



Renal function in β -thalassemia major receiving desferal versus deferasirox

Forough Sabzghabaei¹, Maryam Darnahal^{1*}, Azita Azarkeivan²

¹Department of Internal Medicine, Iran University of Medical Science, Tehran, Iran

²Department of Thalassemia Clinic, Transfusion Research Center, Institute for Research and Education in Transfusion Medicine, Tehran, Iran

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ABSTRACT

Introduction: Deferasirox is a new oral iron chelating agent which has been administered in β -thalassemia major patients in last few years. There is some reports regarding nephrotoxicity of this agent; however, no comparative study has been conducted yet.

Objectives: The aim of this study was to compare the prevalence of kidney dysfunction in β -thalassemia major patients receiving either desferal or deferasirox as iron chelating agents.

Patients and Methods: In this cross-sectional study, adult patients with β -thalassemia major who received 25 mg/kg/d of desferal or 25 mg/kg/d of deferasirox were studied. We compared them for serum calcium (Ca), creatinine (Cr) levels and 24 hours urine collection for proportion of Ca and protein. Estimated glomerular filtration rate (eGFR) was calculated by Cockcroft-Gault formula.

Results: Twenty-seven patients receiving desferal and 23 patients receiving deferasirox were evaluated. There was no significant difference of calciuria ($P=0.19$), glycosuria ($P=0.508$), mean 24-hour urine proteinuria ($P=0.44$), mean serum Cr ($P=0.47$), serum Ca level ($P=0.067$) and mean eGFR ($P=0.42$) between two groups.

Conclusion: There is no significant difference of hypercalciuria, glycosuria, mean eGFR, proteinuria, and also serum Cr between β -thalassemia major patients who received desferal or deferasirox.

Implication for health policy/practice/research/medical education:

In a study on 50 β -thalassemia major patients (27 individuals receiving desferal and 23 with deferasirox) no significant difference of renal function, hypercalciuria, glycosuria and proteinuria between two groups was detected.

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Introduction

Thalassemia is a form of inherited hematologic disorder of hemoglobin synthesis due to α/β -globin chain imbalance. It leads to ineffective hematopoiesis. The most severe form is β -thalassemia major which requires long-term transfusion to correct anemia. Since there is no physiologic active mechanism for the excretion of iron, regular transfusions cause iron overload (1). Excess iron accumulates in heart, spleen, liver and leads to overproduction of free radicals; which causes organ damages (2-4).

Since, the main reason of death in patients with β -thalassemia major is heart failure due to myocardial iron deposition, iron chelating agents have increased the life expectancy of patients (5-7).

Regular administration of deferoxamine as a chelating agent first introduced in 1960, nearly doubled lifetime of patients (8-10). Deferoxamine needs slow subcutaneous infusion over 8-12 hours with high lifetime costs (9-11). In the recent two decades, introduction of two oral chelating agents; deferiprone and deferasirox, much preferred by patients. These two drugs have improved treatment of β -thalassemia major patients significantly (10).

The prevalence of hypercalciuria and renal stones is higher in patients with β -thalassemia major (12,13). Studies have shown that prevalence of renal stone is higher in patients using deferasirox or deferiprone with unknown reason (14,15).

Higher urinary excretion of calcium (Ca) increases the

*Corresponding author: Maryam Darnahal, Email: maryamdarnahal@yahoo.com

risk of Ca phosphate and Ca oxalate stone formation. The risk of stones increases with increased urinary Ca excretion >100 mg/d. However, there is no unique cut off and definition for hypercalciuria (16,17).

There are limited data considering the effect of thalassemia on kidney. Recent data suggests that deferasirox may be nephrotoxic, since high doses intravenous injections of deferoxamine could have adverse renal effects (18).

Since, there are not enough studies on side effects of chelation therapy in patients with β -thalassemia major, we compared the prevalence of renal dysfunction in patients with β -thalassemia major receiving desferal (deferoxamine) compared to deferasirox.

Objectives

The aim of this study was to compare the renal effects of desferal versus deferasirox in β -thalassemia major patients.

Patients and Methods

Twenty-seven patients injecting 25 mg/kg/d of desferal and 23 patients receiving 25 mg/kg/d of deferasirox orally, who also took 1-3 Ca carbonate tablets per day as supplement, were selected based on systematic random sampling method. Serum Ca and creatinine (Cr) were checked and 24 hours urine was collected to analyze proportion of protein and Ca. Random urine analysis was done and glycosuria was checked by dipstick.

Ethical issues

The research followed the tenets of the Declaration of Helsinki. Informed consent was obtained. The study protocol was approved by the Ethics Committee of Iran University of Medical Science (#93-02-30-24649).

Statistical analysis

Analysis was performed in SPSS version 22 software (IBM; Chicago, IL, USA). We used mean and standard deviation (SD) or median and interquartile range (IQR) to describe numerical variables and relative frequency percentage to describe the nominal or categorical variables. Chi-square

test was applied to compare qualitative outcomes between two groups and independent *t* test to compare quantitative outcomes between two groups. The level of significance was 0.05 for two-sided tests.

