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Effect of pantoprazole and *Helicobacter pylori* therapy on uninvestigated dyspeptic patients

STOMACH

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Original Article

ABSTRACT

Background/Aims: This study aimed to test the efficacy of empirical proton pump inhibitor use and *Helicobacter pylori* therapy for uninvestigated dyspepsia in a population with a high prevalence of *H. pylori*.

Material and Methods: The study had a two-stage design. In the first stage, the efficacy of 4-week pantoprazole treatment was compared with placebo in patients with uninvestigated dyspepsia. In the second stage, the efficacies of 2-week treatment with pantoprazole in *H. pylori*-negative patients and *H. pylori* eradication therapy (pantoprazole + amoxicillin + clarithromycin) in *H. pylori*-positive patients were compared. The primary endpoint was sufficient overall symptom relief (Global Overall Symptom score ≤2; no or minimal symptoms) at the end of treatment.

Results: In the first stage, sufficient overall symptom relief was achieved by 25.2% of patients in the pantoprazole group and 15.5% of patients in the placebo group, a difference that was not statistically significant (p=0.06). In the second stage, the rate of sufficient overall symptom relief was higher in the *H. pylori* therapy group than in the pantoprazole group (37.1% vs. 23.4%; p=0.02). After untreated follow-up, sufficient overall symptom relief remained significantly higher in the *H. pylori* therapy group than in the pantoprazole group (39.7% vs. 18%; p<0.001). Almost all patients receiving pantoprazole experienced symptom relapse after treatment.

Conclusions: This study validated the use of a test-and-treat strategy against *H. pylori* in uninvestigated dyspepsia, which may be an advisable treatment approach for uninvestigated dyspeptic patients in countries with a high prevalence of *H. pylori*.

Keywords: *Helicobacter pylori*, uninvestigated dyspepsia, pantoprazole, proton pump inhibitor

INTRODUCTION

The term dyspepsia refers to uneasiness in digestion (1). It consists of a very heterogeneous group of symptoms that are localized to the upper abdomen and range from pain or discomfort to postprandial fullness, abdominal bloating, early satiety, epigastric burning, belching, nausea, and vomiting (1-4). Dyspeptic symptoms are very common in the general population. Their prevalence is approximately 20-25% in the Western world (5-6) and 42.1% in Turkey (7). As advised by guidelines, empirical acid-suppression treatment with a PPI is commonly administered without prior endoscopy in young dyspeptic patients (1,4,8-10). However this approach had several caveats, including that (i) the duration of treatment is not defined, (ii) response is often lost during untreated follow-up periods, and (iii) most of these patients eventually undergo upper gastrointestinal endoscopy. The test-and-treat strategy is advised for uninvestigated dyspeptic patients in countries with a high prevalence of *H. pylori* (1-4,8); however the efficacy of treatment is not certain, resistance to treatment is common, and the reinfection rate is high. Furthermore, test-and-treat may be costly. The rates of response to these two treatment approaches can vary depending on the prevalence of *H. pylori* in the community, and the prevalence of *H. pylori* is around 80% in Turkey (11).

In this study we aimed to test the efficacy of empirical proton pump inhibitor (PPI) use and the efficacy of *H. pylori* eradication for uninvestigated dyspepsia in a society with a high prevalence of *H. pylori* positivity.

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MATERIALS AND METHODS

This prospective study was conducted at the Gastroenterology Clinic of Bezmialem Vakıf University from June 2012 to October 2013. It was approved by the institutional review board (B.30.2 .BAV.005/331-02.05.2012). We obtained written informed consent from all patients before the study began. This study was performed in compliance with the Declaration of Helsinki.

Patients

We enrolled patients who visited our outpatient clinic because of uninvestigated upper gastrointestinal (GI) symptoms. Patients 18-45 years of age were eligible for inclusion if they had at least one of eight specific upper GI symptoms (epigastric pain, burning, postprandial fullness, early satiety, bloating, belching, nausea, and vomiting) with one or more of the symptoms being of at least moderate severity (Global Overall Symptom [GOS] score ≥4) during the previous 3 months.

