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Original Research Article

Impacts of transfusion in β-thalassemia major patients receiving multiple blood transfusions

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ABSTRACT

Background: Beta-thalassemia major is one of major public health problems in India. Thalassemia major is a transfusion-dependent severe anemia and these children experience various problems if the transfusion is inadequate but at the same time repeated blood transfusions are associated with hazards like iron overload.
Methods: This study was conducted at thalassemia ward of S.M.S Hospital and J.K.LON paediatrics Hospital, Jaipur from April 2012 to Nov. 2013. 145 thalassemia patients on transfusion therapy attending outdoor or being admitted were assessed after obtaining due permission from the authorities and consent from the guardian or parents of patients.
Results: Present study comprised 145 beta-thalassemia major patients with 51 (35%) females and 94 (65%) males in which youngest patient is 3 years old and the oldest 33 years. 104 (72%) were Hindus and 41 (28%) were Muslims. Consanguinity was found in a significant proportion 16% (23) of the parents of the patients. 137 (94%) patients had serum ferritin ≥1000ng/ml. Out 145 thalassemic patients, 108 (74.5%) have total serum bilirubin >1(mg/dl), 103 (71%) have SGPT level >35IU, 103 (71%) have SGOT level >40IU), 38 (26.2%) have serum alkaline phosphatase level >390 IU, 35 (24.1%) have serum creatinine level >1.6mg/dl, 42 (29%) have serum urea level >45mg/dl, 28 (19.3%) have serum uric acid level >6mg/dl.
Conclusions: It is suggested to revise and devise suitable transfusion regime so that a balance between adequate transfusion and minimum side effects of multiple transfusions is maintained. Systemic effects of multiple transfusions should be rigorously and meticulously studied.

Keywords: Blood transfusion, Ferritin, Iron chelation, Thalassemia

INTRODUCTION

Thalassemia is most common heterogeneous group of single gene disorders, inherited in an autosomal recessive manner that involves the decreased and defective production of haemoglobin. Beta-thalassemia major is one of major public health problems in India (prevalence 7.48%) especially in some communities such as Sindhis and Punjabis from northern India, Bhanushali's, Kutchis, Lohana's from Gujarat, Mahar's, Neobuddhist's, Koli's and Agri's from Maharashtra, and Gowda's and Lingayat's from Karnataka etc.[1] The carrier rate for β - thalassemia gene varies from 1 to 3% in Southern India to 3% to 15% in Northern India.[2,3]

Every year approximately 100,000 children with thalassemia major are born world over, of which 10,000 are born in India. The general incidence of thalassemia

trait in India varies between 3 and 17%. It is estimated that there are about 65,000-67,000 beta-thalassemia patients in India with around 9,000-10,000 cases being added every year.[2-6] Thalassemia major is a transfusion-dependent severe anemia and these children experience various problems if the transfusion is inadequate but at the same time repeated blood transfusions are associated with hazards like iron overload. The combination of regular blood transfusions and chelation therapy has dramatically increased the life expectancy of thalassemics into 4th and 5th decades of life.

On the other hand, frequent blood transfusion has also led to iron overload with many complications including endocrinopathies (in the form of growth retardation, pubertal delay, gonadal dysfunction and diabetes mellitus), behavioural and neurotic problems, cardiovascular problems, liver disease. Frequent blood transfusion can also lead to increased chances of transfusion-transmitted infections TTIs such as HIV (with risk of progression to AIDS), HBsAg, and HCV (with high risk of developing chronic hepatitis, liver cirrhosis and hepatocellular carcinoma), syphilis (VDRL) and Malaria can also occur.[7]

Severe β thalassemia major (also called Cooley's anaemia) has traditionally had a poor prognosis with 80% dying from complications of the disease in the first five years of life. Until recently, patients who received transfusions only did not survive beyond adolescence because of cardiac complications caused by iron toxicity.[8] The introduction of chelating agents to remove excessive iron has increased life expectancy dramatically. The overall survival following stem cell transplantation has been shown to be 90% with a disease-free survival of 86% over a mean follow-up period of 15 years.[9]

In our study, we observe number of children receiving blood and complications arising in them due to the blood treatment itself, and patient compliance with the treatment regimen.

