 (9.0)	14 (4.0)
Taste problems	41 (12.0)	31 (9.0)	34 (10.0)	13 (4.0)	37 (10.0)	33 (9.0)	40 (11.0)	25 (7.0)
Lack of appetite	65 (19.0)	41 (12.0)	34 (10.0)	24 (7.0)	59 (16.0)	48 (13.0)	37 (10.0)	25 (7.0)
Diarrhea	3 (1.0)	10 (3.0)	3 (1.0)	0 (0.0)	14 (4.0)	11 (3.0)	7 (2.0)	3 (1.0)

reported an 83.7% eradication rate using *L. acidophilus*, and *B. bifidum* strains, and this rate was found to be significantly higher compared with standard triple therapy. In another study, Dinleyici et al²² reported that *Saccharomyces boulardii* (*S. boulardii*) improves compliance, decreases side effects, and moderately increases the eradication rate of *H. pylori*. Goldman et al¹⁸ reported no positive effect on the eradication rate using *B. animalis*, and *L. casei* strains. In the study by Hurduduc et al²³ using the *S. boulardii* strain, probiotics showed no effect on the eradication rate, but did show beneficial health effects. In the present study, the eradication rate was 68.9% in group one, and 66.6% in group 2, suggesting that probiotics had no effect on the eradication rate.

Probiotics are still used in daily practice, not for the purpose of increasing eradication rates, but to limit side effects, and to make use of their beneficial effects against drug intolerance. In one study,²⁴ the use of a probiotic formula (*L. plantarum*, *L. reuteri*, *L. casei* subsp. *rhamnosus*, *B. infantis*, *B. longum*, *L. salivarius*, *L. acidophilus*, *Streptococcus thermophilus*, and *L. sporogenes*) found a significant decrease in side effects, such as epigastric pain, nausea, vomiting, and diarrhea. Another study using *L. rhamnosus* GG did not report any beneficial effects.¹³ Similarly, Szajewska et al²⁵ did not find any difference in terms of eradication rate and side effects using *L. GG*.

There was no significant difference between the groups in the current study, and the low eradication rate may be associated with high antibiotic resistance in Turkey.

The limitations of the current study were: 1) *H. pylori* culture, antibiotic susceptibility, and drug resistance were not performed; 2) only the presence or absence of side effects (for example, abdominal pain, nausea, vomiting, constipation, belching, taste problems, lack of appetite, and diarrhea) were considered without

severity of the symptoms; and 3) the sample size of patients was relatively small.

In conclusion, the combination of probiotic strains of *L. casei* 2401, *L. acidophilus* 2027, and *B. lactis* 2211 did not have any additive effect on *H. pylori* eradication rate, and did not lessen the side effects of the standard triple therapy. A new large randomized controlled trial is needed to clearly understand the clinical efficacy of this probiotic combination with standard triple therapy. Whether other probiotic strains have beneficial effects also needs to be substantiated in further randomized trials.

Acknowledgment. The authors gratefully acknowledge Ayca E. Kuybula for the statistical analysis, and Caroline J. Walker for English language editing.

References

1. Lionetti E, Francavilla R, Castellazzi AM, Arrigo T, Labò E, Leonardi S, et al. Probiotics and *Helicobacter pylori* infection in children. *J Biol Regul Homeost Agents* 2012; 26 (Supp 1): S69-S76.
2. Shiotani A, Cen P, Graham DY. Eradication of gastric cancer is now both possible and practical. *Semin Cancer Biol* 2013; 6: 492-501.
3. Wang F, Meng W, Wang B, Qiao L. *Helicobacter pylori*-induced gastric inflammation and gastric cancer. *Cancer Lett* 2014; 10: 196-202.
4. Akcam M, Elmas O, Yilmaz A, Çağlar S, Artan R, Gelen T et al. Myeloperoxidase, xanthine oxidase and superoxide dismutase in the gastric mucosa of *helicobacter pylori* positive and negative pediatric patients. *Mol Cell Biochem* 2006; 290: 125-130.
5. Papastergiou V, Georgopoulos SD, Karatapanis S. Treatment of *Helicobacter pylori* infection: Past, present and future. *World J Gastrointest Pathophysiol* 2014; 5: 392-399.
6. Montes M, Villalon FN, Eizaguirre FJ, Delgado M, Muñoz-Seca IM, Fernández-Reyes M, et al. *Helicobacter pylori* infection in children. Antimicrobial resistance and treatment response. *Helicobacter* 2014; 10.1111/hel.12187.
7. Boltin D, Ben-Zvi H, Perets TT, Kamenetsky Z, Samra Z, Dickman R, et al. Trends in secondary antibiotic resistance of *Helicobacter pylori* from 2007 to 2014: Has the Tide Turned? *J Clin Microbiol* 2015; 53: 522-527.

