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Original Article

Symptom improvement after helicobacter pylori eradication in patients with functional dyspepsia-A multicenter, randomized, prospective cohort study

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Abstract: Objective: To observe the improvement of functional dyspepsia (FD) after helicobacter pylori (HP) eradication in FD patients. Methods: 644 FD patients were recruited of whom 585 completed follow up. They were divided into postprandial distress syndrome (PDS) group and epigastric pain syndrome (EPS) group. Patients with HP infection were randomly allocated into eradication group and non-eradication group. Patients in the eradication group were randomly assigned into two groups and treated with triple therapy and sequential therapy, respectively. Patients in non-eradication group and HP non-infection group were treated with Domperidone (PDS patients) or Talcid (EPS patients). Clinical symptoms were evaluated. Results: When compared with patients with unsuccessful HP eradication and without eradication, significant improvement in symptoms was found at 8 w, 12 w, and 26 w in patients with successful HP eradication in EPS group ($P < 0.05$). However, in PDS group, improvement in symptoms was comparable among patients expect at 26 w after successful HP eradication ($P < 0.05$). Therapeutic efficacy in patients without HP eradication was poorer than that in HP negative patients in EPS group ($P < 0.05$), while in PDS group, symptoms were relived at 26 w and 52 w ($P < 0.05$). Conclusions: HP is one of pathogenic factors of FD and HP eradication may benefit FD patients, regardless therapeutic regimes, especially in EPS patients.

Keywords: Epigastric pain syndrome, functional dyspepsia, helicobacter pylori eradication, helicobacter pylori infection, postprandial distress syndrome, sequential-therapy, triple-therapy

Introduction

Helicobacter pylori (HP), a kind of gram negative bacteria, have been recognized to be related to duodenal ulcer or gastritis in 1982 by Warren and Marshall. Increasing studies have demonstrated that a variety of diseases including gastrointestinal diseases are related to HP infection. HP is generally accepted to be a major etiologic factor for gastritis, peptic ulcer, gastric carcinoma and lymphoma of mucosal associated lymphoid tissues (MALT) [1]. However, the effect of HP infection on functional dyspepsia (FD) remains controversial. Some studies have been conducted to investigate whether HP eradication can effectively improve the symptoms of FD [2, 3], but they have a small sample size and short term fellow-up. In addition, no study has been carried out to explore the response of FD patients of different subgroups according to the Rome III Criteria to anti-HP therapy.

In addition, there are still some issues worthy solving on the relationships between HP and FD, such as whether HP eradication should be regarded as a routine treatment, whether alleviated clinical symptoms after eradication may be maintained for a long time, and whether the improvement of clinical symptoms is different in FD patients of distinct subgroups, etc. Therefore, we conducted a multicenter randomized

Table 1. Characteristics of patients in different groups

Subgroups	HP infection	Treatment	n	Genders (M/F)	Age (years) ($\bar{\chi} \pm S$)	symptom scores before subdividing ($\bar{\chi} \pm S$)
PDS	HP+	Domperidone	67	23/44	40.00 ± 11.63	6.88 ± 1.20
		sequential therapy	63	19/44	42.55 ± 10.25	7.00 ± 0.97
		Triple therapy	67	28/39	44.40 ± 10.17	7.11 ± 1.07
	HP-	Domperidone	93	35/58	39.42 ± 9.78	7.15 ± 0.98
EPS	HP+	Talcid	67	24/43	36.10 ± 11.88	7.02 ± 0.19
		sequential therapy	61	14/47	38.08 ± 10.70	7.15 ± 1.16
		Triple therapy	71	27/44	38.92 ± 9.84	6.96 ± 0.96
	HP-	Talcid	96	37/59	35.47 ± 10.58	6.85 ± 0.96

clinical trial to elucidate these issues in Chinese FD patients. Our findings may provide evidence for clinical treatment of FD in Chinese patients.

Methods

Patients and characteristics

A total of 644 patients were recruited into this study from February 2008 to September 2010 from four health centers. There are 416 females and 228 males with a median age of 39.34 years (range: 18-67 years). At the end of study, 59 patients were lost to fellow-up, and 585 FD patients finished this study, including 378 females and 207 males with a median age of 39.14 years (range: 18-67 years). According to the Rome III Criteria, these patients were independently divided into EPS group and PDS group. Patients in two groups were then subdivided into HP group and non-HP group on the basis of results from HP detection. In HP group, patients received triple therapy, sequential therapy and non-therapy (**Table 1**).

