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PREVALENCE OF HELICOBACTER PYLORI INFECTION AMONG TRANSFUSION DEPENDENT THALASSAEMIA PATIENTS

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Abstract

Background and objectives: Helicobacter Pylori infection is a common bacterial infection specially in developing countries, this study was designed to find out the frequency of this bacterial infection in transfusion dependent thalassaemia patients and compare it with healthy controls also to associate different clinical and labouratory characteristics with Helicobacter Pylori positive and negative subjects.

Methodology: The study group included 70 symptomatic patients with thalassaemia who require regular blood transfusion and 32 symptomatic controls with the age ranging from (5-18) years. Stool sample was collected from all cases and controls and H.Pylori rapid antigen test was done for all of them. For case group also CBC and serum ferritin measurement was done.

Results: As a result 28 (40%) patients with transfusion dependent thalassaemia and 9 (28.13%) cotrols were tested positive for Helicobacter Pylori but this difference was not significant statistically. Strong relationship was found between positivity of the test and frequency of blood transfusion, frequency of chelation, type of chelation, serum ferritin level and CBC parameters (low Hb, high WBC, high Plt).

Conclusion: Transfusion dependent thalassaemic patients are more prone to Helicobacter Pylori infection than healthy controls and it can be considered as a cause of recurrent abdominal pain in these patient.

Keywords: transfusion dependent thalassaemia, helicobacter pylori, helicobacter pylori stool antigen test.

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Introduction

Thalassaemias are group of inherited disorders of the red cell synthesis caused by the mutation in the globin genes, causing imbalance in the synthesis of alfa or beta globin chains of hemoglobin, resulting in ineffective erythropoiesis and chronic hemolytic anemia varying in severity(1). Thalassaemias are considered as commonest genetic disorder worldwide extending from the Mediterranean basin through the Middle east, India and Southeast Asia(2). Beta thalassaemia is caused by reduced or absence of beta globin chain result in precipitation of alfa globin chains while alfa thalassaemia caused by the deletion of the alfa globin chain resulting in precipitation of beta chains leading to oxidative damage of the cell membrane and apoptosis and ineffective erythropoiesis(1).

The clinical severity of thalassaemias is determined by extend of imbalance between alfa and beta chains of globin, resulting in three distinct disorders: Thalassaemia major (which is transfusion dependent) , Thalassaemia intermedia (may be transfusion dependent or not) and thalassaemia minor (1).

Inherited hemoglobin disorders also include beta thalassaemia association with other abnormal hemoglobins such as HbS (resulting in sickle B -thalassaemia which may require regular blood transfusion), Hb E, Hb C, HbD and others (3). Transfusion dependent thalassaemia patients are patients that require lifelong red blood cell transfusion in order to survive (such as B-thalassaemia major patients.

In thalassaemia major there is excessive red cell (hemolysis) leading to chronic anemia , also large number of red blood cells processed by the spleen causing splenomegaly and symptoms of hypersplenism resulting in need to splenectomy (4). Transfusion dependent thalassaemias due to chronic anemia need recurrent blood transfusion which is another source of iron together with increased iron absorption leading to a state of iron overload and this iron accumulate in various organs especially heart and liver leading to their damage(4).

Helicobacter Pylori is a gram-negative microaerophilic curved bacillus that colonizes the mucosa of the stomach and cause gastritis , peptic ulcer and may predispose to gastric cancer, studies have demonstrated that H. Pylori prevalence increases with increasing age and it is more prevalent in developing countries (5). Helicobacter Pylori infection may ne asymptomatic or symptomatic with symptoms of abdominal pain which is usually at epigastric region and less number having abdominal pain associated with vomiting and lesser number having vomiting alone (6).

There are consequences of chronic anemia and regular blood transfusion include: growth retardation, bone marrow expansion, susceptibility to infection, iron overload, splenomegaly , heart failure and liver failure (7). Heart failure considered the most common cause of death in thalassaemia major followed by infection (4).

The aim of this study is to: Determine the background prevalence of Helicobacter pylori infection in transfusion dependent thalassaemia patients, compare clinical and labouratory findings between H.Pylpri positive and negative patients and determine the relationship between the mean duration of spleenectomy and the positivity of helicobacter pylori infection.

