Splenectomized versus non-splenectomized patients with thalassemia major

Echocardiographic comparison

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ABSTRACT

الأهداف: إجراء مقارنة بواسطة ايكو القلب بين مرضى استئصال الطحال مع هؤلاء المرضى اللذين لم يستئصال لهم الطحال من مرضى الثلاسيميا الكبرى.

الطريقة: أجريت دراسة على مرضى الثلاسيميا بمستشفى الولادة والأطفال– المدينة المنورة – المملكة العربية السعودية خلال الفترة مابين ديسمبر 2006م وحتى ديسمبر 2007م. تم تقييم كل المرضى من خلال الفحص السريري، والفحص الفيزيائي، والدراسات المختبرية، وإيكو القلب.

النتائج: شملت الدراسة 57 مريضاً قسموا على مجموعتين: مجموعة لم يستأصل منها الطحال (36 مريض)، ومجموعة تم استئصال الطحال منها جراحياً (21 مريض). تناظرت المجموعتين بشكل جيد من حيث العمر، الجنس، الوزن والطول. كانت كمية الدم التي أعطيت خلال السنة الماضية (6577.1±206.9ml مقابل 5390.5±220.0ml) (p=0.0005)، والدليل السنوي لنقل الدم (200.9±11.3 مقابل 134.1±7.3) (p=0.0001)، كانت منخفضة بشكل ملحوظ في مجموعة المرضى اللذين استؤصل منها الطحال عن مجموعة المرضى بدون استئصال الطحال. لم يكن هناك أي اختلاف مهم بين المجموعتين في الفحوصات المخبرية. كما لم يكن هناك اختلاف في الوظيفة الانقباضية للبطين الأيسر بين المجموعتين بالنسبة للقياس. كانت نسبة E/A للصمام الميترالي أعلى بشكل ملحوظ في مجموعة المرضى اللذين استؤصل منها الطحال (1.6±0.2 مقابل 1.4±0.2) (p=0.02). كان الضغط الشرياني الرئوي مرتفع في مجموعة المرضى اللذين استؤصل منها الطحال (34.2±9.1mm Hg مقابل 20.8±9.2) (p=0.0001). كان عدد المرضى اللذين يعانون من الضغط الرئوي أكبر في مجموعة المرضى اللذين استؤصل منها الطحال (14 (66.7%) مقابل 6 (16.7%)) (p=0.0004).

خاتمة: يختلف مرضى الثلاسيميا الكبرى مع استئصال الطحال عن أولئك بدون استئصال طحال بأنهم يحتاجون لنقل دم أقل. ولكن من جهة أخرى وجد أن لديهم عامل خطورة لاعتلال الوظيفة الانبساطية للبطين الأيسر، وارتفاع ضغط الشريان الرئوي. وعليه يجب أن يؤخذ ذلك بعين الاعتبار أثناء متابعة هؤلاء المرضى.

Objective: To study the effect of splenectomy in patients with thalassemia major on the cardiovascular system through echocardiographic study.

Methods: A prospective, cross sectional study was carried out from December 2006 to December 2007. Patients from the Thalassemia Center in the Maternity and Children's Hospital, Madina, Kingdom of Saudi Arabia, were screened by means of history, physical examination, laboratory studies, and echocardiography.

Results: Fifty-seven patients were studied: 36 were non-splenectomized, while 21 were surgically splenectomized. The 2 study groups were well matched for age, gender, height, and weight. The total amount of blood given during the previous year (6577.1±206.9 ml versus 5390.5±220.2 ml, p=0.0005), and the annual transfusion index (200.9±11.3 versus 134.1±7.3, p=0.0001) were significantly lower in the splenectomized group. There was no significant difference between the 2 groups regarding laboratory studies. Left ventricular systolic function shows no difference regarding fraction shortening between the 2 groups. The mitral valve E/A ratio was significantly higher in the splenectomized group (1.6±0.2 versus 1.4±0.2, p=0.02). The pulmonary artery pressure was higher in the splenectomized group (34.2±9.1 versus 20.8±9.2 mm Hg, p=0.0001). There was a significantly higher number of patients with pulmonary hypertension in the splenectomized group (14 [66.7%] versus 6 [16.7%], p=0.0004).

