The Efficacy of Pre-Treatment Proton Pump Inhibitors in the Eradication of *Helicobacter pylori*

Helicobacter pylori Eradikasyonunda Tedavi Öncesi Proton Pompa İnhibitörlerinin Etkinliği

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ABSTRACT

Objective: Proton pump inhibitors significantly reduce *Helicobacter pylori* colonization and provide recovery in its activity and inflammation. We investigated; the effects of eradication initiated 28 days after proton pump inhibitor treatment and eradication initiated simultaneously with proton pump inhibitor treatment, on treatment success rates of *Helicobacter pylori*.

Material and Methods: The study took place at our tertiary care hospital, where 42 patients in the study group were given oral lansoprazole treatment for 28 days followed by eradication treatment and 41 patients in the control group were given both treatments simultaneously. Eradication success was monitored using *Helicobacter pylori* polyclonal antigen stool tests.

Results: A total of 83 participants, aged between 8 and 18 years, tested positive for *Helicobacter pylori*. The mean age of the participants was 15.14 ± 2.01 years. The *Helicobacter pylori* cure rate was found to be 92.9% in the study group and 92.7% in the control group. There were no significant differences observed between the two groups in terms of eradicating *Helicobacter pylori* (p=0.976).

Conclusion: We found no significant differences in *Helicobacter pylori* treatment success rates with modified proton pump inhibitor usage in children.

Key Words: Esophagogastroduodenoscopy, Helicobacter pylori, Proton pump inhibitors, Treatment

ÖZ

Amaç: Proton pompa inhibitörleri *Helicobacter pylori* kolonizasyonunu önemli ölçüde azaltarak aktivitesinde ve inflamasyonda azalma sağlar. Proton pompası inhibitörü tedavisinden 28 gün sonra başlatılan eradikasyonun ve proton pompası inhibitörü tedavisiyle eş zamanlı başlatılan eradikasyonun *Helicobacter pylori* tedavi başarı oranlarına etkisini araştırdık.

Gereç ve Yöntemler: Araştırma, üçüncü basamak tedavi merkezi olan hastanemizde gerçekleştirildi; burada çalışma grubundaki 42 hastaya 28 gün boyunca oral lansoprazol tedavisi ve ardından eradikasyon tedavisi verildi, kontrol grubundaki 41 hastaya ise her iki tedavi aynı anda verildi. Eradikasyon başarısı *Helicobacter pylori* poliklonal antijen dışkı testi kullanılarak değerlendirildi.

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Ethics Committee Approval / *Etik Kurul Onayı*: This study was conducted in accordance with the Helsinki Declaration Principles. This research protocol was thoroughly examined and authorized by the Scientific Research Ethics Committee of Gülhane Training and Research Hospital, with approval number 2021-345 on September 23rd, 2021.

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Bulgular: Çalışmamıza yaşları 8 ile 18 arasında değişen ve *Helicobacter pylori* pozitif olan toplam 83 katılımcı dahil edildi. Katılımcıların ortalama yaşı 15.14±2.01'di. Helicobacter pylori iyileşme oranı çalışma grubunda %92.9, kontrol grubunda ise %92.7 olarak bulundu. *Helicobacter pylori*'nin eradikasyonu açısından iki grup arasında anlamlı bir fark gözlenmedi (p=0.976).

Sonuç: Çocuklarda modifiye proton pompa inhibitörü kullanımı ile *Helicobacter pylori* tedavisi başarı oranlarında anlamlı bir fark bulunamadı.

Anahtar Sözcükler: Özofagogastroduodenoskopi, *Helicobakter pylori*, Proton pompa inhibitörleri, Tedavi

INTRODUCTION

Helicobacter pylori (*H. pylori*) is a type of bacteria that has a spiral shape and is gram-negative and microaerophilic. It's prevalence varies depending on geographical location. It is found in more than 85% of people in areas with low socioeconomic status, and 30-40% of people in areas with high socioeconomic status (1). *H. pylori* is associated with gastrointestinal (GI) diseases, such as peptic ulcer disease, mucosa-associated lymphoid tissue lymphoma, and adenocarcinoma, as well as other diseases like growth and developmental retardation, iron-refractory iron deficiency anemia, and idiopathic thrombocytopenic purpura (2).

Based on the European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) guidelines, to diagnose *H. pylori* in children, a positive culture or the presence of *H. pylori* gastritis in a biopsy, as well as another positive test like a rapid urease test or polymerase chain reaction (PCR), is required (3).

