EVALUATION OF THE RELATIONSHIP OF ECHOCARDIOGRAPHIC LEFT VENTRICULAR MASS TO AMOUNTS OF TRANSFUSIONS OF PACKED CELL AND DEFEROXAMINE IN THALASSEMIA MAJOR

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Abstract - The disease of thalassemia major requires management by repeated transfusions of packed cell and iron chelators such as deferoxamine. Today, serum ferritin is used for estimation of adequacy of the management. As the most morbidities and mortalities of the disease are the consequences of cardiac complications, echocardiography is periodically performed along with the management. In this case-control study, our object was to appoint if we can use "left ventricular mass" to evaluate the quality of past longterm managements for the patients.

The variables of weight, height, body surface area, total amounts of transfusions of packed cell and deferoxamine during 5 years ago, crude left ventricular mass, indexed left ventricular mass (left ventricular mass / body surface area$^{1.23}$), ejection fraction, and shortening fraction, were measured in 34 thalassemia major patients of 16 to 18 years of age who had no signs or symptoms of any organ failure, particularly cardiac failure and had received repeated transfusions of packed cell and deferoxamine. In the control group, these variables (except amounts of transfusions of packed cell and deferoxamine) were measured in 34 normal subjects of 16 to 18 years of age too. The variables of left ventricular mass, ejection fraction and shortening fraction were recorded on the echocardiographic paper. Then, the group of thalassemic patients were sectioned into two subgroups of ordered (well managed) and non-ordered (badly managed) patients on the basis of 5 scales. Since, on the basis of international scales, absolute majority of the patients were set in the non-ordered group, the international scales were moderated and comparisons were done.

Only the means of variables of weight, height and body surface area were too less and of indexed left ventricular mass was too more in thalassemics than normal subjects (P-value = 0.000). Almost no significant difference was seen between two ordered and non-ordered subgroups, on the basis of any scale (P-value > 0.05).

By increase the cases and extension of the research the study can be done to reach the better results of more confidence. Acta Medica Iranica 39 (1): 7-13; 2001

Key words: β -Thalassemia, left ventricular mass, ejection fraction, shortening fraction, packed cell, deferoxamine

INTRODUCTION

One of the most prevalent genetic diseases is thalassemia. Affected subjects of its major kind, have threatened life in low ages, due to severe anemia. In order to prevent this, there are necessities for repeated transfusions of packed cell (PC).

After lysis, transfused packed cell releases so much iron which is not excretable and therefore accumulates in different organs and causes death in ages of second decade. In order to prevent these, iron chelators must be used and the most common drug is deferoxamine mesylate (desferal) (Des) today(1,2).

Measurement of serum ferritin (Fer.) levels is a way to assess efficacy, now (3). If lower than 1000 ng/ml, the efficacy is appropriate, and if higher than 1000 ng/ml, the efficacy is inappropriate(1-2,9). Increase or decrease in serum ferritin by influence of transfusions of packed cell and deferoxamine, are done in a releative short time and cannot be representative of longterm situations of their managements. So they cause too many unpredictable cardiac complications in the patients(4,5).

If longterm evaluation of adequacy of transfusions can be done, complications can be preventable with changes and making proper the regimens of therapy.

In the past presented articles, the results have been about the reliability of echocardiography more than clinical signs (6-8). In some studies, some cardiac indices had been measured, such as structural changes of thicknesses of septum and posterior wall, dimensions of atrium and aortic root, and left ventricular systolic and diastolic dimensions, that all of them had been increased(3,4) ; and ejection fraction and shortening fraction had been decreased in those patients(3,4,9). In one article, from electrocardiography, echocardiography, cardiac holter monitoring and radioisotope MUGA scanning, echocardiography had been introduced as the main tool for evaluation of morphology and performance of myocardium in the thalassemic patients

with cardiac complications. Also another article had resulted that by severe therapy with deferoxamine, cardiac toxicities which were the consequences of iron deposition, could be decreased to improve cardiac performance (2) and the echocardiographic changes return to normal (1).