Conclusion: Splenectomized patients with thalassemia major are at high risk of having impaired diastolic left ventricular function and pulmonary hypertension.

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Thalassemia major is one of the most severe genetic defects, which presents as a major public health problem in the world population. Treatment of thalassemia consists mainly of blood transfusion, chelation therapy and bone marrow transplantation.[1] Regular transfusion and chelation therapy is still the only treatment used in many hospitals around the world. Several life threatening complications like iron overloading, hepatitis, hypertension, cardiac dysfunctions and renal failure may develop due to multiple transfusions.[2] Splenectomy is often carried out to avoid these complications associated with repeated transfusions, and to minimize the need and frequency of blood transfusions.[3,4] Splenectomy, on the other hand, may have some effects, which need to be studied. The purpose of our study was to investigate some clinical, laboratory, and echocardiographic parameters between splenectomized and non-splenectomized thalassemia major patients.

Methods. This was a prospective study with cross-sectional design, conducted from December 2006 to December 2007. The work was approved by the ethical committee of the hospital. Patients with thalassemia major from the Thalassemia Center in Maternity and Children's Hospital, Madina, Kingdom of Saudi Arabia who underwent periodic transfusion, on regular chelation therapy, and did not suffer from congenital or rheumatic heart disease were included. Only patients who are 10 years old or more, were enrolled in this study to avoid age difference between the 2 groups. All evaluated patients were screened by means of history taking, physical examination, laboratory studies, and echocardiography. The most recent laboratory values were used. Hemoglobin level was determined before each transfusion and serum ferritin level was determined 4-5 times each year. The average value of both hemoglobin and serum ferritin levels was used. Transthoracic echocardiography was performed in all patients with the use of the Sonos 5500 (Philips) systems (Andover, MA, USA). Complete 2-dimensional M mode, and Doppler (pulsed wave, continuous wave and color) echocardiography was performed. Cardiac measurements were performed according to the guidelines of the American Society of Echocardiography.[5] Peak velocities of the E wave and A wave, and the ratio of the E wave to the A wave were measured in a standard manner.[6] Tricuspid regurgitation was assessed in the parasternal right ventricular inflow, parasternal short-axis, and apical 4-chamber views, and a minimum of 5 sequential complexes were recorded. Continuous-wave Doppler sampling of the peak regurgitant jet velocity was used to estimate the right-ventricular-to-right-atrial systolic pressure gradient with the use of the modified Bernoulli equation (4 x [tricuspid regurgitant jet velocity]^2).[7] The mean right atrial pressure was calculated according to the degree of collapse of the inferior vena cava with inspiration: 5 mm Hg for a collapse of at least 50% and 15 mm Hg for a collapse of less than 50%.[8] The systolic pulmonary artery pressure (PAP) is calculated by adding the transtricuspid pressure gradient to the mean right atrial pressure.[9,10] Pulmonary hypertension was defined as a systolic pulmonary artery pressure greater than 35 mm Hg.[11]

All continuous data are expressed as the mean (±SD). The unpaired t-test was used to compare continuous data, while the Chi-square test was used to compare dichotomous data. Statistical significance was described as $p<0.05$.

Results. We studied 57 patients with thalassemia major who received regular blood transfusion and on iron chelation therapy. Thirty-six patients were non-splenectomized, while 21 patients were surgically splenectomized. The mean age of patients at the time of splenectomy was 9.7±2.5 years. The duration since splenectomy and conduction of this study was 6.8±1.4 years. Indications of splenectomy in our patients were previously published, and included increased transfusion requirements and massive splenomegaly in 20 patients, and splenic abscess in one patient.[12,13] **Table 1** compares the clinical characteristics of both splenectomized and non-splenectomized groups. The 2 study groups were well matched for age, gender, height and weight. No significant difference between the 2 groups regarding oxygen saturation, pulse rate or mean blood pressure. No significant difference was observed between the 2 groups regarding cardiopulmonary symptoms. The total amount of blood given during the previous year (6577.1±206.9 ml versus 5390.5±220.2 ml, $p=0.0005$)

Table 1 - Clinical findings in patients with thalassemia major.