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Materials and Method

This case-control study was carried out in Erbil Thalassaemia center/ Kurdistan region/Iraq, from April 2022 to August2022. Erbil thalassaemia center is the only center in Erbil city where thalassaemic patients visit to recieve their regular blood transfusion, follow up their clinical condition and receive their iron chelation therapy.

Seventy patients were included in the study, the inclusion criterias were patients should be diagnosed with hemoglobinopathy which in need of regular blood transfusion, the age included from5-18 years and patients having symptoms of recurrent abdominal pain and or nausea and vomiting while the exclusion criterias were age <5 years or>18 years and any diagnosed case of Helicobacter Pylori on treatment.

Patients were asked about their name, age, gender,blood group, frequency of blood transfusion, duration of blood transfusion (time calculated from the first transfusion), type of iron chelation therapy, duration of receiving chelation, type of hemoglobinopathy and splenectomy done or not, if done the patient asked about the duration of splenectomy. For all patients complete blood count(Hb ,WBC, Plt) was done with serum ferritin level ad Helicobacter Pylori rapid antigen stool test. For CBC 2ml of venous blood taken from the patient with use of tubes containing EDTA anticoagulant and for serum ferritin at the same time 2ml of venous blood put in tube(not containing anticoagulant) and serum ferritin level measured after centerfugation, while for Helicobacter Pylori stool test specific sterile tubes were used for stool collection and the test performed within the first half hour of stool collection.

While for controls of the study, 32 healthy with age and sex related controls were taken whom suffered from recurrent abdominal pain andlor nausea and vomiting and also Helicobacter Pylori rapid stool antigen test was performed to all of them.

The general and medical characteristics of controls and children with thalassemia were presented in mean and standard deviation or number and percentage. The comparisons of general and medical characteristics between control and thalassemia patients were examined in an independent t-test or Pearson chi-squared tests. The comparison of the helicobacter test between control and children with thalassemia was examined in Pearson chi-squared test. General, therapeutic and biochemical factors associated with helicobacter outcomes among thalassemia patients with different characteristics were examined in an independent t-test or Pearson chi-squared tests. A p-value of less than 0.05 was determined as a statistically significant difference. The statistical calculations were performed by JMP pro 14.3.0.

The ethical approval of the present study was taken from the local health ethics committee in Erbil city (KBMS health ethics committee). The written consent form was taken from all patients before recruitment into the study. The confidentiality of the personal information of the patients was protected throughout the study period.

Results

The median age for thalassaemic patients group was (11.89±3.85) years and for control group was (10.72±3.95) years ranging from (5-18) years for both groups. In thalassaemic patients group the male

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gender patients were 33 patients with percentage of (47.14%) while female patients were 37 with percentage of (52.86%). In control group the male controls were 14 with percentage of (43.75) while female controls were 18 with percentage of (56.25) as seen in table 1. There was no statistically significant difference between age and gender of the case group and control group.

Table 1: Comparisons of general characteristics between control and thalassemia patients

Characteristic	Study groups no (%)		
	Control (n=32)	Thalassemia (n=70)	p-value (two-sided)
Age (5-18 years) mean (SD)	10.72 (3.95	11.89 (3.85	0.1619[a]
Gender Male Female	 14 (43.75 18 (56.25	 33 (47.14 37 (52.86	0.7497[b]
[a] an independent t-test and [b] Pearson chi-squared tests were performed for statistical analyses.			

Table 2: Medical characteristics of patients with thalassemia

Medical characteristics	Thalassemia (n=70)	
	Number	Percent
Frequency of blood transfusion (7-40 days) mean (SD)	20.93	7.59
Frequency of blood transfusion (day) 7-14 days 14-21 days 22-28 days 29 days and more	 10 33 8 19	 14.29 47.14 11.43 27.14
Duration of blood transfusion (3.5-17.5 years) mean (SD)	10.74	3.87
Duration of blood transfusion (year) 1-5 years 6-10 years 11-15 years 16-17.5 years	 8 23 30 9	 11.43 32.86 42.86 12.86
Type of hemoglobinopathy Major Sickle B	 62 8	 88.57 11.43

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Table 3: Treatment and biomedical measurements of thalassemia patients:

