Do Iron Chelators Affect Fertility in Thalassemic Men?

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Abstract

Aim: To evaluate the effect of iron chelator drugs on testicular volume, semen parameters and serum FSH, LH, and Testosterone concentrations in 62 young male patients with major and intermedia thalassemia.

Methods: Sixty two young male patients with major and intermedia thalassemia, aged 18-41 years who had different iron chelator drug using status were evaluated.

Results: At the time of the study their serum ferritin levels ranged from 182-11053 ng/mL (mean 2067 ng/mL). The mean volume of patients' ejaculate was 2.3 cc. The mean concentration of sperm was 61.04 million per milliliter. The mean size of right testis was 11.4 cc and the mean size of left testis was 11.7 cc. Hypogonadism and hypothyroidism was seen in 22.6% and 17.7% of patients, respectively. The mean level of FSH was 3.7 mIU/ml, LH was 4.6 mIU/ml and Testosterone was 4.8 ng/dl. The mean level of serum ferritin was 2067 ng/dl.

Conclusion: This study suggests that in thalassemic men, concentrations of serum Testosterone, LH, FSH has significant correlation with sperm parameters and testicular volume but iron chelators mostly do not impact the elements of fertility in these patients.

Keywords: Thalassemia major; Thalassemia intermedia; Spermatogenesis; Puberty; Testicular volume; Gonadal hormones; Iron chelators

Introduction

Beta thalassemia is a hereditary hemoglobinopathy that can cause severe anemia. The life expectancy of these patients has noticeably extended by the combination use of transfusion and effective chelation therapy. Transfusions can prevent mortality and promote normal development, but the iron in the transfused red cells accumulates and in the long run damages the liver, heart, and other organs. Involvement of different organs including the endocrine system lessens the quality of thalassemic patients' lives. In fact, pubertal failure, sexual dysfunction and infertility, due to hypogonadism have been reported in 51% to 66% of thalassemic patients [1-3]. The etiologies of male infertility in general population are several though in β-thalassemia are classically considered to be the result of iron deposition in the endocrine glands. The adverse reactions of the drugs they use for different reasons including iron chelation could be an important factor influencing thalassemia fertility [4].

The prevalence of acquired hypogonadism in β-thalassemia has been reported to depend mainly on the degree of compliance with blood transfusion and chelation programs [5]. This means
that iron chelator drugs could be a protector against iron deposition in gonads but at the same time could have toxic effects on gonads and sperms. The aim of this study was to evaluate the effect of iron chelator drugs on pubertal development, sexual hormone status and sperm parameters in adolescent and young adult males with Beta-thalassemia major and intermedia.

Materials and Methods

This prospective study was conducted between January 2001 and January 2003 at a teaching hospital in Tehran, Iran. The study included 62 males with Beta-thalassemia major and intermedia, whose ages ranged between 18 and 41 years. Among the patients, 52 had been regularly transfused since early childhood and underwent different chelation therapies using subcutaneous desferrioxamine and/or oral deferasirox and/or deferiprone. The requisite of the study was that the participants being competent and cooperative.

Puberty was evaluated in the patients according to Tanner’s classification of testicular development [6]. Testicular size ≤4 mL (long axis of ≤2.5 cm) was considered stage I (prepubertal genitalia), and size ≥25 mL (≥5 cm in length) was considered adult genitalia [7]. Testicular volumes were calculated with scrotal ultrasound. After overnight fasting, blood samples were collected from patients for evaluation of their basal LH, FSH, and Testosterone.

Iron overload was assessed by direct and indirect methods. It was evaluated by measuring serum ferritin level. Iron status was classified as mild (ferritin < 1000 ng/ml), moderate (ferritin >1000 ng/ml and < 2500 ng/ml) or severe (ferritin >2500 ng/ml). T2* MRI of heart and liver was assessed for iron overload. Standard computer program SPSS for Windows, release 16.0 was used for data entry and analysis. P≤0.05 was considered statistically significant.

The study was approved by the University’s ethical Committee.

Patient informed consent was obtained, as appropriate, before beginning the study.

Results

The patients’ age range was between 18 to 41 years. Their mean age was 27.2 years. Among the patients, 75.8% were major and 24.2% were intermedia and totally 83.9% were transfusion dependent. Among our patients, 4.8% did not use any kind of iron chelator drugs, 54.8% used deferoxamine, 50% used deferasirox and 21% used deferiprone. On an additional glance, 14.5% had history of using both deferoxamine and deferasirox, 12.5% used deferoxamine and deferiprone at the same time and 3.2% used deferasirox and deferiprone simultaneously. The mean volume of patients’ ejaculate was 2.3 cc. Five patients (8.1%) had dry ejaculate and 24.2% o patients had unacceptable ejaculate volume (<1.5 ml).

