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Cardiac Involvement of Major Thalassemia and Evaluation of Total Serum Creatine Kinase and Creatine Kinase-MB Isoenzyme and Cardiac TroponimI in These Patients

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Abstract: The goal of this study was the evaluation of specific markers of myocardial injury that includes CK-MB and troponin I in major thalassemic patients. Regular blood transfusion is the main treatment in major thalassemia. One of the most important complications of regular blood transfusion is iron overload that eventually involves many organs like heart and cause myocardial injury. Sixty patients with transfusion-dependent major thalassemia, at the age range of 8 to 15 years in Tabriz Pediatric Medical Center were chosen. Measurement of Hb, Hct and serum ferritin were performed in hospital laboratory, but total serum Creatine Kinase (CK) by photometric and isoenzyme of CK-MB by immunologic DGKC and cardiac troponin I (cTnI) were tested by ELISA methods in Shaheed Madani heart center laboratory before blood transfusion. For all patients echocardiography and ECG assessment of cardiac function were done by a pediatric cardiologist and results were statistically analyzed. Forty nine patients (group A) had normal left ventricular ejection fraction (LVEF = 50-70%) and 11 patients (group B) had reduced LVEF (20-45%). There was no statistical difference between two groups in average volume of blood transfusion ($p = 0.074$). Although total CK and CK-MB isoenzyme were higher in group B but there was no statistically meaningful difference between two groups ($p = 0.123$, $p = 0.111$). Troponin I also was higher in group B but statistically analysis showed no correlation between cardiac function and troponin I level in these groups ($p = 0.827$). This study showed that cardiac markers are not helpful for recognition of cardiac involvement in major thalassemia.

Key words: Major thalassemia, creatine kinase, CK-MB, Troponin I (cTnI)

INTRODUCTION

Regular transfusion is the main treatment of major thalassemia, prolonged and repeated transfusions result in iron overload and hemosidrosis (Thalassaemia Management, 1999). Currently, cardiac complications are reported to cause 71% of deaths in patients with thalassemia major. Therefore the heart is the target lethal organ in thalassemia. Once heart failure develops, the outlook is usually poor. The cardiomyopathy may be reversible if iron chelation therapy is intensified in time, but the diagnosis is often delayed by the unpredictability of cardiac iron deposition and the late development of symptoms and echocardiographic abnormalities. The early diagnosis of iron-induced cardiomyopathy with established clinical techniques such as echocardiography and stress radionuclide angiography has had limited success (Alan *et al*., 2004).

Complication of Iron overload especially in heart includes pericarditis, arrhythmia, myocarditis and resistant heart failure (Behrman *et al*., 2004). Endomyocardial biopsy by cardiac catheterism is the main definitive diagnostic method for myocardial hemosidrosis but this is an invasive method and is not feasible to be done repeatedly. So other non invasive methods like ECG and echocardiography are performed for evaluation of cardiac involvements (Orkin and Nathan, 2003). Furthermore high ESR (Erythrocyte sedimentation rate), increased enzymes and cardiac proteins in serum may be seen following acute and chronic inflammatory processes of myocard (Caddel, 2000; Dreyer *et al*., 1998). There is variability in iron deposition between and within different organs. Serum ferritin is the most commonly used indirect estimate of body iron store. The relation between myocardial iron and other measures such as serum ferritin and liver iron has been unknown until recently and therefore assessment of cardiac risk from these measures has at best been uncertain (Alan *et al*., 2004).

Aspartate aminotransferase (AST), Creatine Kinase (CK) and MB isoenzyme and troponin T and I are specific

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cardiac enzymes and proteins that are used for evaluation of heart involvement (Caddel, 2000; Defour *et al*., 2001). Holter monitoring of cardiac rhythm for 24 h in major thalassemia patients older than 12 years in the absence of clinical manifestations shows many disorders. One study showed that 75% of patients had disrhythmia from premature atrial contraction to ventricular tachycardia (Panteghini, 2004; Caddel, 2000). In early stage of iron overload echocardiography shows ventricular hypertrophy without ventricular dysfunction. With increase of iron load, left ventricular function reduces and finally results in irreversible dilated cardiomyopathy (Orkin and Nathan, 2003). But in the disease process progression from mildly abnormal echocardiographic parameters to fulminant cardiac failure is often rapid and relentless (Alan *et al*., 2004). Both Magnetic Resonance (MR) and magnetic susceptometry are significantly affected by iron and both show changes in iron overload. However, to date only MR can be applied to a moving organ such as the heart. Fortunately there has been substantial progress in the speed and image quality of cardiovascular MR in recent years (Alan *et al*., 2004). At this study we used chest X-ray, ECG and echocardiography every 6 month for evaluation of cardiac involvement in major thalassemia patients. So this study was planned to measure serum level of specific heart markers such as total Creatine Kinase, CK-MB and cardiac troponin I for determination of cardiac involvement in major thalassemia patients, as an alternative way to reduce their health care charges.