Inclusion criteria

The inclusion criteria were as follows: 1). Diagnosis of EPS and PDS was done according to Rome III Criteria. 2). Age ranged from 18 years to 70 years. 3). Examinations such as gastroscopy, epigastric Doppler ultrasonography, electrocardiograph examination, blood tests (renal and liver function, fasting blood glucose, complete blood count and erythrocyte sedimentation rate [ESR]) and routine urinalysis were carried out at baseline and showed normal to exclude organic diseases, gastric mucosa was normal or presented with mild hyperaemia, and patients with a history of surgery were excluded.

Exclusion criteria

The exclusion criteria included: 1). Patients had warning signs and malignant diseases could not excluded. 2). Patients had concomitant other serious digestive problems including peptic ulcer. 3). Patients had severe diseases of other systems, such as heart, liver, lung, kidney, hematological system, and endocrine system. 4). Patients were pregnant or breast feeding women, or had conception during the study period. 5). Patients refused to participate in this study or had a poor compliance. 6). Patients had symptoms overlapping with PDS and EPS. 7). Antacids and bismuth had been used within two weeks before endoscopy. 8). Patients had drug addiction, alcoholism or other problems unsuitable for study. 9). Patients had drug allergy or idiosyncratic reaction.

Assessment of HP infection

Patients received gastroscopy, and biopsy was done at one antral site and one corpus site for histological examination (Giemsa staining), and biopsy at another antral site was performed for fast urease test. Both tests showing positive were employed to confirm HP infection, and both showing negative to confirm HP non-infection. Once one test showed positive, patients were excluded. Four weeks after eradication treatment, HP infection was assessed by ^{14}C-urea breath test (UBT).

Symptom evaluation

The gastrointestinal symptom rating scale was used to score dyspepsia symptoms before and at 4 w, 8 w, 12 w, 26 w and 52 w after treatment. This validated instrument measures symptoms including abdominal pain and burn-

Table 2. Symptom improvements in patients with successful/unsuccessful HP eradication and patients without eradication in EPS and PDS group

Groups		before	4 w	8 w	12 w	26 w	52 w nt
EPS group	Successful eradication (n = 67)	81.77	69.48	69.04△	69.83△	66.35*	69.49
	Unsuccessful eradication group (n = 22)	77.55	81.59	71.27	77.77	90.34	85.09
	Without eradication (n = 67)	75.54	86.51	90.33	87.41	86.76	85.34
	P	0.697	0.051	0.008	0.043	0.003	0.055
PDS group	Successful eradication (n = 59)	78.03	67.94	64.92	63.08	62.32*	64.91
	Unsuccessful eradication (n = 17)	70.12	63.15	68.53	76.71	85.24	79.21
	Without eradication (n = 67)	67.71	77.80	79.11	78.66	77.16	76.42
	P	0.295	0.228	0.103	0.054	0.025	0.157

△P < 0.05 successful eradication vs without eradication. *P < 0.05 successful eradication vs other patients.

