Pharmaceutical sciences , 2013, 18(4), 199-204

http://pharm-sci.tbzmed.ac.ir

The Adverse Effects of Thalassemia Treatments Including Blood Transfusion and Main Pharmacological Therapies

Mohammadreza Sattari[1], Dorna Sheykhi[2], Alireza Nikanfar[3], Abasali Hosseyn Pourfeizi[4], Maryam Nazari[5], Roya Dolatkhah[6], Hadi Hamishehkar[7], Simin Ozar Mashayekhi[8]*

[1] *Hematology & Oncology Research Center, Faculty of Pharmacy, Pharmacology and Toxicology Department, Clinical pharmacy Department, Tabriz University of Medical Sciences, Tabriz, Iran.*

[2] *Hematology & Oncology Research Center, Student Research Center, Faculty of Pharmacy, Clinical pharmacy Department, Tabriz University of Medical Sciences, Tabriz, Iran.*

[3] *Hematology and Oncology Research Center, Faculty of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran.*

[4] *Hematology and Oncology Research Center, Faculty of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran.*

[5] *Pediatric Hospital, Tabriz University of Medical Sciences, Tabriz, Iran.*

[6] *Hematology and Oncology Research Center, Shahid Ghazi Hospital, Tabriz University of Medical Sciences, Tabriz, Iran.*

[7] *Applied Drug Research Center, Faculty of Pharmacy, Tabriz University of Medical Sciences, Tabriz, Iran.*

[8] *Hematology & Oncology Research Center, Faculty of Pharmacy, Tabriz University of Medical Sciences, Tabriz, Iran.*

ARTICLEINFO

Article Type:
Research Article

Article History:
Received: 29 September 2012
Accepted: 27 January 2013

Keywords:
Thalassemia
Blood Transfusion
Deferoxamine
Adverse Effects

ABSTRACT

Background: Beta-thalassemia major (β-TM) is a disorder which needs lifelong blood transfusions. Our aim was to examine the treatments side effects in thalassemic patients. ***Methods:*** 110 β-TM patients attending two centers were invited to the study. Those who consented were asked to complete a questionnaire. The questionnaire covered demographical information, used medications and their side effects. The data was analyzed using SPSS software version 14. ***Results:*** Data was collected between August 2008 and July 2009. Patients' age was 14.0±1.32 years. The duration of treatment was 11.3±7.5 years. Thalassemic patients received blood transfusions, deferoxamine and supportive medications. Number of medications, received by patients was 3.9±1.9. Hemosiderosis in heart (11%) and endocrine system (8%) were main blood transfusion side effects. A few had hepatitis B or C. ***Conclusion:*** Because of prevalence of side effects of therapies, reviewing and improving treatment protocol by designing new medicines with lower side effects and establishment of an adverse reactions team seemed necessary.

Introduction

Beta Thalassemia (β-TM) is the most common autosomal hereditary disease[1,2] and at least 200,000 patients (homozygote) are born worldwide each year and an estimated 240 million carry thalassemia genes (heterozygote).[3] Thalassemia genes are prevalent in people originating from Mediterranean, Middle East, Asian subcontinent and Southeast Asia. Iran is located in thalassemic global belt.[4] On the coast of Caspian Sea, rate of carriers is about 10%, while in the other parts of Iran; it varies between 4 and 8%.[5] Genetic consulting and screening is performed premarital and during pregnancy and therapeutic abortion is permitted for the diseased embryos, but a large number of thalassemic patients exist in Iran, causing major problem for the health care system of the country.[6] Iran has started its primary care program for thalassemia prevention in 1997[7] and number of thalassemic birth has decreased considerably ever since, but there are many thalassemic patients in Iran.[1]

Because of the nature of this disease, these patients need lifelong treatments such as blood transfusion, iron chelating agents, assistant medicines such as folic acid, calcium and vitamin K and many other medicines depending on the patients condition. As any other pharmacological therapies,[8] the medicinal therapy, especially long term ones, accompanies unwanted effects.