METHODS

This study was conducted at Thalassemia ward of S.M.S Hospital and J.K.LON Paediatrics Hospital Jaipur from April 2012 to Nov. 2013. It is a hospital based observational study. 145 thalassemia patients more than 3 years of age both males and females who were on transfusion therapy attending outdoor or being admitted in J.K.LON Hospital and S.M.S Hospital, Jaipur were assessed after obtaining due permission from the authorities and consent from the guardian or parents of patients, the clinical data was collected. Cases were randomly selected till sample size was completed.

Criteria for selection of cases

Patients of β-thalassemia major registered at Thalassemia ward of S.M.S Hospital, Jaipur and J.K.LON Paediatrics Hospital, Jaipur and receiving blood transfusions regularly at the same institute, irrespective of their age and sex were included in this study. Type of blood to be administered includes fresh blood, washed red blood cells or packed red cell (ideally leucodepleted).

Criteria for exclusion of cases

Under the age of 3 years and multiple blood transfused patients other than thalassemia.

Following laboratory investigations were carried out as under: pretransfusion Hb, S. ferritin, blood sugar (fasting), liver function test (total S. bilirubin, SGOT, SGPT, S. alkaline. phosphatase), renal function test (S. creatinine, S. urea, S. uric acid), test for Transfusion-Transmitted Infections (TTIs) likes HIV, HBV, HCV, Malaria and VDRL.

All investigations were done in Pathology Lab, Immunoassay Lab, Biochemistry Lab and Microbiology Lab, S.M.S. Medical College, Jaipur.

RESULTS

Our study comprised 145 beta-thalassemia major patients with 51 (35%) females and 94 (65%) males receiving regular blood transfusions at Thalassemia ward of S.M.S Hospital, J.K. LON Pediatrics Hospital, Jaipur. youngest patient is 3 years old and the oldest is 33 years with the mean age ±SD being 10.00±4.75 years (mean age ±SD for male was 9.99±4.56 and for female was 10.00±5.13year) (Table 1).

Table 1: Distribution of thalassemia patients according to age and sex.

Age group (Yrs.)	Sex		Total
	Male	Female	
3-5	14	6	20
6-10	44	25	69
11-15	27	15	42
16-20	5	4	9
> 20	4	1	5
Total	94	51	145

Out of 145 thalassemia cases, 104 (72%) were Hindus and 41 (28%) were Muslims. In coherence with the inheritance pattern of autosomal recessive diseases (beta-thalassemia major being one), consanguinity was found in a significant proportion i.e. 23/145 or 16% of the parents of the patients. Muslim community, hereto known for such marital practices, was found to be the major contributor with 23/41 consanguineous marriages having taken place amongst parents of Muslim patients. It was a striking revelation that 56% (23/41) of the Muslim patients were born out of a consanguineous marriage (Figure 1, Table 2).

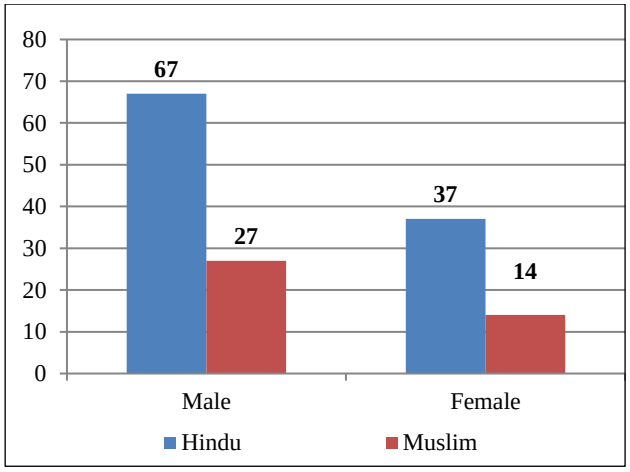

Figure 1: Distribution of thalassemia patients according to religion.