The GOS score has been validated in patients with dyspepsia (12,13), and has previously been used in clinical studies of patients with dyspepsia to assess symptoms and treatment success (14-20). The GOS score measures the severity of the eight symptoms noted above using a 7-point Likert scale, which is defined as follows: 1=no complaint and no symptoms; 2=a minimal complaint that can be ignored easily and without effort; 3=a mild complaint that can be ignored with effort; 4=a moderate complaint that cannot be ignored, but does not influence daily activities; 5=a moderately severe complaint that cannot be ignored and occasionally limits daily activities; 6=a severe complaint that cannot be ignored and often limits concentration on daily activities; and 7=a very severe complaint that cannot be ignored, markedly limits daily activities, and often requires rest.

Patients were excluded if they had an upper gastrointestinal endoscopy and/or non-invasive testing for *H. pylori* or been given eradication therapy for *H. pylori*. Patients were also excluded if they had alarm symptoms (such as significant weight loss, dysphagia, hematemesis, melena, jaundice, or other signs of serious disease), a prior GI operation, heartburn and/or acid regurgitation-dominant symptoms (i.e., probable gastroesophageal reflux disease), irritable bowel syndrome, or other comorbidities (including hepatic, renal, or cardiac disease). PPIs, H2-receptor antagonists, prokinetic agents, gastric mucosal protective agents, steroids, non-steroidal anti-inflammatory drugs, and aspirin were discontinued for at least 2 weeks before study entry.

Study design, follow-up, and outcomes

The study was conducted in two stages. In the first stage, eligible patients were included in a parallel-group, double-blind, randomized, placebo-controlled trial. Here, the efficacy of pantoprazole was compared with that of placebo in patients with uninvestigated dyspepsia. In the second stage, eligible patients were included in a parallel-group, open-label trial. This stage of the study compared the efficacy of pantoprazole in patients with dyspepsia who were *H. pylori* negative and the efficacy of *H. pylori* eradication therapy in patients with dyspepsia who were *H. pylori* positive.

1. Stage one, pantoprazole versus placebo

Patients were randomized 1:1 into the two groups using a computer-generated random allocation. The patients received pantoprazole 40 mg or placebo in one tablet daily, taken before meals in the morning for 4 weeks. Tablets and packages were identical in appearance for pantoprazole and placebo, and both the patients and the treating physicians were blinded to the allocated therapy.

1a. Follow-up and outcomes

Patients visited the clinic at study entry, at the end of the 4-week treatment, and at the end of a 2-week follow-up period without treatment. At each visit to the clinic, the patients completed the GOS assessment. The primary endpoint was defined as sufficient overall symptom relief (GOS ≤2; no symptoms or minimal symptoms) at the end of the 4-week treatment period. The secondary endpoints were sufficient overall symptom relief after 2 weeks of untreated follow-up, as well as symptom improvement (a decrease in the GOS by ≥3 grades for each symptom that had been scored >3 at baseline) after 4 weeks of treatment.

2. Stage two, pantoprazole versus *Helicobacter pylori* eradication therapy

At the end of a 2-week follow-up period without treatment period, all patients were asked to perform a gastroscopy regardless of the outcome of the initial therapy. Only patients who agreed on the endoscopic investigation were enrolled in this second stage. All gastroscopies were performed by one experienced endoscopist (B.B.). The presence of *H. pylori* was determined within 60 min using a rapid urease test (HelicotecUT Plus, Strong Biotech Corp, Taipei, Taiwan) of a biopsy sample that was taken from the antrum. Endoscopic findings were recorded, including the locations, sizes, and number of lesions. Esophagitis, gastric ulcer, duodenal ulcer, gastric erosion, and duodenal erosion were considered clinically significant endoscopic findings (CSEF). Patients who were found to be *H. pylori* positive using the rapid urease test were treated with pantoprazole 40 mg twice per day + amoxicillin 1 g twice per day + clarithromycin 500 mg twice per day for 2 weeks. Patients who were found to be *H. pylori* negative were treated with pantoprazole 40 mg once per day for 2 weeks. Four weeks after the end of the treatment period, response to the treatment of *H. pylori* was investigated using a stool antigen test (SD Bioline *H. pylori* Ag Test, Standard Diagnostics Inc., Kyonggi-do, South Korea).

2a. Follow-up and outcomes

The second stage of the study included a 2-week treatment period and a 4-week untreated follow-up period. Patients vis-

ited the clinic at the second study entry point, at the end of the 2-week second treatment period, and at the end of the 4-week untreated follow-up period. At each visit to the clinic, the patients completed the GOS assessment. The primary endpoint of the second part of the study was sufficient overall symptom relief (GOS ≤2; no symptoms or minimal symptoms) at the end of the 2-week treatment period. The secondary endpoints were sufficient overall symptom relief after 4 weeks of untreated follow-up, as well as symptom improvement (a decrease in GOS by ≥3 grades for each symptom that had been scored >3 at baseline) after 2 weeks of treatment.

