Complications of High Serum Ferritin Level after Splenectomy in β Thalassemic Patients

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ABSTRACT

Objectives: Compare between splenectomized and non splenectomized β -thalassemic patients regarding clinical, biochemical and therapeutic characteristics.

Methods:

This study was conducted on 140 patients with beta thalassemia major and thalassemia intermedia, expressed as two groups (group I) splenectomized patients and (group II) non splenectomized patients, who were attending Thalassemia Center in Karbala Teaching Hospital for Children from the first of November 2007 through 30th of April 2008. Both groups were studied by physical examination, biochemical analysis, hemoglobin level, serum ferritin, hepatitis C virus antibodies, and hepatitis B surface antigen. Echocardiography was done for most of patients.

Results: In group I patients, 82.9% were under transfused and 80% were underchelated, whereas 91.4% of group II patients were under transfused and 74.3% of them were underchelated. Complications including, cardiac complications, diabetes mellitus, bone deformities, and gall stone were higher in group I than group II patients, moreover, only bone deformities was detected in β- thalassemia intermedia patients of both groups. Splenectomy was beneficial in reducing frequency of blood transfusion in 77.1% of group I patients.

Conclusions: There is an aggravating effect of splenectomy on hemosiderosis. High serum ferritin level in splenectomized patients is associated with higher incidence of complications.

Key words: serum ferritin, splenectomy, thalassemia.

Introduction

Splenectomy in thalassemia is justified when the spleen becomes hyperactive, leading to excessive destruction of red blood cells and thus increasing the need for frequent blood transfusion resulting in more iron accumulation. A practical one criteria suggest that splenectomy may be beneficial in patients who require >200 -250 ml / kg packed red blood cells per year to maintain Hb level of 10 g / dl. Presence of leucopenia and thrombocytopenia are other indications. Splenectomy reduces the transfusion requirement to approximately 150 ml / kg / year, with some variation from patient to patient, and the effect has been demonstrated to be long lasting. Traditionally, the procedure is delayed whenever possible until the child aged 4-5 years or older.

Post splenectomy risk of infections is always a concern. Pre splenectomy immunization (4-6 week) and post surgical prophylactic antibiotics have significantly decreased the rate of such complications.

Thrombocytosis, pulmonary hypertension and venous thromboembolic events are reported as complications after splenectomy (1, 2, 3, and 4).

The theory that a residual portion of spleen (partial splenectomy) protects the patient from infections and thrombotic events is still unproven. It has been hypothesized that the spleen could represent a reservoir for transfused iron and that splenectomy would, therefore, expose the patient to the risk of more massive siderosis of the liver (5).

However, the iron content of the spleen, at splenectomy, is low, amounting to no more than one –fifth to one – tenth of the liver iron content. In addition, no difference has been observed in extent of liver fibrosis between splenectomized and non splenectomized patients (1).

Central venous line placement is another surgical procedure for the ease and convenience of administering blood transfusion, chelation therapy, or both (6).

Gall stones have been reported in 4-23 % of thalassemic patients.

High incidence rate of HCV continues in developing, leading to an increased incidence of fibrosis, cirrhosis and hepatocellular carcinoma (7, 8).

Although the cardiac complications of thalassemia are multifactorial, the role of iron is of paramount importance. Most deaths in patients with thalassemia are due to cardiac involvement. The 5 years survival rate after onset of heart failure was 48 % (9).

Liver parenchyma siderosis is present from the very early stages of iron loading and progress to fibrosis and cirrhosis (8).

Patients with thalassemia major frequently exhibits features of insulin–dependent diabetes and impaired glucose tolerance. Age at initiation of transfusion therapy, liver iron load, poor compliance with chelation, and male sex were found to be significant factors in the development of diabetes(10, 11).

During our daily practice in pediatric examinations, we noticed many thalassemic patients who experienced splenectomy had not gained accepted response in regard to frequency of transfusions. In addition, many of them showed other complications. Many literatures had concentrated mainly on some complications, like infections. Other complications have not been concentrated upon.

