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Immunological role of Probiotic in treatment of Helicobacter Pylori Infection

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ABSTRACT

Helicobacter pylori is the most common cause of acute chronic mucosal tumors, peptic ulcer, gastric carcinoma, duodenitis and gastritis. The current work aim to know the effect of probiotics in the treatment of patients with ***Helicobacter pylori*** and measuring the levels of MCP-1, IL-10 of these patients before and after treatment.

The work was conducted in the laboratory of Al_Sharqat Hospital in Salah Al-din governorate, stool and blood samples were collected from 80 patients at ages between (29-59) years, during the period between November 2021 to May 2022.

The study include 80 serum samples were collected from the patients and this samples were devided to two groups first include 40 patients treated with probiotic while other group 40 patients treated with antibiotic, , the levels of IL- 10 and MCP-1 investigated By using ELISA technique to determine acute infection,. According to 61 stool were collected from patient were infected with ***Helicobacter pylori***, 35 (87.5%) patients were treated with probiotics succeeded in eradicating ***Helicobacter pylori***, while 26 (65%) patients were treated with antibiotics.

The result show differences in the level of MCP-1 and IL-10 of patients were treated by probiotics, the levels of MCP-1 increased from 78.07 to 91.18 pg\ml after treatments, in contrast to levels of IL-10 before treatments 10.39 pg\ml to 8.03 pg\ml after treatments.

the correlation between MCP-1 and IL-10 levels in patients who had successfully treated H.pylori, where the MCP-1 levels in patients that had successful *Helicobacter pylori* eradications by using probiotics were 92.6 pg\ml compared to 51.84 pg\ml. Compared with patients who didn't get recovery from the germs, by contrast, patients who didn't have the eradications of the germs and aorectomy have an average a high levels of IL-10 (14.15 pg\ml), whereas the patients that succeeded in getting rid of the germs (7.94 pg\ml).

Key words: *Helicobacter Pylori*, Probiotic, MCP-1 and IL-10 levels

Introduction

Chronic long-term gastritis is almost always caused by *Helicobacter pylori* infection [1]((Khalifa *et al*., 2010) It is also a cause of peptic ulcers [2] (Nam, *et al*, 2010), Related diseases of *Helicobacter pylori* are the main cause of the digestive disorder. Complications include gastritis, stomach ulcers, duodenal ulcers and stomach adenomas, mucosal carcinomas and lymphoid tissues, and lymphoma [3] (Keikha and Karbalaei, 2021), and gastritis known as inflammations, erosions or irritations of the stomach linings. It may happen suddenly (acute) or gradually (chronic))[4] (Huang and Lopes, 2020). It is brought on by more factor, including infection by H.Pylori, induced medications like aspirin, non -steroidal anti inflammatory drugs (NSAIDs), corticosteroid and alcohol [5] (El Zahaby *et al*., 2017). Most common gastritis symptoms include heartburn, upper abdominal pain, vomiting and nausea. Gastritis is considered to affect about half of the people in the world and generate a significant amount in the community [6] (Yu *et al*., 2018). Initially, the idea that this bacterium was associated with gastritis and duodenal ulcers was met with much skepticism by the scientific community, are Gram-negative bacteria, microscopic, motile & helical. Bacteria which colonize the stomach submucosal layer .[7] (Keikha *et al*., 2019). Persistent infections are main characteristics of this microorganisms, studies have shown that *Helicobacter pylori* may live for decades in the stomach of humans.[8] (Yousefi *et al*., 2019). Peptic ulcer disease is a different type of disease consisting of gastric ulcer and duodenal ulcer. This pepsin and acid cause a lesion in the mucous membrane of the stomach and duodenum [9] (Spósito *et al*., 2021). These occur when aggressive agents such as (hydrochloric acid, pepsin, etc.) appear. This bacterium attacks the self-defense mechanisms of the mucosal barrier and causes an

allergic reaction in the abdomen. Existing treatment to control peptic ulcers diseases are associated with high rates of relapse and reduced side effects [10] (Ali & Muhammad, 2018).

The probiotic role in the case of *Helicobacter pylori* is eradication and improve tolerance by reducing treatment frequency and associated side effects. As well, probiotics can help in improving the body's defenses against H. pylori infection. The clinical outcomes of *Helicobacter pylori* infections are determined or reduced by many factors and including *Helicobacter pylori* strains, infections and intensity of *Helicobacter pylori* colonization. It has been observed that the risk of developing peptic ulcers and stomach cancers increase by the level of infections. Therefore, suppressions of *Helicobacter pylori* can reduce risk of *Helicobacter pylori* -associated disease.[11](Yang *et a.l*, 2014).

