Original Article

PROSPECTS AND FUTURE OF CONSERVATIVE MANAGEMENT OF BETA THALASSEMIA MAJOR IN A DEVELOPING COUNTRY

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ABSTRACT:

Objective: To assess the efficacy, prospects and future of conservative management of beta thalassemia major patients in a developing country.

Design: Patients registered at IHBTS were studied over a period of three years. They consented to being managed on moderate transfusion regimen, aiming to maintain a pre-transfusion haemoglobin(Hgb) level of 9.0 ± 1.0g per dL. We studied their transfusion requirements, status for transfusion transmitted infections (TTIs), serum ferritin levels and complications developing as a result of iron overload.

Setting: All patients were registered and managed at the Thalassemia Centre, The Institute of Haematology & Blood Transfusion Service (IHBTS) Punjab, Lahore.

Subjects: Initially all registered patients were included in this study. Sporadic patients as well as dropouts occurring due to any reason, (patients concurrently seeking treatment at other centres as well, or complying poorly to advised chelation therapy) were excluded from the study. The data presented here conforms to a cohort of 60 regular patients who adhered best to our selection criteria.

Main Outcome Measures: 1) The study highlights the deficiencies & problems of conservative management for beta thalassemia major. 2) The major impact of our study is the message that conservative management in a poor country, like ours, is a no-win situation. 3) There is an urgent need to immediately start a prevention programme.

Results: In the younger patients, blood consumption even on the moderate transfusion regimen is 120ml/kg/year, however with ascending age the consumption increases to 240ml/kg/year. A substantive number of the patients are either Hep C (35%) or Hep B (1.7%) positive. There are no HIV positive patients. Serum ferritin levels vary widely and could not be controlled due to poor compliance to chelation. 50% of the patients developed one or other complications of iron overload. The cost of treatment depending on the quality of care, is tremendous and beyond the reach of the common man.

Conclusions: Conservative management may be the best alternative and at times the only hope for patients in our country. However, in order to decrease the disease load, steps need to be taken to introduce preventive measures.

KEY WORDS: Beta thalassemia, Conservative management, Problems, Premarital screening, Genetic counselling, Prevention programme

Pak J Med Sci April-June 2004 Vol. 20 No. 2 105-112

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* Received for publication: November 18, 2003
Accepted: January 3, 2004

INTRODUCTION

The management of thalassemia major in a developing country poses a major challenge to the health services. Lack of resources & lack of coordination hampers the treatment of this multidisciplinary problem in a variety of ways. Awareness and availability of antenatal diagnosis is limited. The decision to terminate

pregnancy is a difficult choice in our society. Premarital counselling especially amongst the uneducated is unheard of. The curative treatment of marrow transplantation is prohibitively expensive. The resultant impact of all these factors combined has led to a situation where conservative management of the child born with this disease is, perhaps not the best but, the only choice.

Beta thalassemia occurs worldwide, with a higher prevalence among Mediterranean populations, in the Middle East, in parts of India, Pakistan, and South East Asia. It is also prevalent in southern parts of former USSR and People's Republic of China. It is less common in Africa except for some pockets in the West and North Africa. It has been seen in all racial groups, even in the homozygous state, in persons of pure Anglo-Saxon stock.[1] In Pakistan, the disease is seen in almost all parts of the country. The estimated carrier status is around 5-7% meaning thereby that there are about 9.8 million carriers in the total population. Although no documented registry of thalassemic patients exists in Pakistan, the estimate is that approximately 9000 beta thalassemia children are born every year. The average life expectancy in Pakistan is 10 years and at present the disease load is of 90000 to 100000 patients throughout the country.[2]

In developing countries patients are not ideally managed on the conservative regimen due to a number of reasons.[3] It is partially the unavailability of safe blood, lack of appropriate treatment facilities, lack of diagnostic facilities, absence of antenatal screening, lack of education and poverty. Conservative management revolves round regular blood transfusions, iron chelation and treatment of complications. All efforts in this regard are over shadowed by poverty, increasing disease load and meagre resources. The result is a dismal feeling of being resigned to accept circumstances as preordained destiny by these patients or their parents. The prospects are better for some of the children due to the relentless efforts of their parents and care providers. This improves the life expectancy somewhat, though morbidity is still considerable.