The aim of the present study was to investigate the side effects of β-TM's main treatments including blood transfusion and iron chelating therapy (ICT) and some

***Corresponding Author:** Siminozar Mashayekhi, Department of Clinical Pharmacy, Faculty of Pharmacy, Tabriz University of Medical Sciences, Tabriz, Iran. Tel. +98(411)3372250, Fax. +98(411)3344798, Email: mashayekhis@yahoo.co.uk

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of other pharmacological therapies received by β-TM patients.

Methods and Patients

All β-TM patients attending two hematology centers in Tabriz were invited to our study, regardless of age or duration of treatment. Patients were provided with an information sheet and those who consented, were asked to completed a questionnaire. For patients under 18 years of age, both child and his/her guardian were asked to sign the informed consent. The questionnaire was a simple one and could be answered mainly by ticking boxes. The questionnaire was completed by gathering information from patients records or direct questions from the patients or their guardians. The questionnaire consisted of three sections. In the first section, demographic information was collected. In the next section, questions were asked about type of their treatments and in the third section, and questions were asked about potential side effects of these medicines. The potential side effects were extracted from Martindale pharmacopeia[9] and British National Formulary (BNF).[10] In order to find the correct relationship between the side effects and used medications, we specifically asked if the patients experienced any of the side effects while receiving a medication. When there was possibility of different routes of administration for a medication, the route of administration was also considered in side effects enquiry.

The present study was not an interventional one and according to our university roles, ethical approval was not needed, but every effort for protecting patients right and confidentiality was applied.

SPSS software, version 14 was used for analyzing data. A descriptive analysis was carried out using proportions for categorical data, mean or median for continuous data, with standard deviation (SD).

Results

Data collection was conducted between August 2008 and July 2009 as part of a larger study in which we examined cost and adverse effect of thalassemia treatment.[11] Out of 148 patients registered to thalassemic association of Tabriz in Iran, 100 (67.6%) had regular visit to the hematology centers and accepted to participate in the study. Eighty seven questionnaires were distributed among patients in the hematology center of pediatric specialized hospital and thirteen in another center specialized for adults. Forty three percent of the subjects were female and 57% were male. The samples had a normal distribution for age; ranging from 4 months to 65 years old and with median age of 14.0 (±11.32). Both youngest and oldest patients were female. Only 10 % of subjects were married and 91% lived with their parents (Table 1).

Table 1. Scocio-demographic characteristics of patients (N=100).

Description of variables		Number
Sex	Female	43
	Male	57
Age (years)	Mean (SD)	15.6 (11.32)
	Median (min-max)	14.0 (4 month-65 years)
N of patients with	< 10 years	32
	10-15 years	31
	16-25 years	23
	26-35 years	8
	≥ 36 years	6
Marital status in over 18 years patients	Married (Female: Male)	10 (9:1)
	Single (Female: Male)	16(7:9)
Living status	Alone	0
	With parent(s) ≤18	74
	With parent(s) > 18	17
	With partner	9
Working/school status	N of patients aged 7-18 years, going to school or preschool	22
	N of patients aged >18 years,	26*
	N of over 18 patients with job/ higher education	13(10/3)
	N of over 18 patients without job	12
	N of over 18 patients having a daily task of running household	3

* One subject did not answer the job question

Up to the age of 16, the education level was consistent with the age of subjects but problem emerged for subjects 16 years old and over. None of 7 years old and older subjects were illiterate, but 46.0% had under 8 years of education, 43.2% had high school education and 10.8% had university degrees. β-TM was diagnosed in 68% at infancy (up to age of 2 years old), in 16% the diagnosis was done at the age of 3 to 5, and for the rest the age of diagnosis was over 5 years of age or during adulthood. The latest diagnosis age was for a

female subject at age of 55. Except for five subjects, the treatment started immediately after diagnosis. The gap for these 5 patients was 1 year (3 patients), 3 years (1 patient) and 10 years (1 patient). The later was the only patients whose diagnosis and initiation of treatment occurred in adulthood. The duration of treatment varied between 4 month and 32 years (11.3 ± 7.5). Forty four patients had familial history of the disease. Eight subjects had two or more siblings with β-TM, and 22 had one sibling with β-TM, while both parents of one of the subjects had β-TM.