Table 2: Distribution of thalassemia patients according to consanguity.

Religion	Consanguity		Total
	No	Yes	
Hindu	104	0	104
Muslim	18	23	41
Total	122	23	145

Thalassemia patients were divided into four groups based on their serum ferritin levels, <1000ng/ml and ≥1000ng/ml) and on their chelation therapy, yes/no. We found that only 8 (6%) patients had serum ferritin <1000ng/ml and all of them were on chelation therapy. The rest 137 (94%) patients had serum ferritin ≥1000ng/ml. Minimum serum ferritin level is 310ng/ml and the Maximum serum ferritin level is 6720 ng/ml with the mean serum ferritin level ±SD being 2264.39±1286.34ng/ml (mean serum ferritin level ±SD for male is 2338.14±1347.37 and for female is 2128.45±1166.06ng/ml) (Table 3).

Table 3: Distribution of thalassemia cases based on serum ferritin level and chelation.

Serum ferritin level (ng/ml)	Chelation therapy		Total
	Yes	No	
< 1000	8	0	8
≥ 1000	133	4	137
Total	141	4	145

Out of 145, Maximum number of patient 100(67%) were being transfused within 21-30 per year (Table 4).

Out 145 thalassemic patients, 108(74.5%) of them have total serum bilirubin >1(mg/dl), 103(71%) have SGPT level >35IU, 103 (71%) have SGOT level >40IU), 38 (26.2%) have serum alkaline phosphatase level >390 IU, 35 (24.1%) have serum creatinine level >1.6mg/dl, 42 (29%) have serum urea level >45mg/dl, 28 (19.3%) have serum uric acid level >6mg/dl (Table 5).

Table 4: Distribution of thalassemia major patients based on serum ferritin level and No. of blood transfusions per year.

Serum ferritin level (ng/ml)	No. of transfusion per year					Total
	1-10	11-20	21-30	31-40	41-50	
<1000	1	1	6	0	0	8
≥1000	0	22	94	20	1	137
Total	1	23	100	20	1	145

Table 5: Distribution of thalassemia patients according to Liver function test and renal function test.

Tests	No. of patients	% of total
Bilirubin >1mg/dl	108	74.5
SGOT >40IU/dl	103	71.0
SGPT >35IU/dl	103	71.0
S. Alkaline Phosphate >390IU/dl	38	26.2
S. Creatinine >1.6mg/dl	35	24.1
Urea >45mg/dl	42	29.0
Uric Acid >6mg/dl	28	19.3

In our study, we found that 14 (9.65%) patients were only anaemic and 128/145 (88%) and 131/145 (90%) patients were having hepatomegaly and spleenomegaly respectively with anaemia (Table 6).

Table 6: Distribution of thalassemia patients based on Clinical features.

	Clinical features			Total
	Anaemia with spleenomegaly and hepatomegaly	Anaemia with spleenomegly & no hepatomegaly	Only anaemia & No hepatospleenomegaly	
Total No. of patients	128	3	14	145

In our study, there are 5/145 (3.44%) known diabetic patients and all of them have serum ferritin levels above >5000ng/ml. All the patients are on insulin therapy. This is in accord with the fact that diabetes in these patients is usually due to iron deposition in the pancreas leading to insulin deficiency. Out of 145 patients, 10 (7%) patients had impaired fasting glucose and all of them belonged to high serum ferritin level group (≥1000ng/ml) (Figure 2).