The purpose of this work is to discover any relation between these complications and splenectomy.

Patients and methods

Seventy patients with β – thalassemia including β –thalassemia major and thalassemia intermedia (group I)who had splenectomy were studied during the period of first of November 2007 through 30th of April 2008, at time of their attendance to Thalassemia Center in Karbala Teaching Hospital for Children. The age of the patients ranged between 7– 18 years.

Another 70 non splenectomized β–thalassemic patients (group II, control group) were studied for the same characteristics of group I, their age ranged between 5–18 years.

The information collected from these patients were:-

Age and sex, age and clinical presentation at time of diagnosis, age at first blood transfusion, age at starting iron chelation (parenteral desferoxamine, frequency per week and duration of infusion in hours). The compliance with the drug was assessed as good (frequency ≥ 5 / week and duration ≥ 8 hours for each time) (12). Other informations were age at splenectomy, blood transfusion frequency per year before and after splenectomy, presence of complications of β -thalassemia (cardiac complications, diabetes mellitus, gallstone and bone deformities).

All patients were examined. Clinical examination was carried out to determine the presence of thalassemic facies (frontal bossing, prominent facial bones and dental malocclusion) (1), liver span was detected and represented as a mean (normal liver span for children aged 6–12 years ranged 6-12cm) (13).

Type of β-thalassemia (major or intermedia) was detected by hemoglobin electrophoresis results and the clinical manifestation of the disease.

Hemoglobin level prior to blood transfusion, HCV antibodies, Hbs Ag, and serum ferritin level were determined in all patients. (Normal value of serum ferritin for 6

months –15 years is 7- 140 ng / ml and adult level is 15- 200 ng / ml) (14). Echocardiography was done for most of patients.

The study is a prospective, case control study. t –test was used in the statistical analysis. P value < 0.05 was considered as a level of significance.

Results

The mean age of splenectomized patients was 14.2 years for β–thalassemia major patients (57 patients) and 15.5 years for patients with thalassemia intermedia (13 patients).

The mean age of group II β – thalassemia major patients was 11.2 years (55patients) and 11.4 years for thalassemia intermedia (15 patients).

Of group I: fourty seven were male, and 23 were female. While of group II: eleven were male, and 46 were female.

Table 1: Selected demographic characteristics of group I β – thalassemic patients.

Mean age of patient (years)	β – thal. major	β – thal. intermedia
At time of study	14.2±3.5	15.5±2.8
At diagnosis	1.14±0.72	4.07±2.6
At 1st blood transfusion	1.2±5.3	5.3±2.4
At starting of iron chelation	5.9±3.42	11.7±5.35
At splenectomy	8.75±4.32	11.38±3.75

Table 2: Selected demographic characteristics of group II patients.

Mean age of patients	β – thal. major	β – thal. intermedia
At time of study (in years)	11.2±4.6	10.4±5.6
At diagnosis	8±2 (mon)	5±2.7(yrs)
At 1st blood transfusion	8±2 (mon)	5±2.7 (yrs)
At starting of iron chelation therapy (in years)	3.2±1.25	7.9±3.42

In this study, patients with β -thalassemia major of group II were received blood every 18 days as a mean and patients with thalassemia intermedia were received blood every 35 days as a mean.

Table 3: Presentation at time of diagnosis of β – thalassemic patients for both group I and group II patients.

Presentation at time of diagnosis		Group I NO. %		Group II NO. %
Pallor	84.29	59	87.1	61
Jaundice	5.71	4	2.9	2
Hepatosplenomegaly	10	7	10	7

This study had revealed that, the mean liver span was higher (13.5 cm) in group I than group II (8 cm). P-value is < 0.05.Moreover, 71.4% (50 patients) of group II had hepatosplenomegaly.

Table 4: other variables of β – thalassemic patients in splenectomized and non splenectomized patients.