The parameter "left ventricular mass" is a unique aspect of echocardiographic power to determine left ventricular wall thickness. It can be evaluated by either techniques of M-mode or 2-D echocardiography. This parameter can be altered by some certain factors such as weight, height, sex, age, race,..., or pathologic factors such as iron deposition(10-15).

In our study, we decided to determine valuability of echocardiography for evaluation of longterm therapy of the patients, and by comparison of thalassemic patients with normal subjects and comparison of the patients with appropriate and inappropriate regimens of management, establish if echocardiography and left ventricular mass can be used for determination of adequacy of the amounts of transfusions of packed cell and deferoxamine in the past and correction of the regimen in the future, and if it can be substituted instead of serum ferritin to evaluate the quality of longterm management or not.

MATERIALS AND METHODS

The method of this study was observational and case - control.

Study population

The thalassemia major patients, were 16 to 18 years of age and under management by transfusions of packed cell and infusions deferoxamine. We selected these ages because of not having the patients in their growth leaping which might influence our variables. They had to have no background of any disease of dependent or independent to thalassemia, whose recorded data about their diaseases had to be complete for past 5 years. Since infusions of deferoxamine in compliant patients make a clear drop in ferritin after one year of treatment with continued decline to a level of <1000ng/ml in 3-5 year(1), we selected the past 5 years data of the patients for our study. The mode of sampling was non-randomized. In this way, we had 34 patients and 34 normal subjects too.

Site and time

Examinations of patients were done in Shohada-e-Tadjrisch, Mofid, and Ahari Children Medical Center and their echocardiographies were done in Ahari Children Medical Center . The period of the study was about 4 months.

Collection of the data

Collection of the data by asking about their symptoms and examinations of patients by a resident of pediatrician were done. Searching their recorded data of past 5 years to account their amounts of transfusions of packed cell and infusions of deferoxamine, average of their hemoglobin concentrations and number of their references to their transfusion clinic in each 6 months of years, and their serum ferritins was done too. After it, performance of their echocardiographies were done by a pediatric cardiologist.

All of the echocardiographic issues in this study [Left Ventricular Mass (LVM), Ejection Fraction (EF) and Shortening Fraction (SF)] were recorded automatically by the instrument and in order to decrease slipping in measurements, three samples of echocardiographic papers were obtained from each subject to calculate the average of them. In order to point the special locations for estimation the indices on M-mode echocardiography, electrocardiography was done simultaneously, on the monitor and paper too. In addition to crude left ventricular mass, we indexed it by the formula:

"Indexed LVM = Crude LVM / $BSA^{1.23}$"
(BSA = Body Surface Area)(35)

It is noticeable that there are some other formulas for indexing left ventricular mass such as

LVM / H, $H^{1.97}$, H^{2}, $H^{2.7}$, H^{3}, $H^{3.3}$, BSA, BMI (body mass index), FFM (fat free mass), LBM (lean body mass), introduced in different books or articles (11,16).

There were no interference in the mode of therapy in the patients, had no excessive blood sampling from them and no expense for them.

Analysis

In order to analyze the data, all of them were recorded on special forms. The group of patients were splitted into two subgroups of well and badly managed by 5 scales:

a). Amount of transfusions of packed cell.
b). Amount of infusions of deferoxamine.
c). Concentrations of hemoglobin.
d). Number of references to transfusion clinic.
e). Serum ferritins.

After code sheathing of the data, we entered them into the computer. Data analysis were performed with the software SPSS9, in these stages : purging the data, offering the descriptive data, and making statistical tests of Levene, T-test, ANOVA, Scheffe, Kruskal-Wallis and Chi-Square.

Difficulties and Limitations

The tests of concentration of hemoglobin and serum ferritin had been done in different laboratories during past years, so they might have been unreliable. Impossibility to split the group of patients into two subgroups by international standard scales, was our other limitation, because almost all of them were put in non-ordered group in this way. So we had to moderate the scales (in order to section it into two subgroups) as below:

a) The amount of packed cell (PC) transfusions : 10 cc/kg every 25 days.

b) The amount of deferoxamine (Des) infusions : 35 mg/kg/day.

c) The average of hemoglobin (Hb) concentrations in each 6 month : 8/5g/dl.

d) The number of references (Ref.) to transfusion clinic in each 6 month: every 28 days.

e) The serum ferritins (Fer.) : 2500ng/ml.