Treatment and biomedical measurements	Thalassemia (n=70) no (%)	
	Number	Percent
Iron chelating agent		
Exjade	41	58.57
Desferal	15	21.43
Both	14	20.00
Duration of receiving chelation (2-15 years) mean (SD)	8.47	3.81
Duration of receiving chelation (year)		
2-5 years	19	27.14
6-10 years	29	41.43
11-15 years	22	31.43
Splenectomy		
No	59	84.29
Yes	11	15.71
Duration of splenectomy (1.5-7 years) mean (SD)	3.59	1.74
HB (5.9-11.8 g/dl) mean (SD)	8.97	1.22
WBC (2.7-15.4 $\times 10^9$**) mean (SD)**	7.31	3.00
Plt (139-491 (no.$\times 10^9$**) mean (SD)**	311.56	93.26
Blood group		
A-	7	10.00
B+	8	11.43
AB-	2	2.86
O-	3	4.29
B-	6	8.57
A+	16	22.86
AB+	6	8.57
O+	22	31.43
Serum ferritin (582-9131 ng/ml)	3481.53	1911.76

From 70 symptomatic patients with thalassaemia major 28 (40%) were tested positive for Helicobacter Pylori antigen while from 32 cotrols 9 patients (28.13%) were tested positive, meaning the percentage of Helicobacter Pylori infection is higher in thalassaemic patients than in controls but this difference is not statisticaly significant (P-value =0.2471).

Table 4: Comparisons of helicobacter test between control and patients with thalassemia

Helicobacter test	Study groups		
	Control	Thalassemia	p-value (two-sided)
Negative Positive	23 (71.88 9 (28.13	42 (60.00 28 (40.00	0.2471
Pearson chi-squared test was performed for statistical analysis.			

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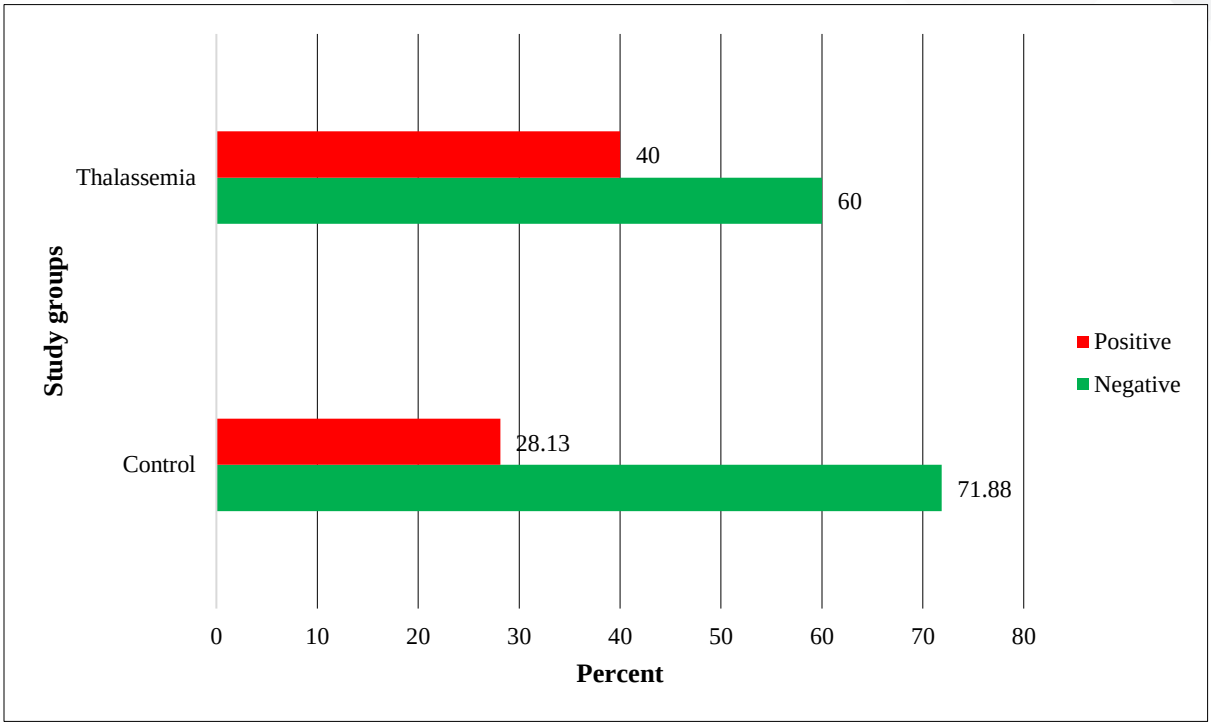

Fig 1: Outcomes of helicobacter of control and thalassemia

According to our results the age had a significant role in the positivity of Helicobacter Pylori infection , the aldolescent age group (53.06%) of them were tested positive while from children age group only (9.52%) were tested positive (P value=0.0007). No significance seen for gender of the patients (P value= 0.5575).