MATERIALS AND METHODS

In this prospective cross sectional study, we selected sixty transfusion-dependent thalassemia major patients (32 male and 28 female) at the age range of 8 to 15 years who had been treated at Tabriz Pediatric Medical Center between March 2006 to Jan 2007. They regularly received packed red blood cell transfusion, 47 patients every month and 13 of them every 3 weeks and desferoxamin as a chelating agent of iron. In this study patients with congenital heart diseases and febrile illness at time of study were excluded. At least 100 units and at most 460 units of blood was transfused to these patients. Before blood transfusion the CBC, Hb, Hct were measured by Abacus cell counter and serum ferritin by Immunoturbidimetric methods and 2 mL blood sample was sent to Shaheed Madani Heart Center laboratory for measurement of the CK, CK-MB isoenzyme and cardiac troponin I. Total CK by photometric, CK-MB isoenzyme by immunologic DGKC and cardiac troponin I by ELISA methods were measured. For determination of normal range of troponin I, sixty normal person without cardiac disorder from 8 to 30 years old were selected and the same investigation was done.

Chest X-ray, colour duppler was requested, ECG and M-mode echocardiography was performed in all patients by a pediatric cardiologist. Patients were divided into two groups, group A with normal and group B with decreased Left Ventricular Ejection Fraction (LVEF). The results were statistically analyzed by SPSS software using Chi-square and ANOVA methods.

RESULTS AND DISCUSSION

Patients age ranged from 8 to 15 years, 47 monthly and 13 patients every 3 weeks had transfusion, 92% of whom had received more than 100 units of packed red blood cell. All of them had been treated with desferal as iron chelating agent. In group A 9 of 49 patients and in group B 3 of 11 patients had no pump and used IV line for desferal infusion, which showed no statistically meaningful difference between two groups ($p = 0.382$). Chest X-ray showed cardiomegaly in 16 (26.6%), acute pulmonary edema in 2 (3.3%) and pleural effusion in 1 (1.6%) of patients. ECG was normal in 39 (65%) and abnormal in 21 (35%) patients, 12 (20%) patients had left ventricular enlargement, right ventricular enlargement in 5 (8.3%), T wave abnormalities in 3 (5%) and PVC in 1 (1.6%) of patients. Echocardiographic findings of patients are shown in Table 1.

Left Ventricular Ejection Fraction (LVEF) as an index of heart function were measured in all of the patients, in 49 (81.6%) of them (group A) it was normal in the range of 50 to 70% (mean 59.9% ±0.9) and in 11 (18.3%) of patients (group B) LVEF was reduced within the range of 20 to 45% (mean 38.18% ±2.45).

Table 2 shows that cardiac function has no statistically meaningful correlation with serum ferritin and volume of blood transfusion, while it has a meaningful correlation with Hb and Hct concentration.

Table 1: Echocardiographic findings in major thalassemic patients

Echocardiography	No.	Percent
Normal LVEF	49	81.6
Decreased LVEF	11	18.3
Left ventricular hypertrophy or dilation	15	25.0
Right ventricular hypertrophy or dilation	7	11.6
Tricuspid insufficiency	42	70.0
Mitral regurgitation	10	16.6
Pulmonary valve insufficiency	8	13.3
Aortic valve insufficiency	6	10.0
Pulmonary hypertension	4	6.6
Right atrial enlargement	4	6.6
Congestive heart failure	2	3.3

Table 2: Statistical relation between mean laboratory results and reduced heart function (LVEF)

Groups	Patients	Blood transfusion (units)	Hb (g dL^{-1})	Hct (%)	Ferritin (ng dL^{-1})	LVEF
A	49	211.00±16	9.51±0.46	29.10±0.46	2759.00±166	59.90±0.59
B	11	278.00±26	8.66±0.35	26.70±1.16	3294.00±233	38.19±2.45
p-value		0.074	0.026	0.038	0.152	

Table 3: Level of total CK, CK-MB and its activity and Troponon I in thalassemic patients

Normal range	Total CK* <195	CK-MB* <24	CK-MB activity** 5-15	Troponin I***
Total patients (mean)	54.33±7.35	3.36±0.37	6.5	0.62±0.05
Group A (mean)	48.82±7.47	3.07±0.33	5/8	0.61±0.05
Group B (mean)	78.91±23.62	4.62±1.38	6.6	0.64±0.13
p-value	0.123	0.111	0.088	0.827