Parameters	Non-splenectomized patients (n=36)	Splenectomized patients (n=21)	*P*-value
Age (years)	16.3±4.3	16.5±2.2	0.83
Girls, n (%)	17 (47.2)	9 (42.9)	0.97
Weight (kg)	36.2±7.4	39.2±7.4	0.15
Height (cm)	145.9±11.1	150.5±8.7	0.1
SPO_2 (%)	99.2±3.3	98.8±1.4	0.64
Pulse (beat/min)	85.6±8.1	82.1±8.6	0.14
Mean BP (mmHg)	81.7±7.1	78.9±4.4	0.1
Total blood given last year (ml)	6577.1±206.9	5390.5±220.2	0.0005
Annual transfusion index	200.9±11.3	134.1±7.3	0.0001

SPO_2 - pulse oxygen saturation

Table 2 - Laboratory investigations in patients with thalassemia major.

Parameters	Non-splenectomized patients (n=36)	Splenectomized patients (n=21)	*P*-value
AST (u/L)	99.1±12.4	93.2±9.3	0.71
ALT (u/L)	93.2±57.3	111.5±28.7	0.18
Total bilirubin (µmol/L)	61.1±33.3	55.6±28.9	0.56
Direct bilirubin ((µmol/L)	8.1±9.1	8.2±5.4	0.96
Albumin (g/L)	36.1±3.8	37.9±5.9	0.18
Glucose (mmol/L)	5.2±0.2	4.9±1.4	0.99
Creatinine (µmol/L)	30.7±13.1	34.1±10.3	0.31
Alkaline phosphatase (U/L)	217±101.4	259.2±74.1	0.12
Ferritin (µg/L)	2255.6±237.4	2333.3±1274.4	0.84
Hepatitis B +ve (n[%])	2 (5.6)	4 (19)	0.25
Hepatitis C +ve (n[%])	22 (61.1)	9 (42.9)	0.28
T4 (ug/dl)	9.3±3.5	8.8±3.4	0.55
TSH (uU/ml)	4.4±1.8	3.8±1.3	0.16
PTH (pg/mL)	24.7±2.3	26.6±4.3	0.69
HB PRE (gm/dL)	8.1±1.2	7.7±1.5	0.21

AST - aspartate aminotransferase, ALT - alanine aminotransferase, T4 - thyroxine,TSH - thyroid stimulating hormone, PTH - parathyroid hormone, HB PRE - hemoglobin pre transfusion

Table 3 - Echocardiographic findings in patients with thalassemia major.

Parameters	Non-splenectomized patients (n=36)	Splenectomized patients (n=21)	*P*-value
IVSTD (cm)	0.8±0.2	0.9±0.2	0.003
LVDD (cm)	4.3±0.6	4.4±0.5	0.49
IVSTS (cm)	0.9±0.2	1.1±0.2	0.01
LVSD (cm)	3.1±0.6	3.1±0.4	0.65
LVPWT (cm)	1.1±0.3	1.1±0.3	0.67
Aortic root(cm)	2.5±0.4	2.5±0.3	0.81
LA (cm)	2.9±0.7	3.1±0.3	0.61
FS (%)	31.0±6.9	33.9±6.7	0.12
Mitral valve E/A ratio	1.4±0.2	1.6±0.2	0.02
Pulmonary artery pressure (mm Hg)	20.8±9.2	34.2±9.1	0.0001
Pulmonary hypertension, n (%))	6 (16.7)	14 (66.7)	0.0004

