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Assessment of Helicobacter Pylori Eradication Treatment On Platelet Count in Patients With Immune Thrombocytopenic Purpura

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Abstract: The impact of Helicobacter pylori eradication on the platelet count in patients with Immune Thrombocytopenic Purpura is controversial. In this clinical trial, the effects of HP eradication on platelet count was assessed and analyzed. Forty Iranian patients with ITP were assessed in two groups. One group was treated with amoxicillin, clarithromycin and omeprazole. The other group received similar amounts of placebo. The platelet counts were analyzed before treatment and during the first, second and third months after treatment. The mean platelet count before treatment in the intervention and control groups were, 67.85×103 mm3 and 69.4×103 mm3, respectively (p=0.82). In the third month after treatment, it was 107.15×103 mm3 in the intervention group and the 71.15×103 mm3 in the control group (p<0.001). Repeated measures analysis confirmed the positive effect of helicobacter pylori eradication on platelet count (p=0.007). In this study, it was found that helicobacter pylori eradication in patients with immune thrombocytopenic purpura induced a dramatic increase in platelets count.
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1. Introduction

Helicobacter pylori is a gram-negative microaerophilic bacterium that colonizes the stomach of more than half of the human population (1 & 2). However, the prevalence of helicobacter pylori worldwide is not homogeneous (3 & 4). In Western countries, the prevalence of infection has decreased over the past few decades (5-7), however, the rate of helicobacter pylori infection in developing countries such as Iran has been reported to be about 80-90% (8-10). Helicobacter pylori is the main cause of chronic active gastritis and ulcers of the stomach and duodenum. Helicobacter pylori is a contributing factor in the development of gastric cancer and mucosa-associated lymphoid tissue lymphoma (1 & 2).

Multiple diseases associated with platelet aggregation have been associated with helicobacter pylori infection. For example, people infected with H pylori are more likely to have a heart attack, coronary heart disease, and stroke (11-16). It has also been suggested that H pylori may initiate Thrombotic Thrombocytopenic Purpura (TTP), inducing platelet aggregation through interaction with the Von Willebrand factor (17). It has also been hinted that the chronic consequences of H pylori infection may be associated with Idiopathic Thrombocytopenic Purpura (ITP), known to eradicate the bacterium from the gastric mucosa in some patients with ITP (18-26).

The causal relationship between H pylori infection and ITP has been stipulated in studies that revealed improved platelet counts after eradication in infected patients (27). The prevalence of H pylori infection in patients with ITP has been systematically investigated. No differences have been discovered with the healthy general population matched by age and geographical area (28). In contrast, a study from Colombia reported a very high prevalence of H pylori infection in patients with ITP (90.6%), which significantly differing from controls (43.8%) (18). Numerous studies in adults have demonstrated a positive effect of H pylori eradication with triple standard treatment on platelet counts in patients (18-21, 24, 34-28). Cohort studies in Japan and Italy have reported higher response rates than others countries (24 & 29 & 31 & 33).

The association between H pylori infection and ITP was first described in 1998, when an Italian group reported a significant increase in platelet count in 8 of 11 ITP patients in whom the bacterium had been eradicated (32). However, in subsequent reports the results were contradictory. Studies often included patients with mild thrombocytopenia who were not

usually treated. Therefore, the role of helicobacter pylori eradication in the management of patients with ITP requires further investigation (24, 32, 35, 36), nevertheless, there is growing evidence of an association between helicobacter pylori eradication and platelet recovery in ITP patients (23 & 26 & 37-39). Clear evidence of an association between H pylori eradication and ITP is not yet available, and there are many inconsistencies in the handful of conducted studies. Prior studies have suggested that additional and more comprehensive research is requisite in this field (42).

Screening and eradicating H pylori infection may be an easier and safer treatment option than suppressing the immune system or removing the spleen in patients with ITP (20 & 40).

The British Society of Hematology now recommends screening and eradicating H pylori as an ITP (Evidence Level III) treatment (41). To date, no reports in regard to these patients have been published in Iran. Because local experiences are important and due to the potential regional variability in helicobacter pylori strains, this study was devised and designed to evaluate the treatment of helicobacter pylori eradication on platelet count in patients with immunosuppressive thrombocytopenic purpura.

Immune Thrombocytopenic Purpura (ITP)

Immune thrombocytopenic purpura (also known as idiopathic thrombocytopenic purpura) is an acquired disorder characterized by immune-mediated platelet degradation and possibly inhibition of platelet release from megakaryocytes. In children, it is usually an acute illness that most commonly occurs after an infection and has a self-limiting course, however, in adults it becomes more chronic. The exact nature of the immune dysfunction in this disease is not known. When ITP is related to an underlying disease, it is referred to as a secondary term. Common underlying disorders, in particular, can include immune disorders such as Systemic Lupus Erythematosus (SLE) and infections such as HIV and hepatitis C. The association of ITP with helicobacter pylori is unknown.