It has to be mentioned that a patient might be in ordered group on the basis of one scale, but in non-ordered group on the basis of other scales. But if we wanted to put the patients who were ordered on the basis of majority of scales, in the ordered group, we had an ordered group with few members and a non-ordered group with a lot of members too. So we could not do this practically.

RESULTS

In this study, we had 34 thalassemia major patients who were 14 females and 20 males, that 22 ones were splenectomized and 12 ones non-splenectomized.

In the control (normal) subjects we had 15 females and 19 males too.

By splitting the group of patients into two groups of ordered and non-ordered groups on the basis of 5 separate scales, in two ways of standard and moderated scales, the descriptive results are summarized and drawn in figure 1.

Comparison of variables' means between thalassemics and normals

As shown in figure 2 the means of weights (W), heights (H) and body surface areas (BSA), were more and the mean of indexed left ventricular masses was less in normal subjects than thalassemics (P-value = 0.000).

The mean of crude left ventricular masses was less in normals than thalassemics but the difference was not significant (P-value > 0.05). The means of ejection fractions and shortening fractions had not any differences in our study (P-value > 0.05).

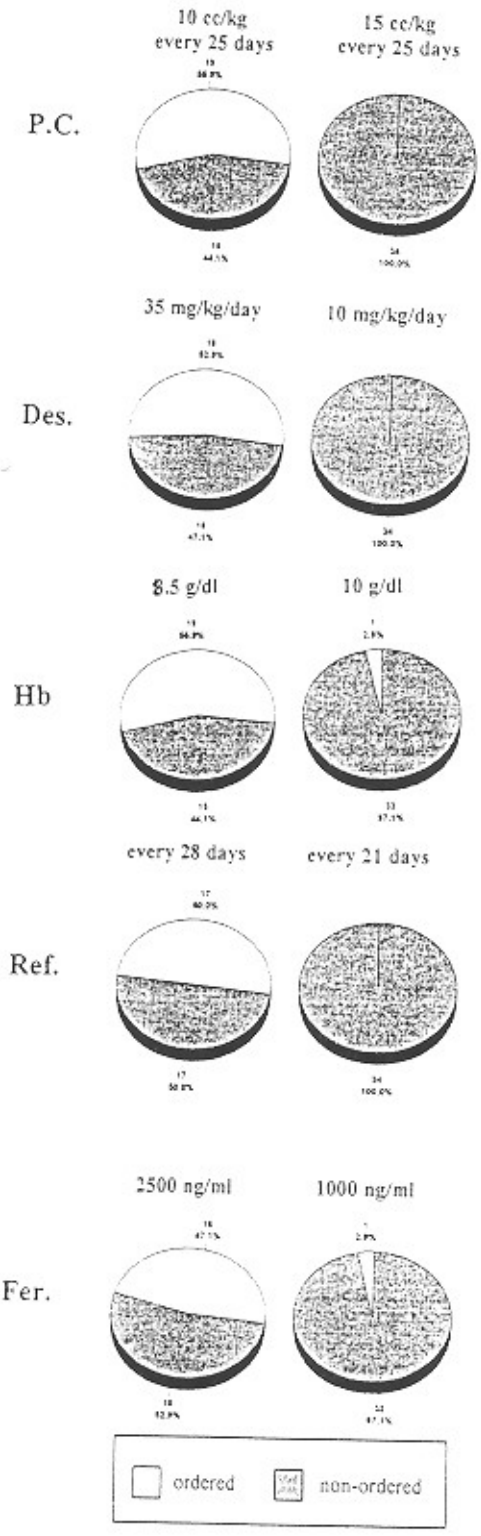

Fig. 1. Discrimination in splitting the thalassemic patients into two groups of ordered and non-ordered ones by standard (right) and moderated (left) scales.