Number of referral to the hospital was once a month for 81% of the subjects and more than once for the rest. Respondents reported having cardiac (38%), endocrine (35%), dental (7%), hepatic (7%), vision (6%), blood (6%), hearing (3%) and renal (1%) problem.

87, 12 and 1 received one, two and four packs of blood each month, respectively. Beside receiving blood transfusion each month, thalassemic patients received several other medications such as iron chelating agent. The used chelating agent included deferoxamine mesylate in 95 subjects. One patient reported receiving deferasirox for a short time in the past. No one received deferasirox or deferiprone alone or as combination therapy and five subjects (four under 5 and one 65 years old female subjects) did not receive any chelating agents. Other common medications used by these patients were vitamins and minerals supplements such as folic acid (86%), vitamin C (56%), vitamin D (8%), vitamin K (35%) or calcium (66%). They also received additional treatments such as propranolol (6%), antibiotic (8%), insulin (4%), furosemide (3%), hormonal therapies (9%), levothyroxin (3%), calcitriol (1%), zinc sulfate (3%), captopril (6%), digoxin (1%), and ribavirin (1%). Number of medications received by the patients was 3.9± 1.9 (0 - 9).

Main reported blood transfusion side effect was hemosiderosis in different organs included heart (11%), pancreas (3%), endocrine system (8%)**,** liver (4%) and thyroid glands (5%) (Table 2). A few numbers of respondents were infected with hepatitis B virus (HBV; 2%), hepatitis C virus (HCV; 3%) while no one was HIV positive. Eighty percent of patients were vaccinated against hepatitis B. 15 patients had splenectomy and there were consisted of 7 female and 8 male subjects.

After rapid intravenous injection deferoxamine mesylate, the reported side effects were as follow: urticaria (65%), flushing (59%), fever (36%), shock and hypotension (8%), itching (6%), gastrointestinal disorders (5%), backache (4%) and dysuria (1%). After intramuscular and subcutaneous injection, local side effects included: swelling (65%), erythma (64%), leg cramps (35%) and itching (6%), while general side effects included allergic skin rashes (43%), tachycardia (15%), convulsions (8%), thrombocytopenia (6%), physical growth disorder (35%), respiratory distress (5%), titnnus (4%), hearing loss (5%) and visual disturbances (11%) while no renal deficiency were seen (Table 3).

Table 2. Clinical characteristic of patients (N=100).

Description of variables		Number
Age at first β-TM diagnosis (years)	Mean (SD)	4.02 (8.6)
	Median (min-max)	1.0 (0 -55)
Duration of treatment (years)	Mean (SD)	15.4 (11.1)
	Median (min-max)	4.0 (4 month-65years)
Number of hospital visit per month	Once	81
	2	17
	4	2
Presence of disease/problems	Cardiac	38
	Endocrine	35
	Dental	7
	Hepatic	7
	Vision	6
	Blood	6
	Hearing	3
	Renal	1

Table 3. Side effects of blood transfusion and ICH in β-TM patients (N=100).

Description of variables		Number
Hemosidrosis	Heart (Female: Male)	11 (1:10)
	Pancreas (Female: Male)	3 (1:2)
	Endocrine system (Female: Male)	8 (1:7)
	Liver (Female: Male)	4 (1:3)
	Thyroid glands (Female: Male)	5 (2:3)
	Parathyroid (Female: Male)	0
Rapid IV injection deferoxamine:	Urticaria	65
	Flushing	59
	Fever	36
	Shock and hypotension	8
	Gastrointestinal disorders	5
	Backache	4
	Dysuria	1
Local side effects of IM and SC injections deferoxamine:	Swelling	65
	Erythma	64
	Leg cramps	35
	Itching	6
	Redness of injection site	
General side effects of IM and SC injections deferoxamine:	Skin rashes	43
	Tachycardia	15
	Convulsions	8
	Thrombocytopenia	6
	Physical growth disorder	35
	Respiratory distress	5
	Titnnus	4
	Hearing loss	5
	Visual disturbances	11
	Renal	0

Respiratory tract constriction (3%), depression (9%), dizziness (4%), thought disorders (3%), change in sleep pattern (9%), loss of appetite (28%), nausea (12%), vulnerability (2%), feeling of bad taste in mouth (5%),

excitement (2%), bloating (4%) were reported as folic acid side effects (Table 4).

