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Benefits of Pharmaceutical Care in Thalassemia

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Abstract

This study was aimed to describe burden of Thalassemia treatment on population, patient's compliance for treatment and determining whether the pharmaceutical care affects quality and life expectancy of patients. A comparative retrospective study design was followed. All the patients were divided into two groups, one group receiving pharmaceutical care like blood transfusion, Chelation therapy and financial aid for treatment while the other group unable to enjoy this pharmaceutical care due to any reason. 50 patients were evaluated and found that B.Thalassemia is one of the major genetic problems in Pakistan affecting both sexes irrespective of literacy rate. 96% patients reported an overall positive opinion about the quality of care provided by proper regimen of blood transfusion with Chelation therapy. Compliance for treatment in poor families was only seen when patients accessed to Baitul Maal or NGOs but not all patients could access them. Overall treatment is much expensive so patient's family can not follow the regimen. Benefits of pharmaceutical-care were only seen among financially settled group of patients. Blood transfusion and Chelation therapy is the only care to offset complications but it is only possible when patients can afford treatment expenses. Government should provide sufficient funds to needy people so that they can enjoy benefits of pharmaceutical-care. The government, NGOs and media should come together on a single platform and work to fight and reduce the burden of disease in the country.

Key Words: - Beta-Thalassemia major, Genetic counseling, Pharmaceutical care, Quality of life.

INTRODUCTION TO THALASSEMIA

THALASSEMIA is an inherited autosomal recessive blood disease. Due to genetic defects there is reduced rate of synthesis of one of the globulin chains that make up hemoglobin. Normal hemoglobin is composed of two chains alpha and beta chains. In thalassemia patients there is deficiency of one of these chains. In alpha thalassemia production of alpha globins chains is affected, whereas in beta thalassemia production of beta chains is affected [1]

Beta thalassemia was originally named as Cooley's anemia, is an inherited blood disorder. It is characterized by reduced synthesis of the hemoglobin subunit beta globin protein[12] that results in microcytic hypo chromic anemia, an abnormal peripheral blood smear with nucleated red blood cells, and reduced amounts of hemoglobin A(Hb A) on hemoglobin analysis.[2,3]

Three clinical and hematological conditions of increasing severity are recognized, i.e., the beta-thalassemia carrier state, thalassemia intermedia, and thalassemia major. The beta-thalassemia carrier state, which results from heterozygosity for beta-thalassemia, is clinically asymptomatic and is defined by specific hematological features. Thalassemia major is a severe transfusion-dependent anemia. Thalassemia intermedia comprehend a clinically and genotypically very heterogeneous group of thalassemia-like disorders, ranging in severity from the asymptomatic carrier state to the severe transfusion-dependent type. The clinical severity of beta-thalassemia is related to the extent of imbalance between the alpha and non alpha globin chains [4]

Beta thalassemia major causes hemolytic anemia, poor growth, severe anemia Poor appetite, Dark urine, Slowed growth, Delayed puberty, Jaundice, Enlarged spleen, liver, heart and skeletal abnormalities during infancy. Affected children will require regular lifelong blood transfusions. Beta thalassemia intermedia are less severe than beta thalassemia major and may require episodic blood transfusions.

There are different tests for Thalassemia. The diagnosis of β-thalassemia relies on measuring red blood cell indices that reveal microcytic hypo chromic anemia, nucleated red blood cells on peripheral blood smear, hemoglobin analysis that reveals decreased amounts of HbA and increased amounts of hemoglobin F (HbF) after age 12 months, and the clinical

severity of anemia. Molecular genetic testing of the gene encoding the hemoglobin subunit beta (HBB) is available in clinical laboratories and may be useful for predicting the clinical phenotype in some cases as well as presymptomatic diagnosis of at-risk family members and prenatal diagnosis. [2]. This include Chronic Villus sampling and Amniocentesis. In Pakistan most commonly used techniques are CBC testing PCR and Hb that is specifically used for screening of this disease.

Treatments for Thalassemia depend on the type and severity of the disorder. People who are carriers or who have alpha or beta Thalassemia trait have mild or no symptoms. They need little or no treatment. Doctors use three standard treatments for moderate and severe forms. These include *blood transfusions, iron Chelation therapy, and folic acid supplements, the judicious use of spleenectomy*.