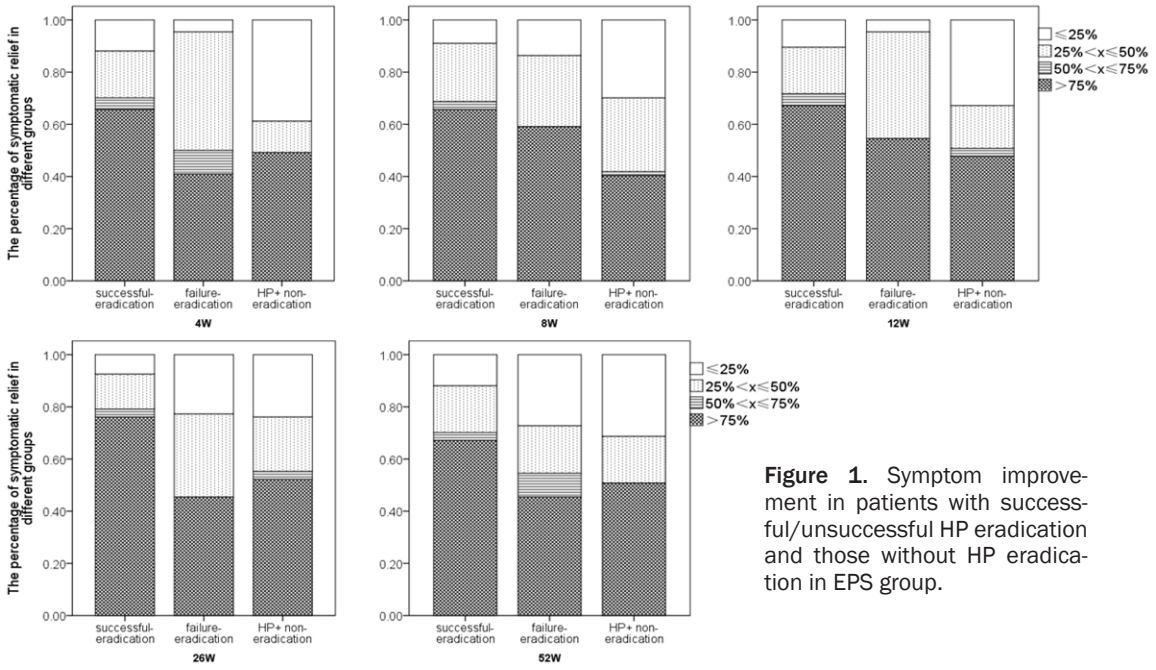

Figure 1. Symptom improvement in patients with successful/unsuccessful HP eradication and those without HP eradication in EPS group.

ing in EPS group, and early satiety and postprandial fullness in PDS group. Every symptom was scored according to its severity on a 4-point scale: 1, none: no symptoms; 2, mild: awareness of sign or symptom, but easily tolerated; 3, moderate: discomfort sufficient to cause interference with normal activities; 4, severe: incapacitating with inability to perform normal activities. The sum of scores of each symptom was calculated for statistical analysis.

The improvement of symptoms was evaluated according to the following formula: (score before treatment - score after treatment) / score before treatment × 100%. The improvement of higher than 75% was defined as complete response; 50%-75% as significant relief; 25%-50% as moderate relief; and < 25% as mild relief. Overall therapeutic efficacy referred to the sum of percentages in moderate relief, significant relief and complete response. The efficiency was calculated as the sum of percentages in significant relief and complete response. Characteristics of patients at baseline are indicated in **Table 1**.

Therapeutic schemes

According to above criteria, 644 patients were enrolled into this study, including 312 in PDS group (205 in HP group and 107 in non-HP group) and 332 in EPS group (216 in HP group and 116 in non-HP group). Patients with HP infection randomly received triple-therapy, sequential-therapy and no treatment.