Frequency of blood transfusion played an important role in positivity of Helicobacter Pylori antigen , most of the patients included in this study were receiving blood every 14-21 days and the largest number of H. Pylori positive cases were located in this group with (39.39%) of them tested positive while the highest percentage of positivity for H. Pylori were included within the group who are receiving blood every 7-14 days which (80%) of them tested positive. Patients that receive blood every 22-28 days and more were less tested positive for H. Pylori antigen(P value= 0.0306). This means that more frequent the patient receive blood more chance to be infected with H.Pylori.

Thalassaemic patients who were receiving blood for longer duration (in years) were more tested positive for Helicobacter Pylori infection. As shown in table 5 the patients receiving blood for 16-17.5 years (77.78%) of them were tested positive and (22.22%) of them were negative, while those who were receiving blood for shorter duration less percentage of them were tested positive (P value=0.0011).

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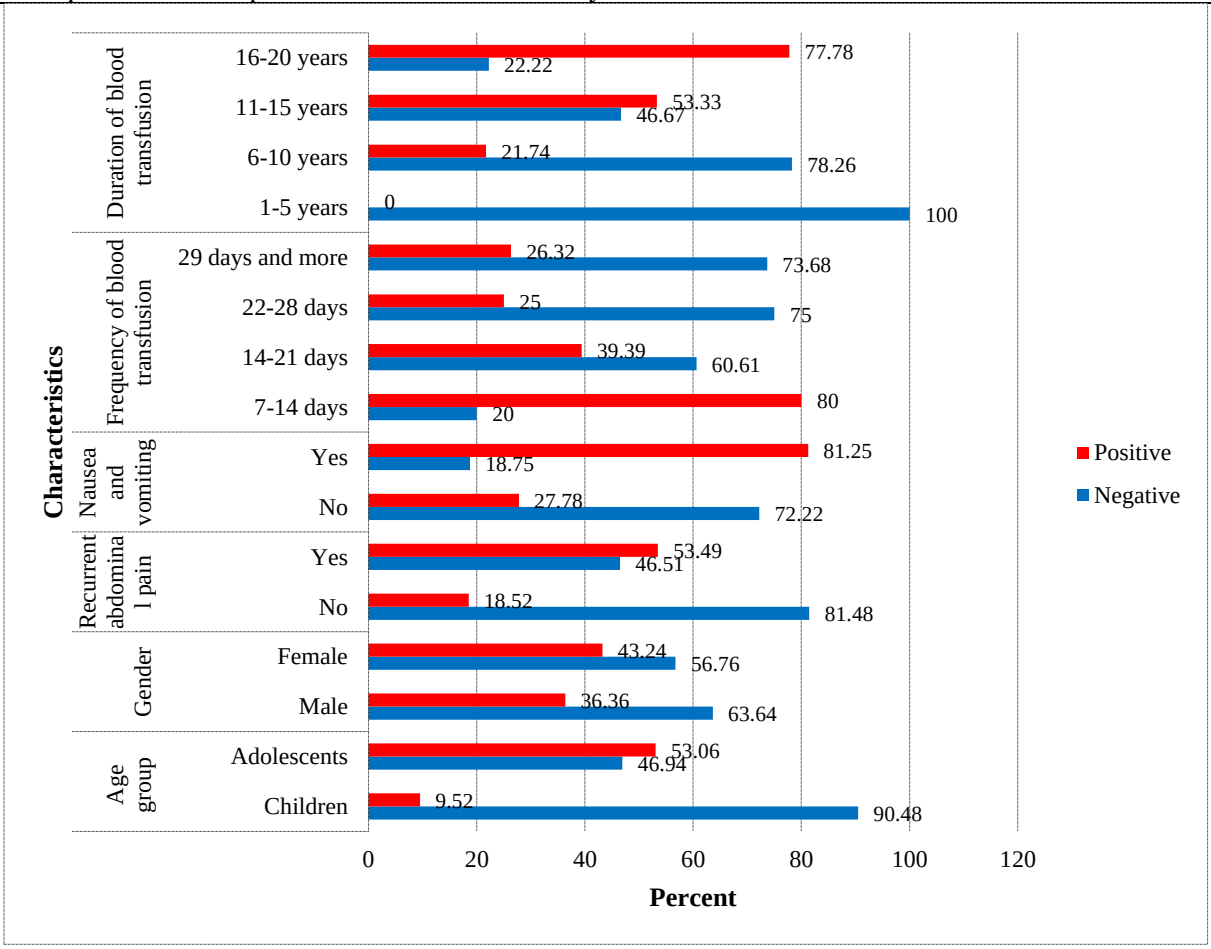
Table 5: Factors associated with helicobacter outcomes among thalassemia patients with different characteristics