In Thalassemia major regular transfusions correct the anemia, suppress erythropoiesis, and inhibit increased gastrointestinal absorption of iron. In Thalassemia intermedia symptomatic therapy based on spleenectomy in most patients, sporadic red cell transfusions in some, and folic acid supplementation is recommended. [29]

Hydroxyurea (HU) is an antineoplastic agent that enhances fetal hemoglobin. These clinical responses are expected to be more in thalassemia intermedia (TI) patients because of lesser alpha/beta globin imbalance. HU therapy in TI patients has significant effects on increasing Hb levels that can cause reducing blood transfusion dependency and transfusion free in some patients, decreasing skeletal deformities and spleenomegaly and increasing energy state. So HU therapy could be a useful alternative to blood transfusion in some TI patients. [5]

Other treatments have been developed or are being tested, but they're used much less often. *Gene therapy* - Researchers are trying to figure out how to correct or modify flawed genes to decrease or cure different types of Thalassemia. *Hemoglobin F therapy* - researchers have tried increasing the level of this type of hemoglobin but it has not had much effect on Thalassemia. *Protein therapy* - A protein (AHSP) has been discovered that helps regulate the amount of alpha protein in red blood cells. Researchers are now looking at using AHSP as a thalassemia treatment.

Regular blood transfusions in thalassemia and other chronic refractory anemia's can result in excessive iron deposition in tissues and organs. This excess iron is toxic, resulting in tissue and organ damage and unless it is removed it can be fatal to those chronically transfused. Iron removal in transfusional iron overload is achieved using chelation therapy with the chelating drugs deferoxamine (DF) and deferipron Effective chelation therapy in chronically transfused patients can only be achieved if iron chelator can remove sufficient amounts of iron, equivalent to those accumulated in the body from transfusions, maintaining body iron load at a non-toxic level. In order to maintain a negative iron balance, both chelating drugs have to be administered almost daily and at high doses. This form of administration also requires that a chelator has low toxicity, good compliance and low cost. DF has been a life-saving drug for thousands of patients in the last 40 years. It is mostly administered by subcutaneous infusion (40-60 mg/kg, 8-12 h, 5 days per week), is effective in iron removal and has low toxicity. However, less than 10% of the patients requiring iron chelation therapy worldwide are able to receive DF because of its high cost, low compliance and in some cases toxicity [6]

According to another study the prognosis of patients with homozygous β-thalassemia (thalassemia major) has been improved by transfusion and iron-Chelation therapy. Regular transfusions and Chelation therapy with the intention to keep serum ferritin concentrations below 2500 ng per milliliter is found to be very effective [7]

With the emergence of oral Chelation therapy a tremendous change in the prognosis of all transfusional iron-loaded patients has been observed. Oral deferipron induces sustained reduction in body iron to concentration compatible with avoidance of complications

from iron overload. However risk of agranulocytosis associated with deferipron may restrict its administration to patients who are unable or unwilling to use deferoxamine [8]
At doses of 50-120 mg/kg/day. It increases urinary iron excretion, decreases serum ferritin levels and reduces liver iron in the majority of chronically transfused iron-loaded patients. Hepatic iron concentration decreased from 14.6 mg/g dry weight of liver before L1 therapy to 1.9 mg/g liver after 9 months of therapy [9]
Despite earlier concerns of possible increased risk of toxicity, all the toxic side effects of L1 are currently considered reversible, controllable and manageable. These include agranulocytosis (0.6%), musculoskeletal and joint pains (15%), gastrointestinal complaints (6%) and zinc deficiency (1%). The incidence of these toxic side effects could in general be reduced by using lower doses of L1 or combination therapy with DF. Combination therapy could also benefit patients experiencing toxicity with DF and those not responding to either chelator alone. (16)Another very important efficacious treatment is the use of once daily oral deferasirox in iron overloaded patients not showing response to Chelation with prior deferoxamine and deferipron.
Although transfusion improves patient's quality of life but it increases the risk of iron burden so concurrent Chelation therapy is done. Iron Chelation therapy improves survival in thalassemia patients but its beneficial effects on survival remain uncertain. According to a research median overall survival was 53 months and 124 months in non-chelated and in chelated patients respectively. [10]
The early use of deferoxamine in an amount proportional to the transfusional iron load reduces the body iron burden and helps protect against diabetes mellitus, cardiac disease, and early death in patients with thalassemia major. [11]
The beneficial effects of deferoxamine therapy on survival and cardiac disease in patients with thalassemia has been observed with reduction in morbidity and mortality examined periods of follow-up too short to provide definitive conclusions regarding the long-term benefits of deferoxamine on cardiac disease.[12,13,14,15]
Reports of reduction in liver iron concentration, improvement in laboratory abnormalities of liver function, and arrest of hepatic fibrosis provide evidence for the beneficial effects of subcutaneous deferoxamine on iron loading within the liver. High-dose IV deferoxamine has been reported to achieve the same benefits in patients with massively elevated hepatic iron concentrations. [16, 17, 18]
Reduction in the risk of diabetes mellitus and glucose intolerance has been reported in patients who used more deferoxamine in relationship to their transfusional iron load, compared to a group who had begun deferoxamine at a more advanced age and had administered therapy less intensively [19]
Iron-induced cardiac disease remains the main cause of death in patients with thalassemia major, despite Chelation therapy with deferoxamine. A study has been suggested that long-term therapy with deferipron provides a greater cardio-protective effect against the toxicity of iron overload than does subcutaneous deferoxamine. [20]
Oral deferasirox therapy is found to increase patient satisfaction and convenience to take medicine. It also lowers impact on daily activities. Oral deferasirox help improve adherence to lifelong Iron Chelation therapy in overloaded Thalassemic patients [11]
However these therapies are also associated with complications especially ocular complications. Deferoxamine is found to be protective for retinal pigment epithelium mottling but associated with increased occurrence of lenticular opacities while RPE degeneration is correlated with use of deferipron. Regular ocular examination can aid in preventing, delaying and ameliorating the complications.
A structured pharmaceutical care program with continuous education from pharmacists on disease control, its treatment, lifestyle changes (that could help control symptoms) and dietary modification improves patient's quality of life, their clinical outcomes and patient's compliance with drug therapy.