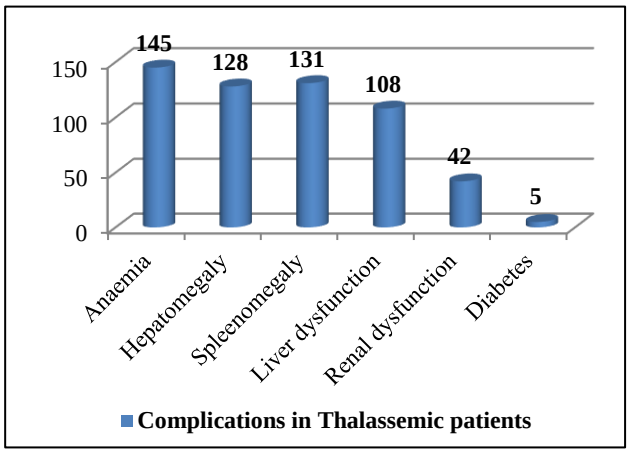

Figure 2: Distribution of thalassemia patients according to complications.

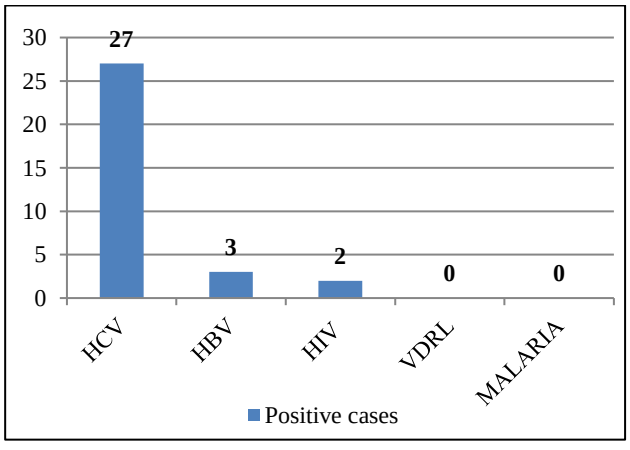

Figure 3: Proportion of positive cases of transfusion transmitted infections (TTIs) in thalassemic major patients.

In this study, out of 32 positive cases, 27 (84.37%) are HCV positive, 3 (9.37%) are HBV positive and 2 (6.36%) are HIV positive. This show that prevalence of HCV infections is greater than other four and HBV is greater than HIV, VDRL and Malaria (Figure 3).

DISCUSSION

Youngest patient is 3 years old and the oldest is 33 years with the mean age ±2SD being 10.00±4.75years (mean age ±SD for male was 9.99±4.56 and for female was10.00±5.13year).

All cases were divided into five groups, 3-5 yrs, 6-10 yrs, 11-15yrs, 16-20yrs and >20years. Maximum numbers, 69 (48%) of thalassemia cases were in age group 6-10years. This result was in accordance with a study done by Shah Sejal J et al.[10] Out of total 145 cases of beta thalassemia major more than one third cases (34.3%) were of 10 or more years of age. Similar age incidence was observed in Ghai OP series, Manchanda and Khanna series, Magotra and Phadke series and Giri, Patra and Patel series.[11-14]

Regarding sex distribution, in our study out of 145 cases, 65 % were male with male to female ratio being approximately 2:1. In accordance with a similar study Ghai reported 63.7% males and 36.3% females, while other study found 70.6% males and 29.4% females.[11,15]

In coherence with the inheritance pattern of autosomal recessive diseases (beta-thalassemia major being one), consanguinity was found in a significant proportion i.e. 23/145 or 16% of the parents of the patients. Muslim community, hereto known for such marital practices, was found to be the major contributor with 23/41 consanguineous marriages having taken place amongst parents of Muslim patients. It was a striking revelation that 56% (23/41) of the Muslim patients were born out of a consanguineous marriage. This result was in accordance with a study done by Shanthi G et al.[16] The β-thalassemia children born to consanguineous parents were 84 (68.58%) and remaining 38 (31.15%) were born to non-consanguineous parents.