Determination of sample size

The sample size was based on the proportion of patients with sufficient overall symptom relief after 4 weeks of treatment with either pantoprazole 40 mg or placebo groups. It was considered desirable to be able to show a difference in the proportion of responders if the true difference was 15% or more. The assumed treatment success rate was 30% for the pantoprazole group and 15% for the placebo group. In order to achieve a two-tailed significance level of 0.05 and a power of 80%, we needed 120 evaluable patients in each arm. To allow for a maximum dropout rate of 10%, 132 patients were needed per arm.

Statistical analysis

Safety variables were analyzed for all randomized patients. Patients who did not return after the initial visit were excluded from the efficacy analyses. All statistical analyses were performed using SPSS version 19 for Windows (SPSS Inc., Chicago, USA). Two- sided p values <0.05 were regarded as statistically significant. Data are presented as mean±standard deviation (SD). The one-sample Kolmogorov-Smirnov test was used to confirm that results followed a normal distribution. The main characteristics of the study group were compared using Pearson's χ^2 test, the Mann-Whitney U test, and Student's t-test. Pearson's χ^2 test was used to compare the proportions of sufficient overall symptom relief and symptom improvement at the end of treatment and at the end of the untreated follow-up period.

RESULTS

1. Stage one: pantoprazole versus placebo

Of the 313 patients with upper GI symptoms who were screened, 49 were excluded (gastro-esophageal reflux disease, n=22; GOS≤3, n=19; other reasons, n=8), and 29 were lost to follow-up after randomization. Thus, 235 patients were included in the study. The flow of patients through the study is illustrated in Figure 1.Their median age was 32 (range 18-45) years, and 61% of the participants were women. The mean number of upper GI symptoms per patient was 4.1 at baseline. In terms of symptoms of at least moderate severity (GOS≥4), bloating was the most frequent, being reported by 78.7% of patients, followed by postprandial fullness (72.3%), epigastric pain (71.5%), epigastric burning (65.1%), belching (57%), early satiety (38.4%), nausea (26.4%), and vomiting (5%). The demographic and clinical characteristics of the patients at baseline were similar in the placebo and pantoprazole groups (Table 1). For each symptom of at least moderate severity (GOS≥4) at baseline, there was no significant difference between the proportions of affected patients in the two groups (Figure 2). At the end of the 4-week treatment, the proportion of patients with sufficient overall symptom relief was 25.2% in the pantoprazole group and 15.5% in the placebo group, which did not amount to a statistically significant difference between the groups (p=0.06) (Figure 3a). After the 2-week untreated follow-up period, the proportions of patients with sufficient overall symptom relief in the pantoprazole and placebo groups were similar (11.7% vs. 13.7%; p>0.05). At the end of the 4-week treatment, the proportions of patients who experienced relief in epigastric burning, epigastric pain, and belching were significantly higher in the pantoprazole group than in the placebo group (58.4% vs. 32.1%, p<0.001; 44.2% vs. 28.5%, p=0.02; and 37.6% vs. 12.8%, p<0.001, respectively). However, after the 2-week untreated follow-up period, the groups did not significantly differ with regard to relief in epigastric pain, epigastric burning, postprandial fullness, early satiety, bloating,

Table 1. Demographic and clinical characteristics of the patients at study entry

	Placebo group (n=116)	Pantoprazole group (n=119)	p value
Women, n (%)	70 (60.3%)	73 (61.3%)	NS
Mean age, years (range)	32 (18-45)	32 (18-45)	NS
Body mass index (kg/m^2), mean (range)	25.5 (17-38)	25.1 (17-36)	NS
Mean history of upper GI symptoms, months (range)	33 (3-108)	37 (3-120)	NS
Current smoker, n (%)	22 (19%)	24 (20.2%)	NS
Consumer of alcohol, n (%)	8 (6.9%)	12 (10.1%)	NS
Number of upper GI symptoms with GOS ≥4, mean (range)	4.1 (1-8)	4.2 (1-8)	NS

GOS: global overall symptom score, NS: not significant (p>0.05)

