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ROLE OF HELICOBACTER PYLORI ERADICATION USING CLARITHROMYCIN-BASED TRIPLE THERAPY IN PATIENTS WITH IRRITABLE BOWEL SYNDROME

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Background: *Association between Helicobacter pylori (H. pylori) and irritable bowel syndrome (IBS) remains controversial. We evaluated the changes in symptoms and quality of life (QOL) in IBS patients following H. pylori eradication using clarithromycin-based triple therapy.* ***Methods:*** *Patients with moderate or severe IBS and positive H. pylori stool antigen were included and received clarithromycin-based triple therapy, followed by testing for H. pylori eradication after one month. IBS symptoms and IBS-QOL questionnaire were evaluated at the baseline and after H. pylori eradication.* ***Results:*** *108 patients had H. pylori eradication. Following eradication, 66 patients reported IBS symptoms improvement, while 42 did not. The improved patients were significantly younger; mean age was 38.1 ± 11.7 (p= 0.03). IBS-C type predominated (42.4%) and postprandial fullness and early satiety as dyspeptic symptoms were higher in the improved group. The non-improved group showed a decrease in IBS-QOL subscales, significantly observed in dysphoria, interference with activity, health worry, and social reaction domains. The total IBS-QOL score was significantly higher in the improved versus the non-improved group (p= 0.000).* ***Conclusion:*** *H. pylori eradication did not improve IBS symptoms or QOL in all patients with IBS. QOL improved in young patients with dyspeptic symptoms and the IBS-C subtype.*

Keywords: *Eradication; Helicobacter pylori; irritable bowel syndrome; quality of life; triple therapy.*

INTRODUCTION

Irritable bowel syndrome (IBS) is characterized by abdominal pain associated with changes in the bowel habits without identified organic pathology[1]. It is estimated that the IBS global prevalence is varying from 9 to 23%[2]. Several reports on IBS and the new Rome IV criteria published in 2016 have changed the diagnostic criteria for IBS. A recent epidemiological survey using the Rome IV criteria revealed that the prevalence of IBS globally is 4.1%[3]. According to the predominant symptom, IBS is categorized into four subtypes: IBS-C (constipation), IBS-D (diarrhea), IBS-M (mixed constipation and diarrhea), and un-classified IBS (non of the previous patterns)[1].

Heterogeneity of IBS pathogenesis is reflected by the long-term interactions of various factors; neuroendocrinal, psychosomatic, changes in immunity, pharmaceutical, and infectious factors[4]. IBS largely impacts the quality of life (QOL), even though clinical interventions remain relatively ineffective. It has been documented in IBS patients that the QOL is even less than the QOL in some chronic diseases, such as diabetes

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mellitus, dialysis-associated renal disease, or gastroesophageal reflux disease[5]. Additionally, in IBS, the biopsychosocial model proposes a significant synergy of physiological, cognitive, and emotional factors[6]. As predictors of health related quality of life (HRQoL), psychosocial factors and symptomatic severity attributed independently to IBS[7].

Helicobacter pylori (*H. pylori*) infection is one of the most common human chronic bacterial infections. The prevalence of *H. pylori* infection in IBS patients varies from 9.7 % to 72.1 %[8]. However, there is still controversy regarding the higher rate of *H. pylori* infection in IBS patients relative to the healthy population[9]. Meanwhile, Liang et al reported in a recent nationwide study in Taiwan that patients with *H. pylori* infection who received eradication therapy had a lower risk of IBS than the untreated patients[10].

The association between *H. pylori* infection and IBS has been extensively investigated, with no established definite relationship. Barrios et al. concluded in their study that *H. pylori* presence in colonic mucosa is an essential co-factor in IBS pathogenesis[11]. Ng QX et al. suggested in one meta-analysis that IBS sufferers may have an increased probability of *H. pylori* infection, but this was not significant statistically[12]. *H. pylori* infection has not been significantly linked to IBS in a recent meta-analysis[8].