Pharmacists are integral part of pharmaceutical care practice. Clinical pharmacy services are defined as direct patient care services provided by pharmacists. Their involvement in providing clinical care involves reduced mortality rate, improved clinical and changed outcomes and fewer disease complications. [21] Pharmacists can impart their role by providing the patients and their relatives with in depth information on disease and on drug dosage, preparations, method of administration, stability, storage, side effects and precautions etc. This type of pharmaceutical care helps patients to receive their proper treatment without need for frequent hospitalization. This would therefore reduce costs of treatment [21, 22]

AIM:-

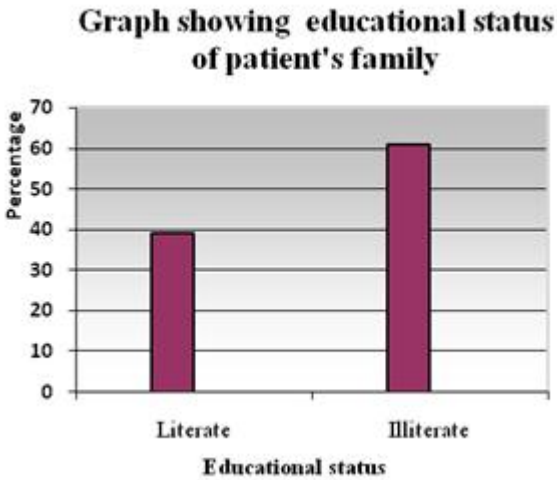
- To evaluate incidence of Thalassemia.
- To ascertain common complications of treatment and their management.
- To describe burden of Thalassemia treatment on population.
- Patient's compliance for treatment.
- Determining whether the pharmaceutical care offsets complications of treatment and affects quality and life expectancy of patients.
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MATERIALS AND METHODS

1. Patients/ Subjects
   Inclusion criteria
   In this study only Beta thalassemia patients suffering from Beta thalassemia major and intermedia of age up to 30 years are selected that are transfusion dependent.
   Patients of each sex and belonging to different socioeconomical status have been observed in this study.
   Exclusion criteria
   Patients of thalassemia minor and patients suffered from Anemic are excluded from this study.
2. Sample Size
   We have gathered data of almost 50-60 patients from different hospitals.
3. Study Setting
   Data was collected from
   a. Thalassemia center of Gangaram hospital
   b. Children hospital
4. Study Design
   A comparative study design has been followed. All the patients were divided into two groups, one of them receiving all pharmaceutical care like blood transfusion, Chelation therapy and financial aid for their proper treatment while the other group was unable to enjoy this pharmaceutical care due to any reason.
   During a period of 15 days we interview different patients at different times of the day.
5. Study Tool
   A questionnaire was developed that evaluate sociodemographic details of such as age, gender, marital status etc. Some questions are related to patient's awareness about diseases; disease history, recent medications, past medical history, medicine side effects, benefits of pharmaceutical care in terms of quality of life etc were also mentioned.

RESULTS:

Of 50 Thalassemic patients 53% were males and 47% females showing both sexes are equally affected by this genetic disorder. [23] (Figure 1)

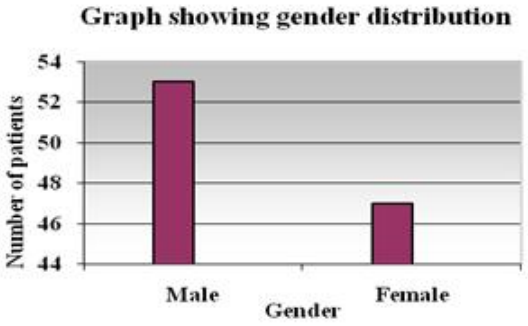


(Figure 1)

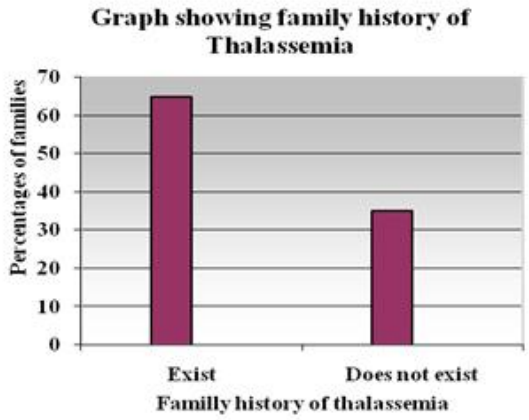
Of 50 patients 61% belonged to illiterate families while 39 % were from literate families. (Figure 2)