The treatment for *H. pylori* typically involves proton pump inhibitors (PPIs), such as lansoprazole or esomeprazole, along with amoxicillin and clarithromycin, or PPIs, amoxicillin, and metronidazole (3). However, antibiotic resistance has become a problem, so new treatment protocols with different antibiotics have been developed for successful eradication (4,5). It is known that *H. pylori* has developed high resistance rates against conventional treatments in some populations, including Turkey (6-8). Therefore, the updated *H. pylori* guideline of ESPGHAN recommends using either a high dose of amoxicillin or the quadruple therapy protocol containing bismuth in health centers where antibiotic susceptibility tests are not available (3).

The mechanism behind the repression of *H. pylori* and the changes in gastric inflammation are not yet entirely clear. However, it is believed that changes in gastric pH caused by PPIs prevent *H. pylori* from growing and surviving (9). Acid suppression therapy performed with PPIs is known to change the anatomic distribution and strength of *H. pylori* in patients with gastritis (10). PPIs reduce the intensity of *H. pylori* in both the antrum and corpus, which can help to alleviate gastritis activity and chronic inflammation (11). PPIs affects the density and distribution of *H. pylori* (3,10). We still do not know if the timing of PPIs treatment has an impact on *H. pylori* eradication.

This study aims to investigate whether applying antibiotic treatment after 28 days of using PPIs increases or decreases treatment success in *H. pylori* eradication treatment.

MATERIALS and METHODS

Our study aimed to include pediatric patients between the ages of 8 and 18, who visited the pediatric gastroenterology outpatient clinic at Gülhane Research and Training Hospital between January 2022 and July 2022 and were diagnosed with *H. pylori* infection after undergoing upper GI endoscopy. Prior to the procedure, all patients and their parents signed an informed consent form. The reason for selecting children at or over the age of 8 was that the treatment protocol for those below the age of 8 differs based on treatment guidelines. The patients diagnosed with *H. pylori* are treated under the guidelines of the ESPGHAN (3).

An experienced pediatric gastroenterologist performed all upper gastrointestinal (GI) endoscopies using an Olympus® gastroscope that had an outer diameter of 9.2 mm. The endoscopies were conducted in the operating room while the patient was under deep sedation. Biopsy samples were obtained from the recommended sites during the procedure, following the guidelines provided by the ESPGHAN (3). A single pathologist analyzed the biopsy samples based on the Sydney System, which assesses chronic inflammation, activity, atrophy, intestinal metaplasia, and the presence or absence of *H. pylori* (12).

The study involved 83 patients who were diagnosed with *H. pylori* and tested positive for it using the polyclonal antigen stool test, rapid urease test, and biopsy materials. Patients with dyspeptic complaints underwent the polyclonal antigen stool test first, followed by the other two tests using biopsy materials obtained during endoscopy, to confirm the histopathological diagnosis of *H. pylori*. Once the diagnosis was confirmed, the planned treatments were initiated. All the patients attended their follow-up sessions regularly, and none of them were excluded from the study. The patients were assigned a number using a web-based computer system and included in the study according to the order they applied to the outpatient clinic for the evaluation of pathology results. Forty-two patients were assigned to the study group, where they were given lansoprazole (1 mg/kg/day) for four weeks. A 4-week pretreatment period was scheduled for the study group based on a previous adult study demonstrating the effectiveness of PPIs in improving elimination success (13). Bismuth base therapy was prescribed to all patients due to common amoxicillin and clarithromycin resistance. From the first day of the fifth week after the biopsy was performed, they were given tetracycline (25-50 mg/kg/

day), bismuth (<10 years of age: 4x262 mg, >10 years of age: 4x524 mg), and metronidazole (30 mg/kg/day) for two weeks. Forty-one patients were assigned to the control group (standard timing group), where they were given antibiotic eradication treatment by being given lansoprazole (1 mg/kg/day, orally), tetracycline (25-50 mg/kg/day), bismuth (<10 years of age: 4x262 mg, >10 years of age: 4x524 mg), and metronidazole (30 mg/kg/day) simultaneously for two weeks. Afterward, the treatment was completed. The eradication treatments were initiated at the doses mentioned in the ESPGHAN guideline (3). After eight weeks of cessation of eradication, the response to the *H. pylori* eradication treatment was evaluated using the *H. pylori* polyclonal antigen stool test, which is a non-invasive method recommended in the ESPGHAN guideline to assess the success of eradication. The patients were not given written information about possible drug side effects but were asked if they experienced any issues during their treatment that could lead to complaints.

