

## Original Article



# Efficacy of *Helicobacter pylori* eradication on recovery of chronic urticaria

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### Abstract

**Introduction:** The studies have been equivocal about the association of *Helicobacter pylori* infection with chronic urticaria (CU) given some controversial evidence in recovery of urticaria following *H. pylori* eradication.

**Methods:** In this clinical trial, 120 patients between the ages of 4 and 20 with intractable CU were recruited. They were grouped into two categories based on urea breath test (UBT) result. UBT positive group received treatment and UBT was repeated after two months while being evaluated for clinical course over a six-month period. On the other hand, UBT negative group received standard treatment for urticaria.

**Results:** All participants with CU have been studied as 40 cases of UBT positive and 80 cases of control group with negative UBT, consisted of 42 (35%) male and 78 (65%) female. Patients had suffered from urticaria on average 29.9 ( $\pm 26.6$ ) months prior to diagnosis. Statistically significant difference was noted between two groups, in terms of severity of urticaria, frequency of episodes, abdominal pain and duration of being symptomatic prior to diagnosis. After receiving treatment for *H. pylori* infection, among case group, 27 (67.5%) of individuals achieved complete recovery of urticaria and 13 (32.5%) cases demonstrated partial resolution of urticaria, meanwhile 59 cases (73.8%) of control group became completely symptom-free, while 21 (26.3%) of the remaining individuals were in incomplete recovery. In comparison of response to treatment between the above-mentioned groups, there was not any statistically significant difference ( $P=0.47$ )

**Conclusion:** Our findings reveal that *H. pylori* infection might contribute to developing CU which highlights the significance of *H. pylori* eradication as an approach for CU.

### Introduction

Urticaria is an outbreak of raised, pruritic and erythematous skin rashes characterized with occasional central pallor. The condition qualifies for chronic urticaria (CU) if the hives remain present for than 6 weeks. Nearly 20%-25% of general population experience a single episode of acute urticaria in their lifetime but CU is much less prevalent (1%) and mostly considered as idiopathic or autoimmune in nature although a wide range of etiologies have been attributed to the development of CU including: physical stimuli, collagen vascular diseases, endocrinopathies, malignancy and allergy.<sup>1-7</sup>

Although, recent studies have taken into consideration the role of infectious agents in CU, such as *Helicobacter pylori* infection and is found to be prevalent among the patients with CU but the association between urticaria and *H. pylori* remains unknown.<sup>8-12</sup> On the other hands, some hypotheses concerning the role of *H. pylori* in

etiopathogenesis of CU.

The prevalence of CU varies in countries that are about 0.6% in Spain (is significantly higher in women than men).<sup>12</sup>

Few data are available on epidemiology of CU in children. Studies on mixed (adult and children) populations reported a prevalence of 0.8%.<sup>11,12</sup> A Korean survey on children aged 4-13 found a prevalence of 1.8%, with no difference among two sex.<sup>13,14</sup> Concerning incidence, an Italian study on children aged 0-14, where the diagnosis of CU was made by a pediatrician, showed an annual incidence of 0.6 to 2.1/1000 children, and a prevalence fluctuating between 0,38% and 0,84%.<sup>15</sup> Overall, the prevalence of CU in children seems to be below 1%, with no significant difference between males and females.<sup>12-17</sup> The aim of this study is to determine of *H. pylori* infection using the UBT in patients with CU to investigate the efficacy of *H. pylori* in Resolution of CU. So, regarding

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recent uncertainties over the role of *H. pylori* infection in developing urticaria, current study has been carried out.

## Methods

Subject enrollment for this clinical trial took place during two years in Tabriz, Iran. They were recruited from sub-specialized pediatric gastroenterology and allergy clinics with inclusion of all patients aged 4-20 years old who were referred with CU. Then patients were divided in to case (UBT+) and control (UBT-) groups according to their urea breath test (UBT) results.<sup>18</sup> Patients with established diagnosis of *H. pylori* infection received triple therapy regimen (a 14-day course of amoxicillin 50 mg/kg with metronidazole 30 mg/kg added to an oral proton pump inhibitor 1 mg/kg for a month).<sup>19</sup> They were offered a repeat UBT two months after treatment completion. Clinical history was obtained including: sex, age, symptoms duration, clinical course, severity of urticaria, previous history of allergic diseases, and presence of any gastrointestinal manifestation such as abdominal pain. Meanwhile clinical signs and symptoms of CU were recorded in a Questionnaire for a 6 month's period and followed by monthly visit of patients.