65% of the patients belonged to families having prior history of thalassemia. It is a genetic defect transferred from one generation to the next. (Figure 3)

96% patients were of Thalassemia major while only 4 % patients were of Thalassemia intermedia. Prevalence of Thalassemia major in Pakistan is greater than intermedia. (Figure 4)



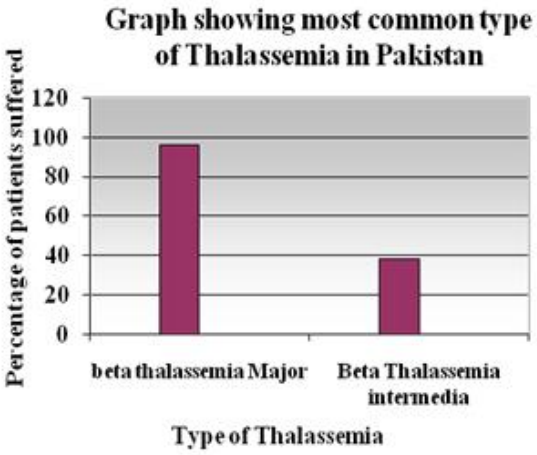
(Figure 2)



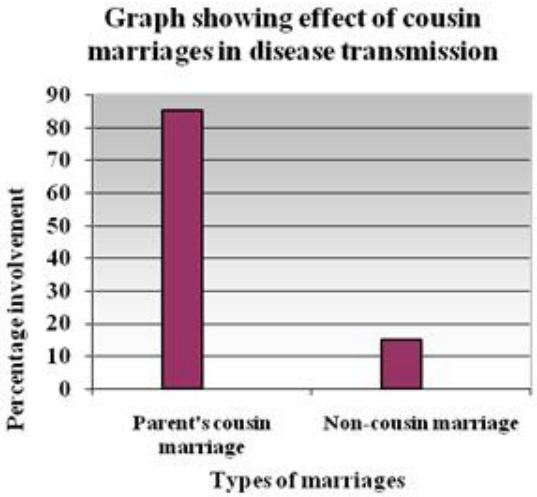
(Figure 3)

85 % cases of cousin marriages were found to be a cause of disease transfer.It shows that there is a definite link of consanguinity for transferring of this disease. Incidence is found to be greatest in case of first cousin marriage. [24] (Figure 5)

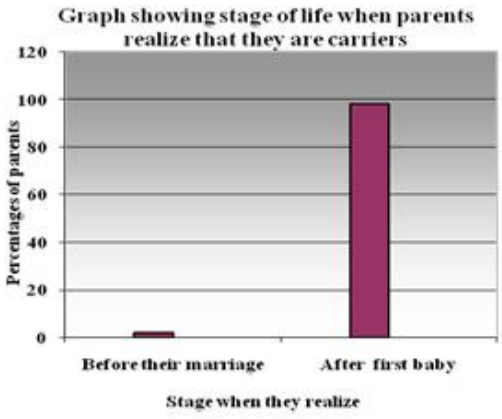
Of 98% of the cases, parents after their first baby could realize that they are Thalassemic carriers irrespective of their literacy rate. While only 2 % cases were observed to have prior knowledge of being carrier. (Figure 6)



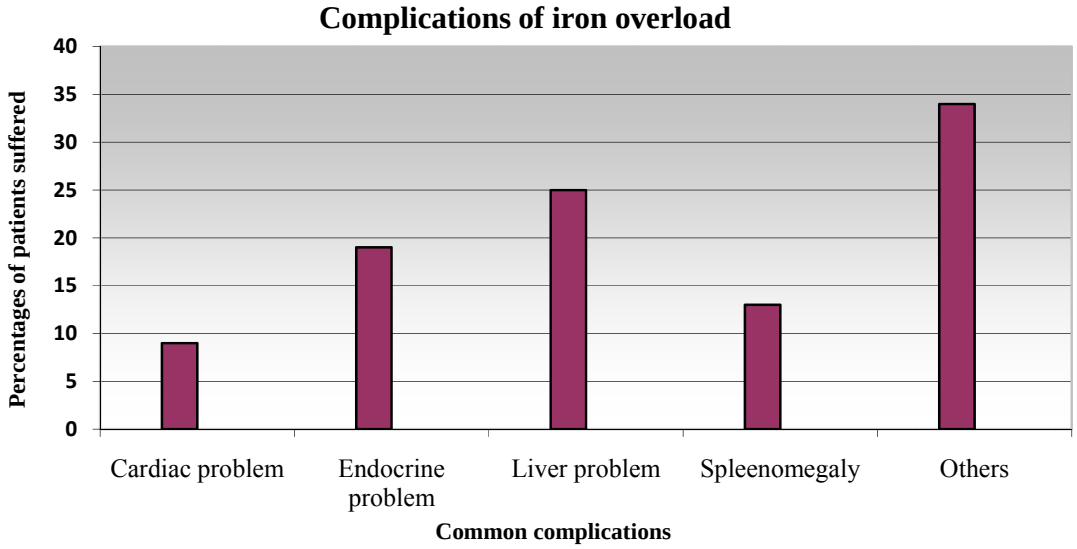
(Figure 4)