Table 4. Side effects of other main treatments in β-TM patients (N=100).

Description of variables		Number
Acid folic supplements:	Respiratory tract constriction	3
	Depression	9
	Dizziness	4
	Thought disorders	3
	Sleep pattern changes	9
	Loss of appetite	28
	Nausea	12
	Vulnerability	2
	Feeling of bad taste in mouth	5
	Excitement	2
	Bloating	4
Vitamin C supplements:	Dizziness	11
	Impotency	11
	Choleliths	4
	Diarrhea	3
	Renal calcium oxalate stones	0
Vitamin K supplements:	Facial flushing	6
	Chest pain	3
	Hypotension	1
	Dizziness	1
	Unusual taste in mouth	1
	Cardiovascular collapse	0
	Hypersensitivity	0
	Anaphylactic shock	0
	Chest constriction	0
	Cyanosis	0
Calcium supplements:	Brodycardia	3
	Cardiac arrhythmias	13

Among patients who used vitamin C supplements, the reported side effects were dizziness and impotency (11%), choleliths (4%) or diarrhea (3%), while no formation of renal calcium oxalate stones was reported (Table 4).

Facial flushing (6%), chest pain (3%), hypotension (1%), dizziness (1%) and unusual taste in mouth (1%) were reported by vitamin K users. No cardiovascular collapse, hypersensitivity, anaphylactic shock, chest constriction and cyanosis were reported as a result of vitamin K supplementation (Table 4). Calcium supplement users reported having brodycardia (3%) and cardiac arrhythmias (13%) (Table 4).

Discussion

Patients with beta thalassemia require blood transfusions on a regular basis to keep the hemoglobin level above 10 g/dl.[12] Transfusion of red blood cells can be a life-saving therapy for thalassemic patients, but chronic transfusion has been associated with accumulation of excess iron (transfusional hemosiderosis).[13] Transfusional hemosiderosis may be clinically silent until it is far advanced[14] and there is wide spread injury to the liver, heart, and endocrine organs.[13] In order to protect patients from the consequences of iron toxicity, iron chelating agents have been introduced in clinical practice.[15] In order to achieve optimal results in these patients, great compliance to these medications is required. The compliance level correlates adversely with duration of treatment,[16,17] number of medications[18] and side effects of medications.[19-21] Low compliance could have harmful consequences on treatment results, patients' health and safety, and could increase costs of therapy.[22] Previous study by Ward and colleagues showed that about 60% of Iranian thalassemic patients received a less than 4 daily dose of desferioxamine per week[23] and another study in the same centers as current study showed that only 53% of patients received ICT once a week,[24] while in Hong Kong, Italy, Taiwan, USA, Cyprus and Greece, the administration of more than 4 days per week was reported in more than 80% of patients.[23] In the same study it was shown that compliance in Iran was lowest amongst nine other countries.

Regular visits to hospital are one way of ensuring receiving appropriate treatment and having suitable preventative measures such as echocardiography or hearing function tests. All of our subjects reported having at least one visit a month but we observed that the number of referral of pediatric patients to the hospitals for controls and treatments was significantly less than that of the other clinic. The higher number of visits among older subjects could be caused by advancing age and increase in duration of thalassemia and its treatments. These may cause further health issues and therefore more therapeutic intervention could be needed. Most of the adult subjects continued visiting pediatric hospital for their routine treatments instead or transferring to the second clinic which is a designated one for adults. The preference of the subjects for visiting pediatric hospital for treatments during adulthood could be because of the familiarity of the pediatric hospital and difficulty of adjustment to the new environment during hospital change. Hospital visits number each month was similar in male and female subjects.