		Group I NO. %		Group II NO. %
Hb level (g/dl)				
(5-7)	14.3	10	34.3	24
(>7-9)	68.6	48	57.1	40
(>9)	17.1	12	8.6	6
Positive hepatitis screen	32.9	23	25.7	18
Hepatitis B	4.3	1	16.6	3
Hepatitis C	95.7	22	83.3	15

An important finding is that 17.1 % of splenectomized patients had Hb level above 9 g/dl, while 8.6 % of non splenectomized patients had Hb level above 9 g/dl. In addition, 32.9 % of splenectomized patients were positive for hepatitis (95.7 % HCV and 4.3% for hepatitis B), while 25.7 % of non splenectomized patients were positive for hepatitis (83.3 % HCV and 16.7 % for hepatitis B).

Mean serum ferritin level was 795.8 ng/ml ranged (280-3213ng/ml) for group I patients, while mean serum ferritin level was 566 ng/ml ranged (200-2150 ng/ml) for group II patients. P-value <0.05.

Table 5: illustrates frequency and duration of iron chelation therapy in relation with number of underchelated patients of group I and group II.

Variables	Group I NO. %	Group II NO. %
Frequency of using iron chelation therapy		
≤2/wk		
3/wk-4/wk	28 40	24 34.3
5/wk	28 40	28 40
Duration of iron chelation therapy(hr)	14 20	18 25.7
≤ 6hr	45 64.3	39 55.7
8hr	15 21.4	18 25.7
≥ 10h	10 14.3	13 18.6
Number of underchelated patients	56 80	52 74.3

Mean number of blood transfusion / year was16 (ranged 8-24) for β -thalassemic major patients of group I and was 22 / year (ranged 12-36) for patients of group II, while mean number of blood transfusion / year was 8 (ranged 6-18) for patients with thalassemia intermedia of group I and was 13 (ranged 6-32) for patients of group I (p-value <0.05). Moreover, 20 % of group I patients used iron chelation therapy for ≥ 4 times per week, while 25.7 % of group II patients used iron chelation therapy for ≥ 4 times per week.

Of group I patients 64.3% used iron chelation therapy for ≤ 6 hours in comparison with 55.7 % of group II patients.

Table 6: illustrates frequency and number of blood transfusion per year before and after splenectomy in group I patients.

Variables	Before splenectomy		After splenectomy	
	mean value	Range	mean value	Range
Number of blood transfusion (per year)				
β – thal. major	24	12-48	16	8-24
β – thal. intermedia	16	12-22	8	6-18
Frequency of blood transfusion (in days)				
β – thal. major	15	7-28	23	15-45
β – thal. intermedia	22.5	16-28	45	20-56

Decreased frequency of blood transfusion / year after splenectomy were found in 54 patients (77.1 %), while 16 patients (22.9%) of the same group of patients had unaffected frequency of blood transfusion / year after splenectomy. After splenectomy, the
frequency of transfusion in β –thalassemic major patients were (8 – 24) / year and (6 – 18) / year for patients with thalassemia intermedia.

Table 7: illustrates chronic complications in both group I and group II patients.

Complications	Group I		Group II	
	NO.	%	NO.	%
Thalassemic face.	38	54.3	14.3	10
Heart failure	5	7.1	1.4	1
Diabetes mellitus	3	4.3	1.4	1
Gall stone	7	10	0	0
No complications	17	24.3	82.9	58

None of these complications (cardiac complications, diabetes mellitus, gall stone) were detected in patients with thalassemia intermedia except thalassemia facies.

Discussion

In our center, many complications have been found in splenectomized thalassemics in significant percent, with clear association with high serum ferritin.

In this study, the mean age of splenectomized patients (group I) was 14.2 years with range of (7-18) years for β - thalassemia major patients and 15.5 years with range of (9 - 18) years for β - thalassemia intermedia patients. This is higher than that reported in Mosul 1999, where the mean age of all patients was 10.4 years with range of (4 -18) years. This may be due to selection of the patients for splenectomy in which the minimum age of splenectomized patients was 7 years for thalassemia major and 10.4 years for thalassemia intermedia patients (15). The mean age of group II patients was lower than that in group I patients in this study.

