

Comparison of Beta-2 Microglobulin Level and Some Variables Between Thalassemia Major Patients Who Treated by Desferal and Control Group

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Abstract

Background: Iron over load will be appearing in kidney following blood transfusion. Desferal as an iron chelator can be ended renal complication.

Objectives: The aim of this study is evaluation the level of β_2 microglobulin in β -Thalassemia major patients for follow up proximal tubular damage.

Methods: In this descriptive and analytic study 40 thalassemic patients who were treated by Desferal and 40 healthy subjects enrolled in this study randomly. For evaluation the proximal tubular damage in these groups, we measured the β_2 microglobulin. Another variable such as: Ca, Mg, P and Urea of blood and K, Cr, protein and volume of urine 24 hours were measured. We compared these variables between two groups. And descriptive and analytic analyses were used.

Results: The level of β_2 microglobulin had significant difference in both groups, also the level of Ca, K and β_2 Globin in serum and Cr, protein and urine volume in 24 hours had significant difference.

Conclusions: The higher level of β_2 microglobulin in Thalassemia major patient who were treated by Desferal, show the proximal tubular damage.

Keywords: Transfusion Dependent Thalassemia Major, Desferal, β_2 Microglobulin

1. Background

Beta Thalassemia is one of the inherited hemoglobinopathy. Patients with this autosomal recessive disease have reduced or restricted production of β strand of hemoglobin [1, 2]. The major treatment of this patients is prolonged blood transfusion [3]. Following blood transfusion, Iron overload can be seen in heart, liver, endocrine, and kidney [1]. For improvement the quality life and survival of these patients the use of iron chelator is necessary [4-7].

One of the injection form of iron chelator is Desferal (DFO), and it cannot absorb from GI tract and have short half-life, and immediately after stop the injection of DFO the iron chelator activity will stop. Although the effectiveness of this drug will accelerate along prolonged injection.

The indication use of DFO is; after 10 - 20 blood transfusion or in patients with ferritin higher than 1000 mg. The effective dose of DFO is 30 - 40 mg/kg/day in 5 days a week, also the duration of injection is 8 - 12 hours sub cutaneous via electronic pump. Of course inflammation of injection site, pulmonary infiltration, night blindness, color blindness, hearing loss are the side effects of this drug are [2].

Renal dysfunction in these patients is possible following: 1) side effect of DFO, 2) iron over load in kidney, 3) lipid peroxidation, stress oxidative, release free radicals and thrombosis [8]. The first case of kidney disability in thalassemia patients was reported in 1975. Following this report, some studies reported regarding poor performance of proximal portion of kidney, proteinuria, aminoaciduria, low smolarity of urine, acceleration of N-acetylcysteine D-glucosaminidase (NAG) and β_2 -microglobulin in thalassemia patients who treated with DFO [9].

β_2 -microglobulin is an unglycosylated polypeptide with 11800 molecular weight, it can be detect in nucleate cells and neutrophil granules. It metabolized and excretion from kidney. The normal level of it in serum is 2 $\mu\text{g/L}$ [10]. Evaluation the level of β_2 -microglobulin can be done following the injury of proximal tubules of kidney [11]. The high level of β_2 -microglobulin can predict oxidative stress and iron overload in kidney [9], and it consider a sensitive marker for evaluation of the capacity of kidney filtration [12].

In spite of progresses in chelating therapy some chief complications of thalassemia are inevitable. It seems that,

in thalassemia patients the complication of this disease such as kidney complication will increase; it probably occur following iron over load in tubular epithelial cells of kidney and hypoxia following RBC hemolysis [4].

Despite a great number of studies have been done on different complications of thalassemia, little investigation renal function in these patients have been limited in number, mainly studying patients on DFO. Moreover, they have not considered novel and earlier markers of renal, such as; β_2 -macroglobulin. Also, it is a sensitive and reliable early marker of tubular dysfunction [6].