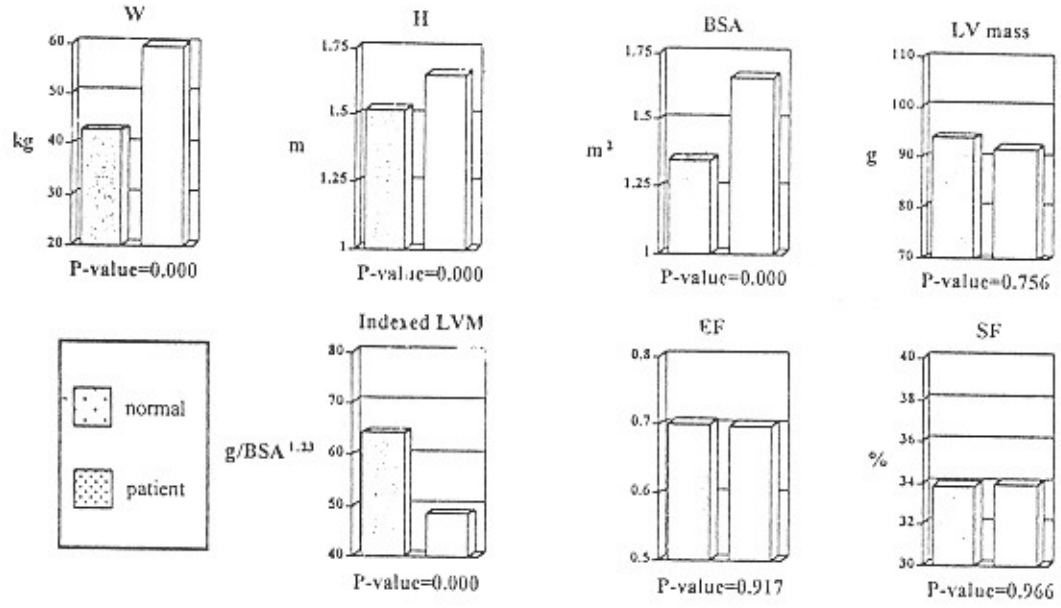

Fig. 2. Differences of means of variables in two groups of normal subjects and thalassemic patients.