Having dry ejaculate significantly correlated with having the history of using deferiprone (p=0.025). However, patients who had the history of using deferoxamine had significantly lower ejaculate volume comparing with patients who did not use deferoxamine (1.7ml versus 2.6 ml). This was also true about the patients who had the history of using deferiprone (1.2ml versus 2.3ml). But having the history of using deferasirox had not impacted ejaculate volume in our study. The mean concentration of sperm was 61.04 million per milliliter. Totally, 61.3% of patients had acceptable sperm concentration (≥15 M/ml) but 21% had azospermia and 22.4% had oligospermia. In patients who used deferiprone, oligospermia was significantly more frequent (P=0.04).

Considering the sperm motility, respectively, in 22.4% and 34.6% of patients the number of motile sperms and progressively motile sperms were less than normal. Considering the sperm morphology, in 44.8% of patients the number of sperms with normal morphology were less than normal. The drugs did not impact the sperms’ motility and morphology in our study. The mean size of right testis was 11.4 ml and the mean size of left testis was 11.7 ml. Only 3.2% of patients had testicular volume less than 4 ml which is indicative of the puberty process not being started and this was significantly correlated with using deferiprone. This means that deferiprone usage was associated with delayed puberty.

The mean level of FSH was 3.7 mIU/ml, LH was 4.6 mIU/ml, and Testosterone was 4.8 ng/dl. The frequency of hypogonadotropic hypogonadism and hypergonadotropic hypogonadism was 16.1% and 6.5%, respectively. The chelator drug usage did not correlate with the gonadal hormones’ serum level. The mean level of serum ferritin was 2067 ng/dl. Serum ferritin level correlated significantly with deferoxamine and deferiprone usage and not with deferasirox usage. In 74.2% of patients cardiac MRI was normal. In 21% of patients hepatic MRI was normal. Interestingly, cardiac and hepatic MRI involvements did not correlate with chelators’ usage. All the same, no significant correlation was found between the iron overload determinants and sperm parameters or having hypogonadism.

Discussion

Iron overload in beta-thalassemia patients is the mutual outcome of multiple blood transfusions and improperly increased iron absorption due to ineffective erythropoiesis. Tissue iron deposition affects all organ systems, especially the cardiac, hepatic, and endocrine systems. Observational records advocate that iron loading in endocrine organs may precede that in the heart and liver. There is now considerable evidence on the role of iron overload in endocrine morbidity in these patients [9,10]. Hypogonadism and

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and having dry ejaculate and oligospermia was more frequent in patients who had the history of using deferiprone had significantly lower ejaculate volume comparing with patients who had never used deferiprone. Considering testicular volume in ultrasound assessment, in patients who used deferiprone testicular volume less than 4ml which is indicative of delayed puberty was much more frequent [30].

Our study has a number of limitations, including the retrospective design and the lack of dose and duration of drug usage being specified. Therefore, further prospective studies on a larger population would improve the quality of the research.

**Conclusion**

In conclusion, we observed that in thalassemic men, concentrations of serum Testosterone, LH, FSH has significant correlation with sperm parameters and testicular volume but iron chelators mostly do not impact the elements of fertility in these patients. Taking into account the important role of reproduction and fatherhood in the quality of lives of these patients, we advocate the necessity of the care givers to be alert of the mentioned side effects.

**References**

1. Galanello R, Origa R (2010) Beta-thalassemia. Orphanet J Rare Dis 5: 11.
2. De Sanctis V, Giovannini M (2011) Endocrine histology findings in a prepubertal thalassemic girl with multiple endocrine complications secondary to iron overload. Georgian Med News 193: 51-55.
3. Soliman A, Yasin M, El-Awwa A, Osman M, de Sanctis V (2012) Acute effects of blood transfusion on pituitary gonadal axis and sperm parameters in adolescents and young men with thalassemia major: a pilot study. Fertil Steril 98: 638-643.
4. De Sanctis V, D’Ascola G, Wonke B (1986) The development of diabetes mellitus and chronic liver disease in long term chelated beta thalassaemic patients. Postgrad Med J 62: 831-836.
5. De Sanctis V, Elsedfy H, Soliman AT, Elhakim IZ, Pepe A, et al. (2016) Acquired hypogonadotropic hypogonadism (AHH) in thalassaemia major patients: An underdiagnosed condition? Mediterr J Hematol Infect Dis 8: e2016001.
6. Tanner JM, Whittehouse RH (1976) Clinical longitudinal standards for height, weight, height velocity, weight velocity, and the stages of puberty. Arch Dis Child 51: 170-179.
7. Kauschansky A, Dickerman Z, Phillip M, Weinreb N, Strich D (2002) Use of GnRH agonist and human chorionic gonadotrophin tests for differentiating constitutional delayed puberty from gonadotrophin deficiency in boys. Clin Endocrinol 56: 603-607.
8. Tuck SM (2005) Fertility and pregnancy in thalassemia major. Ann N Y Acad Sci 1054: 300-307.
9. Noetzli LJ, Panigrahy A, Mittelman SD, Hyderi A, Dongelyan A, et al. (2012) Pituitary iron and volume predict hypogonadism in transfusional iron overload. Am J Hematol 87: 167-171.
10. Belhoul KM, Bakir ML, Saned MS, Kadhim A, Musallam K, et al. (2012) Serum ferritin levels and endocrinopathy in medically treated patients with β thalassemia major. Ann Hematol 91: 1107-1114.
11. Borgna-Pignatti C, Rugolotto S, De Stefano P, Zhao H, Cappellini MD, et al. (2004) Survival and complications in patients with thalassemia major treated with transfusion and deferoxamine. Haematologica 89: 1187-1193.