So far, many studies were done regarding effect and side effect of DFO and renal dysfunction following injection of DFO. But study regarding assessment the level of β_2 -microglobulin is limited. Although a study mentioned there is no significant difference between the levels of β_2 -microglobulin compare to control group [13]. So this study was done with this purpose; evaluation the level of β_2 -microglobulin in thalassemia patients who treated by DFO.

2. Methods

This descriptive and analytic study was done in thalassemia research center of Mazandaran University of Medical Sciences. Patients with thalassemia major who were treated by DFO were selected randomly. The sample size of this study was calculated 40 according power 80% and CI (confidence interval) 45% [13].

$$n \geq \frac{2(z_{\alpha} + z_{\beta})^2 p(1-p)}{(p_0 - p_1)^2} \quad (1)$$

The inclusion criteria of current study were: blood transfusion dependent thalassemia major patients, thalassemia patients who treated with DFO as an iron chelator (the dose of DFO were 25 - 50 mg/kg/day in 5 days a week), age between 15 - 60 years old; and the exclusion criteria were: Non blood transfusion dependent thalassemia major patients, patients who treated by Deferiprone (DFP) and Deferasirox (Exjade) and LCL670, age lower than 15 and higher than 60 years old.

We considered 40 healthy person (non-thalassemia major patients) consider as control group. The samples of control group were selected through their healthy (Non thalassemia) sister or brother with age between 15 to 60 years old. Selected samples were referred to Boali laboratory (the laboratory of Boali hospital, Mazandaran University of Medical Science). Blood and urine sample 24 hours were taken, (the urine were collected from 8:00 AM to 8:00 AM tomorrow, of course after vacate morning urine). We advise to samples during this 24 hours that they were collecting the urine don't have sever exercises, drink enough

liquid and don't need to have special food diet. We evaluated some variables such as; Cr, serum BUN, K, Na, Ca, Mg, P, Urea, β -globin in serum and protein, Na, K, Cr and volume of urine 24 hours in case and control groups. Data were analyzed by SPSS version 16, also we used descriptive and analytic tests (independent T test) for comparing quantitative variables in both groups (the normality of t- test was $P > 0.05$ (Kolmogorov-Smirnov test)). The significant level in this study was $P \leq 0.05$.

3. Results

Forty thalassemia major patients entered in our study; among them 18 (53.4%) and 21 (46.4%) were female and male respectively. Also, 22 (55%) and 19 (45%) were female and male in control group.

Duration the use of DFO and blood transfusion were 9.3 ± 5.06 years and 10.7 ± 5.38 years respectively.

Table 1 shows the age and level of ferritin in patients. It shows that, there is no significant difference regarding age and gender, $P = 0.142$ and $P = 0.502$ respectively, but the level of ferritin were different between two groups ($P < 0.001$).

Table 1. Frequency of Gender, Mean of Age and Ferritin Level in Both Groups

Variables	Case Group	Control Group	P Value
Age, y	27.5 \pm 7.08	25.4 \pm 5.4	0.142
Gender (female-male), No. (%)	18 (53.4)-21 (46.4)	22 (55)-19 (45)	0.502
Ferritin, ng/mL	2392.09 \pm 1839.15	80.15 \pm 32.58	< 0.001

Table 2 shows some blood markers of renal function such as; K, Ca and β_2 -globin.

Table 2. The Level of Blood Markers of Renal Function in Both Groups

Variables	Case Group	Control Group	P Value
BUN, mg/dL	20.7 \pm 1.74	20.9 \pm 0.76	0.15
Cr, mg/dL	0.67 \pm 0.03	0.77 \pm 0.04	1.77
Uric acide, mg/dL	5.08 \pm 0.27	4.99 \pm 0.21	0.05
K, mEq/L	4.39 \pm 0.06	4.13 \pm 0.09	0.007
Na, mEq/L	138.99 \pm 0.37	139 \pm 0.52	0.1
β_2 -globin, μ g/L	2.57 \pm 0.21	1.8 \pm 0.55	0.001 <
Urea, mg/dL	28.59 \pm 1.18	23.09 \pm 1.31	0.4
P, mg/dL	4.14 \pm 0.1	3.29 \pm 0.1	0.3
Mg, mg/dL	1.92 \pm 0.04	2.04 \pm 0.05	0.2
Ca, mg/dL	9.28 \pm 0.07	7.2 \pm 0.16	0.001 <

It shows that the level of these markers had significant difference between the groups.