H. pylori's potential mechanism of association with IBS could be linked to *H. pylori*-induced inflammation, which encourages the secretion of proinflammatory neurotransmitters such as 5-HT and others that influence the brain-gut axis later. This inflammation can also cause changes in intestinal flora or exacerbate the response to stress[13]. Recently, anti-*H. pylori* treatment was found to enhance the clinical remission rates of IBS patients[9]. However, there are limited data on the effect of *H. pylori* eradication on the IBS symptoms and QOL. Therefore, we aimed to evaluate the changes in IBS symptoms and the QOL in IBS patients following eradication of *H. pylori* using clarithromycin-based triple therapy.

MATERIAL AND METHODS

Patients with IBS diagnosed by Rome IV criteria were included in the study. They were recruited from the Tropical Medicine and Gastroenterology Department outpatient clinic in Al Rajhi Liver University Hospital, Assiut over 6 months period. Routine laboratory investigations such as blood picture, liver function, and abdominal ultrasound were done to exclude organic diseases and confirm IBS diagnosis. Patients with moderate or severe IBS according to IBS-severity score were included[14]. IBS-severity score includes 5 questions with a total score of 500, the patient had mild IBS if the total score is< 175, moderate IBS if score between 175 and 300, and severe IBS if > 300.

All patients have been tested for *H. pylori* antigen in the stool, as a simple, more affordable, and more tolerable alternative to urea breath test, especially in the developing countries[15]. There was also clinical evaluation of gastritis or dyspepsia symptoms such as epigastric pain, postprandial fullness, nausea, vomiting, and belching. Positive cases for *H. pylori* were treated in the form of triple therapy by clarithromycin 500 mg b.id, 500 mg tinidazole bid, and 20 mg omeprazole bid for 14 days. Evaluation of the quality of life was done at baseline (before treatment) using the Arabic version of the IBS-QOL questionnaire. To avoid the confounding effect during the interpretation of the results, patients received ant-*H. pylori* therapy only and did not receive treatment for IBS symptoms during the study duration. Also, patients followed the instructions as regard avoiding food that can exacerbate IBS symptoms to avoid this confounding factor.

Follow up was done one month after the end of *H. pylori* therapy according to guidelines[16] to monitor the eradication of *H. pylori* antigen in the stool and also to monitor IBS symptoms. Improvement of patients symptoms was considered if there was a reduction in IBS-severity score relative to the baseline. IBS-QOL questionnaire was used again to assess the QOL after 1 month of therapy. IBS-QOL questionnaire was done and interpreted at the outpatient clinic of Neurology and Psychiatry Department, Assiut University.

The IBS-QOL is a self-report psychometric tool developed and validated to assess the impairment of QOL in IBS. It is specific to IBS and can be used to determine the impact of IBS and its treatment[17]. A systematic review has recommended the IBS-QOL measure as the best of five IBS-specific QOL scores available to establish the change in

HRQoL[18]. The IBS-QOL measure consists of 34 IBS-specific items and is evaluated by the patients through a 5-point Likert scale (1 = not at all, 2 = slight, 3 = moderate, 4 = quite a bit, 5 = extremely or a great deal).

The sum of the items is converted into a score with a range between 34 to 100 and the score of 100 equals to the maximum QOL score. There are eight IBS-QOL subscales or domains in the IBS-QOL measure: dysphoria, interference with activity, body image, health worry, food avoidance, social reaction, sexual concerns, and relationships. Concerning the interpretation of results, the minimum important response (MIR) for IBS-QOL is considered if there is an increase of 10.2 from the baseline score. If there is an increase of at least 14 from the baseline, the meaningful clinical response (MCR) is considered[19].

This study was approved by the Ethical Committee of Faculty of Medicine, Assiut University and was registered on clinical trial by ID: NCT04512898. A written informed consent was obtained from all the participants before enrolment in the study. All procedures performed in this study were in accordance with the ethical standards of the institution and/or national research committee and with the Helsinki Declaration.