8. Hasan SR, Vahid V, Reza PM, Roham SR. Short-duration furazolidone therapy in combination with amoxicillin, bismuth subcitrate, and omeprazole for eradication of *Helicobacter pylori*. *Saudi J Gastroenterol* 2010; 16: 14-18.
9. Mehri N, Kambiz E, Ahmad K, Fatemeh F, Farzaneh M, Hossein FG, et al. The efficacy of a 1-week triple therapy for eradication of *Helicobacter pylori* infection in children. *Arab J Gastroenterol* 2011; 12: 37-39.
10. Misiewicz JJ. Management of *Helicobacter pylori* related disorders. *Eur J Gastroenterol Hepatol* 2012; 9: 17-20.
11. Iwańczak B, Francavailla R. *Helicobacter pylori* infection in pediatrics. *Helicobacter* 2014; 19: 46-51.
12. Pacifico L, Osborn JF, Bonci E, Romaggioli S, Baldini R, Chiesa C. Probiotics for the treatment of *Helicobacter pylori* infection in children. *World J Gastroenterol* 2014; 20: 673-683.
13. Padilla Ruiz M, Fernández Aguiar ME, Arce Nuñez M, Polo Amorín R. [Lactobacillus rhamnosus GG supplementation to reduce side-effects of anti-*Helicobacter pylori* treatment]. *Rev Gastroenterol Peru* 2013; 33: 121-130. Spanish
14. Sabbi T. Short review about *Helicobacter pylori* infection in pediatric age: epidemiological and clinical findings, diagnosis, therapy and role of probiotics. *Pediatr Med Chir* 2011; 33: 221-226.
15. Li S, Huang XL, Sui JZ, Chen SY, Xie YT, Deng Y, et al. Meta-analysis of randomized controlled trials on the efficacy of probiotics in *Helicobacter pylori* eradication therapy in children. *Eur J Pediatr* 2014; 173: 153-161.
16. Wang YH, Huang Y. Effect of *Lactobacillus acidophilus* and *Bifidobacterium bifidum* supplementation to standard triple therapy on *Helicobacter pylori* eradication and dynamic changes in intestinal flora. *World J Microbiol Biotechnol* 2014; 30: 847-853.
17. Tepes B, O'Connor A, Gisbert JP, O'Morain C. Treatment of *Helicobacter pylori* infection 2012. *Helicobacter* 2012; 17: 36-42.
18. Goldman CG, Barrado DA, Balcarce N, Rua EC, Oshiro M, Calcagno ML, et al. Effect of a probiotic food as an adjuvant to triple therapy for eradication of *Helicobacter pylori* infection in children. *Nutrition* 2006; 22: 984-988.
19. He JD, Liu L, Zhu YJ. [Ten-day sequential therapy for *Helicobacter pylori* eradication in children: a systematic review of randomized controlled trials]. *Zhonghua Yi Xue Za Zhi* 2013; 26: 3500-3505. Chinese
20. Federico A, Gravina AG, Miranda A, Loguercio C, Romano M. Eradication of *Helicobacter pylori* infection: which regimen first? *World J Gastroenterol* 2014; 2: 665-672.
21. Ahmad K, Fatemeh F, Mehri N, Maryam S. Probiotics for the treatment of pediatric *Helicobacter pylori* infection: a randomized double blind clinical trial. *Iran J Pediatr* 2013; 23: 79-84.
22. Dinleyici EC, Kara A, Ozen M, Vandenplas Y. *Saccharomyces boulardii* CNCM I-745 in different clinical conditions. *Expert Opin Biol Ther* 2014; 14: 1593-1609.
23. Hurduc V, Plesca D, Dragomir D, Sajin M, Vandenplas Y. A randomized, open trial evaluating the effect of *Saccharomyces boulardii* on the eradication rate of *Helicobacter pylori* infection in children. *Acta Paediatr* 2009; 98: 127-131.
24. Tolone S, Pellino V, Vitaliti G, Lanzafame A, Tolone C. Evaluation of *Helicobacter Pylori* eradication in pediatric patients by triple therapy plus lactoferrin and probiotics compared to triple therapy alone. *Ital J Pediatr* 2012; 38: 63.
25. Szajewska H, Albrecht P, Topczewska-Cabanek A. Randomized, double-blind, placebo-controlled trial: effect of *lactobacillus GG* supplementation on *Helicobacter pylori* eradication rates and side effects during treatment in children. *J Pediatr Gastroenterol Nutr* 2009; 48: 431-436.

Related Articles

Bin Mohanna MA, Al-Zubairi LM, Sallam AK. Prevalence of *Helicobacter pylori* and parasites in symptomatic children examined for *Helicobacter pylori* antibodies, antigens, and parasites in Yemen. *Saudi Med J* 2014 ;35:1408-11.

Pandya HB, Patel JS, Agravat HH, Patel SB, Thakkar MC. Identification of *Helicobacter pylori* by different conventional staining techniques and its comparison with polymerase chain reaction. *Saudi Med J* 2013; 34: 942-948.

Al-Khattaf AS. *Helicobacter pylori* virulence markers in gastroduodenal disorders. Detection of cytotoxin-associated gene A and vacuolating cytotoxin-associated gene A genes in Saudi patients. *Saudi Med J* 2012; 33: 716-721.