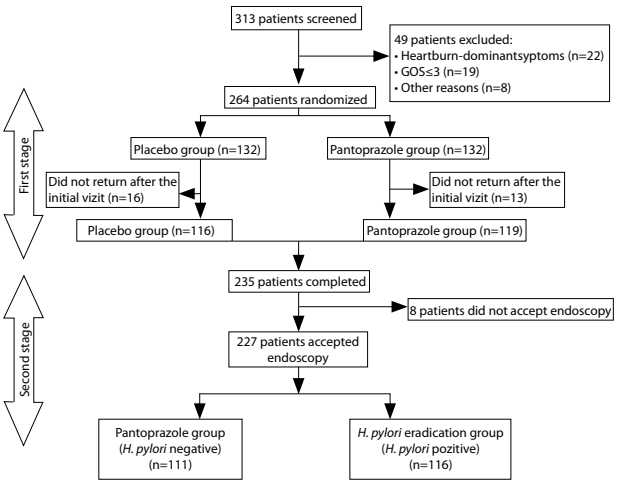

Figure 1. Summary of patient flow. GOS: global overall symptom score.

Table 2. Pantoprazole versus placebo: sufficient overall symptom relief and symptom improvement

		Placebo (n=116)	Pantoprazole (n=119)	p value
Sufficient overall symptom relief, (%)	4 w. treatment	15.5	25.2	NS
	2 w. follow-up*	13.7	11.7	NS
Symptom improvement				
Epigastric pain, (%)	4 w. treatment	28.5	44.2	0.02
	2w. follow-up*	20.7	31.6	NS
Epigastric burning, (%)	4 w. treatment	32.1	58.4	<0.001
	2 w. follow-up*	28.6	41.7	NS
Postprandial fullness, (%)	4 w. treatment	24	23.9	NS
	2 w. follow-up*	18.3	18.5	NS
Early satiety, (%)	4 w. treatment	21.6	28.6	NS
	2 w. follow-up*	17.6	25.4	NS
Bloating, (%)	4 w. treatment	17.6	26.5	NS
	2 w. follow-up*	19.4	18.4	NS
Nausea, (%)	4 w. treatment	16.6	20.4	NS
	2 w. follow-up*	14.2	22.7	NS
Vomiting, (%)	4 w. treatment	26.3	28.5	NS
	2 w. follow-up*	15.7	21.4	NS
Belching, (%)	4 w. treatment	12.8	37.6	<0.001
	2 w. follow-up*	12.8	24.7	NS

w: weeks, NS: not significant (p >0.05); *2-week follow-up after treatment

belching, nausea, or vomiting (all p >0.05). The proportions of patients with sufficient overall symptom relief and improvement in each of the eight symptoms are summarized in Table 2.

2. Stage two: pantoprazole versus *Helicobacter pylori* eradication therapy

Of the 235 patients who reported to the clinic visit after the 2-week untreated follow-up period, 227 patients agreed to perform a gastroscopy. Eight patients refused endoscopy and were excluded from the second stage of the study. The median age of the included patients was 32 (range 18-45) years, and 60.8% were women. Gastroscopy revealed CSEF in 32.5% of the patients. Esophagitis was the most common clinically significant endoscopic finding (17.1% of the patients) (Table 3). Peptic ulcer was found in 16 (7%) patients (11 had duodenal ulcer and 5 had gastric ulcer). No patients were found to have gastric or esophageal malignancy.

Using the rapid urease test, 51% of the patients were found to be *H. pylori* positive. Expectedly, CSEF and peptic ulcer were more common in the *H. pylori*-positive group than in the *H. pylori*-negative group (35.3% vs. 29.7%, and 9.5% vs. 4.5%, respectively), but the differences were not statistically significant (both p>0.05). The demographic and clinical characteristics of the patients at the baseline of the second study were similar in the pantoprazole and *H. pylori* therapy groups (Table 4). For each symptom of at least moderate severity (GOS≥4) at the baseline of the second study, there was no significant difference between the proportions of affected patients in the two groups (Figure 4).