This study was conducted for the purpose of shedding light on its treatment and the use of several therapeutic methods by achieving the following objectives: Investigation of efficacy of probiotic in treating *Helicobacter pylori* infections, Detection of immunomodulators that can be stimulated by probiotics inside the body, and Determining the factors that can affect the rate of recovery from stomach bacteria like gender, age, place of residence, marital status, body weight and presence of associated diseases.

Materials and methods

Collect of samples

Samples were collected from Stool and Serum of patients which infected with *Helicobacter pylori* and attending to Shirqat General Hospital/ Salah al-Din, which numbered 80 cases, males and females, their aged were ranged (18-50) years, and diagnosed by an internist during the period from 1.11.2021 to 1.7.2022, as they divided into 2 groups, Each group included forty patient infected with *Helicobacter pylori* bacteria.

Diagnosis Samples and classify

A- Determination of the antigen *Helicobacter pylori*: The diagnosis of samples was made by detecting the antigens of the bacteria in the patient's stool using a kit to detect *Helicobacter pylori* antigen in the stool .

B- B- bacterial culture :Also take the stool sample for bacterial culture from patients on some culture media like blood agar,EMB agar,Macconkey agar to detect for normal flora and count it According to .[12] (Pakpour& Horgan,2021).

C- Blood samples: While the serum part: 5ml of blood was withdrawn from the vein and left for 15 minutes in a gel tube, then placed in a centrifuge for 15 minutes and the serum was obtained. The serum was kept in the freezer until the required tests in the study were performed,

D- Groups classification:The first group: Forty patients infected with *Helicobacter pylori* bacteria, as the diagnosis was made by detecting the antigens of bacteria in the patient's stool using a kit that detects the bacteria in the stool and after confirming the positive analysis and the presence of the germ, as these people are supposed to be given a prescription of antibiotics from the doctor specialist. Which is pylori kit consists of a group of antibiotics that are Tindazole, clarithromycin and Lansoprazole.

The second group: also forty patients infected with *Helicobacter pylori* bacteria, as the diagnosis was made by detecting the antigens of bacteria in the patient's stool using a kit that detects bacteria in the stool and after confirming the positive analysis and the presence of the bacteria, then a stool sample was taken for culture and bacterial count was taken and 5 ml was withdrawn Blood from a vein and left 15 minutes in a gel tube and then put in a centrifuge for 15 minutes and get the serum, where the serum was kept in the freezer until used.

Serological markers

It measure the level of macrophage chemoattractant proteins-1 (MCP_1), and level of interleukin_10 (IL_10) before and after treatment with probiotics and the levels are measured using ELISA as these people are supposed to be given bio-enhancers(probiotics) containing beneficial bacteria (*Lactobacillus plantarum, Lactobacillus Rhamnosus, Lactobacillus casei, Lactobacillus Gasseri, Lactobacillus acidophilus, Lactobacillus salivarius, Bifidobacterium Bifidum, Bifidobacterium lactis, Bifidobacterium Infantis, Bifidobacterium Longum*).

Statistical analyses

Statistical test was done with SPSS softwares version (SPSS, Chicago, 25.0). Continuous data was subjected to test of normality (ShapiroWilk test), Data with normally distributions were presented as mean and standard deviations, analyzed with Student t-test. Data with non-normal distributions were presented as median and range, analyzed with Mann Whitney U test. Categorical variable was expressed as number and percentages which analyzed with Chi_square test. Pearson's correlations test were done to explore the possible correlations of MCP-1 & IL-10 with age, weight and disease duration of the patients. A P- value low than 0.05 was considered to indicate a statistically significant differences.

Results and Discussion

Demographic Characteristic of the Patient

Mean age of the patients in probiotic group was 29.03±8.18 years (range 20-45 years) compared with 33.55±7.29 years (range 21-47 years) for those in antibiotic group with a significant difference. Likewise, the males were more common among probiotic than antibiotic group (50% versus 25%) with a significant difference. Though, there is no significant difference between the 2 groups regarding weight, comorbidities and disease duration. Although ex/current smokers were more frequent among antibiotic than probiotic group (67.5% vs. 47.5%), the difference was not a significant (Table\1).