12. Taher AT, Musallam KM, Karimi M, El-Beshlawy A, Belhoul K, et al. (2010) Overview on practices in thalassemia intermedia management aiming for lowering complication rates across a region of endemicity: the optimal care study. Blood 115: 1886-1892.

13. Vogiatzi MG, MacKlin EA, Trachtenberg FL, Fung EB, Cheung AM, et al. (2009) Differences in the prevalence of growth, endocrine and vitamin D abnormalities among the various thalassemia syndromes in North America. British Journal of Haematology 146: 546-556.

14. Gamberini MR, de Sanctis V, Gilli G (2008) Hypogonadism, diabetes mellitus, hypothyroidism, hypoparathyroidism: Incidence and prevalence related to iron overload and chelation therapy in patients with thalassemia major followed from 1980 to 2007 in the Ferrara centre. Pediatric Endocrinology Reviews 6: 158-169.

15. Hershko C (2010) Pathogenesis and management of iron toxicity in thalassemia. Ann NY Acad Sci 1202:1-9.

16. Farmaki K, Angelopoulou N, Anagnostopoulou G, Gotsis E, Rombopoulos G, et al. (2006) Effect of enhanced iron chelation therapy on glucose metabolism in patients with beta-thalassemia major. British Journal of Haematology 134: 438-444.

17. ElAlfy M, Ragab E, Abdel-Aziz E, Massoud W, Elsedfy H (2013) Deferiprone and deferoxamine combined chelation could improve puberty of adolescent males with beta-thalassemia major with preserved pituitary and testicular function. Egyptian Journal of Haematology 38: 4.

18. Al-Rimawi HS, Jallad MF, Amarir ZO, Obeidat BR (2005) Hypothalamic-pituitary-gonadal function in adolescent females with beta-thalassemia major. Int J Gynaecol Obstet 90: 44-47.

19. Moeschlin S, Schneider U (1963) Treatment of primary and secondary hemochromatosis and acute iron poisoning with a new, potent iron-eliminating agent (Desferrioxamine-B). New England Journal of Medicine 269: 57-66.

20. De Virgiilis S, Cossu P, Toccafondi C, Sanna G, Frau F, et al. (1983) Effect of subcutaneous deferoxamine on iron balance in young thalassemia major patients. Am J Pediatr Hematol Oncol 5: 73-77.

21. Davies SC, Marcus RE, Hungerford JL, Miller MH, Arden GB, et al. (1983) Ocular toxicity of high-dose intravenous desferrioxamine. Lancet 2: 181-184.

22. Olivieri NF, Buncic JR, Chew E, Gallant T, Harrison RV, et al. (1986) Visual and auditory neurotoxicity in patients receiving subcutaneous deferoxamine infusions. N Engl J Med 314: 869-873.

23. De Virgiilis S, Congia M, Frau F, Argioli F, Diana G, et al. (1988) Deferoxamine-induced growth retardation in patients with thalassemia major. The Journal of Pediatrics 113: 661-669.

24. Cappellini MD, Cohen A, Piga A, Bejaoui M, Perrotta S, et al. (2006) A Phase III study of deferasirox (ICL670), a once-daily oral iron chelator, in patients with beta-thalassemia. Blood 107: 3455-3462.

25. Jensen PD, Jensen FT, Christensen T, Nielsen JL, Ellegaard J (2003) Relationship between hepatocellular injury and transfusional iron overload prior to and during iron chelation with deferoxamine: a study in adult patients with acquired anemias. Blood 101: 91-96.

26. Mula-Abed WA, Al-Hashmi HS, Al-Muslahi MN (2011) Indicators of Renal Glomerular and Tubular Functions in Patients with Beta-Thalassemia Major: A cross sectional study at the Royal Hospital, Oman. Sultan Qaboos Univ Med J 11: 69-76.

27. Hoffbrand AV, Al-Refaie F, Davis B, Sirihanakatkul N, Jackson BFA, et al. (1998) Long-term trial of deferiprone in 51 transfusion-dependent iron overloaded patients. Blood 91: 295-300.

28. Bartlett AN, Hoffbrand AV, Kontoghorghes GJ (1990) Long-term trial with the oral iron chelator 1,2-dimethyl-3-hydroxypyrid-4-one (L1). II. Clinical observations. British Journal of Haematology 76: 301-304.

29. Agarwal MB, Gupte SS, Viswanathan C, Vasandani D, Ramanathan J, et al. (1992) Long-term assessment of efficacy and safety of L1, an oral iron chelator, in transfusion dependent thalassemia: Indian trial. British Journal of Haematology 82: 460-466.

30. De Sanctis V, Elawwa A, Angastiniotis M, Kattamis C, Karimi M, et al. (2012) Highlights from the First Thalassaemia Forum on Growth and Endocrine Complications in Thalassemia Doha, (October 2-3,