A day-care Thalassemia centre in the public sector was established at the Institute of Haematology and Blood Transfusion Services, Punjab in April 2000. The aim was to alleviate the problems being faced by the patients and provide them appropriate and affordable health care under one roof. Over a period of three years, the Institute has registered 180 patients on regular basis apart from meeting the transfusion requirements of another 700 children registered elsewhere.

The main stay of conservative management is blood transfusion, iron chelation and prevention or management of complications of iron overload. The patient's haemoglobin level is generally utilized as an indicator for transfusion and blood is transfused at the lowest Hgb level at which they experience acceptable relief of symptoms. There are different transfusion regimens being followed each with their own advocates and there is considerable controversy in the choice of regimens.[4] In our centre, we adopted the moderate transfusion regimen recommended by The Thalassemia International Federation.[5] We attempted to maintain the pretranfusion Hgb at 9.0 ± 1.0 g per dL. The logic in employing this regimen is that the decreased amount of blood transfused leads to lesser iron overload and consequently lesser complications. It also decreases the chelation requirement and consequently the cost of treatment.

We have analysed our data with regard to blood consumption, patient status for TTI, iron overload and clinical assessment of complications. We have also attempted to estimate the cost of the treatment. Developing countries face a host of organizational, logistic and funding problems. The experience we acquired in this background points out multiple deficiencies in the conservative management in our country and we feel convinced that this is a no win situation.

The inertia of the health care system in introducing preventive remedial or curative measures has led to the increase in the burden of this disease. It is extremely important to

sensitise the public regarding prevention of the disease. Many countries like Cyprus and Iran have successfully controlled the incidence. Such steps will never be late in the day and are urgently needed in Pakistan, in order to alleviate the dismal psychological and socio-economic burden of this disease.

Large scale population screening is neither possible nor feasible; a pilot study in some countries has already failed.[6] Efforts, therefore, need to be directed towards pre-natal screening for detection of carrier status. This entails screening of expectant mothers at their first prenatal visit; the father is screened in cases in which the mother is detected to be a carrier. Genetic counselling and antenatal diagnosis with the choice of therapeutic abortion is offered to the couple if they are both carriers.

These measures will help curtail the disease, while children already born can continue to be managed either conservatively or, if they can afford, by curative treatment.

PATIENTS AND METHODS

We conducted this study on a cohort of thalassemic children being managed conservatively at the Institute of Haematology & Blood Transfusion Service, Punjab, Lahore. We studied the blood consumption, patient status for the major transfusion transmitted viral infections(HIV,HBV & HCV), serum ferritin levels and clinical assessment of associated iron overload.

We have also estimated the approximate cost of conservative management of thalassemic children in order to give an idea of the economic magnitude of the problem. The cost of transfusion given here does not include cost of blood as it was all obtained through non-remunerated voluntary donation or replacement donation.

Sixty patients divided into three age groups of 2-5 ,6-10 and 11-17 years were selected from the children registered for conservative management at IHBTS and followed for a period of three years. To be included in the study, the patients had to meet the following criteria:

1. *Only beta thalassemia major patients were included.*
2. *Only those patients who consented to being managed on moderate transfusion regimen, which aimed at maintaining a pretransfusion haemoglobin at 9.0 ± 1.0 g/dl were studied.*
3. *The patients had to restrict themselves to receiving transfusion only at IHBTS & iron chelation at IHBTS or at home/family care provider.*
4. *Maintain regularity in order to maintain pretransfusion haemoglobin of 9.0 ± 1.0 g/dl.*