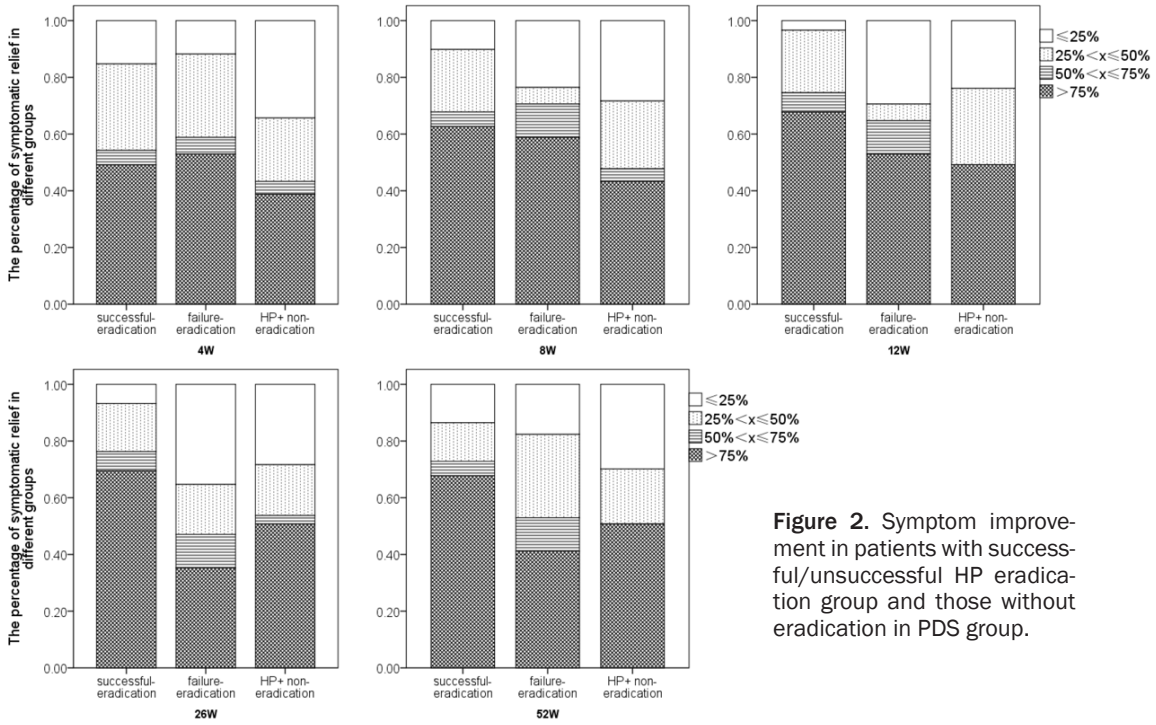

Figure 2. Symptom improvement in patients with successful/unsuccessful HP eradication group and those without eradication in PDS group.

Table 3. Symptom improvement in patients without HP eradication and HP negative patients in EPS and PDS group

Groups	Patients	before	4 w	8 w	12 w	26 w	52 w
EPS group	Without HP eradication (n = 67)	84.22	90.40	95.13	92.90	90.34	91.41
	HP negative (n = 96)	80.45	76.14*	72.84*	74.40*	76.18*	75.43*
	P	0.596	0.039	0.001	0.006	0.033	0.016
PDS group	Without HP eradication (n = 67)	75.19	82.67	86.67	87.51	89.46	89.34
	HP negative (n = 93)	84.32	78.94	76.05	75.45	74.05*	74.13*
	P	0.195	0.599	0.121	0.071	0.018	0.019

*P < 0.05 patients without HP eradication vs HP negative patients.

Triple-therapy was done with Esomeprazole 20 mg, clarithromycin 500 mg and Amoxil 1.0 g (bid for 10 days), and sequential therapy with Esomeprazole 20 mg and amoxicillin 1.0 g (bid for 5 days), and then with esomeprazole 20 mg, clarithromycin 500 mg and tinidazole 500 mg (bid for following 5 days). HP positive patients without anti-HP treatment and those without HP infection were treated with Domperidone 10 mg (PDS group) or Talcid 1.0 g (EPS group) (tid for 10 days).

Statistical analysis

Chi-square test was used to compare the HP eradication rate between two subgroups of FD patients, and between triple-therapy group and sequential-therapy group. For comparison of clinical symptoms before and after treatment among groups, Wilcoxon rank sum test was adopted. Data in different group were expressed as mean rank. A value of $P < 0.05$ was considered statistically significant. Statistical analysis was performed using SPSS version 17.0 for Windows.

Results

HP infection rate

There were 396 patients positive for HP among 585 patients (n = 197 in PDS group, and n = 199 in EPS group). HP infection rate was 67.70% in Chinese FD patients. No significant