Table 3. Clinically significant endoscopic findings

	Pantoprazole group (n=111)	*H. pylori* therapy group (n=116)	Total (n=227)
Clinically significant endoscopic findings, n (%)*	33 (29.7%)	41 (35.3%)	74 (32.5%)
Esophagitis, n (%)*	21 (18.9%)	18 (15.5%)	39 (17.1%)
Peptic ulcer, n (%)*	5 (4.5%)	11 (9.4%)	16 (7%)
Gastric ulcer, n (%)#	1 (0.9%)	4 (3.4%)	5 (2.2%)
Duodenal ulcer, n (%)#	4 (3.6%)	7 (6%)	11 (4.8%)
Gastric erosions, n (%)#	4 (3.6%)	2 (1.7%)	6 (2.6%)
Duodenal erosions, n (%)#	3 (2.7%)	10 (8.6%)	13 (5.7%)

* p>0.05, #Statistical analysis could not be performed due to small sample size.

At the end of the 2-week treatment period, the proportion of patients with sufficient overall symptom relief was higher in the *H. pylori* therapy group than in the pantoprazole group (37.1% vs. 23.4%; p=0.02) (Figure 3b). This overall benefit was

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Table 4. Demographic and clinical characteristics of the patients at entry into the second study

	Pantoprazole group (n=111)	*H. pylori* therapy group (n=116)	p value
Women, n (%)	70 (63.1%)	68 (58.6%)	NS
Mean age, year (range)	32 (18-45)	31 (18-45)	NS
Body mass index (kg/m^2), mean (range)	24.8 (17-36)	25.8 (18-38)	NS
Mean history of upper GI symptoms, months (range)	38 (3-120)	33 (3-114)	NS
Current smoker, n (%)	19 (17.1%)	25 (21.6%)	NS
Consumer of alcohol, n (%)	9 (8.1%)	9 (7.8%)	NS
Number of upper GI symptoms with GOS ≥ 4, mean (range)	3.4 (1-8)	3.3 (1-8)	NS
Previous pantoprazole treatment	61 (55%)	54 (46.6%)	NS

GOS: global overall symptom score, NS: not significant (p >0.05

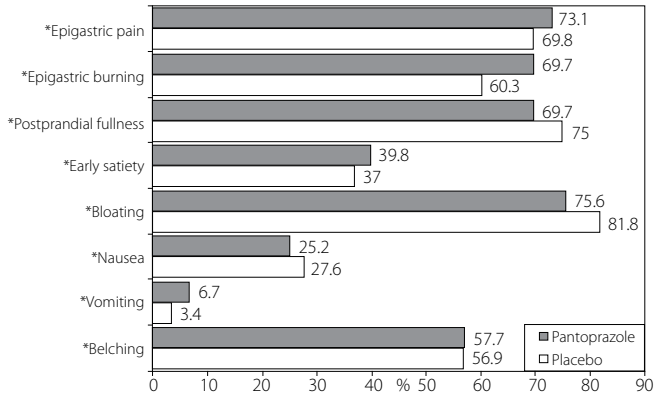

Figure 2. The proportion of patients with each symptom of at least moderate severity (GOS ≥4) in the pantoprazole and placebo groups at study entry. There was no significant difference between two groups .* p >0.05

even more pronounced and significant after the 4-week untreated follow-up period (39.7% vs. 18%; p<0.001). Likewise, this superiority was also demonstrated with the various dyspeptic symptoms at the end of the 2-week treatment: the proportions of patients who experienced relief in epigastric pain, postprandial fullness, belching, early satiety, and bloating were significantly higher in the *H. pylori* therapy group than in the pantoprazole group (51.3% vs. 33.9%, p=0.03; 39.2% vs. 19.8%, p<0.001; 37.9% vs. 20%, p=0.03; 33.3% vs. 14.9%, p=0.04; and 31.7% vs. 15.9%, p=0.01, respectively). The proportions of patients with sufficient overall symptom relief and symptom improvement in the second stage of the study are summarized in Table 5. Values are presented for each of the eight symptoms.

After the 4-week untreated follow-up period, the presence of *H. pylori* was investigated using a stool antigen test. After *H. pylori* eradication therapy, 63.8% of the patients were found to be *H. pylori* negative. Of the patients who received eradication therapy and became *H. pylori* negative, 51.4% achieved sufficient overall symptom relief. By contrast, overall symptom relief was achieved by 21.4% of the patients who received eradication therapy but remained *H. pylori* positive, which constituted a significant difference (p=0.002).