Table 1: Demographic and clinical characteristic of the study populations

Variables	Probiotics (n=40)	Antibiotics (n=40)	p-value
Age, years Mean± SE Range	 29.03±1.29 20-45	 33.55±1.15 21-47	**0.011**
Weight, kg Mean±SE Range	 77.88±9.59 63-98	 80.15±7.12 69-95	0.232
Gender Male Female	 20(50%) 20(50%)	 30(75%) 10(25%)	**0.021**
Smoking Never Ex/current	 21(52.5%) 19(47.5%)	 13(32.5%) 27(67.5%)	0.070
Comorbidity No DM Hypertension	 35(87.5%) 5(12.5%) 0(0%)	 34(85%) 4(10%) 2(5%)	0.345
Duration, months Mean±SD Range	 3.08±1.59 1.0-7.0	 3.35±1.27 2.0-6.0	0.391

There are some proposed theories about role of bacteria in pathogenesis of peptic ulcers. These theories refer to the role of bacteria in stimulating gastric acid secretions, reducing blood flow to the gastric mucosa, inhibiting gastric bicarbonate secretion, inhibiting gastric mucus secretion, inhibiting prostaglandin secretion and transforming Gastric epithelial cells in gastric ulcer into intestinal epithelial cells and in duodenal ulcer conversion of duodenal epithelial cells into gastric epithelial cells Gastricmetaplasia .[13](Fischbach *etal*., 2016). : [14] (Magni *etal*.,2021). Patients treated and cured with probiotics had a higher percentage of patients treated and cured with antibiotics, and the cause of multi-drug resistance by *Helicobacter pylori* These results are in agreement with .[15] (Goderska *et al*., 2018) who confirmed the multiple resistance of this bacteria . On the other hand, sex may be one of the influencing and predisposing factor for developing peptic ulcer diseases. A number of researchers have indicated that peptic ulcer disease is related to the male sex. Longinov and his group (1998) mentioned that, ratio of males to females with peptic ulcers disease is 3.5:1, the researchers explained The reason for the increase in peptic ulcers disease in males is the effect of the stress and work, that the male is exposed to more than the female .[16] (Deding *etal*., 2016). also the results in agreement with (Balakrishnan et al 2004)which showed differences with comorbidities and serum MCP_1,IL-10 levels.

Rate of Successful Eradication

According to the test of stool antigens, 35 patients among probiotic group (87.5%) had successful eradication of *Helicobacter pylori* 26 patients (65%) were successfully treated by antibiotics. Chi square revealed a significant differences between 2 groups in eradication rate (Figure -1).

Fig. 1: Rates of successful eradication of *Helicobacter pylori* in probiotics and antibiotic-treated patients

Serum levels of MCP-1 and IL-10 before and After Treatment with Probiotic

Data regarding serum levels of MCP_1 and IL-10 found to be abnormal distributed. The data were median, expressed and range, then analyzed with nonparametric Mann Whitney U test. The median levels of MCP_1 had increased from 78.07 pg/ml before treatments to 91.18 pg\ml after treatments with a significant difference. In contrast, the median levels of IL-10 before treatments were 10.39 pg\ml which reduced to 8.03 pg\ml after treatments with a significant differences (Table -2).

Table 2: Serum levels of MCP-1 and IL-10 before and After Treatment with Probiotic

Cytokine	Before treatment	After treatment	p-value
MCP-1, pg/ml Mean±SE Median Range	 101.06±62.0 78.07 38.4-267.7	 163.18±128.12 91.18 37.68-483.5	**0.039**
IL-10, pg/ml Mean±SE Median Range	 14.15±10.71 10.39 2.63-53.6	 8.45±5.16 8.03 1.56-19.24	**0.015**

Cytokine differences during *Helicobacter pylori* infections have a significant impacts on the development of gastric diseases due to their broad and multiple effect on cells of immune and epithelials .[17] (Bockerstett *et al*., 2017). The results in the above table demonstrated the ability of probiotics to improve IL-10 level in subjects with *Helicobacter pylori* infections.[18] (Garcia-Castillo, V et al 2018). whose concentration is increased in the serum and stomach of infected persons, MCP-1 levels are low during *Helicobacter pylori* infection but probiotics raise levels of this cytokine after treatment. These bound cytokines are primarily important because they inhibit Injury to the mucous membranes as a result of increased inflammatory response.[19] (Wang *et al*., 2017), [20] (Viladomiu *et al*., 2017).