Characteristics	Helicobacter outcomes no (%)		p-value (two-sided)
	Negative (n=42)	Positive (n=28)	
Age group			
Children	19 (90.48	2 (9.52	**0.0007**
Adolescents	23 (46.94	26 (53.06	
Gender			
Male	21 (63.64	12 (36.36	0.5575
Female	21 (56.76	16 (43.24	
Frequency of blood transfusion			
7-14 days	2 (20.00	8 (80.00	**0.0306**
14-21 days	20 (60.61	13 (39.39	
22-28 days	6 (75.00	2 (25.00	
29 days and more	14 (73.68	5 (26.32	
Duration of blood transfusion (year)			
1-5 years	8 (100	0 (0.00	**0.0011**
6-10 years	18 (78.26	5 (21.74	
11-15 years	14 (46.67	16 (53.33	
16-17.5 years	2 (22.22	7 (77.78	
Pearson chi-squared test was performed for statistical analyses.			



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It was found that found that the patients who were receiving oral chelation (exjade) plus injectable chelation (desferal) were more liable for H. Pylori infection (71.43%) of the were positive and (28.57%) were negative, while who were receiving desferal alone and exjade alone were (53.33%) and (24.39%) of them tested positive, respectively (P value=00.40). Also the longer duration of receiving chelation therapy was associated with higher rate of infection with H. Pylori as seen in (table 6) patients who is recieving iron chelation therapy 11-15 years (63.64%) were tested positive while who were receiving chelation for shorter duration were less infected with H. Pylori (P value=0.0006).

Patients who did spleenectomy more of them (63.64%) were tested positive for H. Pylori antigen while (36.36%) of them were tested negative but this was not statisticaly significant (P value=0.1018). The duration of splenectomy also was not found to be statisticaly significant.

The type of hemoglobinopathy (Beta thalassaemia major or sickle beta thalassaemia) was not found to be statisticaly significant in H. Pylori positivity (P value=0.4620) also the blood group of the patient was not found to be statisticaly significant (P value=0.7921).

The mean level of hemoglobin in thalassaemic patients with H.Pylori was lower than negative cases (8.34±0.97g\dl), white blood cell count higher in positive cases (8.75±3.95.× 10^9) and platelet also higher (346.92±91.48.× 10^9) with P-values of 0.0001,0.0136,0.0370 for them respectively. Mean serum ferritin level for positive cases was (2564.6ng\ml) while it was (3773.43ng\ml) for negative cases (P value=0.058) which means significantly lower serum ferritin level in positive cases of H.Pylori.

Table 6: Therapeutic and biochemical factors associated with helicobacter outcomes among thalassemia patients with different characteristics

Characteristics	Helicobacter outcomes		p-value (two-sided)
	Negative (n=42)	Positive (n=28)	
Iron chelating agent			
Exjade	31 (75.61	10 (24.39	**0.0040**[b]
Desferal	7 (46.67	8 (53.33	
Both	4 (28.57	10 (71.43	
Duration of receiving chelation (year)			
1-5 years	18 (94.74	1 (5.26	**0.0006**[b]
6-10 years	16 (55.17	13 (44.83	
11-15 years	8 (36.36	14 (63.64	
Splenectomy			
No	38 (64.41	21 (35.59	0.1018[b]
Yes	4 (36.36	7 (63.64	
Type of hemoglobinopathy			
Major	36 (58.06	26 (41.94	0.4620[b]
Sickle B	6 (75.00	2 (25.00	
Blood group			
A-	3 (42.86	4 (57.14	0.7921[b]
A+	4 (50.00	4 (50.00	
AB-	1 (50.00	1 (50.00	

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AB+ B- B+ O- O+	1 (33.33 4 (66.67 12 (75.00 4 (66.67 13 (59.09	2 (66.67 2 (33.33 4 (25.00 2 (33.33 9 (40.91	
HB (g/dl)	9.54 (0.84	8.34 (0.97	**<0.0001[a]**
WBC (no.× 10^9)	6.78 (2.46	8.75 (3.95	**0.0136[a]**
Plt (no.× 10^9)	294.21 (99.55	346.92 (91.48	**0.0370[a]**
Serum ferritin (ng/ml)	3777.43 (1915.19	2564.6 (1147.69	**0.0058[a]**
[a] an independent t-test and [b] Pearson chi-squared tests were performed for statistical analyses.			