Patients with indefinable cause for their condition as well as recent medication history of antibiotics, angiotensin-converting enzyme inhibitors, *proton pump* inhibitors, and nonsteroidal anti-inflammatory drugs were excluded from study. The data of patients who were not followed up were not analyzed in the study. Severity of urticaria was evaluated by number of wheals and degree of pruritus experienced by patients that affected their daily activities. For this reason, we used the modified urticaria activity score to assess severity of disease by asking: "How many wheals were there when patient's urticaria was most severe?" Wheals were classified as none, mild (20 or fewer wheals per 24 hours), moderate (20 to 50 wheals per 24 hours), or intense (50 or more wheals per 24 hours or large confluent areas of wheal). Pruritus was classified as none, mild (present but not annoying or troublesome), moderate (troublesome but not interfering with normal daily activities or sleep), or intense (very troublesome and interfering with normal daily activities or sleep).<sup>5</sup>

Following a comprehensive explanation covering the aim of study and details related to possible side effects of eradication regimen, a written consent was obtained from each of the participants' guardians. Present study has involved no intervention except for oral administration of the standard *H. pylori* triple therapy to the case group. This trial is registered with the Iranian Clinical Trials Registry (identifier: IRCT 201012065330).

## Statistical analysis

Collected data were analyzed using IBM SPSS Statistics V21.0. Basic features of data set were summarized with the use of descriptive statistics (frequencies, proportions, and measures of central tendency). Chi-square and

McNamara tests were performed to compare qualitative variables and independent-samples *t* test was exerted to contrast quantitative data. The Kolmogorov-Smirnov test was utilized to test whether our dataset could match the characteristics of a normal distribution and *P* values less than 0.05 were considered as statistically significant.

## Results

In this clinical trial study, 120 participants with CU has been studied as 40 cases of UBT positive and 80 controls of UBT negative. Our study sample consisted of 42 (35%) male and 78 (65%) female patients, with a sex ratio of 70% (28) female to 30% (12) male subjects in the case group of UBT positive patients while 62.5% (50) of individuals in control group (UBT negative) were female, leaving 37.5% (30) of male patients behind. The mean age was 14.1 ( $\pm 5.43$ ) years old with a minimum and maximum value of 4 and 20, respectively. The majority of subjects aged 15-20. The mean age of case group and control group was found to be 14.47 ( $\pm 0.05$ ) and 13.92 ( $\pm 5.64$ ).

While only 22 (18.3%) of patients reported unremitting symptoms of urticaria, the bulk of participants (81.7%,  $n=98$ ) did not experience incessant urticaria. Previous medical history of allergy and family history of allergy was noted in 30 (25%) and 50 (41.7%) of patients, respectively. The severity of urticaria was assessed to be mild in 5.8% ( $n=7$ ) and moderate in 80% ( $n=96$ ) of individuals and only 17 patients (14.2%) complained of excruciating attacks of urticaria. Total of 77% of patients with severe urticaria were revealed to be infected with *H. pylori*.

Patients had suffered from urticaria symptoms on average 29.9 ( $\pm 26.6$ ) months prior to diagnosis with minimum and maximum values of 1 and 180 months. From all patients with CU, 80 (66.6%) and 40 (33.3%) patients had tested negative and positive for *H. pylori* on UBT, respectively. Totally, after receiving treatment for *H. pylori* infection, 86 patients (71.7%) were completely cured of urticaria and the remaining 34 patients (28.3%) showed partial resolution. After case group's getting treated for *H. pylori*, a second UBT was conducted for them, in which 39 patients (97.5%) was cleared of infection and only one patient (2.5%) still did test positive for *H. pylori*. Among the case group, 67.5% ( $n=27$ ) showed signs of complete resolution (with complete resolution of wheal and pruritus) and 32.5% ( $n=13$ ) experienced a partial (with occasionally wheal and pruritus) recovery. On the other side, 73.8% ( $n=59$ ) of controls had recovered from urticaria and 26.3% ( $n=21$ ) of them had achieved partial relief. These findings failed us to appreciate any statistically meaningful difference in the rates of response to treatment between cases and controls (*P* value = 0.47). Demographics of case and control group are compared in Table 1.