Immune thrombocytopenic purpura is characterized by mucosal cutaneous bleeding and generally very low platelet counts, while other peripheral blood cells and their smears are normal. Patients are usually admitted with eczema and petechiae, or their thrombocytopenia is accidentally detected in a comprehensive blood cell test. In these patients, mucosal cutaneous bleeding such as bleeding from the oral mucosa, gastrointestinal tract, or heavy bleeding during menstruation may occur. In rare instances, life-threatening hemorrhages may also occur in the central nervous system. Wet purpura (blood blisters in the mouth) and retinal bleeding may also indicate life-threatening bleeding.

Epidemiology

ITP is the most common acquired hemorrhaging disorder. It is more common in children than adults. Among children, the prevalence of ITP is similar in girls and boys. A study conducted in Denmark from 1973 to 1995 estimated the annual incidence of ITP among adults at about 22 per million population, taking into account the cut-off point of 50,000 platelets per microliter. Research indicates that the prevalence of ITP among adults is more than 22 per million population. A UK study of all diagnosed cases of ITP between 1990 and 2005 reported a rate of 39 among men and 44 for women (per million).

Since ITP is a chronic disease in adults, its prevalence is higher than its incidence. A study conducted in the United States on the prevalence of the disease found that the prevalence is about 100 per million population, ranging from 41 to 160 people per million population (mostly senor citizens).

Approximately 70% of adults with ITP are women (72% under the age of 40). Moreover, in a Danish study, gender differences in the incidence of ITP was only observed in people under 60.

Clinical Symptoms

Among ITP patients, significant differences in clinical symptoms were observed. Even though the onset of ITP may be acute and sudden, the disease's occurrence is often unclear and latent. Bleeding in symptomatic patients can range from petechiae and bruising to severe, life-threatening hemorrhaging. The proliferation and prevalence of automated blood cell counting devices has led to the detection of asymptomatic cases with mild thrombocytopenia, expanding the range of ITP clinical symptoms. Clinical symptoms in patients with ITP-induced thrombocytopenia include the following:

-Petshi, purpura & tendency to bruise
-Epistaxis, bleeding gums & menorrhagia
-Severe gastrointestinal bleeding & hematuria (rare)
-Intracranial hemorrhage (uncommon but fatal)

Diagnosis

There is no ITP-diagnosis gold standard method. Antibody tests (serological methods) are usually not effective due to their low sensitivity/specificity. Bone marrow assessments can be utilized for older adults (over 60), those with abnormal laboratory symptoms or findings that are not justified/explainable by ITP, or for patients who do not respond to initial treatment. Peripheral blood smears are morphologically normal and may only

contain large platelets. Depending on the history of hemorrhaging, iron deficiency anemia may also exist.

Lab tests are conducted to identify ITP's secondary cause and include HIV infection testing, hepatitis C (plus other infections if necessary), serological SLE tests, serum protein electrophoresis, and immunoglobulin levels to detect hypogammaglobulinemia or gonadotropin deficiency. In the event of anemia, a direct antiglobulin (Coombs) test is performed to rule out autoimmune hemolytic anemia with ITP (Evans Syndrome).

Treatment

ITP treatment encapsulates the utilization of medications that reduce the uptake of antibody-bound platelets by the reticuloendothelial system or decreasing antibody production. However, ITP diagnosis does not necessarily translate into prescription of treatment. The risk of thrombocytopenia-related mortality does not increase in patients with platelet counts above 30,000 per microliter. Initial treatment of patients with no symptoms of significant bleeding, severe thrombocytopenia (less than 5,000 per microliter) and/or symptoms of impending hemorrhaging (such as retinal bleeding or severe bleeding from the oral mucosa), is usually prescribing them some 1 mg/kg prednisone, although immunoglobulin (D) Rho (WinRho SDF) can also be used (dosage: 50-75 µg\kg). Rho immunoglobulin (D) should be injected only in +Rh patients since the of action mechanism of this drug is to create a limited hemolysis and saturation of Fc receptors and inhibition of their function with antibody-coated cells. Upon consumption of this medication, hemoglobin levels are usually reduced (average 1.7 g/dl) and severe intravascular hemolysis is a rare complication. In anemic patients, the dodge should be lowered.