Safety

Safety data were available for 264 patients during the first stage of the study and 227 patients during the second stage of the study. Treatment with study medication was generally well tolerated. No patient was withdrawn as a result of incompliance or because of adverse events. No deaths occurred in the study. A total of 34 (12.8%) patients (20 [7.5%] with pantoprazole and 14 [5.3%] with placebo) reported at least one adverse event during the first stage of the study. Headache, nausea, taste perversion, diarrhea, and flatulence were the most common events reported. During the second stage of the study, a total of 38 (16.7%) patients reported adverse events: 14 (6.1%) in the pantoprazole group and 24 (10.6%) in the *H. pylori* therapy group. Taste perversion, increased abdominal pain, diarrhea, headache, and flatulence were the most common events reported. A total of 5 (2.2%) endoscopy-related adverse minor events (sore throat, nausea, or breathing difficulty) were reported, all of which resolved spontaneously.

DISCUSSION

Although dyspepsia is rarely associated with a serious etiology, it can often significantly affect the quality of life. Moreover, it is an extremely common presentation encountered in outpatient clinics, thus its management should be based on a solid evidence based approach. The AGA guidelines recommends for empirical acid-suppression treatment with a PPI without prior endoscopy in young dyspeptic patients presenting with no alarm features in areas with low H. Pylori prevalence (4,10). On the other hand, the test-and-treat strategy is advised for uninvestigated dyspeptic patients in countries with a higher prevalence of *H. pylori* (1-4,8); however the efficacy of treatment is not certain, resistance to treatment is common, and the reinfection rate is high.

We performed a two-stage study to assess the efficacy of pantoprazole and *H. pylori* treatment in cases of uninvestigated dyspepsia. In the first stage of the study, there was a trend of an overall beneficial response with pantoprazole as compared with placebo however this did not reach statistical significance. Only the acid-related symptoms appeared to significantly improve, and this effect was lost during the untreated follow-up period. This is in contrast with several other studies where PPI treatment has been found to be superior to placebo (21-24). In a randomized, placebo-controlled study of 140 uninvestigated dyspeptic patients, Rabeneck et al. (21) found that patients receiving omeprazole experienced a higher rate of treatment success than patients receiving placebo at the end of 6 weeks of treatment. The response rate was reduced in both groups after untreated follow-up, but the benefits remained more evident

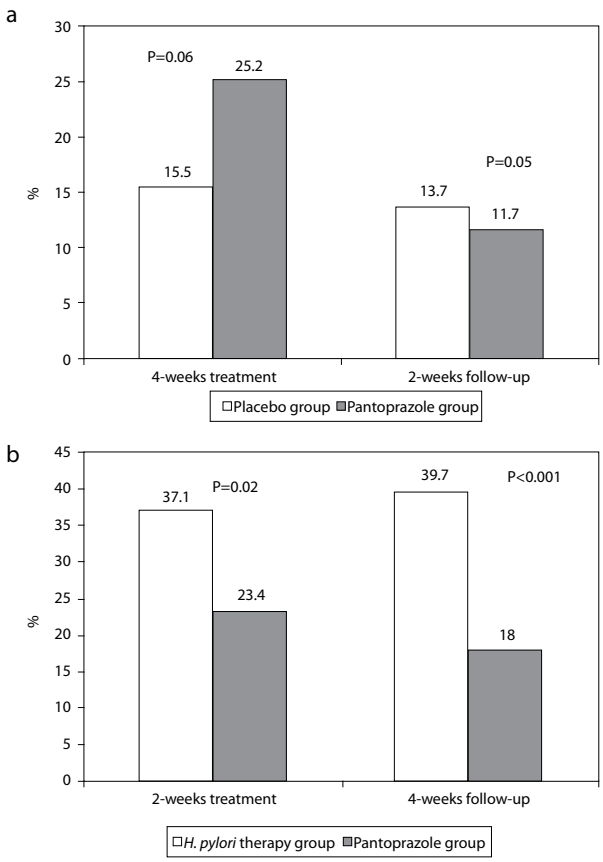

Figure 3. a, b. The proportions of patients with sufficient overall symptom relief in the first stage of the study **(a)** and the second stage of the study **(b)**.