This research protocol was thoroughly examined and authorized by the Scientific Research Ethics Committee of Gülhane Training and Research Hospital, with approval number 2021-345 on September 23rd, 2021. The research was conducted in compliance with the principles outlined in the Helsinki Declaration.

Statistical analysis

The data were processed and analyzed with the Statistical Package for the Social Sciences (SPSS) for Windows 21.0 package software. In the presentation of the descriptive statistics, frequency and percentages are used for the discrete variables, while mean ± standard deviation (SD) values are used for the continuous variables. Pearson's chi-squared (χ^2) test was used in comparing the discrete variables, while the Crosstabs procedure was used in comparing two different variables in the study and control groups. The correlation between the variables was evaluated with the Spearman's correlation coefficient. $p<0.050$ was acknowledged as statistically significant.

A power analysis was conducted to determine the necessary sample size for the study. The G*Power 3.1 program was used to calculate the statistical power of the test. Based on a similar study published by Janssen et al. (14), where the odds ratio of eradication rates was 0.201, and the actual α was 0.020. To achieve a statistical power of at least 80%, the study required a minimum of 70 participants, with 35 people in each group, at a significance level of 5%. Fortunately, we could include more participants than the minimum number required.

RESULTS

The study involved 83 patients aged between 8 to 18 years who had been diagnosed with *H. pylori* through histopathology (Figure 1). None of the patients had been admitted to the hospital before due to dyspepsia. Out of the 83 patients, 54 (65.1%) were female and 29 (34.9%) were male. Heartburn (74.7%), abdominal pain (67.5%), nausea (30.1%), eructation (8.4%), loss of appetite (6%), and bad breath (2.4%) were the most common symptoms that led to upper GI endoscopy. All patients had antral gastritis or pangastritis, but none of them had a peptic ulcer as confirmed by the endoscopy results (Table I). All patients were given *H. pylori* eradication treatment, and 92.8% of them (77 patients) were successfully treated (Table II). However, six patients who did not respond to the treatment still had the same complaints after it. The parents confirmed that all patients had taken their medications as prescribed, on time and in full. None of the patients developed any side effects from the treatment, and the treatment process was not terminated for any reason. The biopsy materials obtained

Table I: Upper gastrointestinal endoscopy results of the participants

Endoscopy result	Total*	Study group*	Control group*
Antral gastritis	35 (42.2)	12 (28.6)	24 (58.5)
Antral gastritis + Esophagitis	1 (1.2)		
Pangastritis	42 (50.6)	30 (71.4)	17 (41.5)
Pangastritis + biliary reflux	5 (6)		
Total	83	42	41

***:** *n(%)*

Table II: Efficacy of treatment modalities on cure rates

Treatment	Result*			p*
	Cure	Positive	Total	
Study group	39 (92.9)	3 (7.1)	42	0.976
Control group	38 (92.7)	3 (7.3)	41	
Total	77 (92.8)	6 (7.2)	83	

***** *Pearson's chi-squared (χ^2) test*

Table III: The correlation of the eradication results to the activity, colonization, and inflammation of *Helicobacter pylori*

	Result	
	Correlation	p*
H. pylori activity	0.054	0.627
H. pylori inflammation	0.088	0.429
H. pylori colonization	0.173	0.118

***Spearman's correlation*

Table IV: Results accompanying or not accompanying esophagitis, pangastritis, and biliary reflux

Endoscopy result	Cured Ones*	Positive*	χ^2	p
Antral Gastritis	32 (91.4)	3 (8.6)	0.116	0.734
Pangastritis	40 (95.2)	2 (4.8)	0.116	0.734
Antral gastritis + Esophagitis	1 (100)	0 (0)	0.079	0.779
Pangastritis + biliary reflux	4 (80)	1 (20)	1.294	0.255

