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Comparison of the Role of Helicobacter Pylori Eradication in the Treatment of Chronic Urticaria with Conventional Therapies

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ABSTRACT

Introduction: Helicobacter pylori (H. pylori) is the cause of the most common chronic bacterial infection in humans of all ages across the world. The majority of the patients with chronic urticarial have been reported to carry H. pylori. The present study aimed to compare the role of H. pylori eradication in the treatment of chronic urticaria with conventional therapies.

Materials and Methods: This randomized, double-blind, controlled trial was conducted on 120 patients with chronic urticaria infected with H. pylori receiving urea breath test referring to Qaem Hospital in Mashhad, Iran. The participants were randomly assigned to two groups of treatment and control. The control group received conventional therapy for urticaria with H1 and H2 blockers. The treatment group received triple drug therapy with rabeprazole (20 mg, twice daily), clarithromycin (500 mg, twice daily), amoxicillin (1 g, twice daily) for 14 days. One, three, and six months after the treatment, the symptoms of the patients in both groups were analyzed based on the urticaria severity score.

Results: No significant difference was observed between the treatment and control groups in terms of age (P=0.863). However, mean age was significantly higher in the male patients (P=0.006). The majority of the patients receiving combination drug therapy were significantly better cured compared to the control group (P<0.001), which was demonstrated by many components of the urticaria severity score (P<0.001).

Conclusion: According to the results, the therapies used in the treatment group were more effective in the eradication of H. pylori infection in the patients with chronic urticaria compared to conventional therapies with H1 and H2 blockers for symptom resolution.

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Introduction

Helicobacter pylori (H. pylori) is the cause of the most common chronic bacterial infection in humans of ages across the world (1, 2).

Attempts have been made to associate some common chronic infections with chronic urticaria, including H. pylori infection (3-6). In developing countries, such as Iran, H. pylori infection has been reported to affect 80% of the population aged less than 20 years, while in industrialized countries, the rate has been estimated at 20-50% (7). Furthermore, a correlation has been reported between H. pylori infection, socioeconomic status, and education level.

H. pylori could be detected in peptic ulcers. This bacterium is also one of the major causes of gastritis. Maltoma (mucosal lymphoma) and gastric adenocarcinoma are also attributed to H. pylori (7). One of the adverse consequences of H. pylori colonization in the stomach is its association with chronic urticaria, which leads to hives for more than six weeks in the patients (8-10). It is also notable that chronic urticaria may also be developed by autoimmune, idiopathic pseudo-allergies or infectious agents (8, 11-13).

Several studies have confirmed the key role of H. pylori bacterial infections (e.g., dental sepsis, sinusitis,

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urinary tract and gallbladder infections, and gastric infections) in developing variable degrees of chronic urticaria (8, 14, 15). The present study aimed to investigate the role of a triple drug regimen in eradicating H. pylori infection and its effects on the treatment of chronic urticaria.

Materials and Methods

Characteristics of the Patients

This randomized, double-blind, controlled trial was conducted at Ghaem Hospital in Mashhad, Iran during 2011-2013. Sample population consisted of the patients affected by chronic urticaria for a minimum of six weeks prior to enrollment. The participants were aged more than 14 years and provided informed consent. Diagnosis was confirmed by an allergy and immunology physician.

Study Design

The urea breath test (UBT) was performed on the patients regardless of etiology. To do so, 13C-urea capsules and distilled water (100 cc) were administered to the patients. After 10 minutes, their breath was analyzed using an envelope containing an absorber and a Heliprobe® device (Kibion). After 250 seconds, the analysis of the results was presented based on a specific equation in the form of the numerical value d, which was the sum of d1 and d2 analysis.

Based on the results of the d index, the patients were divided into three groups of no infection (d<25), borderline infection (50> d>25), and high/severe infection (d>50). It is notable that to perform UBT, the patients were required to avoid antibiotics or bismuth within one month prior to the test. In addition, they were not allowed to use proton pump inhibitors, H2 blockers or antacids for two weeks prior to the test. Another requirement was abstinence from eating for six hours before the test (16).