Statistical analysis

Data analysis was performed using version 21 of SPSS software (SPSS Inc, Chicago, IL, USA). As appropriate, the means ± standard deviations, frequencies, and percentages were used. The independent t-test and paired t-test were performed for comparison of quantitative variables between the two groups and within the same group, respectively. The Chi-square ($\chi 2$) test was used for the comparison of categorical data. When P is < 0.05, a significant p-value was considered.

Results

One hundred and twenty-four IBS patients were included at the start of the study. They received the anti-*H. pylori* triple therapy. A total of 16 patients showed failure to eradicate *H. pylori* antigen while 108 patients had *H. pylori* eradication. The demographic and clinical features of patients with *H. pylori* eradication, as illustrated in table 1, show that the mean age was 40.11 ± 12 years, and males predominated (61.1%). The most frequent IBS type was IBS-C type (38.9%), and bloating was a frequent complaint in 68 patients (54.8%). Dyspeptic symptoms were common in the included patients, and postprandial fullness was the most observed in 68.5%.

Table 1: The demographic, clinical, laboratory and ultrasonographic features of the patients with *H. pylori* eradication.

Items	IBS patients (n=108) (n, %)
Age (mean ± SD)	40.11±12
Sex:	
Male	66(61.1%)
Female	42(38.9%)
Residence:	
Rural	42(38.9%)
Urban	66(61.1%)
Smoking	32(29.6%)
Co-morbidity:	
Diabetes Mellitus	14(13%)
Hypertension	10(9.3%)
Type of IBS:	
IBS-C	42(38.9%)
IBS-D	32(29.6%)
IBS-M	34(31.5%)
IBS-U	0
Bloating	68(54.8%)
Dyspeptic symptoms:	
Postprandial fullness	74(68.5%)
Early Satiety	68(63%)
Epigastric pain	54(50%)
Belching	64(59.3%)
Laboratory data:	
WBCs (mean ± SD) ($x10^3$/ μL)	6.4± 1.7
Hb (mean ± SD) gm/dl	12.7±1.3
PLT (mean ± SD) (x 10^3/μL)	253.8±59.7
Bilirubin (mean ± SD) mg/dl	1.1±0.1
ALT (mean ± SD) IU/l	29.8±8.7
AST (mean ± SD) IU/l	29.1±5.9
Abdominal ultrasound:	
Normal	56(51.9%)
Gaseous distension	30(27.8%)
Fatty liver	22(20.4%)

IBS-C: constipation predominant; IBS-D: diarrhea predominant; IBS-M: mixed type; IBS-U: unspecified type; WBC: white blood cells; Hb: hemoglobin; PLT: platelets; ALT: alanine aminotransferase; AST: aspartate amino transferase.

One month following *H. pylori* therapy, among patients who had *H. pylori* eradication, 66 patients reported improvement of their IBS symptoms, and 42 did not improve symptoms. Therefore, patients with *H. pylori* eradication were categorized into two groups according to their improvement of IBS symptoms: a group with improved symptoms and a non-improved group. As shown in table 2, patients with improved symptoms were significantly younger than the non-improved; their mean age was 38.1 ± 11.7 (p= 0.025). The majority in both groups were males. As regard the type of IBS,

there was a significant difference between both groups (p= 0.003) with a predominance of IBS-C type in the improved group (42.4%), while IBS-D was common in the non-improved group (47.6%). Postprandial fullness and early satiety as dyspeptic symptoms were higher in those who have improved IBS symptoms than the non-improved group, with a significant difference for early satiety (p= 0.035).

A significant difference in the total IBS-QOL score one month after *H. pylori* therapy (p= 0.000) between patients with *H. pylori* eradication and those without eradication (53.9 ± 1.8 vs. 34.5 ± 4.4, respectively) was observed with higher score recorded in patients who had *H. pylori* eradication (Fig. 1).