(Figure 5)

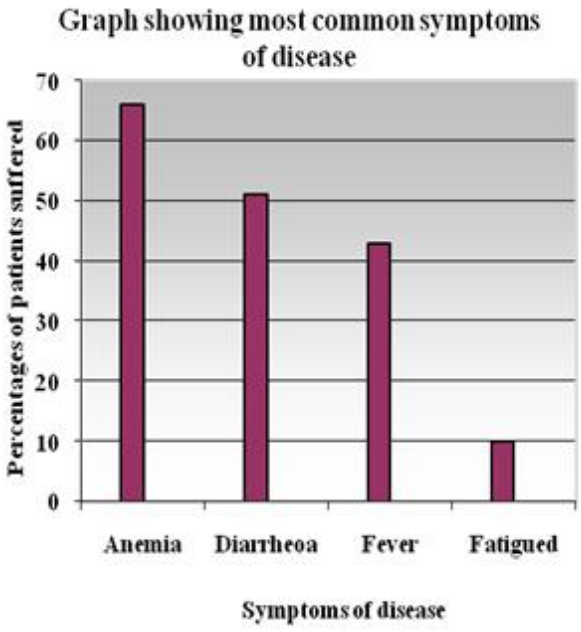


(Figure 6)



(Figure 9)

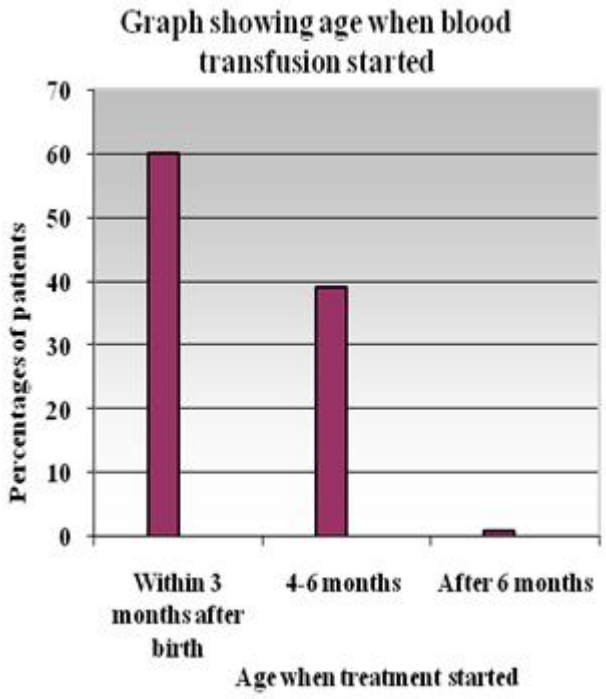
Initial symptoms observed among patients are Anemia (66%), Diarrhea (51%) others include Fever 43%, and Fatigue10 %.(Figure 7)



(Figure 7)

Among 60% of the patients, blood transfusion, as first intervention, was observed to be started within 3 months after birth while among 39% of the patients, transfusion was started within 4-6 months and only 1 % cases were observed when transfusion started after 6 month. (Figure 8)

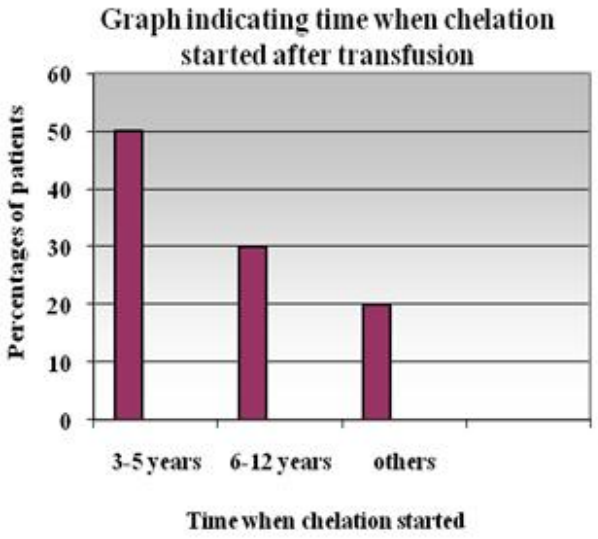
The most commonly observed complaint among these patients taking regular blood transfusion was liver problem (25%), Endocrine abnormalities (19%), Cardiac problems (9%) while others less frequently encountered symptoms were kidney abnormalities and bone deformations etc.(Figure 9)