***:** *n(%),* ***χ^2:** *Pearson's chi-squared test*

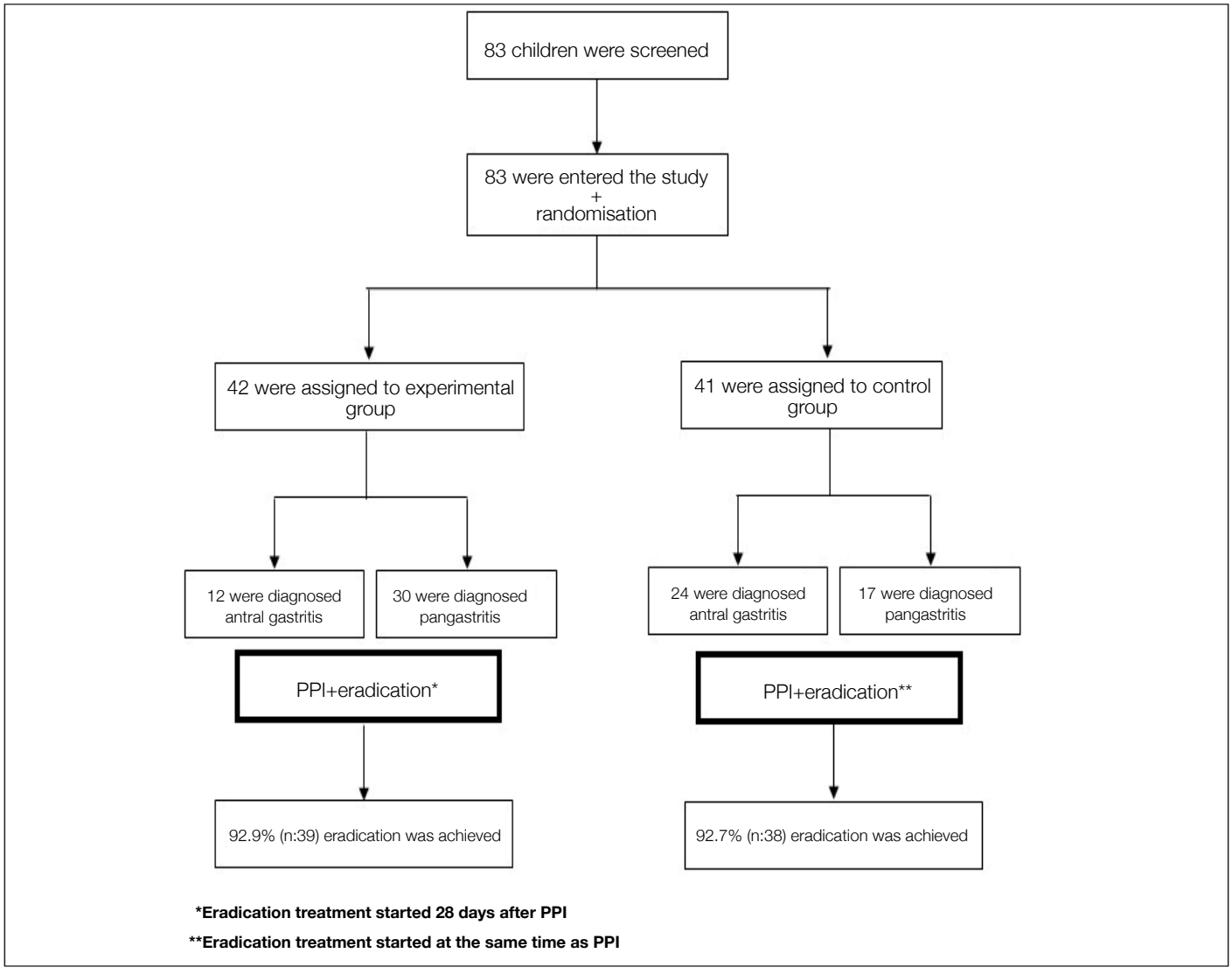

Figure 1: Determination of eradication ratio study group and control group.

during endoscopy were analyzed and evaluated based on the advanced Sydney System, and there was no statistically significant correlation between the activity, inflammation rate, and colonization intensity of *H. pylori* and the success of the eradication process (Table III). The success of eradication was not correlated with only antral gastritis or pangastritis, or the presence of esophagitis or biliary reflux along with antral gastritis or pangastritis (Table IV).

DISCUSSION

To successfully eradicate *H. pylori*, it is crucial to complete the treatment as prescribed and on time. Patients and their families should be informed about the potential side effects of the medications and educated about the treatment process. Extending the treatment plan from 7-10 days to 14 days could increase the likelihood of success (3,15). Additionally, other factors can affect the success of the treatment. In this study, we analyzed the success rates of eradication treatment for patients who tested positive for *H. pylori*. We compared the outcomes of patients who took lansoprazole at the same time as the treatment to those who took it after using lansoprazole for 28 days.

There have been various reasons reported for the failure of treatment for *H. pylori*. Some of these include the patient not following the treatment as instructed, resistance to antibiotics, and excessive bacterial load (3,16). However, it is unfortunate that antibiotic susceptibility tests are often expensive and not available in many health centers. At our institution, we use histopathological and rapid urease tests to check for positive results. Based on the test results, we diagnose the patient and recommend the same treatment as advised in the guideline (3).