Association of serum MCP-1 and IL-10 with successful eradication in patients treated by Probiotic

Median serum level of MCP-1 in the patients with successful eradication was 92.6 pg/ml (range= 71.84 pg/ml 231.5 pg/ml) compared with 51.84 pg/ml (range= 38.4 pg/ml 267.9 pg/ml) in those with no eradication. However, the difference exceeded the acceptable level of significant. In contrast, patients with no eradication showed a relatively higher median level of IL-10 (14.15 pg/ml, range= 4.19 pg/ml 53.6 pg/ml) than those with successful eradication (7.94 pg/ml, range= 2.67 pg/ml 38.06 pg/ml) although the differences were not significant (Figure2).

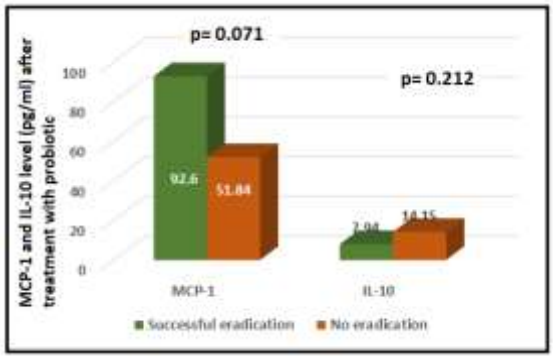


Fig. 2: Serum levels of MCP-1 and IL-10 in patients with successful eradications of *Helicobacter pylori* and those with no eradication

Correlations of MCP-1 and IL-10 with other Variables before treatment

Pearson's correlation test used to explore the possible correlations of MCP-1 and IL-10 with other variables.

Before Treatment

In general, no significant correlation between MCP-1 or IL-10 with any included variables before treatment (Table-3).

Table 3: Pearson's correlations of MCP-1, IL-10 and disease duration with age and weight of the patients before treatment

Variable	MCP-1		IL-10		Disease Duration	
	coefficient	p-value	coefficient	p-value	Coefficient	p-value
Age	-0.192	0.234	0.039	0.811	-0.118	0.299
Weight	-0.052	0.749	0.130	0.422	0.093	0.410
Disease duration	0.281	0.079	-0.129	0.427		
IL-10	-0.089	0.584				

After Treatment: After treatment, MCP-1 demonstrated a negative significant correlation with IL-10 (r =-0.368, p =0.019) as in table 4and figure 3

Table 4: Correlations of MCP-1 and IL-10 with other Variables after treatment

Variable	MCP-1		IL-10		Disease Duration	
	R	p-value	R	p-value	R	p-value
Age	0.014	0.933	-0.045	0.783	0.093	0.410
Weight	0.124	0.447	-0.056	0.729	-0.118	0.299
Disease duration	0.130	0.424	-0.011	0.945		
IL-10	**-0.368**	**0.019**				

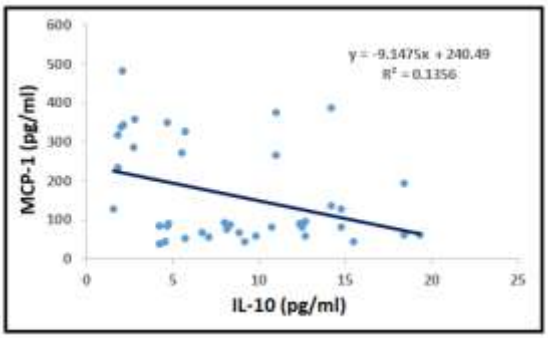


Fig. 3: Scatter plot & regression lines between IL-10 & MCP-1

Association of MCP-1 & IL-10 with Gender, smoking and Comorbidity before treatments

Median level of IL-10 in male was 14.63 pg\ml that was less from that of female (8.62 pg\ml) with a significant difference. Furthermore, the median IL-10 in patients without comorbidities was 9.76 pg\ml in comparison with 12.46 pg\ml in those with comorbidities with a significant differences. Although IL-10 levels were high in ex/current smokers than non-smokers (14.46 pg\ml vs. 8.75 pg\ml), the difference was no signifcant (Table-5).