The comparison of two groups displayed significant difference in terms of presence of abdominal pain, frequency of episodes, severity of attacks, history of allergy

**Table 1.** Comparison of different demographic findings between 2 groups

Variable	UBT (positive)	UBT (negative)	P value	
Sex	Male	12 (30%)	30 (37.5%)	0.41
	Female	28 (70%)	50 (62.5%)	0.60
Age (year)	14.47 ± 5.05	13.92 ± 5.64	0.001	
Duration of symptoms before diagnosis (month)	37.14 ± 36.47	22.06 ± 25.52	0.47	
Answer to treatment	Partial recovery	27 (67.5%)	59 (73.8%)	0.21
	Complete recovery	13 (32.5%)	21 (26.3%)	0.15
Abdominal pain	13 (32.5%)	31 (38.8%)	0.001	
History of allergy	19 (47.5%)	7 (8.75)	0.001	
Alteration of symptoms	Persistent	21 (52.5%)	0 (0%)	0.001
	Intermittent	19 (47.5%)	80 (100%)	
Severity of urticaria	Mild	5 (12.5%)	2 (2.5%)	0.001
	Moderate	24 (60%)	72 (90%)	
	Severe	11 (27.5%)	6 (7.5%)	

and duration of symptoms prior to diagnosis.

**Discussion**

We studied 120 patients with CU and divided them into two groups of cases (40 UBT positive patients) and controls (80 UBT negative cases), out of which 42 individuals (35%) were male and 78 of participants (65%) were female. Hook-Nikanne et al<sup>20</sup> conducted a study with enrollment of 235 (CU), consisting of 48 male and 147 female subjects, Ghazzawi and Obidat<sup>21</sup> carried out a similar study on 100 CU patients with 38 male and 62 female and also in the study of Hellmig et al<sup>22</sup>. including 32.4% male individuals enrolled. Likewise, the majority (n = 80) of 125 participants in the study of Valsecchi and Pigatto<sup>23</sup> were female. Current study was in accordance with all of the above-named studies, in terms of predominance of female participants. In the bulk of studies, the age of participants ranged from 30 to 50 which is conversely higher than that reported in our study (14.10 ± 5.43). However, our study is in an agreement with Valsecchi and Pigatto’s sample concerning the mean age.

Present study signifies a statistically relevant difference between cases and controls in tests of mean duration of symptoms prior to diagnosis, which was 37.14 ± 36.47 months among *H. pylori* positive subjects and 25.52 ± 22.06 months for uninfected patients (P < 0.05). Correspondingly, the average period was calculated to be 25.52 (ranging from 8 months to 10 years) and 36.2 months (with a range of 6 months to 15 years) by Dauden et al and Ghazzawi et al, respectively.<sup>1,24</sup> The estimated duration in current study is perhaps the closest to the former.

We found 52.5% of UBT positive patients to be suffering from unremitting urticaria, whereas all of their control counterparts (UBT negative) experienced intermittent symptoms of urticaria, which was statistically remarkable (P < 0.05).

This study indicated a statistically demonstrable difference in severity of urticaria between two groups,

as only 2.5% of control subjects exhibited rather severe manifestations of urticaria compared to 12.5% of cases who displayed severe features (P < 0.05). Previous history of allergy was present in a quarter (n = 30) of patients with CU, and the remainder of urticaria patients (n = 90, 75%) had no allergic comorbidity. The distribution of frequency of allergy between cases and controls was statistically noteworthy (P < 0.05), with 47.5% positive history of allergy among *H. pylori* infected patients versus 13.9% among the uninfected controls, which is in alignment with Hellmig’s study.<sup>22</sup> In another statistically remarkable discrepancy, in contrast to 32.5% of UBT positive cases, only 3.8% of UBT negative controls had complained of abdominal pain (P < 0.05).

Helmig et al in a statistically insignificant finding uncovered that after treatment, 67.5% of cases and 73.8% of controls achieved full recovery, which leaves the rest of participants in an incomplete resolution of symptoms.<sup>22</sup> Hook-Nikanne et al concluded that eradication of *H. pylori* does not affect the resolution of CU, as only 8 out of 30 patients with eradicated *H. pylori* (27%) could recover from CU. Meanwhile, 5 of 18 untreated subjects (28%) achieved recovery.<sup>20</sup> In the study of Ghazzawi and Obidat only 32% of patients (24 out of 76) made full recovery after being started on anti *H. pylori* medications and the remaining patients showed various degrees of resolution. They described no statistically prominent difference in the prevalence of *H. pylori* infection among subjects with and without CU, nonetheless the authors didn’t dismiss the role of *H. pylori* eradication in treatment of urticaria altogether and have suggested that *H. pylori* infection may fulfill a crucial role with regards to disease causation.<sup>21</sup> Fukuda et al studied a total of 26 patients with *H. pylori* infection and urticaria, then 19 patients received eradication regimen and 17 of them expressed varying degrees of symptom relief. On the other hand, among 9 patients who did not receive treatment for their *H. pylori* infection, solely 2 patients (22%) recovered from urticaria and 7 cases displayed no improvement of their urticaria attacks,