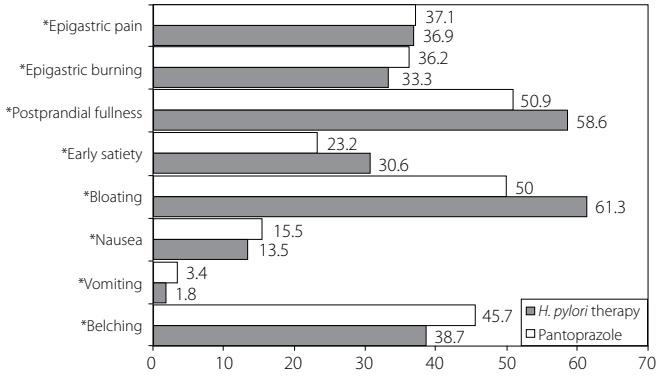

Figure 4. The proportion of patients with each symptom of at least moderate severity (GOS ≥4) in the pantoprazole treatment and H. pylori therapy groups at entry into the second stage of the study. There was no significant difference between two groups.
*p>0.05

in the omeprazole group (21). In another study, the efficacies of 20-mg omeprazole, 40-mg omeprazole, and placebo were compared in 829 dyspeptic patients, and the success rate was higher in both omeprazole treatment groups (22). In that study, symptoms that suggested gastro-esophageal reflux disease were not excluded, and the primary endpoint was complete relief of the predominant symptom. At the end of the untreated follow-up period, high rates of symptom relapse were seen. Van Zanten et al. (23) compared esomeprazole and placebo treatments in 1118 uninvestigated dyspeptic patients with epigastric pain and epigastric burning. At the end of the 4-week treatment, esomeprazole was found superior to placebo.

The low response rates to pantoprazole and placebo in the present study may have resulted from the following basic causes: (i) the primary endpoint was defined as sufficient relief of all eight symptoms, and (ii) patients with heartburn and acid regurgitation symptoms were not included. The main treatments for these two symptoms are PPIs (9-25). If heartburn, acid regurgitation, and other symptoms that suggest gastro-esophageal reflux disease had not been excluded from the dyspepsia symptoms, PPI treatment could have been more effective (24). Additionally, approximately 70% of uninvestigated dyspeptic patients are diagnosed with functional dyspepsia (1-4,26). In functional dyspeptic patients, the efficacy rate of placebo is high (around 20-60%) (2). Therefore, response to placebo is not surprising in uninvestigated dyspeptic patients.

Endoscopies were performed to avoid missing CSEF however this did not affect the randomization process or the final results. In our study, 32.5% of the patients had CSEF. Esophagitis was the most common (17.1%) CSEF. Peptic ulcer was found in 16 (7%) patients. However no malignancies were identified, confirming the high reliability of the absence of alarm features to exclude serious underlying etiologies and the recommendation against early endoscopic examination in these patients. In the CADETPE study (27), which assessed 1040 uninvestigated dyspeptic patients, the rates of CSEF (58%) and esophagitis (43%) were higher, but the rate of peptic ulcer (5.3%) was lower than in the present study. A lower rate of esophagitis may have been observed in our study because heartburn and acid regurgitation symptoms were clearly defined as exclusion criteria. Furthermore, the higher incidence of peptic ulcer in our study may have resulted from the greater prevalence of *H. pylori*.

The rates of response to these two treatments can vary depending on the prevalence of *H. pylori* in the community (28). We found a 51% prevalence of *H. pylori*, and a higher proportion of patients achieved sufficient overall symptom relief in the *H. pylori* eradication group than in the pantoprazole group (37.1% vs. 23.4%, p=0.02). The *H. pylori* eradication group also included higher proportions of patients who experienced relief of epigastric pain, epigastric burning, epigastric fullness, belching, early satiety, and bloating symptoms as compared with the pantoprazole group. Interestingly, the beneficial effect of *H. Pylori* treatment was persistent after the 4-week untreated follow-up period, whereas most symptoms relapsed in those who received pantoprazole alone, suggesting a durable response to *H. Pylori* eradication.

The proportion of patients with sufficient overall symptom relief was significantly higher among those who became *H. py-*

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Table 5. Pantoprazole versus *Helicobacter pylori* eradication therapy.