*Unit L^{-1}, **CK-MB activity = CK-MB × 100/Total CK (%), ***ng L^{-1}

Table 3 shows that mean total CK and CK-MB isoenzyme serum levels in group B were more than group A patients but statistically there was no meaningful correlation between those enzymes and patients cardiac function. Normal level of troponinI based on data of original manufacture information sheet was less than 0.5 ng L^{-1} and based on data from 60 normal persons (age 8 to 30) in laboratory of Shahid Madani Hospital was less than 1.89 ng L^{-1}, results shown in Table 3. No statistically meaningful correlation between troponinI level and cardiac function in two groups of thalassemic patients. Several studies have shown patients that received more than 100 units of red blood cell transfusion without using Iron chelator had obvious iron precipitation in their heart. According to study in Israel, 80 units red blood cell transfusion is enough for right and 100 units for left ventricular dysfunction (Orkin and Nathan, 2003). In this study 92% of patients have received more than 100 units of red blood cell transfusion and left ventricular dysfunction was induced in 18.3% of them. The range of pre transfusion hemoglobin in our patients was 6.5 to 11.5 g dL^{-1} with mean Hb level 9.35±0.14, this is lower than a study in USA with mean Hb level 10.1±0.2 (Panteghini, 2004). Comparison of this two study showed that our patients had not favorable pre transfusion conditions. Present study showed there is statistically meaningful correlation between anemia and reduced cardiac function, anemia not only increases iron absorption from GI tract and leads to hemosidrosis, but also increases cardiac complication by hemodynamic effects in thalassemic patients (Behrman *et al*., 2004). Even though present study showed there was no statistically meaningful correlation between ferritin level and LVEF, But mean ferritin level in our patients (2857±146 ng mL^{-1}) comparing with those of industrial countries (1894±396 ng mL^{-1}) (Missov *et al*., 2001) and (1600 ng mL^{-1}) (Freeman *et al*., 1983) was higher, which indicates that our patients do not receive enough iron chelator. Previous studies have showed that cardiac involvement and complications like dysfunction of left ventricle and arrhythmias are more common in young thalassemic patients who had hyper transfusion programs and did not receive regular iron chelator, our finding correlate with these studies (Caddel, 2000). In several studies, LVEF has been used as a diagnostic indicator and control of complication of thalassemic patients (Caddel, 2000; Missov *et al*., 2001). Caddel (2000) studied 36 patient (5-25 years) for five years and found that progressive cardiac complications like reduced LVEF, arrhythmia and T wave abnormalities were common in iron overload patients. In this study left ventricular function was studied in all patients, 11 (18.3%) of them had reduced LVEF. Since reduced cardiac muscle function is due to damage and necrosis of cardiac muscle fibers, so we can conclude that our 11 patients had damage and necrosis of myocardium. Creatine Kinase is a protein in mammalians muscle and its plasma level increases in early stage of myocardial damage which can be used in diagnosis of heart disease (Delanghe *et al*., 1988). Increased cardiac troponin I is one of the best diagnostic index in myocardial necrosis. In some cases of myocardial necrosis without elevation of ST segment in ECG, we can use cardiac troponinI for diagnosis (Betrand *et al*., 2002). In many pathological conditions without clinical findings of myocardial ischemia such as hemoglobinopathies and hemosidrosis due to blood transfusion, elevation of troponinI can help in diagnosis (Gupta *et al*., 2002; Spies *et al*., 1998). Missov *et al*. (2001) measured serum level of CK-MB and cardiac troponin before and after blood transfusion in 17 thalassemic patients with normal LVEF, they found that in 7 patients with high level of serum ferritin (2669±125 ng mL^{-1}), cardiac troponin also is high (8.4±6.3 pg mL^{-1}). Dreyer *et al*. (1998) found a direct correlation between CK-MB level and volume of blood transfusion. Sandri (2003) reviewed 19 patients with cancer who had received antracycline, they found that LVEF will decrease about 12 months after increase of cardiac troponin, so they concluded that troponinI has a

predictive value for LVEF. In contrast, Kismet *et al.* (2004) study in turkey did not find any relation between cardiac troponine and cardiac damage due to Doxorubicin.

CONCLUSION

In this study although mean levels of CK-MB and cardiac troponin I in patients with decreased LVEF were higher than patients with normal LVEF, but there were not any statistical difference between two groups. We concluded that total CK, CK-MB and cardiac troponin dose not predict of cardiac damage of thalassemic patients, but serial measurements of them may be helpful.

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