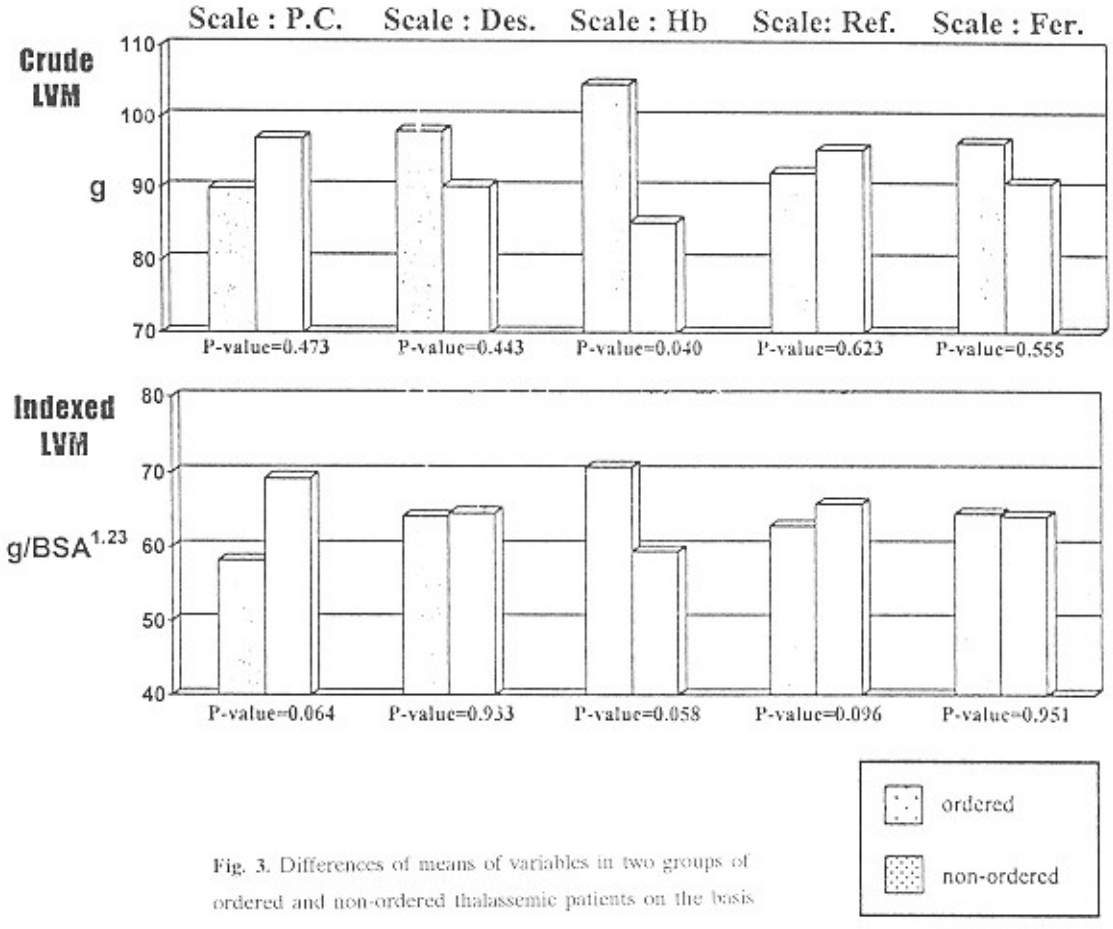

Fig. 3. Differences of means of variables in two groups of ordered and non-ordered thalassemic patients on the basis of 5 different scales

Table 1. Qunantity of significance of means' differences of variables between three groups of normal subjects and orderd and non-ordered thalassemic patients

		P-value				
Variable	Scale / Unit	P.C. Trans.	Des. Infus.	Hb Concen.	Ref. Num.	Serum Ferr.
W	kg	0.0000	0.0000	0.0000	0.0000	0.0000
H	m	0.0000	0.0000	0.0000	0.0000	0.0000
BSA	m^2	0.0000	0.0000	0.0000	0.0000	0.0000
Crude LVM	g	0.7238	0.6751	0.1073	0.8985	0.7912
Index LVM	$g/BSA^{1.23}$	0.0000	0.0002	0.0000	0.0002	0.0002
EF		0.9746	0.9717	0.9746	0.3097	0.9935
SF	%	0.9817	0.9799	0.9716	0.3181	0.9968

Comparison of amounts of significance of the means' differences of variables between three groups of normals and ordered and non-ordered thalassemics

As shown in table 1, by using each moderated scale which were discussed before, the means of weights, heights and body surface areas had significant differences between three groups which were significant (P-value = 0.0000). Also, the means of indexed left ventricular masses had significant differences too (P-value < 0.0002). But in the means of crude left ventricular masses, ejection fractions and shortening fractions, significant differences were not seen. In searching the causes of significancy of the differences between the groups, with the use of special statistical tests, it was noticed that the main causes were the differences between normal subjects in contrast to each group of ordered and non-ordered thalassemic patients.

comparison of means between ordered and non-ordered thalassemics

There were almost no main differences between the means of weights, heights and body surface areas in ordered and non-ordered groups. The means of these variables were even a little more in non-ordered than ordered group too. In comparison of left ventricular masses (Fig. 3).

By the scale 1 (amounts of packed cell transfusions = 10cc/kg every 25 days): The means of crude and indexed left ventricular masses in non-ordered group were less than ordered one.

By the scale 2 (amount of deferoxamine infusions = 35 mg/kg/day): The more mean of crude left ventricular masses in non-ordered group than ordered one, though no difference in the means of indexed left ventricular masses were seen. Differences were not significant.

By the scale 3 (concentrations of hemoglobin = 8.5 g/dl): The means of left ventricular masses

were more in non-ordered group than ordered one which difference was significant about crude left ventricular mass too.

By the scale 4 (number of references to the transfusion clinic = every 28 days): The less means of crude and indexed left ventricular masses in non-ordered group than ordered one were seen.