All the patients were diagnosed with chronic urticaria and had positive UBT for H. pylori with the d index of more than 50. According to the literature, the prevalence of H. pylori is approximately 80% (23), and the sample size of the present study was estimated at 120 patients at 95% confidence level.

Medications

The patients were randomly assigned to two groups of 60. Randomization of the participants was performed using simple random sampling and a table. In the first group (control), the patients received the conventional therapies for chronic urticaria, which involved H1 and H2 blockers (e.g., ketotifen and ranitidine) (9, 10), which continued for six months as needed.

In the second group (treatment), the patients received an additional triple-drug eradicative treatment for H. pylori infection, which involved rabeprazole (Pariet®; 20 mg, twice daily), clarithromycin (500 mg, twice daily), and amoxicillin (1 g, twice daily) for 14 days (7, 8, 19).

One month after the treatment, the UBT was repeated to confirm the eradication of H. pylori in the treatment group. The patients were evaluated for the signs and symptoms of urticaria recurrence based on the urticaria severity scoreone, three, and six months after the treatment

Statistical Analysis

Data analysis was performed in SSPS version 13.0 (SPSS Inc., Chicago, IL, USA) using t-test, Mann-Whitney U test, Kruskal-Wallis test, Friedman's test, and nonparametric correlational tests to compare the quantitative variables between the study groups. Moreover, Chi-square was used for the comparison of the categorical variables. In all the statistical analyses, P-value of less than 0.05 was considered significant.

Results

In total, 120 patients with chronic urticaria, including 52 males (43.3%), with the mean age of 37.8±13.8 years (age range: 14-80 years). Mean age of the male patients was significantly higher than the females (P=0.01), and no significant difference was observed between the treatment and control groups in terms of the mean age (P=0.56) (Table 1).

Table1: Mean Age of Patients Based on Gender and Treatment Group

	Confidence Interval		Standard Deviation	Mean Age (year)	N
	High limit		Low limit		
Total	40.7	35.6	13.8	37.8	120
Male	46.3	38.1	14.2	41.4	52
Female	38.2	32.1	13.1	35.1	68
Standard Treatment	42.5	34.3	14.2	38.5	60
Eradication + Standard Treatment	41.1	34.8	13.6	37.1	60

In addition, no significant difference was observed between the groups in terms of gender (P=1.00). Variables of the participants based on the pretreatment urticaria severity scores are presented in Table 2.

According to the findings, symptom improvement in the treatment group was more significant compared to the control group three and six months after the treatment (Table 3). One month after the treatment, the urticaria localization score improved in 13 patients in the control group (21.7%) and 45 patients in the treatment group (75.0%) (P=0.01). However, no significant differences were observed between the two groups in terms of the other components of the urticaria severity score (P>0.05). Meanwhile, the results of the repeated UBT showed improvement in 54 patients in the treatment group (90%).

Three months after the treatment, the signs and symptoms of urticaria improved in 23 patients in the control group (38.3%) and 48 patients in the treatment group (80.0%) based on the components of the urticaria

severity score. All the values based on the urticaria severity score had significant differences between the treatment and control groups (P<0.05), with the exception of the disease duration score (P=0.86). Furthermore, these findings were repeated six months after the treatment.

According to the results of Mann-Whitney U test, the healing ratio in the patients who were exposed to combination drug therapy was significantly higher compared to those who were exposed to conventional therapies three and six months after the treatment (P<0.001).

Although a positive, significant correlation was observed between the age and total score of the patients (Spearman's rho=0.86; P<0.001) between the male and female patients in the treatment and control groups (P<0.001). It is notable that in the present study, even after the adjustment of the demographic variables (e.g., age and gender), the improvement in the treatment group was more significant compared to the control group. In addition, our findings indicated the improvement of the urticaria severity score was more significant in the female and younger patients, especially in the combination drug therapy group (Table 4).

We also investigated the role of additional standard regimens in the eradication of H. pylori in the patients with chronic urticaria. Moreover, we examined the correlations between different variables, such as localization, frequency, pruritus intensity, wheal duration, and disease duration with demographic variables (e.g., age, gender), which might have affected the process of treatment and healing.