Table 2: Comparison between patients with improved symptoms of IBS and patients who did not-improve after *H. pylori* eradication.

Variables	Improved IBS symptoms (n, %) (n=66)	Non-improved IBS symptoms (n, %) (n=42)	P value
Age (mean ± SD)	38.1±11.7	43.3±11.8	0.025*
Sex:			
Male Female	44(66.7) 22 (33.3)	22(52.4) 20(47.6)	0.16
Residence:			
Rural	28(42.4)	14 (33.3)	0.42
Urban	38(57.6)	28(66.7)	
Smoking	22(33.3)	10(23.8)	0.39
Types of IBS:			
IBS-C	28(42.4)	14(33.3)	0.003*
IBS-D	12(18.2)	20(47.6)	
IBS-M	26(39.4)	8(19)	
Bloating	32(48.5)	24(57.1)	0.43
Dyspeptic symptoms:			
Postprandial fullness	48(72.7)	26 (61.9)	0.29
Early satiety	48 (72.7)	20(48.6)	0.035*
Epigastric pain	30(45.5)	24(57.1)	0.13
Belching	38(57.6)	26(61.9)	0.95

* significant p value.

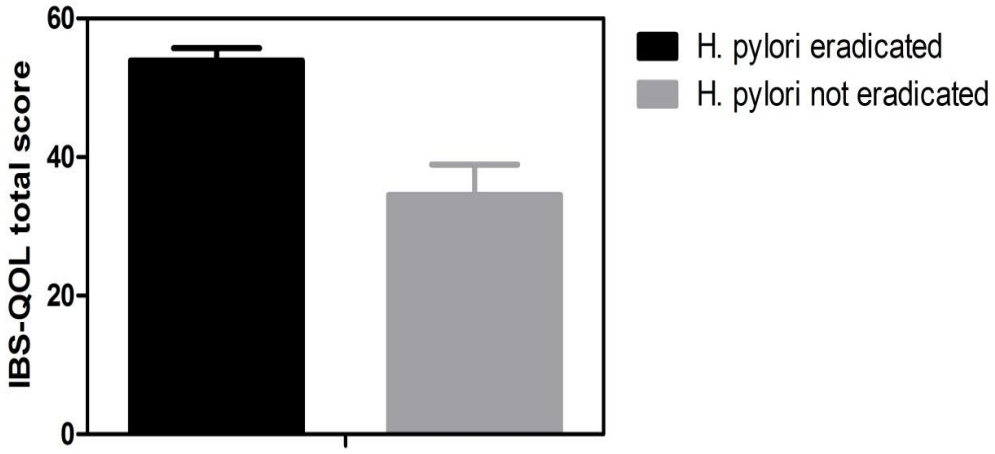

Fig. 1: Comparison of IBS-QOL between patients with *H. pylori* eradication and patients without eradication.

On comparison between IBS-QOL score before and after *H. pylori* therapy among patients with eradicated *H. pylori*, as shown in table 3, there was a highly significant increase in the scores of IBS-QOL for all the subscales in the group of improved IBS symptoms. On the other hand, the non-improved group showed a decrease in IBS-QOL subscales, which was significantly observed in dysphoria, interference with activity, health worry, and social reaction. Meanwhile, the score of the food avoidance subscale significantly increased (p= 0.016). Subsequently, the improved group's total score showed a meaningful clinical response by a significant increase from the baseline score by more than 20 (baseline score was 46.9 ± 2.1 vs. 69.7 ± 2.8 after therapy). Meanwhile, the total IBS-QOL score in the non-improved group did not significantly show a meaningful clinical response from baseline (baseline score was 44.3 ± 2.9 vs. 47.6 ± 3.8 after therapy). Therefore, as demonstrated in fig. 2, the total IBS-QOL score was significantly different between the improved versus the non-improved groups after *H. pylori* eradication (p= 0.000).