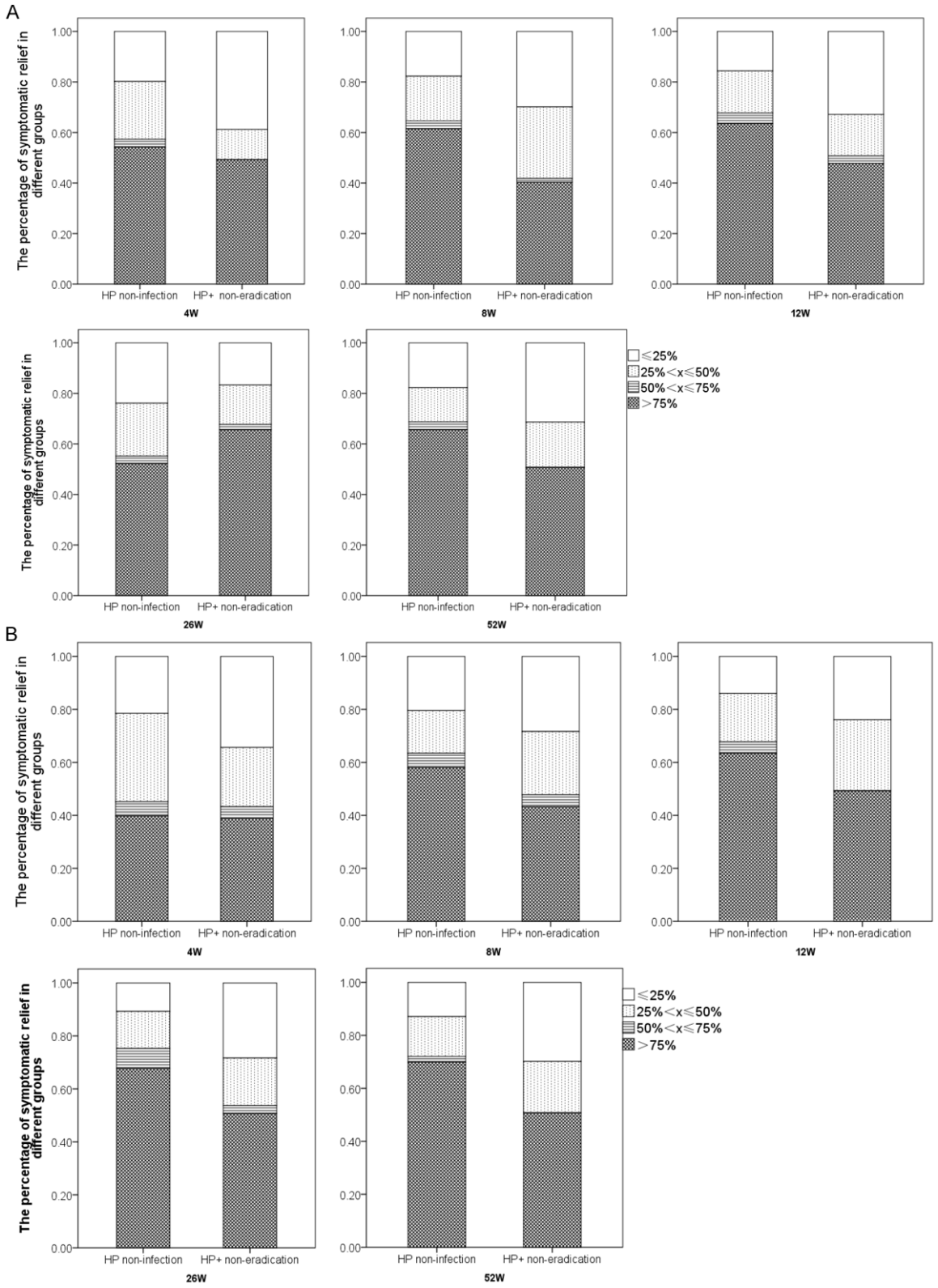

Figure 3. Symptom improvement between patients without HP eradication and HP negative patients in EPS group and PDS group (A: EPS group, B: PDS group).

Table 4. Symptom improvement in patients receiving triple-therapy or sequential-therapy and those without HP eradication in EPS group and PDS group

Groups		before	4 w	8 w	12 w	26 w	52 w
EPS group	triple therapy (n = 71)	98.36	92.54	91.42	92.88	91.90	94.99
	sequential therapy (n = 61)	105.03	94.00	88.43	92.18	95.61	93.68
	without eradication (n = 67)	97.16	113.37*	119.62*	114.66*	112.58*	111.06
	P	0.682	0.032	0.001	0.015	0.036	0.095
PDS group	triple therapy (n = 67)	105.18	93.05	95.36	97.60	98.02	101.03
	sequential therapy (n = 63)	100.37	93.10	92.42	92.52	93.64	89.91
	without eradication (n = 67)	91.54	110.50	108.83	106.50	105.01	105.51
	P	0.334	0.096	0.158	0.295	0.451	0.211

*P < 0.05 without eradication vs other groups.

difference was noted in HP infection rate (67.93% vs 67.46%; P = 0.752) between PDS group (197/290) and EPS group (199/295).