Intravenous gammaglobulin (IvIgG) also blocks Fc receptors in the reticuloendothelial system, but appears to do so via a different mechanism from Rho immunoglobulin (D). In splenectomy patients, IvIgG is more effective than (D) Rho. The total dose is IvIg g/kg2, provided in several doses over 2-5 days. Side effects are usually contingent on the volume/quantity of the injection and include aseptic meningitis and kidney failure. All immunoglobulin products are extracted from human plasma and the viral agents in them are removed.

In patients with severe ITP or symptoms of bleeding, hospital admission and a combination therapy approach including high-dose glucocorticoids with IvIg or Rho anti-D and, if necessary, immunosuppressive agents may be prescribed. Rituximab, an anti-CD20 (B cell) antibody, has been demonstrated to be effective in treating resistant ITP.

Splenectomy is utilized to treat patients who develop a recurrent decrease in glucocorticoids. Contrary to popular belief, more patients recover over time, but the importance of splenectomy has not diminished. If the platelet count is high enough, monitoring the patient or intermittent treatment with IvIgG or Rho anti-D is a sensible approach to determine if ITP is improving. Prior to splenectomy, vaccination against encapsulated organisms (especially pneumococcus, meningococcus, and haemophilus influenzae is recommended depending on the patient's age and possible contacts). Diversionary spleen is a rare cause of the disease's recurrence.

Newer drugs for ITP are thrombopoietin receptor agonists. This treatment stems from the finding that many patients, contrary to previous assumptions, do not have elevated levels of thrombopoietin and do not indicate increased platelet degradation. Two products, one oral and the other subcutaneous, have been demonstrated to be effective in patients with ITP, although their role in ITP treatment is unclear.

Treatment

Several treatment regimens have been recommended for the treatment of helicobacter pylori infection, listed in the here below table:

Table 1 : treatment regimens for the treatment of helicobacter pylori infection

Medication	Dose	Treatment Period
H2 Antagonist	-	4 Weeks
Bismuth Salicylate	525-mg Four Times a day	2 Weeks
Metronidazole	250-mg Four Times A Day	2 Weeks
Tetracycline	500-mg Four Times A Day	2 Weeks
Omeprazole	20-mg Once Daily	4 Weeks
Clarithromycin	500-mg Twice Daily	2 Weeks
Amoxicillin	1000-mg Twice Daily	2 Weeks
Omeprazole	20-mg Once Daily	2 Weeks
Clarithromycin	500-mg Twice Daily	2 Weeks
Metronidazole	500-mg Twice daily	2 Weeks
Omeprazole	20-mg Once Daily	2 Weeks
Bismuth	525-mg Four Times A Day	2 Weeks
Metronidazole	500-mg Three Times A Day	2 Weeks
Tetracycline	500-mg Four Times A Day	2 Weeks

Research Methodology

This was an interventional study. The statistical population consisted of all patients diagnosed with immune thrombocytopenic purpura and hospitalized in Kermanshah's Imam Khomeini Hospital.

Research Environment: Blood & Oncology Department of Imam Khomeini Hospital, Kermanshah

Sampling

Permuted-Block Randomization

How Sample Size Was Calculated

Using the comparison formula, 2 means and taking into account the mean and standard deviation from similar studies, and 95% confidence and 80% strength in finding the differences between groups, the maximum number required in each group (20 cases) was calculated.

Data Collection Method

Patients with conclusive ITP diagnosis (consistent with the American Hematology Association criteria), examined by an experienced hematologist, hospitalized in Kermanshah's Imam Khomeini Hospital and met the inclusion and exclusion criteria were included in the study. The diagnosis consisted of condition, physical examination, CBC, peripheral blood smear and bone marrow exam. Pursuant to providing information on how the study would be conducted, all patients were notified regarding the informed written consent for participation in the study. Demographic data of patients (including age, sex and duration of disease onset) was recorded in a questionnaire. Stool samples were taken from all patients for evaluation (regarding presence of helicobacter pylori antigen). Patients who tested negative for fecal antigen were excluded from the study. The patients were divided into intervention and control groups utilizing permuted-block randomization (blocks of 4 & 6). The research was a double-blind study and the patients and the medical individual in charge of the patients were all from the treatment group. In the intervention group, helicobacter pylori eradication regimen contained the following prescribed medications:

Clarythromycin 500 mg BD N= 28
Amoxicylin 1 gr BD N= 28
Omeprazol 20 mg BD N= 90

The control group received the same placebo in terms of number and shape as the case group. At the end of the treatment period, the patients underwent fecal examination again to ensure helicobacter pylori had been eradicated. During the treatment period, platelet count was monitored three times (intervals of one, two and three months) and if the platelet count increased before the end of the treatment period, the individual would be excluded from the study (and considered as spontaneous improvement). The impact of treatment was evaluated consistent with the platelet count.