Table 3: Comparison of the IBS-QOL before treatment of *H. pylori* and after *H. pylori* eradication.

IBS-QOL	Improved IBS symptoms (n=66) (mean ± SD)		P value	Non- improved IBS symptoms (n=42) (mean ± SD)		P value
	At baseline	After therapy		At baseline	After therapy	
Dysphoria	42.2±2.2	60.5±1.7	0.000**	45.2±3.6	37.1±3.3	<0.001**
Interference with activity	39.4±2.7	62.1±1.8	0.000**	39.5±3.4	36.1±3	0.001*
Body image	62.1±2.8	81.3±1.4	0.000**	58± 4.3	58.9±4	0.279
Health worry	43.4±3.2	59.6±2.5	0.000**	45.2±3.5	38.1±3.6	0.008*
Food avoidance	31.1±3.7	38.4±3.3	0.000**	28.6±5	32.1±4.8	0.016*
Social reaction	49.8±2.8	66.7±2.2	0.000**	49.4±4.5	44.9±4.2	0.004*
Sexual concerns	58±5.5	66.7±5.1	0.001*	42.3±7.3	42.9±7.6	0.836
Relationships	49.5±2.9	64.4±2.1	0.000**	49.6±4.3	46.4±4.1	0.058
Total score	46.9±2.1	69.7±2.8	0.000**	44.3±2.9	47.6±3.8	0.294

* Significant p value <0.05

**Highly significant p value <0.001

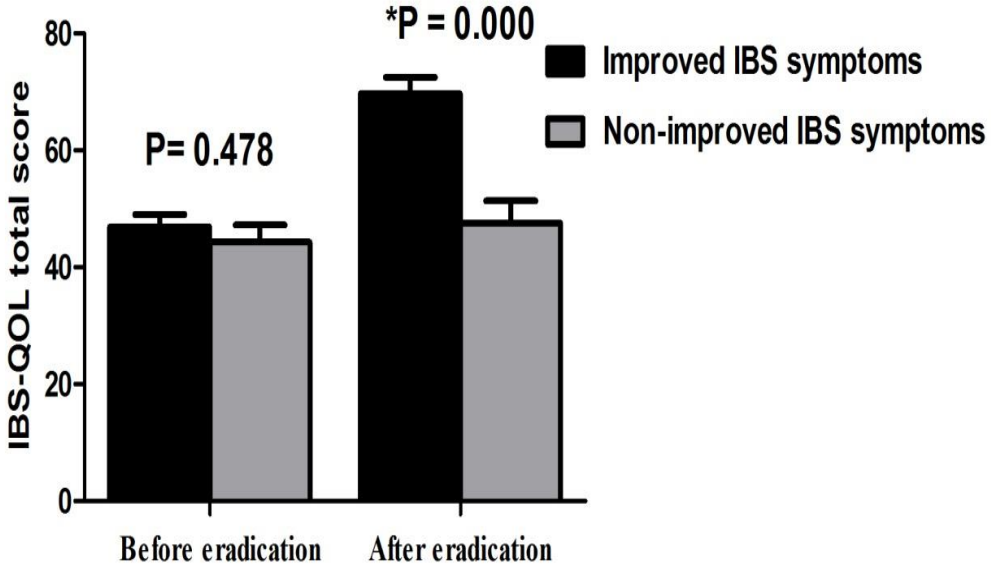

Fig. 2: Comparison between patients with improved IBS symptoms and non-improved regarding the total QOL score before and after *H. pylori* eradication.

Discussion

The IBS prevalence shows a significant variation among different countries depending on the diagnostic criteria, gender, and age[20]. IBS and *H. pylori* are highly prevalent in Egypt, in one study, IBS prevalence among Egyptian patients was 34.2%[21]. Meanwhile, the prevalence of *H. pylori* in Egypt is estimated to range from 13% to 72% in children, with adults ranging from 26% to 90%[16]. However, the prevalence of *H. pylori* in IBS was not reported in Egypt. In this study, we used the clarithromycin-based triple therapy for 14 days to treat *H. pylori*. According to the Egyptian recommendations for the management of *H. pylori*, clarithromycin-based triple therapy for 14 days is still recommended as the first-line regimen for *H. pylori* eradication[16].