Also, shows the level of Na, K, Cr, protein and volume of urine 24 hours in two groups of study. This shows that the levels of protein and volume urine 24 hours had significant difference.

Table 3. Comparing Variables of Urine 24 Hours in Both Groups

Variables	Case Group	Control Group	P Value
Cr, mg/24hrs	757.85 ± 54.85	1070 ± 59	0.04
K, mEq/24hrs	53.4 ± 5.1	75.78 ± 4.1	0.4
Na, mEq/24hrs	138.13 ± 8.04	139.1 ± 8.5	0.29
Protein, mg/24hrs	97.49 ± 11.42	81.19 ± 4.14	0.001 <
Volume, mL	1182.97 ± 53.42	1445.12 ± 70.44	0.007

4. Discussion

There is limited and conflict results regarding renal dysfunction in thalassemia major patients who treated by DFO. This study evaluated the renal function in thalassemia major patients following chorionic anemia, iron overload and dose-related toxicity of DFO. This study showed that there were significant differences between two groups as to markers of proximal tubular dysfunction (β -2 microglobulin) and markers of glomerular dysfunction (urine protein), also between the level of serum BUN creatinine but regarding Na, there were no significant differences.

Hamed et al. (2010) demonstrated that the glomerular and tubular renal dysfunction are presented in thalassemia major patients who treated by DFO [14]. This result was similar to our findings. Jalaly et al. demonstrated that there is a positive relation between renal dysfunction in thalassemia major patients and acceleration of age, increased frequency of blood transfusion and hypercalciuria [15]. Jafari et al. demonstrated that, there is no evidence of proximal tubular in major β -thalassemia patients who were treated by DFO. Also, they believed that this patients who were treated with high dose of DFO and high level of ferritin the level of serum BUN, serum K, and in some cases in uric acid can be increase [13].

The investigation of relation between anemia and increase overloading of renal function with iron from DFO in patients showed that although there were significant relation between these factors, serum K, Na, Ca, uric acid, β -2 globulin and urinary creatinine, protein and urinary volume, the evidence of significant relation between and markers of renal tubular dysfunction were detected in our

patients. Some studies demonstrated the effect of DFO on renal dysfunction on β -thalassemia [16-20]. Although some studies show degree of tubular dysfunction in minor thalassemia [21-24].

Of course the nephrotoxicity of DFO is related to dose of this drug [6]. In this study we show that; the level of Cr had not significant difference in both groups. Although the serum level of Cr is not trustworthy marker of renal function, because it is under the influence of many factors such as; muscle mass, protein intake, inflammatory disease and liver disorder [6].

The level of proteinuria showed glomerular renal function; and the proteinuria in urine 24 hours and serum level of β -2 globulin showed tubular renal function. Also, the level of β -2 microglobulin indicated the kidney filtration capacity. On the other hand the level of ferritin couldn't predict the rate of renal damage, also, the level of ferritin is not important factor for diagnose of hemosiderosis in thalassemia major patients, and we can concluded that DFO hadn't effective role in excretion of kidney iron overload.

The main cause of renal dysfunction in thalassemia major patients is unknown, probably it is multi-factor disorder. Of course some factors such as; chorionic hypoxia following anemia, hemosiderosis and cellular damages following lipid peroxidation are possible causes [6].

The limitation of this study was no measurement of some markers such as; N acetyl β di glucoseaminidase, hematuria, GFR, C Cystatin and calciuria and determination kidney size by sonography. We suggest the measurement of these markers in future studies.

4.1. Conclusions

In conclusion it is needed to state that this study demonstrated evidence of renal tubular damage in β -thalassemia major. Although more wide studies are suggested.

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Footnotes

Authors' Contribution: Mandana Zafari conducted this study and Azar Aghamohammady collected the data.

Conflicts of Interests: The authors don't have conflict of interest.

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