IVSTD - interventricular septum thickness in diastole, LVDD - left ventricular diastolic diameter, IVSTS - interventricular septal thickness in systole, LVSD - left ventricular systolic diameter, LVPWT - left ventricular posterior wall thickness, LA - left atrium diameter, FS - fraction shortening, E/A - Ratio of transmitral peak velocity of early and late diastolic flow

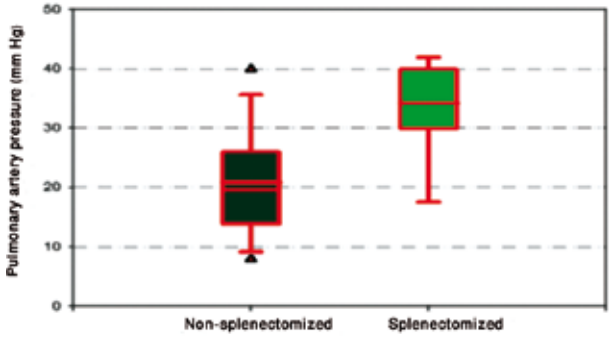

Figure 1 - Comparison of pulmonary artery pressure between splenectomized and non-splenectomized patients with thalassemia major.

and the annual transfusion index (200.9±11.3 versus 134.1±7.3, *p*=0.0001) were significantly lower in the splenectomized group than non-splenectomized group). **Table 2** shows the laboratory findings in both splenectomized and non-splenectomized groups. There were no significant differences between the 2 groups regarding serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, direct bilirubin, glucose, creatinine, alkaline phosphatase, albumin, thyroxine, thyroid stimulating hormone and parathyroid hormone. There were no significant differences between serum ferritin level and hemoglobin in both groups. Positivity for hepatitis B and hepatitis C virus were not significantly different between the 2 groups. **Table 3** shows the echocardiographic findings in both splenectomized and non-splenectomized groups. The ventricular septal thickness in both diastole (0.9±0.2 versus 0.8±0.2 cm, *p*=0.003), and systole (1.1±0.2 versus 0.9±0.2 mm, *p*=0.01) was significantly higher in splenectomized patients than non-splenectomized patients. There was no significant difference between the 2 groups regarding left ventricular posterior wall thickness, left ventricular dimension in diastole and systole, aortic root diameter or left atrial diameter. Left ventricular systolic function shows no difference regarding fraction shortening between the 2 groups. The mitral valve E/A ratio was significantly higher in splenectomized group than that of non-splenectomized group (1.6±0.2 versus 1.4±0.2, *p*=0.02). The PAP was higher with marked significance in splenectomized group than non-splenectomized group (34.2±9.1 versus 20.8±9.2 mm Hg, *p*=0.0001) (**Figure 1**). The chi-square test was used to compare patients with pulmonary hypertension between the 2 groups, and we found significantly higher number of patients with pulmonary hypertension in the splenectomized group than the non-splenectomized group (14 [66.7%] versus 6 [16.7%], *p*=0.0004).

Discussion. Among our 57 patients with thalassemia major, 21 patients underwent splenectomy. We could not find any difference regarding age, gender, weight or height between the 2 groups. Our study takes into consideration that splenectomy was usually carried out at the age of 8-10 years.[4] We selected patients to be at least 10 years of age in both groups to exclude the effect of age on the results. In a previous study, results were obscured by the confounding effect of age when the 2 groups were compared.[14] The total amount of blood given during the last year and the annual transfusion index were significantly lower in splenectomized patients than non-splenectomized patients. This means that the goal to which splenectomy was initiated was achieved.