Kumar et al, and Devi RR et al, concluded that consanguineous marriages are strongly favoured in the Dravidian population, while Rao and Inbaraj and Rao, reported that in South India the level of consanguinity will vary considerably from 4.5 to 6.1% depending upon the factors such as religion, caste and socio-economic status.[17-20] The β-thalassemia children born to consanguineous parents (68.85%) was higher than non-

consanguineous parents, clearly indicates that consanguinity, which is prevalent from time immemorial in Tamil Nadu, has a greater role to play in the expression of various forms of β-thalassemia.

In our study, there are 5/145 (3.44%) known diabetic patients and all of them have ferritin levels above >5000 ng/ml. All the patients are on insulin therapy. This is in accord with the fact that diabetes in these patients is usually due to iron deposition in the pancreas leading to insulin deficiency. Out of 145 patients, 10 (7%) patients had impaired fasting glucose and all of them belonged to high ferritin level group (≥1000ng/ml). Comparable prevalence was reported by Karahanyan E et al, Aysegul Kurtoglu U et al, Thuret I et al, Najafipour F while prevalence was found to be higher by El Hazami MA et al and Khalifa AS et al.[21-26] This difference in prevalence can be explained by different patient characteristics (ethnicity, timely chelation).

In our study, we found that 14 (9.65%) patients were only anaemic and 128/145(88%) and 131/145(90%) patients were having hepatomegaly and spleenomegaly respectively with anaemia. which may be due to result of extramedullary haemopoisis and iron overload, lack of proper monitoring of chelation therapy or expensive of treatment to afford by every person especially in this era of inflation and may be due to TTIs (HCV, HBV, HIV).[27]

A study on complications in thalassaemia patients receiving blood transfusion shows hepatomegaly 72.5% and spleenomegaly 92.5% respectively.[28] The percentage of hepatomegaly in a study was (94%) reported by Ahmad A in Mosul.[29]

We found that 108 (74.5%) patients have total serum bilirubin >1mg/dl, 103 (71%) have SGOT level >40IU), 103 (71%) have SGPT level >35IU and 38 (26.2%) have serum alkaline phosphatage level >390 IU.

Total S. bilirubin, SGOT, SGPT, serum alkaline phosphatase levels were raised (liver dysfunction) in most of thalassemic patients. As a result of deposition of iron in liver, which may be due to lack of proper monitoring of chelation therapy or expensive of treatment to afford by every person especially in this era of inflation and may be due to TTIs (HCV, HBV, HIV). Serum ferritin level was >1000ng/ml in all case of liver dysfunction.

A study of assessment of liver functions as reflected by the serum levels of bilirubin, AST, ALT and ALP and iron status as reflected by serum ferritin. A significant increase in the serum levels of AST, ALT, ALP and bilirubin was found in thalassemic patients.[30]

A study on "Associated Complications in Beta Thalassemia Patients" Commonest complication was growth failure and was observed in 81 (46%) patients. Next common were cardiac complications and were observed in 41 patients (23.3%). Hepatic enzymes were raised in 12 patients (6.8%). Endocrine complications were found in 30 (17.1%) patients. Transfusion related infections such as Hepatitis B were found in 12 (6.8%) cases.[7]

Thalassemia patients were divided into two groups based on their serum creatinine level (<1.6mg/dl and >1.6mg/dl), on their serum urea level (<45mg/dl and >45mg/dl) and based on their serum uric acid level (<6mg/dl and >6mg/dl). Serum creatinine, serum urea and serum uric acid levels were raised (renal dysfunction) in 35 (24%), 42 (29%), 28 (19.3%) cases of thalassemia patients respectively. As a result of deposition of iron in renal, which may be due to lack of proper monitoring of chelation therapy or expensive of treatment to afford by every person especially in this era of inflation and may be due to TTIs (HCV, HBV, HIV). Serum ferritin level was >1000ng/ml in all case of renal dysfunction.