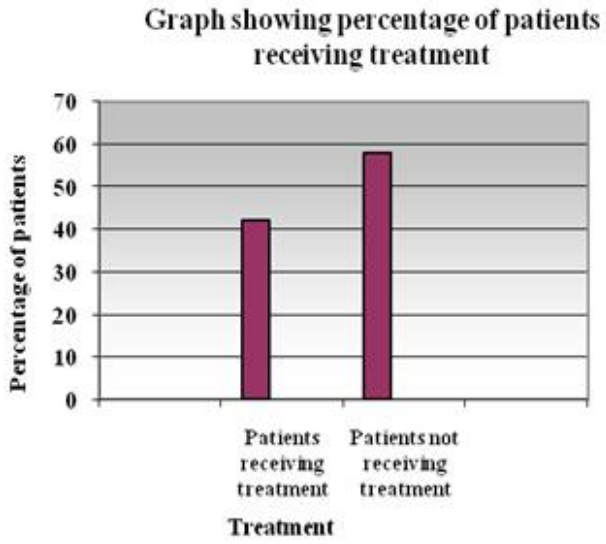
(Figure 8)

Of 50 patients, chelation therapy was started in 40% cases after 3-4 years of transfusion. (Figure 10)

Of 50 patients 42 % were able to afford proper pharmaceutical care (blood transfusion and appropriate regimen of chelation therapy) [Figure 11]

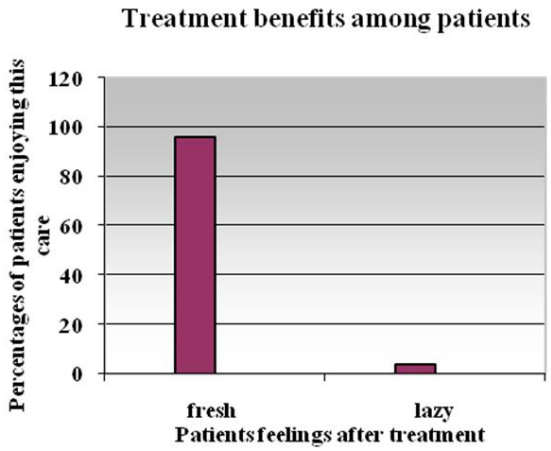


(Figure 10)



(Figure 11)

Of 42 % patients enjoying pharmaceutical care 96 % patients were seemed to experience fresh feeling and they really enjoyed daily activities as normal persons. (Figure 12)



(Figure 12)

DISCUSSION

Thalassemia, an autosomal recessive disorder is also known as Mediterranean anemia.

Of 50 patients, both sexes were seen to be equally affected. Broadly there is no area specification but fatal disease is more common in areas where cousin marriages are a trend for example tribal areas of FATA, Baluchistan, Waziristan and sindh.

85% cases were seen in which cousin marriages were a big reason for Thalassemia transmission. 96% patients were found suffering from Thalassemia major. This chronic disease starts showing the initial symptoms three months after birth. Initial symptoms observed were Diarrhea (51%), fever (43%) and mostly anemia (66%) depending upon the severity of affected Hb change. In most of the cases (60%) transfusion was started within three months after birth but in others late start of transfusion was due to economical reason. Complication of blood transfusion found in patients include Spleenomegaly 13%, renal 8%, cardiac 6%, endocrine abnormalities e.g. Menstrual problem 9%, and liver 25%.Complications of Thalassemia are mainly due to iron overload, excess iron deposits as Hemosidrin and ferritin in the liver, spleen, endocrine organs and myocardium. The accumulation of toxic quantities of iron causes endocrine, cardiac and liver disorders. However new regimen of blood transfusion with

Chelation therapy proves to be very helpful not only delaying these abnormalities but also avoid their occurrence. Chelation therapy, which usually have to be started within 3-4 years after first blood transfusion but due to crippled healthcare system and poor economical status of patients it was also seen to be started very late in many patients. Benefits of pharmaceutical care (Blood transfusion and proper regimen of chelation therapy) were mostly observed among financially stable (43%) families that were in better position to purchase medicines for expensive chelation therapy. Of those receiving proper treatment 96% patients were found to be as active and fresh as healthy individuals.

CONCLUSION:

B-thalassemia major is a serious genetic disorder which results in a considerable increase in both acute and chronic morbidity and mortality. Thalassemic patients cannot be cured but they are just provided with proper pharmaceutical care in terms of Blood transfusion and proper regimen of chelation therapy. It improves patient's life expectancy and quality as they feel better like healthy individuals. But the treatment is too expensive to afford by every person especially in this era of inflation. It is the duty of government, NGOs and the rich to help needy people through funds and donations so that they can also enjoy the benefits of pharmaceutical care. The government, NGOs and media should work together to reduce the burden of disease in the country and to eradicate it from the world.