To the best of our knowledge, this is the first study to evaluate the effect of *H. pylori* eradication on the QOL of IBS patients. In this study, the improvement of IBS symptoms after *H. pylori* eradication was noticed in 61.1% of IBS patients. This is in concordance with a meta-analysis that found *H. pylori* treatment can enhance the clinical remission rates of IBS patients[9]. Similar to our results, a recent meta-analysis revealed that *H. pylori* infection was associated with increase in the risk of IBS and *H. pylori* eradication can improve IBS symptoms[22].

In the current study, patients who had improved IBS symptoms following *H. pylori* eradication were significantly younger than those without improved symptoms. IBS-C type was more common in patients who had improved instead IBS symptoms after *H. pylori* eradication, while IBS-D was predominant in those who did not improve. This would suggest that the IBS-C type will benefit from *H. pylori* eradication which could be attributed to the prokinetic effect of clarithromycin. In a previous study it was found that clarithromycin could stimulate cyclic inter-digestive gastroduodenal motility in patients with functional dyspepsia and *H. pylori* related-gastritis[23]. A positive association between *H. pylori* and IBS was revealed in an Egyptian study by Ali et al. In IBS constipation-predominant patients, *H. pylori* infection incidence was high in this study[24]. Likewise, Xiong et al. found no significant correlation between *H. pylori* and IBS-D and found that *H. pylori* eradication could not benefit IBS-D patients[13].

Treating *H. pylori* could improve IBS symptoms by changing gastrointestinal pH and intestinal flora, encouraging the recovery of the intestinal mucosal immune system, and restoring the gut-brain axis to regulate the hormone system[25]. Malinen *et al.*, on the other hand, studied the fecal flora of IBS and non-IBS-patients and found no link between IBS and *H. pylori* infection[26].

Another possible explanation is that *H. pylori* infection may induce the inflammatory markers or increase mast cell activation, and then affect the gastric mucosa and nerve remodeling, which causes visceral hypersensitivity symptoms like IBS[27].

Moreover, the improved patients in our study had more frequency of dyspeptic symptoms, particularly postprandial fullness, and early satiety, which suggests that *H. pylori* was implicated in these dyspeptic symptoms. Similar to our study, Su et al. demonstrated that *H. pylori* infection was a risk factor for functional dyspepsia in IBS patients in Taiwan[28]. The probability of medical counseling by primary care physicians increases with presence of functional dyspepsia in IBS patients[29].

IBS has a substantial impact on HRQoL[30]. A consensus review panel found that the IBS-QOL is accurate, valid and reliable psychometric measure in IBS[31]. The present study showed considerable improvements in the IBS-QOL score following the eradication of *H. pylori* when IBS symptoms improved. This confirms also that the symptoms of the patient are subjectively improved. In IBS, no objective component, for example, can be measured by a structural pathology. HRQoL is not based on assessing the patients' health experiences or their subjective health status but it represents a significant measure of their health status. IBS-QOL as an IBS-specific QOL measure has the advantage of containing questions related to abdominal pain or bowel habits and how these affect HRQoL[32]. Therefore, the improvement in QOL in this study could not be merely attributed to the effect of *H. pylori* drugs, but is attributed to the improved IBS symptoms which was measured by IBS specific IBS-QOL questionnaire.