Discussion

Thalassaemia firstly was described as a form of severe anemia that occurs in young children and associated with bone changes and splenomegaly, the only cure for thalassaemia is bone marrow transplantation if transplant not done then regular blood transfusion protocol is the only treatment that is available to these patients [8].

Regular and early usage of blood transfusion protocol will decrease the rate of complications and will prolong survival while long term protocol of blood transfusion can limit its beneficial effect and cause complications such as chronic infections, transfusional siderosis, alloimmunization against RBC antigens , liver and heart failure [9].Most of the patients infected with H.Pylori are asymptomatic and may cause chronic gastritis and peptic ulcer[10]. Urea breath test and stool for H. Pylori atigen are regarded as uninvasive tests to diagnose H.Pylori infection [11].

The results of our study stated that the prevalence of Helicobacter Pylori in symptomatic transfusion dependent thalassaemia patients is (40%) while the prevalence in healthy symptomatic controls is (28%) meaning thalassaemic patients are more prone to H.Pylori infection than healthy people but these percentages are not statisticaly significant, as in a study published in Iran (Mehran Karimi) the prevalence of H.Pylori infection in Beta thalassaemia major patient was (68%) while (60%) in controls and this difference also was not statisticaly significant [12]. Another study published stated that the prevalence of Helicobacter Pylori was (58.1%) among thalassaemic patients with recurrent abdominal pain while it was (48.8%) in normal controls which is not statisticaly significant [5].

A study done in Egypt stated that the prevalence of H.Pylori in symptomatic patients with thalassaemia major by HP IgG antibody was positive in (58.3%) while in symptomatic controls was (29.2%) , also there was higher prevalence of H.Pylori IgG antibody in asymptomatic thalassaemic patients (41.7%) than asymptomatic controls (20.8%) and these results were significant statisticaly (P value=0.04) [13].

It is believed that the high frequency of H.Pylori is thalassaemic patients who need regular transfusion is related to the state of iron overload suggesting that there is a link between iron overload and risk of infections [14,15].

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In this study the prevalence of H.Pylori infection increases with increasing age of the patient while there was no relation between H.Pylori infection and the gender of the patient. Also in this study no relation found between the blood group and Rh of the patient with H.Pylori infection, while the relation was stated in some studies [16].

In current study relation found between H.Pylori infection and frequency of blood transfusion, duration of blood transfusion and duration of receiving iron chelation stating that the longer duration of transfusion and chelation more risk for infection with H.Pylori [12]. Also relation found between H.Pylori and the type of chelation agent given to the patient possibly also related to the state of iron overload.

There was no clear relation found between spleneectomy and H.Pylori infection however the percentage of positivity of H.Pylori was higher than negativity in spleenectomized patients but not significant statisticaly, while in some studies discovered that there was a significant relation between H.Pylori infection and spleenectomy stating that there is change in the immune system after spleenectomy [6,17].

The mean level of serum ferritin was significantly lower in positive than negative cases of H.Pylori while in another published studies show no relation between H.Pylori infection and seum ferritin level [6].

Besides, the mean hemoglobin level of transfusion dependent thalassaemic patients was lower in H.Pylori positive group than in negative group , some published articles suggest that H.Pylori lead to a state of iron diffeciency and iron diffeciency anemia [17]. Also there was higher WBC and platelet count in positive thalassaemic patients than in negatives.

Conclusion

According to our study we conclude that transfusion dependent thalassaemia patients are more prone to be infected with Helicobacter Pylori infection than normal people, and we can regard Helicobacter Pylori infection as a common cause of abdominal pain and\or nausea and vomiting in transfusion dependent thalassaemia patients.

There is clear relationship between duration of blood transfusion ,receiving iron chelation and frequent transfusion protocols with probability of H.Pylori infection.

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