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# Can *Saccharomyces boulardii* treat and eradicate *Helicobacter pylori* among children instead of bismuth?

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## ABSTRACT

**Aim**: The objective of this study is to compare the use of *Saccharomyces boulardii* (*S. boulardii*) in eradicating *Helicobacter pylori* (*H. pylori*) in children as an alternative to bismuth, which has a limited scope of application due to its side effects.

**Material and Method**: Included in the study were 220 pediatric patients with symptomatic *H. pylori* gastritis. The patients were randomized into three treatment groups. Patients who received bismuth or *S. boulardii* in addition to the standard triple therapy for 14 days were compared with the control group who received only triple therapy.

**Results**: Analysis of the bismuth, *S. boulardii*, and control groups' treatment success showed that the *H. pylori* eradication rate was highest among study participants who received bismuth (95.2%), followed by patients who received *S. boulardii* (92.4%). The most frequent side effects were observed in the patient group that received bismuth (17.5%).

**Conclusion**: Although bismuth continues to be successful in eradicating *H. pylori*, alternative treatment protocols are necessary because of its side effects and limited use in pediatric patients. *S. boulardii* can be administered instead when bismuth can not serve as alternative due to its side effects.

**Keywords**: Eradication, Helicobacter, *S. boulardii*, side effects, triple therapy

## INTRODUCTION

*Helicobacter pylori* (*H. pylori*) may lead to superficial gastritis, peptic ulcer, mucosa-associated lymphoid tissue (MALT) lymphoma, and gastric adenocarcinoma (1). While the worldwide rate of *H. pylori*–infected individuals is 50%, the corresponding rate in Turkey is 65% (2). Moreover, *H. pylori*'s prevalence rate has been reported at around 40% among children with symptoms (3). Various diagnostic methods and treatment models have been developed for the early detection of *H. pylori* infection and the prevention of chronic complications resulting from the infection. A study conducted in Turkey reported that *H. pylori*'s antimicrobial resistance to clarithromycin was 24.86%, while its resistance to metronidazole, levoflaxacin, amoxicillin, and tetracycline was 33.75%, 23.77%, 0.97%, and 3.51%, respectively (4). In another study carried out in Turkey, H pylori resistance to clarithromycin and fluoroquinolones were 27% and 15%, respectively (5). Since 2000, the success rate of triple therapy has fallen below 80% (50–79%) due to *H. pylori* resistance to metronidazole and clarithromycin (6). In cases of robust antibiotic resistance, bismuth, PPI, and two antibiotics are recommended. If bismuth is not available, quadruple treatments of three antibiotics and PPI are advised.

Recently, *H. pylori* eradication failure has increased to 20% in quadruple treatments comprising bismuth (7). Since bismuth treatments have high side effects, alternative treatment methods are necessary. Recently, probiotic treatment alternatives are receiving emphasis to improve both treatment compliance and success. *Saccharomyces boulardii* (*S. boulardii*)'s mechanism of action in the eradication of *H. pylori* is not clear yet. It is thought that it prevents the colonization of *H. pylori* and other bacteria and it strengthens the mucosal defense (8). Moreover, it is claimed that it can increase patient compliance due to fewer side effects relative to bismuth. There is not enough research on this subject. Randomized controlled studies in pediatric patients are insufficient in particular. This study compares the treatment efficacy and side effects of bismuth and *S. boulardii* in children with symptomatic *H. pylori* gastritis with the control group.

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In this study, it was aimed to compare the use of *S. boulardii* in the eradication of *H. pylori* in children instead of bismuth, which has a limited application area due to its side effects.

## MATERIAL AND METHOD

The study was carried out with the permission of Taksim Training and Researches Hospital Ethics Committee (Date: 25.12.2019, Decision No: 177). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. The patients, or their parents or guardians, signed written statements of informed consent.

This research involved a prospective, parallel design, single-center study. It included 220 pediatric patients aged between 12 and 18 years old who applied to the hospital's pediatric gastroenterology outpatient clinic due to chronic dyspeptic complaints. All patients had dyspeptic complaints for at least 3 months and received neither diagnosis nor treatment for *H. pylori* previously. A total of 26 patients were taken out (i.e., 8 patients with drug allergies and 18 patients lost to follow-up). Patients were randomly assigned to three treatment groups by a physician who had no involvement with the study. Each patient was assigned a number. The patients were then followed up on treatment and side effects based on these numbers.

Patients with upper gastrointestinal bleeding, patients who had undergone stomach or intestinal surgery, patients with a history of antibiotic or probiotic use in the previous three months, patients taking aspirin, and patients suffering from bleeding-coagulation disorders were excluded from the study.