PPIs are an essential component of every *H. pylori* eradication therapy, as they increase the success rate of the treatment by creating a suitable pH level for the antibiotics used to eradicate the bacteria. Although they have a weak eradication potential

on their own, PPIs contribute positively to the success of the treatment by creating a synergistic effect when used in combination with antibiotics (9). PPIs can be highly effective when taken at the right times, even in high doses when gastric acid levels are high, or when taken once every 12 hours instead of 24 hours (15). Jeong Gong et al. (10) have reported that PPIs treatment significantly reduces colonization in the antrum and leads to significant recovery in terms of *H. pylori* activity and inflammation. According to Labenz et al., (17) *H. pylori* cannot increase its colonization when gastric acid levels are low and is rendered susceptible to amoxicillin and clarithromycin with acid suppression, resulting in an increased treatment success rate. In contrast to previous studies that focused on the aftermath of the treatment, we examined the correlation between the activation, inflammation degree, and colonization intensity of *H. pylori* in the pre-treatment period and the eradication success results. Our findings indicate that there is no statistically significant correlation between these factors and the success of the treatment. In our pursuit to improve the success of *H. pylori* treatment, we examined changes in treatment outcomes by altering PPIs usage. Our findings showed that the treatment success rate was 92.7% (n=38) in the study group and 92.9% (n=39) in the control group. Therefore, we concluded that there was no statistically significant difference between the two treatment modalities (p=0.976). Similarly, a meta-analysis conducted by Kuang et al. (18) also found that pre-treatment use of PPIs did not impact the success of *H. pylori* eradication. Celebi et al.(19) reported that a lansoprazole-based regimen is more influenced by CYP2C19 in comparison to esomeprazole and rabeprazole. They found that esomeprazole had the highest success rate in achieving an intragastric pH value higher than 4 (19). In our study, we chosed to use lansoprazole for both the study and control groups due to easier access. We set the lansoprazole treatment as 1 mg/kg/day for both groups to avoid any variations. Therefore, we attribute the eradication success rate in our study to the antibiotherapy rather than lansoprazole. While PPIs can reduce *H pylori*'s density and quickly alleviate dyspeptic complaints in adult studies, we believe that altering the treatment time or increasing the dosage may not be significant in terms of eradicating the bacteria in children. None of our patients in the study group experienced an increase in complaints while taking lansoprazole. Complaints regressed in all patients in both study and control groups while taking lansoprazole.

Although Sydney scoring is an important method for evaluating inflammation severity, *H. pylori* colonization intensity, and atrophy presence through microscopic analysis, our study found that microscopic findings did not significantly affect the eradication rate (12). Szőke et al. (20) also found that biliary reflux did not intensify endoscopy results or lead to pre-malignant lesions in *H. pylori*-positive patients. Similarly, Agin et al. (21) reported that biliary reflux did not affect the presence or intensity of *H. pylori*. Our studies showed that biliary reflux, which occurs with antral gastritis or pangastritis, did not significantly impact *H. pylori* eradication treatment success. While we recognize that the compared scenarios are different, we observed that biliary reflux does not positively contribute to *H. pylori* intensity nor have a negative effect on *H. pylori* eradication.

It's important to note a few limitations in this study. Firstly, due to the way the biopsy samples were grouped as "antrum-corpus", it was not possible to make an anatomical comparison. Secondly, gender discrimination was not made due to the limited number of patients compared to adults. Lastly, all patients received bismuth-containing treatment as there was no detection of antibiotic resistance in our hospital.

Our research has revealed that administering PPIs either before or concurrently with antibiotics to pediatric patients aged 8-18 years may not have a significant impact on eradicating *H. pylori*, despite PPI's known influence on *H. pylori* colonization. These findings differ from those observed in adult patients. Further comprehensive research is necessary to gain a deeper understanding of this issue.