Results

Twenty-seven patients receiving daily desferal injection and 23 patients receiving daily oral deferasirox were evaluated. In desferal group 55.5% were male and in deferasirox group 52.17% were male.

Patients in desferal group received 850 mg Ca averagely, and patients in deferasirox group received 800 mg averagely which was not significantly different between the groups ($P=0.78$).

Overall 70% of patients had hypercalciuria by definition of 24 hours urine Ca >100 mg. The proportion of 24 hours urine Ca of more than 100 mg/d is significantly higher in female group who received desferal (Table 1).

Additionally, the proportion of glycosuria was different among two groups. In desferal group, only 7.4% had glycosuria while, in deferasirox group 13% had glycosuria, however, it is not significant ($P=0.508$).

The estimated glomerular filtration rate (eGFR) in desferal group and deferasirox group were 120.45 ± 35.25 mL/min/1.73 m² and 112.80 ± 31.27 mL/min/1.73 m² respectively ($P=0.42$). Accordingly 24 hours urine protein excretion in desferal and deferasirox groups were 110 mg/day and 188.09 mg/d respectively ($P=0.44$).

Furthermore, the mean serum Cr level between two groups were 0.68 ± 0.12 mg/dL and 0.67 ± 0.11 mg/dL respectively ($P=0.47$). Likewise, the mean serum Ca in desferal and deferasirox groups were 8.11 ± 0.32 mg/dL and 8.04 ± 0.2 mg/dL respectively ($P=0.47$).

Discussion

The result of our study showed that mean 24 hours urine Ca was not significantly different between groups. Among patients who had hypercalciuria, 60% were administered desferal and 40% received deferasirox, however, this difference was not significant. It should be noted that our study was conducted on a small proportion of patients.

Table 1. Comparison of laboratory data between two groups

Gender	Variables		Desferal group	Deferasirox group	P value
Male	Urine calcium (mg)	<100	26.6%	25%	0.92
		≥ 100	73.3%	75%	
Female	Urine calcium (mg)	<100	16.6%	54.5%	0.06
		≥ 100	83.3%	45.4%	
Male	Urine calcium (mg)	<250	86.7%	66.7%	0.35
		≥ 250	13.3%	33.3%	
Female	Urine calcium (mg)	<250	91.7%	81.8%	0.59
		≥ 250	8.3%	18.2%	
	Glycosuria (mg)		7.4%	13%	0.51
	GFR (mL/min/1.73 m ²)		120.45 ± 35.25^b	112.80 ± 31.27^b	0.42
	Proteinuria (mg)		110 ± 91.77^b	188.09 ± 514.38^b	0.44
	Serum Cr (mg/dL)		0.68 ± 0.12^b	0.67 ± 0.11^b	0.47

^b Mean \pm SD.

Additionally, the proportion of glycosuria, proteinuria and eGFR was not significantly different among groups. Several studies have reported tubular dysfunctions – including proteinuria, hypercalciuria, and hyperphosphaturia – in thalassemia patients with normal GFR (19-21). In our study, the GFR of all patients were in normal range.

Numerous studies have reported concerns on the potential nephrotoxic effects of deferasirox. Tubular dysfunctions and proximal renal tubular dysfunction (Fanconi syndrome) have also been reported among deferasirox users (21).

Pathologic studies on rats have shown that deferasirox could cause vacuolization of proximal tubular epithelial cells and has direct toxic effect on cortical tubular cells. Acute tubular necrosis and tubular dysfunction was reported (22).

Cianciulli et al studied 19 patients with thalassemia who had administered deferoxamine. They found excreting large amounts of beta-2-microglobulin which was positively correlated with duration and dosage of therapy (23).

A phase III clinical trial comparing deferoxamine and deferasirox showed a rise in serum Cr in 38% of patients receiving deferasirox (mostly at doses of 20 and 30 mg/kg and in patients who had the most dramatic decrease in liver iron concentration and serum ferritin level). However, 14% of patients who received deferasirox had a similar increase in serum Cr. Importantly, this rises were occasionally transient and mostly within the normal range (24,25).

Conclusion

The proportion of hypercalciuria and glycosuria, proteinuria and eGFR were not significantly different in β -Thalassemia major patients with receiving desferal or deferasirox as a chelating agent.

Limitations of the study

The low proportion of patients is a limitation of our study. We hope that such studies will be repeated with larger sample size to confirm the renal safety of oral iron chelating agents for widespread use.

Authors' contribution

FS; participated in study design and research plan, organized the study and prepared the final manuscript. MD and AA, contributed to acquisition of data, data interpretation and writing the manuscript. All authors read and signed the final paper.

Conflicts of interest

The authors declare no conflict of interest.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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