Table2: Frequency of Variables of Patients Based on Pretreatment Urticaria Severity Score

Intensity	Localization Score		Episode Frequency Score		Pruritus Intensity Score		Size Score		Wheal Duration Score		Disease Duration Score	
	N	%	N	%	N	%	N	%	N	%	N	%
0	0	0	0	0	0	0	0	0	0	0	20	16.7
1	32	26.7	10	8.3	9	7.5	10	8.3	6	5	24	20.0
2	78	65.0	92	76.7	82	68.3	93	77.5	82	68.4	53	44.2
3	10	8.3	18	15	29	24.2	17	14.2	31	26.6	23	19.2

Table3: Comparison of Response to Therapy between Treatment and Control Groups Based on Clinical Variables

Variables	Treatment Group	First Month			Third Month			Sixth Month		
		Asym. Sig	Z	Mean Rank	Asym. Sig	Z	Mean Rank	Asym. Sig	Z	Mean Rank
Localization Score	Standard	0.017	-2.38	67.59	0.002	-3.07	68.97	0.000	-5.49	75.25
	Standard + Eradication			53.41			50.88			45.75
Episode Frequency Score	Standard	0.056	-1.91	66.28	0.001	-3.33	70.32	0.000	-5.46	75.16
	Standard + Eradication			54.73			50.68			45.84
Pruritus Intensity Score	Standard	0.156	-1.38	64.72	0.000	-3.73	71.70	0.000	-5.50	75.61
	Standard + Eradication			56.28			49.30			45.39
Size Score	Standard	0.095	-1.66	65.52	0.000	-3.68	71.33	0.000	-5.66	75.67
	Standard + Eradication			55.48			49.67			45.33
Wheal Duration Score	Standard	0.081	-1.74	56.76	0.000	-3.53	70.86	0.000	-5.55	75.40
	Standard + Eradication			55.24			50.14			45.60
Disease Duration Score	Standard	0.785	-0.273	59.68	0.868	-1.66	60.00	0.868	-0.16	60.00
	Standard + Eradication			61.32			61.00			61.00

Table4: Comparison of Improvement in Urticaria Severity Score in Treatment and Contorl Based on Age*

Treatment Group		Pretreatment	First Month	Third Month
Standard	**Z Score**	-1.7	-1.5	-1.2
	Asymp. Sig	0.07	0.12	0.20
Standard + Eradication	**Z Score**	-2.0	-3.4	-3.5
	Asymp. Sig	0.06	0.00	0.00

*Wilcoxon test

Discussion

The findings of the current research were unique since the previous studies in this regard have only assessed the signs and symptoms of urticaria, as well as their intensity and treatment, disregarding the comparison of demographic characteristics (17-21).

In the present study, symptom improvement was observed in the majority of the patients with chronic urticaria after H. pylori eradicative treatments within one, three, and six months of follow-up . Therefore, it could be concluded that there is a significant association between H. pylori eradication and the quality of chronic urticaria treatment.

In the present study, the frequency of the signs and symptoms of urticaria in the treatment and control groups was assessed at various intervals (one, three, and six months). According to the obtained results, symptom improvement in the treatment group was more significant compared to the control group, which is consistent with the results of the previous studies in this regard (20, 21). To draw an analogy, the studies conducted under more standard conditions (i.e., sufficient samples and effective methodology) regarding the eradicative treatment of H. pylori in the patients with chronic urticaria have denoted noticeable improvement (22), which is in line with the current research despite the discrepancies in some studies (23).

Conclusion

Although urticaria could have various causes and avoiding the stimulus may be the optimal treatment, in the chronic urticaria cases where the main cause of the disease cannot be determined, the examination, diagnosis, and treatment of H. pylori infection could effectively prevent and diminish the disease episodes or its toleration. Therefore, it is recommended that this matter be taken into account in the case of the patients with H. pylori infection. It is presumed that such empirical treatments require further investigations to prove their efficacy, while in refractory CU, the eradication of H. pylori should be further considered, especially in the case of young, female patients.

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