In addition, IBS-QOL was used to assess treatment changes over time[30]. In this study, the total IBS-QOL score significantly increased after therapy above the clinically meaningful difference ranges in patients with improved

symptoms. Meanwhile, the non-improved patients showed a significant decrease in dysphoria, interference with activity, health worry, and social reaction domains. However, the noticed increase in the food avoidance subscale score could be related to improving the dyspeptic symptoms after *H. pylori* eradication rather than to IBS symptoms. In a similar study, the IBS-QoL demonstrated a clinically meaningful difference in the domains of social reaction, food avoidance, health worry, body image, and dysphoria in a randomized double-blinded clinical trial assessing the efficacy of lubiprostone in constipation-predominant IBS patients[33].

There were some strengths to our study as it was a prospective study, also we assessed the impact of anti-*H. pylori* therapy through the IBS-QOL and we did not rely only on the subjective assessment of the patients symptoms. In addition, our study did not have any confounding influence from other IBS treatments. However, one of the limitations is the small size of the *H. pylori* non-eradicated group relative to the eradicated group which makes the comparison statistically not comprehensive. Another limitation is the lack of comparison of the effects of different anti-*H. pylori* therapeutic regimens other than clarithromycin-based treatment on the QOL.

In conclusion, *H. pylori* eradication did not improve IBS symptoms or QOL in all patients with IBS. Young IBS patients with dyspeptic symptoms and IBS-C type can have more benefit from anti-*H. pylori* therapy. Subsequently, *H. pylori* eradication in these patients probably improve the clinical symptoms and QOL.

Conflict of Interest

None to declare.

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دورالتخلص من بكتريا هيليكوباكتر بيلوري باستخدام العلاج الثلاثي القائم على كلاريثروميسين في المرضى الذين يعانون من متلازمة القولون العصبي

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المقدمة: لا تزال العلاقة بين بكتريا هيليكوباكتر بيلورى ومتلازمة القولون العصبى محل جدال. وقد قمنا بقييم التغيرات فى أعراض القولون وجودة الحياة الخاصة بمرضى متلازمة القولون العصبى بعد التخلص من بكتريا هيليكوباكتر لديهم باستخدام العلاج الثلاثى القائم على كلاريثروميسين.

طرق البحث: لقد تم اشتراك المرضى المصابين بمتلازمة القولون العصبى بدرجة متوسطة أو شديدة والذين لديهم بكتريا هيليكوباكتر بيلورى فى تحليل البراز وعلاجهم باستخدام العلاج الثلاثى القائم على كلاريثروميسين. تم التأكد من التخلص من البكتريا بعد شهر. تم تقييم أعراض القولون العصبى واستبيان خاص بجودة الحياة قبل بداية العلاج لبكتريا الهيليكوباكتر بيلورى وبعد التخلص منها.

النتائج: كان ١٠٨ مريضا قد تخلصوا من بكتريا هيليكوباكتر. بعد التخلص من البكتريا كان ٦٦ مريضا لديهم تحسن فى أعراض القولون العصبى بينما ٤٤ مريض لم يتحسنوا. المرضى الذين تحسنوا كانوا أصغر سنا ومتوسط العمر.القولون العصبى الغالب عليه الامساك كان الاكثر شيوعا بنسبة ٤٢,٤% ٣٨,١±١١,٧ (p = ٠,٠٣) والشعور بالامتلاء بعد تناول الطعام والشبع السريع هى اكثر أعراض عسر الهضم لدى المجموعة التى تحسنت أعراضها. الجموعة التى لم تتحسن أعراضها كان لديها نقص فى تقييم استبيان جودة الحياة وكان واضحا فى عدم قبول الحياة، اضطراب النشاط ، القلق على الصحة والتفاعل الاجتماعى. التقييم الاجمالى لاستبيان جودة الحياة كان أعلى بشكل واضح فى المجموعة التى تحسنت أعراضها عن المجموعة التى لم تتحسن.

الخلاصة: التخلص من بكتريا الهيليكوباكتر بيلورى لا يحسن أعراض او جودة الحياة لدى جميع مرضى القولون العصبى. جودة الحياة تتحسن لدى المرضى الاصغر سنا والذين لديهم اعراض عسر هضم والقولون العصبى الغالب عليه الامساك.