		Pantoprazole (n=111)	*H. pylori* therapy (n= 116)	p value
Sufficient overall symptom relief, (%)	2 w. treatment	23.4	37.1	0.02
	4 w. follow-up*	18	39.7	<0.001
Symptom improvement				
Epigastric pain, (%)	2 w. treatment	33.9	51.3	0.03
	4 w. follow-up*	22.6	46.2	<0.001
Epigastric burning, (%)	2 w. treatment	57.6	48.4	NS
	4 w. follow-up*	20.3	43.5	<0.001
Postprandial fullness, (%)	2 w. treatment	19.8	39.2	<0.001
	4 w. follow-up*	16	40.5	<0.001
Early satiety, (%)	2 w. treatment	14.9	33.3	0.04
	4 w. follow-up*	14.9	39.1	0.02
Bloating, (%)	2 w. treatment	15.9	31.7	0.01
	4 w. follow-up*	14.8	34.1	<0.001
Nausea, (%)	2 w. treatment	20.8	27.8	NS
	4 w. follow-up*	20.8	31.8	NS
Vomiting, (%)	2 w. treatment	27.2	33	NS
	4 w. follow-up*	27.2	25	NS
Belching, (%)	2 w. treatment	20	37.9	0.03
	4 w. follow-up*	16.4	40.9	<0.001

w: weeks, NS: not significant (p>0.05); * 4-week follow-up after treatment

*lori n*egative at the end of eradication treatment compared to those whose *H. pylori* positivity was maintained after their eradication treatment (51.4% vs. 21.4%, p=0.002), suggesting an active role of H. Pylori in the pathogenesis of dyspepsia. In the Canadian adult dyspepsia empirical treatment-*H. pylori* positive (CADET-Hp) study (14), eradication treatment was found to be superior to omeprazole treatment in 294 dyspeptic patients (success rate: 50% vs. 36%, p=0.02). However, only *H. pylori*-positive patients were included in that study, and thus the rate of response to omeprazole may have been higher. In a study by Manes et al. (29), *H. pylori* eradication treatment was found to be superior to omeprazole treatment. In that study, the prevalence of *H. pylori* was similar to the prevalence observed in our study, and almost all patients experienced relapse of symptoms after PPI treatment. Relapse of symptoms was less common in the group that received *H. pylori* eradication treatment. These data support our findings. The superiority of *H. pylori* treatment to pantoprazole treatment is likely to result from the high prevalence of *H. pylori*. In communities with low prevalence of *H. pylori*, eradication treatment is expected to result in lesser improvements in dyspepsia symptoms.

Limitations of this trial

(i) In the first stage of the study, pantoprazole and placebo treatment caused some reductions to the severity of symptoms. However, at the beginning of the second stage of the study (which compared pantoprazole and *H. pylori* eradication treatment groups), there was no significant difference in general patient characteristics or the rates of symptoms between the two groups. (ii) Endoscopies were performed on all patients prior to the second stage which might have increased the risk of bias as well as playing a 'placebo' effect to the patient who were reassured after this intervention, thus probably affecting/increasing the response rate in both treatment groups. However the endoscopic findings did not affect the randomization process, as this was dependent on the objective result of the urea breath test. In fact, we elected to include this step in the study for safety reasons to detect any serious underlying condition that can be missed in some cases (30), as well as to further validate the usefulness and accuracy of the alarm features mentioned in the guidelines. (iii) In Turkey, clarithromycin resistance has a prevalence of around 24-48% (31-33). The use of a triple treatment that included clarithromycin for the eradication of *H. pylori* may have resulted in both a lower eradication rate and a lower proportion of patients who achieved sufficient overall symptom relief. But we did not test for susceptibility as this was beyond the scope of this study. However these results are of utmost importance for clinicians and researchers in our country and region to avoid this regimen and to adopt and study other options such as the quadruple, sequential or

bismuth-based therapies. Despite these limitations, our study presents the notable advantage of assessing the two basic treatment approaches that are used in practice (pantoprazole and *H. pylori* eradication treatment) in the same patient group. To the best of our knowledge, this study is the first in the literature with this characteristic.

This study validated the use of the test-and-treat strategy against *H. pylori* in uninvestigated dyspepsia. The results indicated that the effect of pantoprazole was similar to that of placebo in uninvestigated dyspeptic patients, and that *H. pylori* eradication treatment was superior to pantoprazole treatment. Notably, the percentage of patients achieving sufficient overall symptom relief was much higher among patients who underwent *H. pylori* eradication treatment and were *H. pylori* negative at the end of the treatment. Recommendation of the test-and-treat strategy in uninvestigated dyspeptic patients appears to be appropriate in countries with a high prevalence of *H. pylori.*

Ethics Committee Approval: Ethics committee approval was received for this study.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

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