HP eradication rate

Four weeks after eradication treatment, ^{14}C-UBT was used to detect HP. The total HP eradication rate was 76.36% (126/165) in FD patients. There were no significant difference in HP eradication rate between triple-therapy group (77/87) and sequential-therapy group (56/78) (80.46% vs 71.79%; P = 0.191), and between PDS group (59/76) and EPS group (67/89) (77.63% vs 75.28%; P = 0.723).

Improvement of clinical symptoms and symptom relief ratio

Before and 4 w, 8 w, 12 w, 26 w and 52 w after treatment, comparisons were done among patients with successful HP eradication, unsuccessful HP eradication and without eradication in EPS and PDS group.

In EPS group, patients achieved significant remission of symptoms at each time point in follow up period after successful HP-eradication, especially at 8 w, 12 w and 26 w. However, in PDS group, symptom relief was comparable among three groups except at 26 w after successful HP eradication (**Table 2**).

As shown in **Figure 1**, in EPS group, during follow-up period, therapeutic efficiency in patients with successful HP eradication was better than that in patients with unsuccessful HP eradication and those without eradication. On the basis of total effective rate, the proportion of overall therapeutic efficacy in patients who received eradication treatment (regardless results [success or failure]) was obviously higher than that in those without eradication at 4 w, 8 w and 12 w, but not at 26 w and 52 w; Patients with successful HP eradication had better efficiency than other patients.

As shown in **Figure 2**, in PDS group, the total effective rate in patients with successful HP eradication was significantly higher than that in other patients at 8 w, 12 w and 26 w. The significant efficiency in patients receiving HP eradication treatment (regardless results) at 4 w, 8 w and 12 w was markedly higher than that in patients without eradication. At 26 w and 52 w, the significant efficiency in patients with successful HP eradication was also higher than that in patients with un successful HP eradication and in those without eradication.

On the basis of above findings, successful HP eradication is better in EPS group than PDS group, at least within half a year. However, on the basis of symptom remission, successful HP eradication plays an important role in both subgroups at the late stage of follow up.

As shown in **Table 3**, the therapeutic effect decreased over time after treatment in HP positive patients without eradication when compared with HP negative patients in EPS group. While in PDS group, symptom relief was found at 26 w and 52 w. Moreover, as shown in **Figure 3**, both significant efficiency and total effective rate were higher than those in HP positive patients without eradication group in EPS group. In addition, in PDS group, the total effective rate in HP negative patients was higher than that in at different time points after treatment, while significant efficiency in HP negative patients was markedly higher than that in HP