SUGGESTIONS

DIETRY MANAGEMENT:-

A person who has Thalassemia must stick to a specific diet. Food that is considered healthy for most people can cause serious complications for Thalassemic patients.

1. Avoid food containing iron. Proteins higher in iron content should be avoided e.g. liver, Oysters, Pork and Beans. Grains rich in iron e.g. peanut butter, infant's cereal and cream of wheat should not be taken. Fruits and vegetable containing iron should be avoided e.g. Peas, green leafy vegetables, spinach and water melon. Tea can inhibit iron absorption.
2. Eat plenty of food that contains Calcium. This is extremely important for keeping the bones strong and health. Dairy products are a good source. An added benefit is that they reduce the body's ability to absorb iron.
3. Include Vitamin-D in diet; it is required for calcium absorption and deposition of Ca in bones. It is present in eggs, dairy products and Fish.
4. Vitamin E and C should be taken by the patients as they have antioxidant properties and lowers LDL oxidation.

SOCIAL CHALLENGES FACED BY PATIENT AND HIS FAMILY

Chronic illness in child challenges him and his family at three levels.

1. The Cognitive level:
   The family has to learn about the cause of illness, its course, prognosis, likely complications and the treatment.
2. Emotional level:
   The family has to work through anxiety and uncertainty caused by illness, as well as their fears that the health of seek man may further deteriorate and he/she will die. Normally the illness is experienced by the parents as a Narcissistic trauma which concerns their creativity and potency and this affects their emotional life and their behavior towards the seek child.
3. The level of every day routine:
   The normal way of life and routine of family are affected by events such as visits to doctor, medical examinations and interventions, admission to hospital and events and practices which have to be incorporated into the daily routine and life of the family.

PREVENTION

Prevention of Thalassemia seems to be the best and necessary option when treatment is difficult, expensive and painstaking. With effective preventive strategies we can overcome the problem.

Screening

Everyone should get screened for Thalassemia. This is the basic step in detecting carriers of the disease. Screening at school level should be initiated.

Pre-marriage tests

The spread of the deadly dieses can be stopped by having medical tests of bride and groom.

Avoid marriage between two minors

One in every fourth child will be born with Thalassemia major in case of two minor spouses. So just avoid these inter marriages.

Diagnosis before birth

The risk of giving birth to Thalassemia major is eliminated with a diagnosis before birth.

A role of media and government

- National plan to provide knowledge of Thalassemia to hospital administrator in order to recognize problem.
- Establish responsible team leader and program evaluation.
- Establish a referral center in each region which provides a complete cycle of services.
- Use easy to understand media and language for communication and financial support.
- Train genetic counselors with well establish guidelines for the whole country.
- Enable primary care provider to provide the basic counseling.
- Provision of education on Thalassemia into high school and college curriculum.
- Establish Thalassemia support groups.
- Furnish specific funds for clinical research in Thalassemia prevention and control.

Pharmacists Role in Thalassemia

- There should be a proper program where pharmacists can train patients with Cooley's anemia to self-administer deferoxamine via an intermittent infusion pump.
- A pharmacist should provide the patient and his family with in-depth information on the disease state through genetic counseling.

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REFERENCES

[1] Muncie HL, Campbell J Alpha and beta thalassemia. [Journal Article, Review] *Am Fam Physician 2009; 80(4):339-44.*

[2] Cao A, R. in:RA, TC, CR, Stephens k, editors. Gene reviews [internet]. Seattle (wa): university of Washington, Seattle; 1993-.2000 [updated 2007 Oct 23].

[3] Cunningham MJ *hematol oncol clin north am 2010; 24(1):215-27.*

[4] Cao A, Galanello R Beta-thalassemia. [Journal Article, Research Support, Non-U.S. Gov't, Review] *Genet Med 2010; 12(2):61-76.*

[5] Karimi M, Hydroxyurea in the management of thalassemia intermedia. [Journal Article] *Hemoglobin 2009.:S177-82.*

[6] Kontoghiorghes GJ, Pattichi K, Hadjigavriel M, Kolnagou A.Postgraduate Research Institute of Science, Technology, Environment and Medicine, 3 Ammochostou St, Limassol 3021, Cyprus.