Upper-gastrointestinal-system endoscopy and biopsies were performed on all patients. Biopsy samples were evaluated for *H. pylori* according to Sydney classification (0=absent, 1=mild, 2=moderate, 3=severe) (9). Patients' *H. pylori* eradication rates were analyzed via a stool antigen test four to six weeks after treatment. Stool antigen test is a qualitative immunochromatography test (CERTEST BIOTEC SL, Spain).

According to the most recently published ESPGHAN/NASPGHAN guidelines, patients underwent a treatment period of 14 days, during which they were randomly assigned to treatment groups. Treatment for the control group included pantoprazole (1mg per kg per day) (max. 40 mg) twice a day, amoxicillin (50 mg per kg per day, twice a day), and metronidazole (15 mg per kg per day, twice a day) (10). The two other groups received bismuth subsalicylate or *S. boulardii* treatments, for the comparison of *H. pylori* eradication across the three groups. These treatments were administered simultaneously with the standard antibiotic treatment. The bismuth treatment group consisted of 63 children, whereas the *S. boulardii* group and the control group had 66 and 65 children, respectively (**Figure 1**). For the bismuth subsalicylate treatment, four 262 mg tablets were administered daily (Bizmopen, 262 mg tab, manufactured by Dincsa İlac san. ve tic. A.S., Istanbul, Turkey). Bismuth subsalicylate was prefered over other bismuth salts due to its lower absorption within gastrointestinal system and weaker interaction with patient diet. For the *S. boulardii* treatment, two 250 mg *Saccharomyces boulardii* tablets (Reflor, manufactured by Sanofi-Synthelabo Ilac A.S., Istanbul, Turkey) were administered for 14 days.

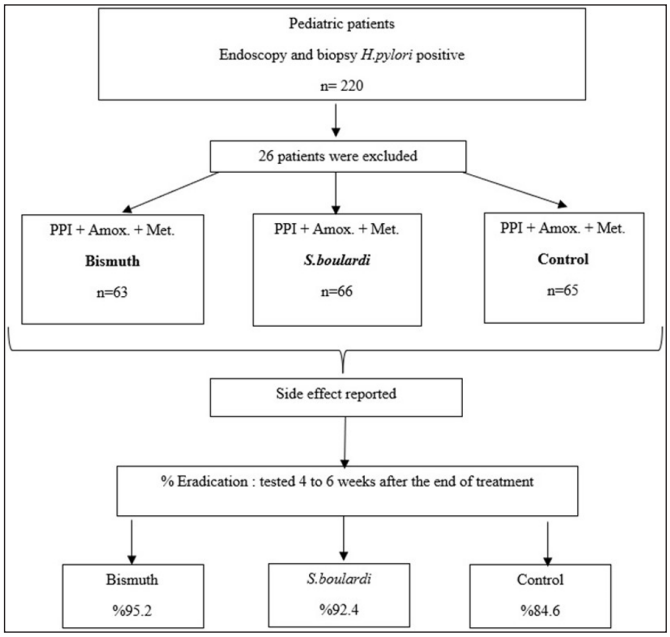


**Figure 1.** Flow chart of the current study

Treatment side effects were analyzed by an independent and blinded pediatrician during the 1st and 2nd weeks of treatment with open-ended questions and side-effect diaries of the patients.

### Statistical Analysis

Statistical analysis was performed with SPSS software for Windows version 22.0 (SPSS Inc., Chicago, IL, USA). The normality condition in quantitative variables' was checked with a Kolmogorov-Smirnov test. Kruskal-Wallis H test was conducted to examine whether any difference in quantitative variables had occurred between the independent groups. The independence hypothesis between qualitative variables was tested using chi-square analysis. Since the quantitative variables did not resemble a normal distribution, their descriptive statistics were explained with the median (25th to 75th percentiles), and the descriptive statistics of the qualitative variables were expressed in terms of frequency (%). P values below 0.05 ($p<0.05$) were considered statistically significant.

## RESULTS

**Table 1** compares the control, bismuth, and *S. boulardii* groups in terms of age, gender, family history, *H. pylori* activity, and complaint duration. The three treatment groups did not differ from one another with respect to age, family history, gender, *H. pylori* activity, or complaint duration (p>0.05).