Inclusion & Exclusion Criteria

Inclusion Criteria

-ITP diagnosis (compliant with the criteria of the American Hematology Association, plus examination by an experienced hematologist
-Platelet count between 30 & 150 thousand
-Non-wet purpura
-Non life-threatening bleeding/hemorrhage
-Helicobacter pylori antigen stool positive test
Exclusion Criteria
-History of allergy to penicillin

-Irregular medication use by the patient
-Malabsorption related diseases

Data Description & Analysis Method

The data obtained from this study were statistically analyzed via utilizing the SPSS Software (Version 16. Chi-Square, Independent T Test and repeated measures. The significance level of P was considered less than 0.05.

Table 2: research Variables

		Backgroun d	Disturbanc e	Independen t	Dependen t	Quantitativ e	Qualitativ e	
1	Platelet count							Number Of Cells Per Cubic Milliliter
2	Age							Year
3	Gender							Male & Female
4	Date Since Onset Of Disease							Month
5	Therap y Group							Interventio n, Control

Findings & Research Results

In this study, 40 patients with immune thrombocytopenic purpura (in intervention and control groups) were treated with helicobacter pylori eradication. The mean age of the patients was 34.82±9.06 years (35.2±9.64 in the intervention group & 34.45±8.68 in the control group; p=0.8).

Table 3 : Frequency Of Study Patients By Gender

Gender	Group	Group	Total
	Intervention	Control	
Male	10	14	24
Female	10	6	16
Total	20	20	40
P Value	0.2 * Chi Square	20	40

According to the above table, 50% of the patients in the intervention group and 70% of the patients in the control group were male. The two groups were in a similar situation in terms of gender (p=0.2).

Table 4 : Comparison Of Disease Duration In The Study Groups

Group	Quantity	Mean	Standard Deviation	P Value
Intervention	20	18.45	12.66	0.26
Control	20	22.45	9.67	0.26

The mean duration of immune thrombocytopenic purpura in all patients was 20.45±11.14 months (median of 23 months), 18.45±12.46 months in the intervention group and 22.45±9.45 months in the control group. The difference between the two groups was not statistically significant (p=0.26).

Table 5 : Mean Platelet Count Comparison Prior To Intervention

Group	Quantity	Mean	Standard Deviation	P Value
Intervention	20	67750	19770	0.82
Control	20	69950	23685	0.82

Comparison of the mean platelet count before the intervention in the study groups revealed that the two groups were in a similar position in terms of platelet count (p=0.82).

Table 6 :Mean Platelet Count Comparison In The First, Second & Third Months After Treatment

Time	Group	Mean	Standard Deviation	P Value
1st Month	Intervention	74200	20255	0.7
1st Month	Control	71550	23520	0.7
2nd Month	Intervention	88600	27660	0.03
2nd Month	Control	71350	21947	0.03
3rd Month	Intervention	107150	31843	≤ 0.001
3rd Month	Control	71150	20171	≤ 0.001

Compliant to the findings of the above table, it was discovered that the mean platelet count in the first month after treatment was similar in the two groups, while in the second and third months after treatment, the mean in the intervention group was significantly higher than the control group.

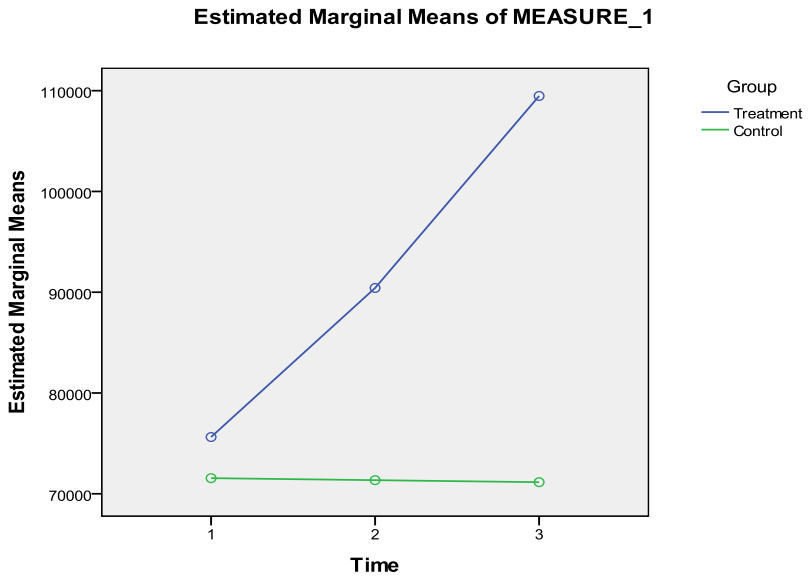

Figure 1: Comparison Of Mean Scores Of Depression During Treatment In The Two Treatment Groups

Repeated measures analysis of platelet count at various times of the study demonstrated that the two groups were different in terms of platelet count changes (p=0.007), specifically, the intervention group had superior results compared to the control group in all stages of the study.