[7] Nancy F. Olivieri, David G. Nathan, James H. MacMillan, Alan S. Wayne, PeterP.Liu,Allison McGee, Marie Martin, Gideon Koren, and Alan R. Cohen

[8] Nancy F. Olivieri, M.D., Gary M. Brittenham, M.D., Doreen Matsui, M.D., Matitiahu Berkovitch, M.D., Laurence M. Blendis, M.D., Ross G. Cameron, M.D., Robert A. McClelland, Ph.D., Peter P. Liu, M.D., Douglas M. Templeton, Ph.D., M.D., and Gideon Koren, *M.D. N Engl J Med 1995; 332:918-922, 1995*

[9] NF Olivieri, G Koren, D Matsui, PP Liu, L Blendis, R Cameron, RA McClelland and DM Templeton Division of Hematology/Oncology, Hospital for Sick Children, Toronto, Canada. Reduction of tissue iron stores and normalization of serum ferritin during treatment with the oral iron chelator L1 in thalassemia intermedia, *Volume 79, Issue 10, pp. 2741-2748,*

05/15/199; The American Society of Hematology

[10] Caterina Borgna-Pignatti[1,*], Simone Rugolotto[2], Piero De Stefano[3], Antonio Piga[4], Felicia Di Gregorio[5], Maria Rita Gamberini[6], Vincenzo Sabato[7], Caterina Melevendi[8], Maria Domenica Cappellini[9], Giuseppe Verlato[10]Article first published online: *2006, DOI: 10.1111/j.1749-6632.1998.tb10479.x* ([1] Department of Clinical and Experimental Medicine, University of Ferrara,[2] Department of Pediatrics, University of Verona,[3] Department of Pediatrics, IRCCS "San Matteo," Pavia ,[4] Department of Pediatrics, University of Turin ,[5] Department of Pediatrics, University of Catania, [6] Annunziata Di Palma, Division of Pediatrics, Ospedale Sant'Anna;[7] Department of Pediatrics, University of Bari, [8] Division of Pediatrics, Ospedale Galliera, Genova, [9] Department of Internal Medicine, University of Milan, [10] Institute of Medical Statistics, University of Verona)

[11] Gary M. Brittenham, Patricia M. Griffith, Arthur W. Nienhuis, Christine E. McLaren, Neal S. Young, Eben E. Tucker, Christopher J. Allen, David E. Farrell, and John W. Harris;*N Engl J Med 1982; 307:1671-1675*

[12] Zurlo MF, De Stefano P, Borgna-Pignatti C, Di Palma A, Piga A, Melevendi C, Di Gregorio F, Burattini MG, Terzoli S: *Survival and causes of death in thalassemia major. Lancet 2:27, 1989[Medline] [Order article via Infotrieve]*

[13] Graziano JH, Piomelli S, Hilgartner M, Giardian P, Karpatkin M, Andrew M, Lo Iacomo N, Seaman C*: Chelation therapy in β -thalassemia major. III. The role of splenectomy in achieving iron balance. J Pediatr 99:695, 1981[Medline] [Order article via Infotrieve]*

[14] Buja LM, Roberts W: Iron in the heart: Etiology and clinical significance. *Am J Med 51:209, 1971[Medline] [Order article via Infotrieve]*

[15] MacDonald RA, Mallory GK: Haemochromatosis and haemosiderosis: *Study of 21 autopsied cases. Arch Int Med 105:686, 1960*

[16] Barry M, Flynn D, Letsky E, Risdon RA: *Long term chelation therapy in thalassemia major: Effect on liver iron concentration, liver histology and clinical progress. Br Med J 2:16, 1974*

[17] Hoffbrand AV, Gorman A, Laulicht M, Garidi M, Economikdou J, Georgipoulou P, Hussain MAM, Flynn DM: Improvement in iron status and liver function in patients with transfusional iron overload with long-term subcutaneous deferoxamine. *Lancet 1:946, 1979*

[18] Aldouri MA, Wonke B, Hoffbrand AV, Flynn DM, Laulicht M, Fenton LA, Scheuer PJ, Kibbler CC, Allwood CA, Brown D, Thomas HC: Iron state and hepatic disease in patients with thalassemia major treated with long term subcutaneous desferrioxamine. *J Clin Pathol 40:1352,* 1987

[19] Brittenham GM, Griffith PM, Nienhuis AW, McLaren CE, Young NS, Tucker EE, Allen CJ, Farrell DE, Harris JW: Efficacy of deferoxamine in preventing complications of iron overload in patients with thalassemia major. *N Engl J Med 331:567, 1994*

[20] A Piga, C Gaglioti, E Fogliacco, and F Tricta (Department of Pediatric Hematology, University of Turin, Italy.) *Haematologica, Vol 88, Issue 5, 489-496*

[21] MacLaren R, Bond CA.(Department of Clinical Pharmacy, School of Pharmacy, University of Colorado Denver, Aurora, Colorado 80045, USA.)

[22] Levine HG, Hanan ZI, Gordon FS, Tomasulo WJ. *Am J Hosp Pharm.1979 ;36(6):788-90.*

[23] Alshifa international monthly magazine.

[24] Imran-u-din Khattak, Samia Tanweer Khattak, Jehanzeb Khan, Heterozygous beta Thalassemia in parents of children with beta Thalassemia*(Saudi Medical College, Swat and Postgraduate Medical institute, Lady reading hospital Peshawar, Pakistan).Gomal journal of medical science 2006, Vol 4, No.2*