Table 5: Association of MCP-1 & IL-10 with Gender, smokings and Comorbidity before treatments

Variables	MCP-1, pg/ml	IL-10, pg/ml
Gender		
Male	78.9(39.21-254.7)	14.63(2.63-53.6)
Female	76.67(38.4-267.7)	8.62(4.19-30.16)
p-value	0.583	**0.024**
Smoking		
Never	75.0(38.4-267.7)	8.75(4.19-32.87)
Ex/current	80(40.79-254.7)	14.46(2.63-53.6)
p-value	0.893	0.057
Comorbidity		
No	77.8(38.4-267.7)	9.76(2.63-53.6)
Yes	81.6(51.58-254.7)	12.46(6.55-30.16)
p-value	0.854	**0.039**

The current study shows that smoking have a clear effect on incidence of peptic ulcers, and this is agreed with.[21] (Lampit *et al*., 2014) and Taha and his group (1994) who support the existence of a relationship between them, as these researchers believed that the effect of smokings on the incidence of peptic ulcer comes through the effect of smokings on the incidence of peptic ulcer. Reducing the production of prostaglandins as well as its effect on reducing the effect of gastric and intestinal bicarbonate. As stated by.[22] (Büttner & Bonas, 2010) that smoking impairs the healing of the mucous layer of the stomach and thus helps to continue infection with *Helicobacter pylori*, as it reduces the local immunity of the gastric lining.

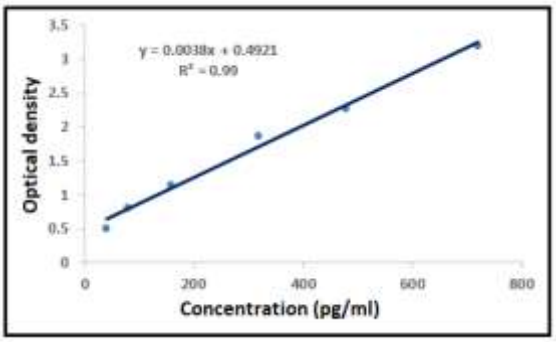
Association of MCP-1 and IL-10 with Gender, smoking and Comorbidity After treatment

The median level of MCP-1 in patients with no comorbidities was 96.84 pg\ml that was higher than that of the patients with comorbidities (59.21pg/ml) with a significant difference. On the other hand, patients with comorbidities displayed higher median level of IL-10 (13.11 pg/ml) than those without comorbidities (7.06 pg/ml) with a significant differences (Table-6).

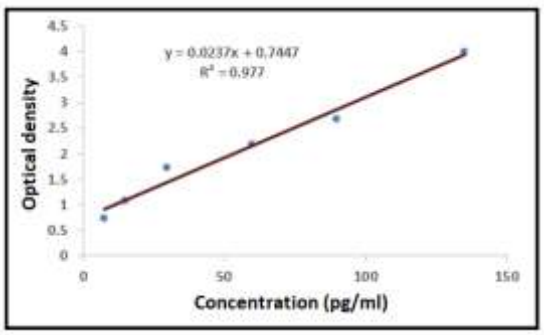
Table 6: Associations of MCP-1 and IL-10 with gender, smoking and comorbidity after treatment

Variables	MCP-1, pg/ml	IL-10, pg/ml
Gender		
Male	132.8(43.16-483.5)	5.57(1.56-18.34)
Female	81.84(37.68-387.5)	9.3(1.78-19.24)
p-value	0.211	0.102
Smoking		
Never	82.1(37.68-387.5)	8.83(1.78-19.24)
Ex/current	136.8(43.16- 483.5)	5.67(1.56-18.34)
p-value	0.178	0.236
Comorbidity		
No	96.84(37.68-483.5)	7.06(4.2-12.67)
Yes	59.21(43.16-83.4)	13.11(1.56-19.24)
p-value	**0.017**	**0.048**

Perez-Perez and Portal-Celhay (2006) [23]. concluded that the immune system is sensitive to the presence of bacteria through special receptors called Toll-like-receptors (TLRs). the receptors are found on the surface of some immune cells called antigens presenting cell, including monocytes. Including infection with *Helicobacter pylori* bacteria, these receptors work to increase the release of cytokine, including tumor necrosis factors (TNF) and IL-10 as an attractant to white cells locally (in the stomach) and also in the serumWhile the increase in interleukin in the serum is due to the production of antigenic substances by these bacteria, such as the production of the enzyme urease and lipopolyscharides (LPS). These cells are T cells and phagocytic cells (such as macrophage and plasma cells). Many researchers have also indicated an increased risk of *Helicobacter pylori* infections in diabetic patients compared to non-diabetics [24] (Pareek, 2014). This is because diabetics can be considered immunosuppressed with weak humoral and cellular immunity, which makes them more predisposed to infection with fungal, viral and bacterial diseases, including *Helicobacter pylori* [25] (Sherwal *et al*., 2014). Because the increase in the level of blood sugar hyperglycemia increases the process of bacterial adhesion to the surface of the epithelial membranes of the stomach, thus enhancing the density of bacterial settlement [26] (Sheu *et al*., 2014). Many researchers also indicated that people with high blood pressure diseases have a cure rate of *Helicobacter pylori* is 80% compared to healthy people, where their cure rate is 85% [27] (Migneco et al., 2003). [28] (Starrett et al, 2011) pointed out indicates that smoking stimulates the epithelial cells to secrete chemokines, especially MCP-1, which recruit and bring neutrophils and macrophage into the lungs. These inflammatory cells then release additional cytokines and chemokines, and this will lead to chronic inflammation and start the stage of programmed cell death. Apoptosis of epithelial and endothelial cells, while [29] (Al-Ghurabi, B. H. (2013)) indicated that there are no actual differences in IL_10 levels between smokers and non-smokers**.**