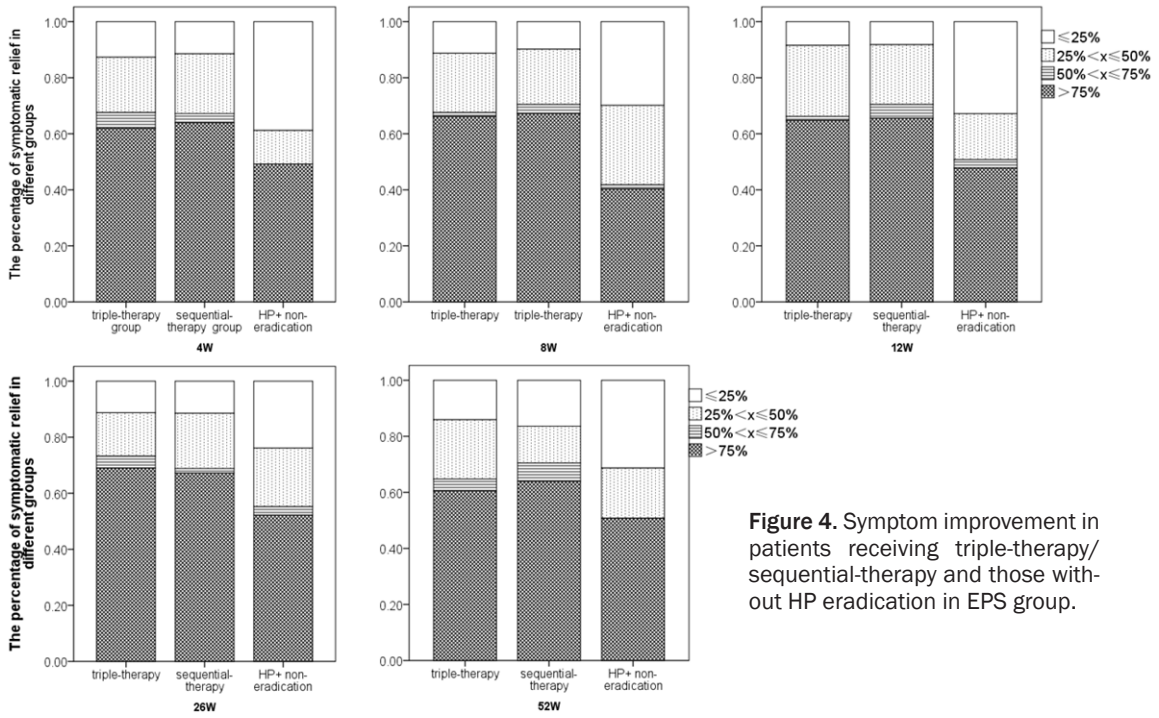

Figure 4. Symptom improvement in patients receiving triple-therapy/sequential-therapy and those without HP eradication in EPS group.

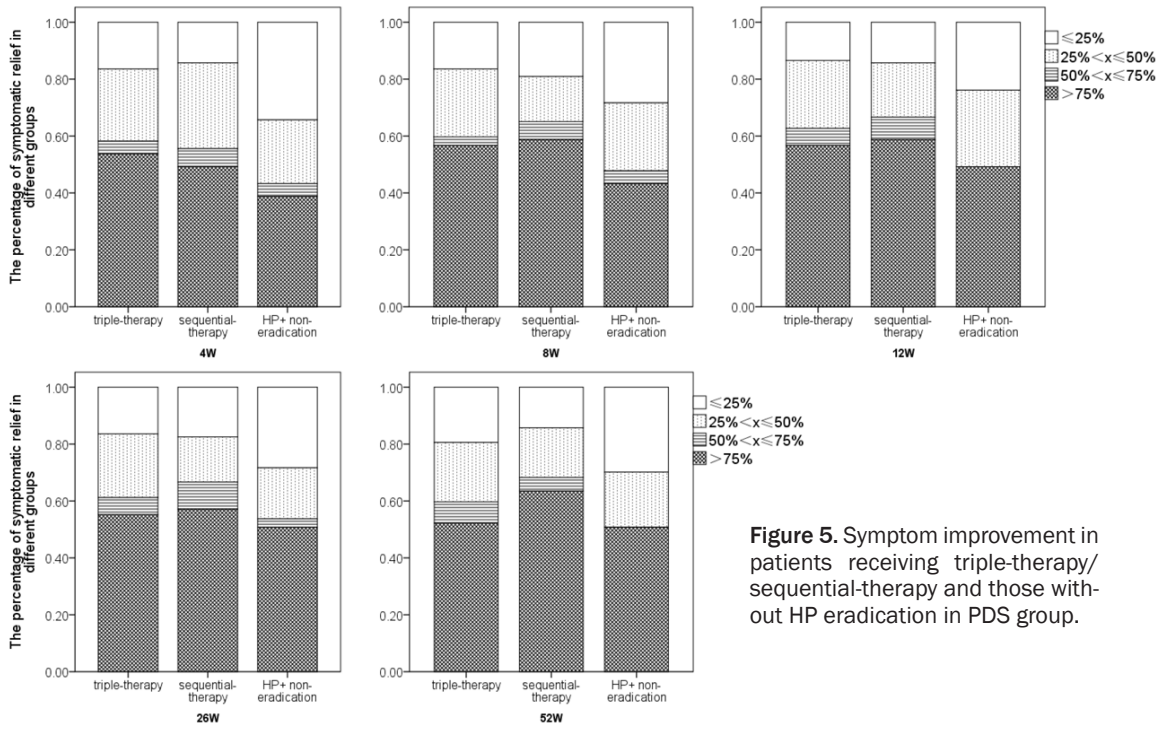

Figure 5. Symptom improvement in patients receiving triple-therapy/sequential-therapy and those without HP eradication in PDS group.

positive patients without eradication since 8 weeks after treatment.