which is indicative of a statistically relevant difference in recovery rates between patients treated for *H. pylori* infection and those not treated.<sup>24</sup> Gaig's<sup>11</sup> study resulted in similar findings, as 4 out of 9 patients (44.4 %) completely recovered from urticaria following a course of *H. pylori* eradication therapy. Expectedly among those not treated for *H. pylori* infection, only one patient (corresponding to 12.3%) achieved recovery. They have emphasized on *H. pylori* eradication to be a component of treatment strategy for patients with a long history of urticaria.<sup>19</sup> Likewise, in the study of Di Campli et al 88% of patients who received treatment for *H. pylori* experienced complete or partial resolution of symptoms, while individuals who were not infected with *H. pylori* continued to suffer from constant symptoms of urticaria.<sup>24</sup> On the contrary, Valsecchi and Pigatto followed up the treated *H. pylori* patients for 12 months, only to find 9% (n=3) of them recovered from urticaria. They subsequently arrived at the conclusion that eradication of *H. pylori* does not affect the recovery from CU.<sup>23</sup> In the study of Rasooly et al on 204 patients of CU, no more than 10% were infected with *H. pylori*. They arrived at the finding that eradication of *H. pylori* leads to resolution of urticaria while limiting the progression of complications associated with peptic ulcer disease and gastric cancer.<sup>25</sup> Loh et al. conducted a study in Canada, with participation of 266 patients of CU, 16.5% (n=44) of whom had tested positive for *H. pylori*. After completion of treatment for *H. pylori*, 44.4% of them had no attacks of urticaria, which highlighted the necessity for widespread testing for *H. pylori* in the work-up of CU.<sup>26</sup> Erel et al studied 38 cases of CU and diagnosed 29 of them with *H. pylori* infection, but only one *H. pylori* positive patient had symptoms subsiding following the standard triple therapy. This study enabled them of denying presence of any meaningful relationship between *H. pylori* infection and CU.<sup>27</sup> Kim et al deduced that patients who were undergone antibiotic therapy for *H. pylori* eradication showed significant higher urticaria remission with or without *H. pylori* eradication.<sup>28</sup>

In the present study with participation of 120 patients of CU, 40 cases (33.3%) had *H. pylori* infection and 80 subjects (66.6%) tested negative for *H. pylori* on UBT. The 40 cases (consisting of 12 male and 28 female individuals) received anti *H. pylori* medications, then underwent repeat UBT. Not more than one cases tested positive on the second UBT and 97.5% (n=39) were cleared of infection. Among the cases of *H. pylori* positive, 67.5% (n=27) had fully recovered from CU while 32.5% (n=13) achieved only a partial resolution. As a statistically unremarkable finding, subjects of control group demonstrated complete and incomplete relief in 73.8% (n=59) and 26.3% (n=21), respectively. In an overall agreement with the aforementioned studies, current study was unable to find any significant relationship between *H. pylori* eradication and resolution of CU.

## Study Highlights

### What is current knowledge?

- Studies have shown the impression of *H. pylori* infection in chronic urticaria.

### What is new here?

- *H. pylori* should be included in urticaria, especially in patients who have not responded to regular treatment of chronic urticaria or in those with concurrent gastrointestinal symptom.

## Conclusion

Current study elucidated the meaningful difference between cases and controls (*H. pylori* positive and negatives) regarding features of urticaria such as duration of symptoms, frequency of symptoms, degree of itchiness, history of allergy and presence of abdominal pain. We could not find any correlation between response to treatment and age/sex. Even though our findings failed to denote the exact role of eradication of *H. pylori* in the natural history, treatment and ultimate resolution of CU, it will be difficult to deny that *H. pylori* eradication exerts some influence over resolution of urticaria at least in a proportion of patients. All in all, it still can be deduced that *H. pylori* infection contributes either directly or indirectly to disease formation. Our limitation was that this study was done in one center and it is better to do it in a multicenter study.

## Conflicts of Interest

The authors declare no conflicts of interest

## Ethical Approval

This study was approved by Ethics Committee in Tabriz University of Medical Sciences (Ethics No. N1.5/4/7578).

## Author's contributions

M.S-SH & M. R contributed in patients visiting and follow up of them as well as writing the article; B. N contribution was static analysis of paper; Z. J and N.HK joined to edit the English article.

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