Summary & Conclusion

This study was performed to assess the effects of helicobacter pylori eradication treatment on platelet count in patients with immune thrombocytopenic purpura. The findings revealed that elimination of helicobacter pylori significantly increases the number of platelets in patients.

Various research in this field have had disparate results in different geographical areas. In accrdance with the findings of our research, a study conducted by Kohda & Associates discovered that 62.5% of ITP patients were infected with helicobacter pylori. Pursuant to being treated (via eradication), the platelet counts in more than 63.2% of patients showed a significant increase, up to 15 months after treatment (21). Hino & Associates reported helicobacter pylori infection in 85.7% of ITP patients, and eradication treatment being successful in more than 55% of patients. Analysis of patients revealed that with the elimination of the infection, platelet count increased significantly in the months following (19). This is similar to our present study as well as findings from other research heretofore alluded to (20, 29, 33, 34 & 43-47).

In contrast to the above studies, a number of researches have pointed to the ineffectiveness of helicobacter pylori eradication treatment in increasing platelet count. Jarque & Associates, by examining the impact of helicobacter pylori eradication on platelet count in patients with chronic ITP, found that only 5% of them had increased platelet count following treatment for helicobacter pylori (48). In a study conducted by Payandeh & Associates on 92 ITP patients in Iran, it was discovered that eradication of helicobacter pylori infection significantly improved platelet count in mild ITP patients, when prescribed the three drugs, amoxicillin, clarithromycin and omeprazole,. However, in patients with severe ITP, this treatment had little effect on platelet count (49). This discrepancy has been delineated in other studies as well (2, 24 & 50).

Even though the number and quality of studies pointing to the positive role of helicobacter pylori elimination within the course of ITP treatment is higher, but the observed discrepancy can be justified in some ways. Pathogenic differences in various strains of helicobacter pylori are among the most important possible causes of the existing conflict. Studies have shown that helicobacter pylori genotypes have significant differences in the development of gastrointestinal symptoms (51, 52). Although it is not clear to what extent bacterial genotypic differences are involved in the development of extra-gastrointestinal symptoms, the geographical dispersion of the positive findings of studies suggests the effect of these differences. Most of the studies mentioned earlier (confirming the positive effect of helicobacter pylori eradication on platelet count) have been performed in East Asia, and the majority of studies with negative results were in Europe and the Americas (2, 24 & 48). Even though a review of the regional differences has been studied, it is difficult to draw conclusions due to the lack of sufficient data concerning the infectious strains of ITP patients (53).

Another possible factor in the assorted responses of ITP patients to helicobacter pylori infection treatment is the disease's duration. In a limited number of studies in this field, the ITP duration is noted. Comparison of mean platelet count changes after eradication of helicobacter pylori indicates that platelet counts are higher in patients with shorter disease duration than in chronic ITP patients (26, 34, 35, 43, 44, 50 & 54). Further studies in this area and meta-analysis of the findings shall be helpful in better understanding this relationship.

The infection duration and how the helicobacter pylori infection develops in patients is another possible factor that can affect the response to eradication treatment. Various mechanisms have been proposed to explicate the role of helicobacter pylori in the creation and/or exacerbation of ITP, such as antibody production, Von Willebrant factor interference, B lymphocyte activation, increased phagocytic activity of monocytes, etc. (35 & 55-58). It appears that eradication treatment prior to establishing the alluded to immunological processes, increases the success of controlling the course of platelet depletion. It was difficult/challenging to examine and test this factor due to the existing limitations.

Even though the etiological role of helicobacter pylori in ITP's pathogenesis has been established, one should bear in mind that other factors such as viral infections (HIV, CMV & VZV) and immune system disorders have also been implicated in the pathogenesis of this disease (59-61). The interaction of these factors can also be impactful in response to any type of treatment, including helicobacter pylori eradication treatment.

Among the present study's constraints was its small sample size, due to the challenge and difficulty of finding patients with the right conditions (this limitation also existed in previous studies). The lck of possibility of performing endoscopy as well as the

inability to directly study helicobacter pylori (due to condition of patients) was another limitation of the study, making it impossible to utilize a method with high sensitivity and specificity to check and verify the presence and thereafter elimination of helicobacter pylori.

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