**Table 1.** Comparison of the general characteristics of the treatment groups

| | Treatment | | | p |
|---|---|---|---|---|
| | Control | Bismuth* | *S. boulardii** | |
| Age (year) | 14 (13-16) | 15 (14-16) | 14.50 (13-16) | 0.745[a] |
| Family history | | | | |
| Yes | 35 (53.8) | 31 (49.2) | 35 (53) | 0.855[b] |
| No | 30 (46.2) | 32 (50.8) | 31 (47) | |
| Gender | | | | |
| Male | 33 (50.8) | 22 (34.9) | 30 (45.5) | 0.185[b] |
| Female | 32 (49.2) | 41 (65.1) | 36 (54.5) | |
| *H. pylori* activity | 2 (1-2) | 2 (1-2) | 2 (1-2) | 0.947[a] |
| Complaint duration (month) | 10 (7-12) | 10 (8-12) | 10 (9-13) | 0.199[a] |

a: Kruskal Wallis H test ; b: Pearson Chi Square test, *: In addition to standard triple treatment

**Table 2** shows the frequency and percentage distributions of the study's endoscopic findings by treatment group. The most common endoscopic finding across all three treatment groups was antral hyperemia. No statistically significant difference in endoscopic findings was observed between treatment groups (p=0.960). Among the control, bismuth, and *S. boulardii* groups, the most common pathological diagnosis was antral gastritis. A comparison of the treatment groups based on biopsy diagnosis revealed that the groups shared similar diagnosis distributions, with no difference between them (p=0.175).

**Table 2.** Comparison of endoscopic findings and biopsy diagnosis according to treatment groups

| | Treatment | | | p |
|---|---|---|---|---|
| | Control | Bismuth | *S. boulardii* | |
| Endoscopic Findings | | | | 0.966[c] |
| Normal | 8 (12.3) | 4 (6.3) | 4 (6.1) | |
| Atrophy | 3 (4.6) | 2 (3.2) | 3 (4.5) | |
| Erosion | 5 (7.7) | 4 (6.3) | 5 (7.6) | |
| Hyperemia | 33 (50.8) | 38 (60.3) | 41 (62.1) | |
| Nodularity | 13 (20) | 13 (20.6) | 11 (16.7) | |
| Ulcer | 3 (4.6) | 2 (3.2) | 2 (3) | |
| Biopsy diagnosis | | | | 0.175[b] |
| Antral gastritis | 30 (46.2) | 31 (49.2) | 42 (63.6) | |
| Chronic gastritis | 15 (23.1) | 9 (14.3) | 9 (13.6) | |
| Pangastrit | 20 (30.8) | 23 (36.5) | 15 (22.7) | |

b: Pearson Chi Square test ; c: Fisher-Freeman-Halton test

As **Table 3** shows, an evaluation of the control, bismuth, and *S. boulardii* treatment groups' *H. pylori* stool antigen tests pointed out that *H. pylori* eradication success was highest among the bismuth group at 95.2%. The patients who received *S. boulardii* treatment followed, with a 92.4% eradication rate, and the difference between these two groups was not statistically significant. Among the control group, the eradication rate was 84.6%. This rate is near the acceptable level recommended for *H. pylori* eradication.

**Table 3**. Comparison of eradication rates of treatment groups

| | | Treatment | | | p |
|---|---|---|---|---|---|
| | | Control | Bismuth | *S. boulardii* | |
| Stool antigen test | Negative | 55 (84.6) | 60 (95.2) | 61 (92.4) | 0.099[b] |
| | Pozitive | 10 (15.4) | 3 (4.8) | 5 (7.6) | |

b: Pearson Chi Square test

**Table 4** exhibits the frequency of side effects—such as headache, nausea, diarrhea, constipation, abdominal pain, and taste disturbances—across the treatment groups. While abdominal pain and taste disturbances were not present in the control group, headache and diarrhea were not reported in the *S. boulardii* group. A comparison of the treatment groups' side effects revealed that the most common side effects were prevalent in the bismuth group (17.5%). However, the three treatment groups experienced a similar frequency of side effects, and no statistically significant difference was observed (p=0.123).

**Table 4.** Distribution of side effects by treatment groups

| | Treatment | | | p |
|---|---|---|---|---|
| | Control | Bismuth | *S. boulardii* | |
| Side effects | | | | 0.123[b] |
| Headache | 1 (1.5) | 2 (3.2) | 0 (0) | |
| Nausea | 2 (3.1) | 2 (3.2) | 1 (1.5) | |
| Diarrhea | 2 (3.1) | 2 (3.2) | 0 (0) | |
| Constipation | 2 (3.1) | 1 (1.6) | 1 (1.5) | |
| Abdominal pain | 0 (0) | 2 (3.2) | 1 (1.5) | |
| Taste disturbance | 0 (0) | 2 (3.2) | 1 (1.5) | |

b: Pearson Chi Square test

## DISCUSSION

*H. pylori* remains a serious public health problem due to its high prevalence in the population, and it continues to increase the number of symptomatic pediatric patients as well as antibiotic resistance (11,12). Treatment regimens containing bismuth are emphasized because of rising eradication rates. In a pediatric study carried out in Turkey, a bismuth containing sequential treatment has achieved *H. pylori* eradication rate over 90% (13). Reports by the Fifth National China Consensus and the Maastricht-V Consensus have also recommended quadruple therapy containing bismuth. Nevertheless,

bismuth is not preferable because of its side effects and its unavailability in some countries (14,15). Limitations also affect the use of bismuth in pediatric patients. Therefore, a search for alternative *H. pylori* eradication treatment in pediatric patients is ongoing.