Standard curve of MCP-1



Standard curve for IL-10

Conclusions

Probiotics have a significantly higher efficiency than the traditional treatment in eliminating *Helicobacter pylori* bacteria for the same period of time. Treatment with probiotics is associated with a significant increases in MCP-1 level and a decrease in IL-10 levels. The therapeutic effect of probiotics can be attributed to the fundamental change that it causes in the bacterial composition of the gastrointestinal tract, represented by an increase in the number of *E.coli* and Lactobacillus bacteria and a decrease in the number of other bacteria. The increase in the levels of MCP-1 and the decrease in the level of IL-10 can also contributes to cure of H. pylori bacteria as well as the protective role of this change in cytokines from other complications. Smoking can be one of the important factors in delaying recovery from infection with this germ, whether in traditional treatment or in the case of probiotics. Being a male patient and/or having comorbidities, especially diabetes, may be associated with increased level of IL-10, which means impairing the effectiveness of the humoral immune response and its negative effects on the efficiency of treatment, whether it is conventional treatment or probiotics

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الدور المناعي للمعززات الحيوية في معالجة الاصابة ببكتريا اللولبيات البوابية

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الملخص

الملتوية البوابية هي السبب الأكثر شيوعًا للأورام المخاطية الحادة المزمنة والقرحة الهضمية وسرطان المعدة والتهاب الاثني عشر والتهاب المعدة. يهدف العمل الحالي إلى معرفة تأثير البروبيوتيك في علاج مرضى الملوية البوابية وقياس مستويات MCP-1 و IL– لهؤلاء المرضى قبل وبعد العلاج، أجري العمل في مختبر مستشفى الشرقاط بصلاح الدين حيث تم جمع عينات من البراز والدم من 80 مريضا (20–59) سنة ، خلال الفترة من تشرين الثاني 2021 الى أيار 2022.

اشتملت الدراسة على مجموعتين تشمل الأولى 40 مريضًا تم علاجهم بالبروبيوتيك بينما تم علاج المجموعة الأخرى من 40 مريضًا بالمضادات الحيوية باستخدام تقنية ELISA ، تم فحص مستويات الأجسام المضادة (Igm M) لتحديد العدوى الحادة ، كما تم تحديد مستويات IL_10 و MCP-1 وفقًا لاختبار مستضد البراز ، نجح 35 مريضًا باستخدام البروبيوتيك (87.5٪) في القضاء على جرثومة المعدة ، بينما عولج 26 مريضًا (65٪) بالمضادات الحيوية.

أظهرت النتائج اختلافات في مستوى MCP-1 و IL-10 للمرضى الذين عولجوا بواسطة البروبيوتيك ، وزادت مستويات MCP-1 من 78.07 إلى 91.18 بيكوغرام / مل بعد العلاج ، على عكس مستويات IL-10 قبل العلاج. 10.39 بيكوغرام / مل إلى 8.03 بيكوغرام / مل بعد العلاج.

العلاقة بين مستويات MCP-1 و IL-10 في المرضى الذين عولجوا بنجاح من جرثومة المعدة حيث كانت مستويات MCP-1 في المرضى الذين نجحوا في استئصال بكتيريا الملوية البوابية باستخدام البروبيوتيك 92.6 بيكوغرام / مل مقارنة بـ 51.84 بيكوغرام / مل، أما أولئك الذين لم يتعافوا من البكتريا، على النقيض من ذلك ، فإن المرضى الذين لم يتم يتشافوا كانت لديهم متوسط مستويات عالية من (14.15 IL-10 بيكوغرام / مل) ، بينما المرضى الذين نجحوا في ذلك التخلص من الجراثيم (7.94 بيكوغرام / مل).