Splenectomy is recommended in patients with thalassemia major receiving chronic transfusions to reduce the excessive transfusion requirements. Many centers recommend splenectomy as the transfusion requirement exceeds 250 ml of packed red cells/kg/year.[3,4,15] We previously published that splenectomy in our patients effectively reduced transfusion requirements.[12] Both groups of patients did not differ regarding studied laboratory parameters. Our data could not find any difference on hemolysis severity between the 2 groups. Reticulocytic count was not complete in most studied patients, so we omitted this in the results section. Although serum AST and ALT levels did not differ between the 2 groups, the mean value is higher than the normal value. This may be explained by the high prevalence rate of hepatitis among our patients. Hepatitis C is positive in a large number of our patients. This is especially seen in older patients. This can be explained by the fact that screening of the transfused blood against hepatitis C was not carried out in the early period of thalassemia management. Although left ventricular systolic function was similar in both splenectomized and non-splenectomized patients, diastolic function was different. The left ventricular fraction shortening was not significantly different between the 2 groups. Abnormalities of ventricular systolic function on echocardiogram are nearly universal and are often not detectable until patients are in overt congestive heart failure. Echocardiographic assessment of myocardial function is useful in such conditions. While systolic dysfunction carries a bad prognosis, patients can be rescued by continuous chelation therapy, provided they are willing to comply with several years of this therapy.[16]

The mitral valve E/A ratio was significantly higher, indicating diastolic dysfunction, in splenectomized than in non-splenectomized patients. The reported left cardiac status in thalassemia patients consists of a pronounced increase in left ventricular diameters, volumes and mass, with impairment of diastolic function before systolic function. This condition represents an early, sub-clinical manifestation of left heart failure.[17,18] We also found that diastolic dysfunction was present in patients with reserved systolic function. Our results are similar to a previous study, which demonstrated that left ventricular diastolic dysfunction was higher in splenectomized thalassemia patients.[14] We speculate that left ventricular diastolic dysfunction may represent myocardial damage resulting from microvascular vaso-occlusive disease. Left ventricular dysfunction and left ventricular restrictive filling should be observed more carefully when examining thalassemia patients. Systolic PAP was significantly higher in splenectomized patients than non splenectomized patients (**Figure 1**). Also, the number of patients who have pulmonary hypertension was significantly higher in splenectomized patients. The frequency of pulmonary hypertension in patients with thalassemia ranges from 10-74% in previous studies.[19-22] The frequency of pulmonary hypertension in our study population falls within this range. Moreover, our findings indicate a significant association of pulmonary hypertension with splenectomy. The mechanisms leading to pulmonary hypertension in thalassemia patients are not yet clear and are likely multifactorial. Chronic hypoxia, a combination of anemia and left ventricular dysfunction causing increased ventricular pressure, and pulmonary vascular remodeling have all been postulated.[19,20,22] Lung injuries due to infections and iron depositions resulting in interstitial fibrosis have also been suggested.[23,24] More recently, chronic hemolysis in patients with sickle cell disease and other hemolytic anemia was suggested as an important factor in the pathogenesis of pulmonary hypertension.[25] Pulmonary hypertension has also been attributed to the presence of a pulmonary thromboembolism resulting from platelet activation and hypercoagulable state occurring in patients with thalassemia.[26-28] One of our patients developed portal vein thrombosis after splenectomy.[29] Many cases with pulmonary hypertension have been noted after splenectomy in patients with hereditary stomatocytosis,[30] pyruvate kinase deficiency,[31] and Gaucher disease.[32] Also in a previous study, 7 out of 61 patients admitted due to severe pulmonary hypertension had splenectomy. In 3 of these patients splenectomy was carried out due to trauma without any underlying disease.[33] These data indicate that splenectomy is a risk factor for pulmonary hypertension regardless of the cause of splenectomy. The risk of pulmonary hypertension may be enhanced by the presence of the previously mentioned factors in thalassemia patients. These observations suggest close monitoring of PAP in thalassemia patients, particularly those with splenectomy. Our study was limited by being a cross sectional study. A longitudinal study to follow up such patients is advised.

In conclusion, splenectomized patients with thalassemia major differ from non-splenectomized patients, in that they receive fewer blood transfusions. On the other hand, they are at high risk of having impaired diastolic left ventricular function. Impaired left ventricular diastolic function can occur in patients with reserved left ventricular systolic function. Pulmonary hypertension exists in a significant number of splenectomized thalassemia major patients. Careful attention to pulmonary hypertension and diastolic left ventricular function should be carried out while following these patients.

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