The mean age at diagnosis of group I patients was 1.14 years for β - thalassemia major patients and 4.07 years for thalassemia intermedia patients, this result is higher than that reported in Mosul 1999, in which the mean age at diagnosis was 9.8 months (15).

In this study, the mean age of patients at splenectomy was 8.75 years for β -thalassemia major patients and was 11.38 years for thalassemia intermedia patients. Other studies in the United Kingdom by Modell and Berdoukas, found that the mean age at splenectomy of thalassemia intermedia was 8 years, and in North America, the mean age at splenectomy was 9 years. Both are lower than the result found in this study (16). This may be due to lower mean age of patients included in their studies.

Seventy seven percent of splenectomized patients were responding to splenectomy by requiring less number of blood transfusion per year (24 per year presplenectomy to 16 per year postsplenectomy for β - thalassemia major patients and from 16 per year presplenectomy to 8 per year postsplenectomy for β - thalassemia intermedia patients). This result is nearly similar to that obtained by other researchers in Iraq (15, 17, 18).

The mean age of starting iron chelation therapy was higher in group I compared to group II patients, and only 20 % of those patients used therapy properly regarding the frequency (5 times / week or more) and only 14.3 % of group I patients used chelation therapy properly regarding the duration of infusion (10 hours or more). As the duration of infusion is more important than the dose and the frequency, this may explain partially the higher level of serum ferritin in splenectomized patients than non splenectomized patients despite the decrease of frequency of blood transfusion in group I compared to group II patients.

Although the role of splenectomy in worsening iron overload is controversial, an aggravating effect of splenectomy on hemosiderosis has been suggested by some authors (1).

Complications (including cardiac complications, bone deformities, diabetes, and gall stone) were higher in group I when compared to group II and this may be attributed to the higher level of serum ferritin in group I patients. Moreover, complications including cardiac failure, diabetes and gall stone were found only in β - thalassemia major patients and not detected in β - thalassemia intermedia patients.

Bone deformities (thalassemic facies) was the only complication found in β – thalassemia intermedia patients, this result is in agreement with Denser Pollack R. et al, who reported 65% of patients with thalassemia intermedia had bone deformities due to increased erythropoiesis (19). Although diabetes mellitus was not reported in β – thalassemia intermedia patients in this study, it was reported in some studies (20). Cardiac complication was not reported in this study in patients with β – thalassemia intermedia, but a large multicenter study has described a worrisome picture, in which variation of serum ferritin was explained by age and by change in soluble transferring

receptor, with an aggravating effect of splenectomy on hemosiderosis has been suggested (21).

The present study had revealed that 32.9 % of group I patients were positive for hepatitis B and hepatitis C whereas 25.7 % of group II patients had positive result, this is nearly similar to the result reported in Basrah in (2005) 30.4% (22).

The higher percent of splenenectomized group I patients with positive hepatitis screen result may explain the higher percent of diabetes 4.3 % compared to 1.4% in group II patients, in addition to the factor of iron overload. It has been suggested that liver damage could contribute to the impairment of islet cell function. Other study in U.S.A. by Melody et al had revealed nearly similar percent of positive hepatitis C result in thalassemic patients 35% (23), while Cooley Care Cooperative Group in 1990, reported that 23 % of thalassemic patients tested in United Kingdom and 21 % in India as well as 15 % of patients in Italy were positive for hepatitis C, which is lower than the result reported in this study. Another nearly similar result was reported in France 34 % (1, 23) In conclusion, although splenectomy was beneficial in reducing requirement of blood transfusion in 77 % of splenectomized β - thalassemic patients, the study revealed that complications (cardiac complications, diabetes mellitus, gall stone and bone deformities) were significantly higher in splenectomized patients compared with non splenectomized β - thalassemic patients.

The presence of higher serum ferritin in splenectomized patients compared with non splenectomized patients may be related partially to decreased duration of using iron chelation therapy in our study, an aggravating effect of splenectomy on hemosiderosis is possible.

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