REFERENCES

1. Quaglia NC, Dambrosio A. *Helicobacter pylori*: A foodborne pathogen? World J Gastroenterol 2018;24:3472-87.
2. Floch P, Mégraud F, Lehours P. *Helicobacter pylori* Strains and Gastric MALT Lymphoma. Toxins (Basel) 2017;9:132.
3. Jones, NL, Koletzko S, Goodman K, Bontems P, Cadranel S, Casswall T, et al. Joint ESPGHAN/NASPGHAN guidelines for the management of *Helicobacter pylori* in children and adolescents (update 2016). J Pediatr Gastroenterol Nutr 2017;64:991-1003
4. Kaplan M, Tanoglu A, Duzenli T, Tozun AN. *Helicobacter pylori* treatment in Turkey: Current status and rational treatment options. North Clin Istanb 2019;7:87-94.
5. Mišak Z, Hojsak I, Homan M. Review: Helicobacter pylori in pediatrics. Helicobacter 2019;24 Suppl 1:e12639.
6. Graham DY, Lee YC, Wu MS. Rational *Helicobacter pylori* therapy: evidence-based medicine rather than medicine-based evidence. Clin Gastroenterol Hepatol 2014;12:177-86.e3; Discussion e12-3.
7. Thung I, Aramin H, Vavinskaya V, Gupta S, Park JY, Crowe SE, Valasek MA. Review article: the global emergence of *Helicobacter pylori* antibiotic resistance. Aliment Pharmacol Ther 2016;43:514-33.
8. Caliskan R, Tokman HB, Erzin Y, et al. Antimicrobial resistance of *Helicobacter pylori* strains to five antibiotics, including levofloxacin, in Northwestern Turkey. Rev Soc Bras Med Trop 2015;48:278-84.
9. Scott DR, Sachs G, Marcus EA. The role of acid inhibition in Helicobacter pylori eradication. F1000Res 2016;5:F1000 Faculty Rev-1747.
10. Gong EJ, Kim DH, Ahn JY, Na HK, Jung KW, Lee JH, et al. Effects of Proton Pump Inhibitor on the Distribution of *Helicobacter pylori* and Associated Gastritis in Patients with Gastric Atrophy. Digestion 2020;101:279-86.
11. Moayyedi P, Wason C, Peacock R, Walan A, Bardhan K, Axon AT, Dixon MF. Changing patterns of Helicobacter pylori gastritis in long-standing acid suppression. Helicobacter 2000;5:206-14.

12. Dixon MF, Genta RM, Yardley JH,Correa P. Classification and grading of gastritis. The updated Sydney System. International Workshop on the Histopathology of Gastritis, Houston 1994. Am J Surg Pathol 1996;20:1161–81.
13. Shinozaki S, Osawa H, Sakamoto H, Hayashi Y, Kobayashi Y, Miura Y, et al. Pre-treatment with proton pump inhibitors decreases the success of primary *Helicobacter pylori* eradication using a vonoprazan-based regimen. Kaohsiung J Med Sci 2018;34:456-60.
14. Janssen MJ, Laheij RJ, Jansen JB, de Boer WA. The influence of pretreatment on cure rates of *Helicobacter pylori* eradication. Neth J Med 2004;62:192-6.
15. Yuan Y, Ford AC, Khan KJ, Gisbert JP, Forman D, Leontiadis GI, et al. Optimum duration of regimens for *Helicobacter pylori* eradication. Cochrane Database Syst Rev 2013;12:CD008337
16. Malfertheiner P, Megraud F, O'Morain CA, Gisbert JP, Kuipers EJ, Axon AT, et al. Management of *Helicobacter pylori* infection-the Maastricht V/Florence Consensus Report. Gut 2017;66:6-30
17. Labenz J. Current role of acid suppressants in *Helicobacter pylori* eradication therapy. Best Pract Res Clin Gastroenterol 2001;15:413-31.
18. Kuang S, Xu J, Chen M, Zhang Y, Shi F, Lu X. The influence of pretreatment with PPI on *Helicobacter pylori* eradication: A systematic review and meta-analysis. Medicine (Baltimore) 2021;100:e27944.
19. Çelebi A, Aydın D, Kocaman O, Konduk BT, Şentürk Ö, Hülagü S. Comparison of the effects of esomeprazole 40 mg, rabeprazole 20 mg, lansoprazole 30 mg, and pantoprazole 40 mg on intragastrıc pH in extensive metabolizer patients with gastroesophageal reflux disease. Turk J Gastroenterol 2016;27:408-14.
20. Szőke A, Mocan S, Negovan A. *Helicobacter pylori* infection over bile reflux: No influence on the severity of endoscopic or premalignant gastric lesion development. Exp Ther Med 2021;22:766.
21. Agin M, Kayar Y. The Effect of Primary Duodenogastric Bile Reflux on the Presence and Density of *Helicobacter pylori* and on Gastritis in Childhood. Medicina (Kaunas) 2019;55:775.