Blood transfusion was carried out at IHBTS by providing packed red cells at 10-20 ml/kg body weight of the child. Transfusion was started in these patients after the age of one year. Most of our patients were transfused every four weeks. Attempts were made to maintain the pre–transfusion haemoglobin of 9.0 ± 1.0 g/dl by decreasing the interval of transfusion. Antibody screening for allosensitization could not be carried out. All patients were screened for HIV, HBV & HCV at the time of registration and periodically thereafter after every three months. All HBV negative patients were advised vaccination. All blood transfused was screened for HIV, HBV & HCV. Sporadic dropouts occurring due to various reasons were excluded from the study. Blood consumption per year was calculated (assuming a null RBC production) by multiplying the volume transfused by the number of transfusions given over this period divided by the weight of the child in kilograms. This was averaged for the three age groups studied. Only three out of 8 patients in the age group 11-17 years underwent splenectomy.

Chelation therapy was carried out either at IHBTS simultaneously by bolus infusion, when the patients were being transfused, at a dose of 25-45mg/kg/day, with a single maximum dose of 1g. The patients were advised to follow up with chelation therapy at home by daily infusions or abdominal administration by pump. Compliance to advised regimen could not be assured.

Serum ferritin was evaluated regularly and average serum levels were calculated for each group. As the levels varied widely, we have attempted to present these in three proportions of measurement of serum ferritin levels in the different age groups studied.

Over this period, patients were periodically evaluated for development of complications related to iron overload (diabetes mellitus over 13 years of age), heart disease, absence or delay in attainment of puberty, spleen size and skeletal abnormalities.

RESULTS

The data with regard to a cohort of 60 thalassemic patients receiving conservative management at the Institute of Haematology & Blood Transfusion Service, Punjab divided into three age groups has been analysed and is presented below.

On a pretransfusion haemoglobin of 9.0 ± 1.0 g/dl, the blood consumption in the different groups is given in Table-1. The need for transfusion was after every four weeks in the two younger age groups and at times rose to every fortnight in the third group, especially in those patients who had not undergone splenectomy.

Table-I also shows that 21/60 (35%) of the patients are HCV positive; and 1/60(1.7%) is HBV positive. There are no HIV positive patients in the study. The largest number of HCV positive patients and the only HBV positive patient are aged 6-10 years (11/60 or 18.3%) while 07 patients (11.7%), in the age group11-17 years, are also HCV positive. It can also, be seen from this table that the largest number of patients are in the ages of 2-5 years. It will be noticed that the number of patients are decreasing with ascending age. The longest surviving patient is aged 17 years.

Table-II shows the average serum ferritin levels as well as the proportion of measurements in the three age groups studied. It can be seen that in the 2-5 years age group the average serum ferritin level is lower and the serum ferritin level increases with ascending age as does the blood consumption. This reflects on failure to comply with chelation therapy. As the need

Table-I: Blood consumption and TTI status of thalassemic patients studied

Age groups in years	*No. of Patients*	*Average weight(Kgs)*	*Average red cells consumed in ml/kg/year**	*No of patients positive for TTIs at initial registration*		
				HIV	*HBV*	*HCV*
2-5	29	14.3	120.0	Nil	Nil	03
6-10	23	22.4	180.0	Nil	01	11
11-17	08	35.4	240.0	Nil	Nil	07

* mls of blood transfused X number of transfusions / weight in kgs / period in years.

Table-II: Serum ferritin levels in the study group

Age groups in years	*No. of Patients*	*Av. serum Ferritin levels ug/dl*	*Proportion of measurements*		
			<1500	*<2500*	*>3500*
2-5	29	1849	22	04	03
6-10	23	2763	Nil	17	06
11-17	08	3972	Nil	Nil	08

Table-III: Clinical assessment of patients with regard to development of complications

Age groups in years	*No. of patients*	*Diabetes Mellitus*	*Heart disease*	*Marked Splenomegaly*	*Skeletal abnormalities*	*Delayed onset of puberty*	*%age complications*
2-5	29	Nil	Nil	Nil	01	—	3.4
6-10	23	Nil	Nil	07	11	—	78.3
11-17	08	01	01	05	02	02	100.0
2-17	60	01	01	12	14	02	50.0