A similar study was done to detect renal dysfunction in beta-thalassemia major patients. Abnormal levels of serum creatinine, serum urea and serum uric acid were detected in 35.9% of patients.[31]

In our study group of 145 pts, we studied the prevalence of five important TTIs (HCV, HBV, HIV, VDRL and Malaria) which is compared to the prevalence of these infections in voluntary blood donors (taken as indicative of general population). A striking 18% of the patients are HCV positive which is significantly more than the prevalence in general population (P<0.05). There is no significant difference in HBV positivity in the thalassemic patients and general population (P>0.05). The prevalence of HIV positivity is not statistically significant compared to the general population (P>0.05). All the 32 patients who are HCV, HBV and HIV positive are not coinfected to each other.

In two studies from Western India, the prevalence of HCV in multiple transfused thalassemics were 16.7% and 17.5%, respectively.[32,33] In a similar study from department of Pathology, M.P. Shah medical college, Jamnagar (Gujarat, India) the seroreactivity for HIV was 3% (06/200); 1% (02/200) were males and 2% (04/200) were females.[10] The seroreactivity for HBV was 2% (04/200) all were males. The seroreactivity for HCV was 2% (04/200); 1.5% (03/200) were males and 0.5% (01/200) was female.[34]

CONCLUSION

In our study, in terms of pre-transfusion hemoglobin levels (taking 10 gm% as cut off), 100% of patients are under transfused. In terms of serum ferritin levels (taking 1000 ng/ml as cut off), nearly 94% of patients need their chelation regime to be reviewed. In terms of the prevalence of endocrinopathies like diabetes mellitus and growth retardation, the chelation therapy received by the patients is inadequate. Looking at the high prevalence of

HCV, screening of the blood units for TTIs especially HCV needs to be improved.

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Ethical approval: The study was approved by the Institutional Ethics Committee