By the scale 5 (serum ferritins = 2500ng/ml): Crude and indexed left ventricular masses were a little more in non-ordered group than ordered one. However, their differences were not significant too. On the basis of all the 5 scales, the means of ejection fractions and shortening fractions were almost equal and were in normal ranges for their ages.

DISCUSSION

This study exhibited no relationship between the manner of managements in thalassemia major (transfusions of packed cell and infusions of deferoxamine) and their left ventricular masses. What were discovered in previous studies in other countries were the differences of the thicknesses of ventricular walls between thalassemics and normal subjects which we reached them too (9). But in contrast to less ranges of ejection fractions and shortening fractions in thalassemics than normals in that studies(7), we hadn't these results in our study. Although in a study by Lattanzi and et-al, their conventional echocardiographic parameters of systolic left ventricular function were undistinguishable from normal controls(17). In comparement of weights, heights, and body surface areas between two groups of thalassemics and normal subjects, it was noticed that these growth indices were significantly less in thalassemics than normals, Though a little excess of the mean of crude left ventricular masses in thalassemics in contrast to normals, the lower difference between them than the level of significancy indicates the absence of real difference (P-value > 0.05). The cause of higher level of the mean of indexed left ventricular masses in thalassemics than normal subjects, in attention to its significant difference, might be due to the lower level of body surface area in thalassemics, which is due to their lower level of weights

and heights (because we had indexed the left ventricular mass by body surface area1.23).

In Lattanzi (17), and Favilli (18) studies, left ventricular mass indexes were significantly higher in thalassemics than normals too. Sau (6) and Henry (19) found left ventricular mass increased in the majority of their thalassemic patients too. In comparison of the variables in two groups of ordered and non-ordered thalassemic patients, 5 scales were considered. When the mean of amount of packed cell transfusions or of number of references were more (the ordered groups), the mean of left ventricular masses were more too. It's justification may be due to the more entrance of packed cell and so the more enterance of iron to their body. When more infusions of deferoxamine (the ordered group) and so less siderosis, less mean of crude left ventricular masses was resulted, too. On the scale of hemoglobin, the patients whose pre-transfusional hemoglobin were more and had more red blood cell in their body, and so less receiving of packed cell, and less entrance of iron, had less mean of left ventricular masses and the difference in two ordered and non-ordered groups was significant about crude left ventricular mass too.

When the mean of serum ferritins was less (the ordered group) which purports about the lower overload of iron, the means of left ventricular masses were less too.

All of these indicate that there are possibilities of relationships, but majority of these differences were not statistically significant and this means no difference. Altogether the results show no significant differences in the variables of two ordered and non-ordered thalassemic patients and they cannot be absolutely judged. There were no main differences in the means of ejection fractions and shortening fractions in any groups of normal subjects and ordered and non-ordered thalassemics in our study, in contrast to significant differences between normal subjects and thalassemics and also ordered and non-ordered thalassemics in other previous studies(2,6,7).

From the identified difficulties in our study, the main difficulty was the low number of patients with complete previous 5 years data in explained ranges of ages which we had considered. The other problem was absence of standardization of the exams of hemoglobin concentration and serum ferritin which the patients had done previously. Also, some of the patients hadn't do their infusions of deferoxamine on the basis of their phisician orders, but they said that they had.

Since there isn't any article about investigations and splitting the transfusion dependent thalassemic patients into two parts of ordered and non-ordered groups on the basis of definite scales and comparison of their left ventricular masses, so we cannot compare our study with another study until today. Which are seen in the previous other articles, are about decrease of left ventricular mass due to full and regular deferoxamine infusions (4,6) and returning to normal cardiac function by it (2,4). This is seen by serial examinations functionally.

We conclude, that if the patient is managed in the best manner (by adequate packed cell transfusions and deferoxamine infusions), so his or her concentration of hemoglobin will be appropriate and his or her serum ferritin will be less than standard level and of course this patient will have the least cardiac complications of the disease and its therapies, and so the echocardiographic researches will have more approximate results to normal.

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