Upper gastrointestinal endoscopy and biopsy remain the gold standard in diagnosing *H. pylori*. An antral nodularity appearance in endoscopy is associated with *H. pylori* (16). Antral nodularity (93%) was the most common endoscopy finding in a study on children less than 20 years of age. Moreover, other endoscopy findings related to *H. pylori* such as mucosal edema, diffuse rash, and antral hyperemia were also observed in these patients. It is acknowledged that *H. pylori* positive children may present various endoscopy findings besides antral nodularity (17). In our study, the most common endoscopic finding was antral hyperemia, followed by antral nodularity.

The most common method for evaluating *H. pylori* eradication success is the $^{13}C$ urea breath test or stool antigen test for *H. pylori* (18). In our study, an evaluation of the control, bismuth, and *S. boulardii* treatment groups' *H. pylori* eradication success via stool antigen tests identified the highest success rate in bismuth treatment (95.2%). Liu et al. (19) reported the eradication rate of quadruple therapy containing bismuth at 98.8%. The eradication rate for 10-day sequential treatment reached 92.4% in their study. In another pediatric study conducted in Turkey, the eradication rate with bismuth-containing quadruple therapy was 92% (13). We found the similar success rate among patients who received *S. boulardii* in our study. However, with sequential treatment, varying eradication rates have been reported in Asian countries. For instance, Korea has 81.9% eradication rates, China 82.6%, and Taiwan 90.5%. Researchers have associated these different eradication rates with poor patient compliance in sequential therapy. A recent study conducted in Taiwan showed that extending sequential therapy from 10 days to 14 days increased eradication rates by 3-4% (20). Therefore, we decided to prescribe a 14-day combined treatment for our patients. As a result, we detected an eradication rate of 84.6% for our patients in the control group. This rate is near the acceptable level recommended for *H. pylori* eradication.

Lee et al. (21) reported epigastric pain (23.6 %) and diarrhea (16.7%) as the most common side effects in a 14-day quadruple therapy containing bismuth. This rate was more common among the patient group who received bismuth, in parallel with our study. In our study, the rate of side effects was 17.5%, and nausea and abdominal pain were among the most frequent side effects. In conventional *H. pylori* eradication treatments, side effects are observed at a rate of 5–30%, which reduce treatment success. The frequency of side effects was 6.7% for patients who received quadruple bismuth treatment for 10 days, versus 11.7% for patients who received quadruple therapy containing bismuth for 14 days (22). In a study conducted on children in China, side effects were reported in 15.3% of patients whose treatments included bismuth (23). This situation affects treatment compliance and success. Therefore, the use of probiotics to increase eradication success among children with *H. pylori* gastritis is an important topic of discussion. Therefore, some studies have involved yeast as probiotics, such as *S. boulardii* (24). A study by Zhou et al. (25) found that the administration of *S. boulardii* decreased nausea, vomiting, diarrhea, and abdominal distention compared to the control group; however, no significant difference was detected between the two groups. Another study in children showed that *S. boulardii* increased treatment compliance by reducing diarrhea during eradication treatment. Furthermore, a slight increase was detected in the *H. pylori* eradication rate relative to the control group (26). Similarly, in our study, the side effects decreased, and the eradication rate increased compared to the control group. Unlike other studies, children receiving *S. boulardii* treatment and bismuth treatment were put into comparison. The eradication rate in children on *S. boulardii* treatment was close to those who received bismuth treatment.

In conclusion, the use of probiotics in the treatment of gastrointestinal problems has been popular in recent years. Probiotic bacteria and *S. boulardii* fungi have been used for *H. pylori* eradication in adult studies. Their positive contributions to treatment have been noted. Therefore, they may be used to increase eradication success, particularly among pediatric patients when bismuth is not a feasible option. With fewer side effects, *S. boulardii* increases treatment compliance and success for pediatric patients, a sensitive group that needs additional consideration for treatment. The most important limitation of this study is that a *H. pylori* culture could not be obtained. Moreover, antibiotic resistance could have been checked, and the treatment groups could have been randomized accordingly.

## ETHICAL DECLARATIONS

**Ethics Committee Approval**: The study was carried out with the permission of Taksim Training and Researches Hospital Ethics Committee (Date: 25.12.2019, Decision No: 177).

**Informed Consent**: All patients signed the free and informed consent form.

**Referee Evaluation Process**: Externally peer-reviewed.

**Conflict of Interest Statement**: The authors have no conflicts of interest to declare.

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**Author Contributions**: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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