REFERENCES

1. Patel J, Patel A, Patel J, Kaur A, Patel V. Prevalence of haemoglobinopathies in Gujarat, India: A cross-sectional study. Int J Hematol. 2008;5(1):1-6
2. De SV. Growth and puberty and its management in thalassemia. Horm Res. 2002;58(Suppl 1):72-9.
3. World Health Organization: Human genetics programme. Division of communicable disease. community control of hereditary anemia memorandum for a WHO meeting. Bull WHO. 1983;61:63-80.
4. Manglani M, Lokeshwar MR, Vani VG, Bhatia N, Mhaskar V. 'NESTROFT'- an effective screening test for b- Thalassemia trait. Indian Pediatrics. 1997;34:703-8.
5. Verma IC, Choudhry VP, Jain PK. Prevention of thalassemia: A necessity in India. India J Pediatr. 1992;59:649-54.
6. Yaish HM. Medscape. Fact sheet: Pediatric Thalassemia, 2017. Available at: https://emedicine.medscape.com/article/958850-overview. Accessed 6 August 2007.
7. Kirti G, Pankaj A. Associated complications in beta thalassemia patients. IOSR J Pharmacy. 2013;3(1):22-5.
8. Cazzola M, Borgna PC, Locatelli F, Ponchio L, Beguin Y, De Stefano P. A moderate transfusion regimen may reduce iron loading in beta-thalassemia major without producing excessive expansion of erythropoiesis. Transfusion. 1997;37:135-40.
9. Peters M, Heijboer H, Smiers F. Diagnosis and management of thalassaemia. BMJ. 2012;344(1):e228.
10. Shah SJ, Chauhan SC, Rathod HK, Patel AB, Sharma VY. A profile of cases of hemoglobinopathies at a Medical college. National J Med Res. 2012;2(2):137-40.
11. Ghai OP, Gupta P, Paul VK. Essential Pediatrics. 6th ed. Delhi: CBS Publishers and Distributors; 2005:302-315.
12. Manchanda SS, Khanna HL. Severe Anemia in childhood. Ind J Child Health. 1961;11:462.
13. Magotra ML, Phadke MV. Anemia in infancy and childhood. Ind Ped. 1975;12:493-98.
14. Giri DD, Patra SB, Patel RZ. Hemoglobinopathies in childhood. Ind J Pathol Microbiol. 1984;27(2):81-9.
15. Coelho G, Setna S, Simmons C. HFE mutation on iron metabolism in beta thalassemia. Ind J Child Health. 1958;7:378.
16. Shanthi G, Balasubramanyam D, Srinivasan R. Studies on the haematological aspects of beta (β)-thalassemia in Tamilnadu. RJPBCS. 2013;4(3):784-90.
17. Kumar S, Pai RA. Swaminathan MS. Consanguineous marriages and the genetic load due to Iethal genes in Kerala. Ann Humn Genet. 1967;31:141-5.
18. Radha RDA, Appaji RN, Bittles AH. Inbreeding in the state of Karnataka. South India. Humn Hered. 1982;32:8-10.
19. Rao PSS. Inharaj SG. Inbreeding in Tamil Nadu, South India. Soc Biol. 1977:24:281-8.
20. Rao PSS. Religion and the intensitv of inbreeding in Tamil Nadu. South India. Soc Biol. 1983;30:413-22.
21. Karahanyan E, Stoyanova A, Moumdzhiev I, Ivanov I. Secondary diabetes in children with thalassaemia major (homozygous thalassaemia). Folia Med (Plovdiv). 1994;36:29-34.
22. Kurtoglu AU, Kurtoglu E, Temizkan AK. Effect of iron overload on endocrinopathies in patients with beta-thalassaemia major and intermedia. Endokrynologia Polska/Polish J Endocrinol Tom. 2012;63(4):260-63.
23. Thuret I, Pondarré C, Loundou A, Steschenko D, Girot R, Bachir D. Complications and treatment of patients with β-thalassemia in France: Results of the national registry. Haematologica. 2010;95(5):724-29.
24. Najafipour F. Evaluation of endocrine disorders in patients with thalassemia major. Int J Endocrinol Meta. 2008;2:104-13.
25. El-Hazmi MA, al-Swailem A, al-Fawaz I, Warsey AS, al-Swailem A. Diabetes mellitus in children suffering from beta-thalassaemia. J Trop Pediatr. 1994;40(5):261-6.
26. Khalifa AS, Salem M, Mounir E, El-Tawil MM, El-Sawy M, Abd Al-Aziz MM. Abnormal glucose tolerance in Egyptian betathalassemic patients: possible association with genotyping. Pediatr Diabetes. 2004;5:126-32.
27. Hoffbrand AV, Pettit JE. Essential hematology. 4th ed. UK: Black Well Science; 2001:71-90.
28. Hira T, Syeda Amna S. Complications in thalassaemia patients receiving blood tranfusion. J Biomed Sci Res. 2011;3(1):339-46.
29. Adaay MH, Al-Anzy MM, Al-Samarrai AMH, Al-Tikriti KA, Al-Samarrai FA. Some observations on the occurrence of β-thalassemia in Mosul. Iraqi J Med Sci. 2011;9(3):270-74.
30. Israa IM, Fadhila S. Assessment of liver functions in thalassaemia. Tikrit J Pharma Sci. 2012;8(1):87-95.
31. Mohkam M, Shamsian BS, Gharib A, Nariman S, Arzanian MT. Early markers of renal dysfunction in patients with beta-thalassemia major. Pediatri. Nephrol. 2008;23:971-6.
32. Agarwal MB, Shah S, Vishwanathan C, Rajadhyaksha G, Bhave AA, Dube SR et al. Thyroid dysfunction in multi-transfused iron loaded

thalassemia patients. Ind Pediatr. 1992;29(8):997-1102.
33. Arankalle VA, Chadha MS, Jha J, Amrapurkar DN, Banerjee K. Prevalence of anti-HCV antibodies in western India. Ind J Med Res. 1995;101:91-3.
34. Vidja PJ, Vachhani JH, Sheikh SS, Santwani PM. Blood transfusion transmitted infections in multiple blood transfused patients of beta thalassaemia. Ind J Hematol Blood Trans. 2011;27(2):65-9.

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