Table-IV: Cost of conservative management on moderate regimen

Age groups in year	*Cost of Transfusion per child per year in Rs.**	*Cost of chelation per child per year in Rs.***	*Total cost per child Approx. per year in Rs.**
2-5	12000	5740	17740
6-10	18790	12562	31352
11-17	37500	25566	63066

* calculated on the basis of blood consumption

** calculated on chelation requirement in the dose of 25-45mg / kg / day and cheapest available brand.

for desferroxamine rises, the increasing costs lead to large number of drop-outs as many patients cannot afford chelation therapy and become erratic in seeking treatment. As estimation of urinary excretion of iron of only a few patients were available, we have not taken it into account in assessing the effectiveness of chelation therapy.

Table-III shows the percentage of complications that the patients developed in the different age groups as well as the overall number and percentage of patients who developed complications. 78.3 % of patients aged 6-10 years showed marked splenomegaly or skeletal abnormalities like frontal bossing, short stature or malar prominence. In the age group 11-17 years 100 % showed one or multiple complications. Overall 50.0% of the patients had developed complications. Apart from these complications, almost all patients showed some level of growth retardation as is evident from their average weights.

Table-IV highlights the cost of conservative management on moderate regimen. It is quite understandable given the poverty in our country that this cannot be strictly followed and the majority of the patients succumb either to the economic effect or to its toxicity with ascending age.

DISCUSSION

Blood consumption:

Long term transfusion support is the backbone of conservative management in beta thalassemia major patients. These patients require regular transfusions to alleviate anaemia. The haemoglobin level is utilized as an indicator for transfusion; as the haemoglobin falls patients experience discomfort and attempts are made to elevate the haemoglobin level through transfusion to provide acceptable relief of symptoms. It seems logical and predictable that a lower endpoint target haemoglobin will allow a reduced use of blood; in thalassemia, especially in our country, the situation is not that simplistic. The objective in employing the moderate transfusion regimen is to keep the blood consumption to a minimum in order to curtail the iron overload. In the different age groups, the blood consumption varied between

120ml/kg/year to 240ml/kg/year, which is far higher than that reported by other studies[4].

This could be due to a number of factors that affect the intervals of transfusion. Firstly, though maximum efforts are made to provide freshest possible packed cells to these patients, at times this becomes difficult due to the large number of patients and fewer donations. Due to cost constraints, we could not carry out antibody screening although ABO and rhesus compatible blood was provided. Regularly transfused patients develop red cell antibodies (Rhesus, Kell or others) that also reduce red cell survival and increase the demand for transfusions[7]. Blood bags were not irradiated nor were blood filters utilized; though, at times washed red cells were provided.

Whenever the blood consumption rises to 200ml/kg/year to 250ml/kg/year, splenectomy is advisable as this markedly reduces the demand for transfusions. Patients in our set up are reluctant to undergo splenectomy. In spite of repeated cajoling & counselling we could convince only three patients who underwent surgery. A large spleen with ascending age dramatically affects the red cell transfusion requirements and splenectomy helps to decrease it. Whether this reluctance is due to fear or monetary restraints or just being resigned to accept fate over the years, nonetheless it poses a great problem in the long run.

Ignorance and desperation on the part of the patients or their parents coupled with prevalent malpractices in our society has unfortunately affected the safety of these children in so far as transfusion transmitted infections are concerned. Attention focussed on the use 'safe blood' has to a large extent conveyed a good message with the result that at least now blood is being screened, by and large, for the three major viral TTIs. Many other studies have also reported high prevalence of TTIs in thalassemic patients[8,9].

However it is not only screening of blood but a number of other factors which are involved in the transmission of these diseases especially to thalassemics. One important factor is the use or re-use of disposables by unscrupulous elements in the society when these patients seek chelation therapy. We have found that 36.7% of our patients are Hep C or Hep B positive. Fortunately, there are no HIV positive patients. Most of these patients, especially in the older age group were already positive at the time of registration when our centre started working three years ago. Some of our younger patients were negative at the time of registration but converted later. We traced the donors through lookback techniques and found none to be positive on re-testing. We feel that most probably these children became positive as a result of use of infected or improperly sterilized disposables at home or by health care providers.