Despite regular referral to the clinics, 33 organ hemosiderosis was seen in 16 subjects. Organ hemosiderosis was reported more among male subjects but the difference failed to reach a significant level. One, 4, 5 and 5 patients suffered from 4, 3, 2, and 1 type of organ hemosiderosis, respectively. We failed to show a significant relationship between age and duration of treatment with number of organ hemosiderosis. It seems that in some patients, deferoxamine was not enough for preventing organ hemosiderosis. In Iran deferoxamine is given to

thalassemic patients free of charge but patients have to pay for other ICTs. Prevention of further hemosiderosis in these patients could be achieved by prescribing 2 chelating agents, but because of the high price of extra ICTs, our patients did not have tendency towards receiving these treatments, and therefore we had no report of dual ICTs. Recent researches showed that deferiprone had a better activity on removal of iron from heart[25,26] and it seems that combining of this ICT with others could reduce hemosiderosis considerably especially the cardiac one; the most common hemosiderosis seen in our patients.

Five patients receiving deferoxamine reported no side effects while two reported having 11 of deferoxamine side effects. On average patients reported having 5.1 (±3.3) types of deferoxamine side effects.

Previous studies had shown beneficial effects of folate supplementation in thalassemic patients[27] and out of 100 patients, 86 were taking folate supplements at the time of the study. Thirty nine of these subjects reported having experienced folic acid side effects, which accounted to a total of 84 side effects. Three previously users reported having 4, 2 and 1 side effects, which could be the cause of discontinuation of the medication. The highest reported side effect was loss of appetite in more than quarter of the subjects.

Patients with hemosiderosis often develop tissue deficiency of vitamin C due to accelerated catabolism. Administration of vitamin C significantly augments iron excretion in response to deferoxamine, particularly, in patients who have vitamin C deficiency.[28] Prolonged administration of Vitamin C has caused side effects in 32 of 56 subjects who used vitamin C supplement. Main reported side effects were dizziness and impotency, while renal calculus was not reported. Gallstone was mentioned as vitamin C's side effects by 4 patients but a prior study has shown that consumption of foods containing high vitamin C could prevent gallstone disease in man.[29] Gallbladder enlargement, bile stasis, and impaired emptying of sludge may be important events in the pathogenesis of pigment gallstones in beta-thalassemic patients[30] and not as result of vitamin C consumption.

Vitamin K was used less than other vitamins and its side effects was also limited. Out of 35 subjects who used Vitamin K supplement, only 6 reported experiencing five different side effects. 24 subjects were supplemented with calcium but 16 different side effects were reported with arrhythmia as the highest reported one.

Some of the side effects reported by the patients are signs or symptoms of thalassemia itself or overlap with other medications side effects, therefore, establishing the relationship between these side effects and the disease or the medications could be difficult, but since we asked if the patients experienced the side effects after starting or at the time of using that specific medication, it is most likely the reported side effects were results of questioned medications. Examples of such symptoms are loss of appetite; which was seen in folate users or leg cramp; which was seen in deferoxamine users.

In summary, thalassemia is a costly illness which needs lifelong treatment and addition of unwanted effects of the therapy could harden the therapy and also reduce patients adherence to the therapy. Improving the patient services and treatment controls will improve these. Regular checkups such as regular echocardiography in asymptomatic patients could result in early diagnosis and better treatment of cardiac involvement.

The limitation of the study was the lack of a registry system for drug adverse effects reports in our clinics. An ADRs team including a clinical pharmacist is needed in all hospitals including thalassemia clinics in order to prevent more complications along routine treatment protocol.

Acknowledgements

The present study is the results of Pharm.D thesis of Dr Dorna Sheykhi (Thesis No 3481, registered in Faculty of Pharmacy, Tabriz University of Medical Sciences).

Conflict of Interests

There has been no Conflict of interests for authors of present article.

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