There was no significant difference in improvement of clinical symptoms between triple-therapy patients and sequential-therapy patients in two subgroups. However, in EPS group, triple therapy patients and sequential therapy patients on the extents of the clinical symptoms were better than HP positive patients without eradication at different time points after treatment, particularly at 4 w, 8 w, 12 w

and 26 w (**Table 4**). Moreover, in two subgroups, the total effective rate and significant efficiency in triple therapy patients and sequential-therapy patients were significantly higher than those in HP positive patients without eradication and no marked difference was noted between triple therapy patients and sequential therapy patients (**Figures 4** and **5**).

On the basis of above findings, we speculated that HP exerts a more potent effect on EPS subtype than on PDS subtype.

Discussion

HP is a common pathogen that infects about one-half of word's population, and the prevalence of HP infection is about 30% in developed countries [4] and 80-90% in developing countries [5]. In addition, 30%-70% of HP infection patents were reported to have FD [6, 7]. In our study, the HP infection rate was as high as 67.70% in Chinese FD patients, which was consistent with the rate in general population as previously reported. Moreover, the HP infection rate was comparable between FD patients of different subgroups (EPS and PDS). Thus, it is necessary to study whether HP should be eradicated or not in FD patients, but there is still a worldwide controversy on this issue [2, 3].

Considering a high prevalence of HP infection and to avoid unnecessary waste of medical resources in our country, a multicenter cohort study is required to investigate whether HP should be eradicated in FD patients and what the best regime is for HP eradication. This trail was done in four health centers in China. There were three objectives in our study: 1) to investigate the prevalence of HP infection in FD patients; 2) to investigate whether clinical symptoms can be relived in FD patients after successful HP eradication and the difference in symptom improvement between two subgroups (EPS and PDS); 3) to compare the therapeutic efficacy of triple-therapy and sequential-therapy.

On the basis of Rome III criteria, FD is defined as presence of epigastric pain, epigastric burning, postprandial fullness and/or early satiety in absence of any organic, systemic or metabolic disease likely to explain the symptoms [8], and these symptoms should be present for 12 weeks, with onset at least 6 months before diagnosis [8]. FD is divided into two subgroups: EPS and PDS [9]. Due to the frequently occurring symptoms, FD significantly affects the quality of life in a variety of patients [10]. To date, many studies have been conducted to investigate the prevalence of FD. It was reported that the prevalence of FD was 25% in western adult patients [11], and 7.58% in a report from Wuhan Union Hospital [12].

Traditionally, EPS patients are treated with antacids and PDS patients with gastrointestinal prokinetic drugs. However, the improvement of symptoms is transient. Thus, to achieve long term relief of FD symptoms is still a challenge for physicians in the Department of Gastroenterology.

As shown in the symptom scores before and at 4 w, 8 w, 12 w, 26 w and 52 w after treatment, FD patients benefited from HP eradication treatment greatly, especially those with EPS achieving a long-term symptom improvement while PDS patients obtaining a short-term improvement. The pathogenesis of FD is still unclear, and several mechanisms have been proposed, including visceral hypersensitivity, delayed gastric empting, HP infection, impaired gastric accommodation, and central nervous dysfunction, etc [13, 14]. Moreover, the pathogenicity of HP in FD is also poorly understood. Some studies have shown [15-17] that HP infection can cause chronic gastritis with different severities resulting in clinical symptoms. Other studies [18-20] also reveal that HP infection can lead to delayed gastric empting as it reduces the electric wave of stomach and slows down the antrum peristalsis. The preferable effect of HP eradication on EPS group may be attributed to the relief of high-acid environment, but this is needed to confirm. However, FD patients acquire a great beneficial after HP eradication according to our multicenter study in Chinese people.

In addition, the therapeutic efficacy of triple-therapy and sequential therapy was compared in FD patients. No significant difference was found in HP eradication rate between two regimes (80.46% vs 71.79%; $P = 0.191$). In addition, the improvement of clinical symptoms was comparable between them. This finding provides evidence for physicians in selection of therapeutic regimens according to the antibiotic-resistance of HP in local area, cost-effectiveness, and side effects of drugs and compliance of patients.

Thus, considering a high prevalence of HP infection in Chinese FD patients (67.70%), HP detection is necessary. HP is one of pathogenic factors of FD and HP positive patients may benefit from HP eradication treatment with triple therapy or sequential therapy, especially in EPS patients.

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Disclosure of conflict of interest

None declared.

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