Hepatitis B vaccination in thalassemics is another important area. Parents are however, reluctant to spend money on this aspect; perhaps because they have not been sensitised enough to appreciate its value. One of the major reasons is of course financial constraint. The parents feel that the costs should be borne by the public sector. Although this would be the ideal scenario, yet at the present time the government can do little, apart from providing counselling. It is pertinent to point out here that screening in the public sector blood banks in Punjab for HIV & HBV was started in 1995 and for HCV in 2000. Recently, the government has also included hepatitis B vaccination in the EPI schedule and it will take some time to show results. The majority of patients included in this study however have been vaccinated. We have only one patient (1.7%) who is hepatitis B positive. He has been positive ever since he registered with us.

It will be noticed that the number of older patients is less, while the number of younger patients is increasing. This could be due to increasing disease load and shortened life expectancy. The oldest patient in this study is aged 17 years. We could not evaluate the life expectancy as some patients dropped out and re-appeared later, becoming erratic or started seeking treatment elsewhere. However, in Pakistan it is generally believed to be around 10 years[2].

Iron chelation:

Our patients even in the younger age group showed markedly high serum ferritin levels. In the 2-5 years age group the average serum ferritin level is 1849ug/dl, this rises on the average to 3972 ug/dl in the older patients with higher blood consumption. At the Institute we infused 1g of desferroxamine for each transfusion and advised home chelation at 25-45mg/kg body weight depending on serum ferritin level. Table-2 also shows the variability in the proportion of measurements of serum ferritin in the different groups studied. Clearly, the serum ferritin level could not be controlled as only few patients fully complied with recommended regimen. The major reasons for poor compliance to chelation therapy are that it is painful, costly, burdensome and the method of administration is time consuming. Chelation therapy is perhaps the most deficient area of thalasemia management.

Iron chelation is usually started when serum ferritin level exceeds 1000ug/dl. Only the injectable preparation is available in Pakistan. There are two manufacturing sources with prices of both varying in the ratio of 10:1. The cost of the drug, in most of the patients, leads to poor compliance and failure to maintain serum ferritin levels within acceptable range. The oral preparation, available in some countries, might help change this scenario, for some of the patients, if introduced in Pakistan, although concerns have been raised about its side effects.

Development of complications:

Thalassemic patients invariably develop complications mostly attributable to iron overload. 50.0% of our total patients developed complications. In the older age groups all patients(100%) had developed one or more complications. 23.3% showed skeletal abnormalities, 1.6% developed diabetes mellitus, 1.6% developed heart disease 20% showed marked splenomegaly while 3.3% showed delayed sexual maturation. Our patients have developed far more complications than reported literature[7].

Cost of treatment:

Table-4 highlights the economic aspect of this disease. It can easily be appreciated that it is almost impossible for an average person to afford this amount which has been estimated very conservatively. If we target ideal treatment, the cost will increase two fold if not more. Curative treatment of stem cell or allogenic marrow transplantation is tremendously expensive and is beyond the reach of almost all our patients.

Prospects & Future:

To say the least, the prospect for patients on conservative management is very bleak. Even the diagnosis at times is doubtful and an over-enthusiastic approach has made many intermedia cases transfusion dependent; appropriate timely decision to start conservative treatment, and proper guidelines for conservative management therefore need to be disseminated widely. At the same time, impetus on prevention and development of more centres for curative treatment should be stressed. Without a change in the proper direction, these patients will continue to suffer a slow & agonising journey to death.

CONCLUSIONS

These are some of the bitter truths about thalassemia management in Pakistan. We feel convinced that this is a no win situation as it prolongs the agony and pain of both the patient and the family. It is our opinion that the time has arrived when concerted efforts need to be put in to eradicate or at least reduce the disease load through a planned prevention programme. This programme should aim at sensitising the public to voluntarily seek premarital screening & genetic counselling. Centres need to be set up for prenatal diagnosis and appropriate prevention as well as for curative treatment.

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