POST SPLENECTOMY OUTCOMES OF B-THALASSEMIA MAJOR; A SINGLE CENTER EXPERIENCE

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ABSTRACT

About 5000-9000 babies with B-Thalassemia major are born in Pakistan every year, signifying a major health care burden. And further-on when these patient become symptomatic, the mainstay treatment is blood transfusions, Iron Chelation therapy and Splenectomy as a last resort. Most of these patients are referred to a tertiary care center for splenectomy.

Our aim of this study was to share our one-year experience of splenectomy cases referred to us, the base line status of these patients, the operative methods, post-op complications and follow-up.

Study Design: This was a prospective study of thalassemia major patients referred to the department of general surgery, Hayatabad Medical Complex, Peshawar, Pakistan, from January 1st 2018 to December 31, 2018.

Materials & Methods: out of total of 208 cases referred to us 174 were operated. The most frequent indication for splenectomy was massive splenomegaly, followed by neutropenia and frequent blood transfusion for more than 4 times in a month. Patients with minor and intermediate thalassemia, sickle cell or other blood disorders were excluded from the study. 174 patients were operated upon for elective open splenectomy via left Sub-costal incision.

Results: Out of 174 patients, 113(64.90%) were male, and 61(35.06%) were female. The age ranged from 5-12 years of age with mean age of 08 years. 153(87.93%) patients had complete recovery with no adverse events, while 21 patients developed post-operative complications. The overall Adverse Events were 12.1%, with no deaths recorded. Post- operative long term follow-up showed 13.2% (n=23) infection rate as Long Term Adverse Event, with Malaria being the most common, followed by upper respiratory tract infection, influenza, para-influenza and sepsis in decreasing frequency respectively. 86.8 % of patients on follow-up had adequate hemoglobin levels with decreased maintenance transfusions.

Conclusion: We conclude that, Splenectomy is a safe and a beneficial procedure in select group of patients. The Short Term post-op complications can be reduced by following proper vaccination protocol and post-operative antibiotic cover. And with proper counseling of patient families, the long term adverse events can be significantly reduced.

Keywords: Splenectomy, B-Thalassemia Major, Post-Operative Outcomes.

The word thalassemia is of greek origin meaning "Sea in Blood" due to its presence among the Mediterranean population called Mediterranean Anemia first described by Cooley[1,2]. Thalassemia is an inherited disorder with which 5000-9000 children are born every year in Pakistan[3] an autosomal recessive hemoglobinopathy, is one of the commonest genetically transmitted disorders throughout the world. Collective measures including carrier identification, genetic counseling and prenatal diagnosis are required for preventing β-thalassemia. To achieve this objective, Identification of the spectrum of genetic mutations, especially for various ethnic backgrounds in Pakistan is necessary. Therefore, we designed a cross sectional prospective study to identify the frequency of various gene mutations in different ethnic groups of Pakistan. Over a 5-year period, DNA from 648 blood samples [including specimens of chorionic villus sampling (CVS, this disorder is characterized by defective RBC's with shortened life span that is less than 120 days, this is due to error in the genetic coding for the Alpha or Beta globin chain resulting in chronic hemolytic anemia characterized by hemolysis, premature destruction of RBC's in the bone marrow and in addition to shortened life span[4] hereditary, chronic hemolytic anemia due to a partial or complete deficiency in the synthesis of α-globin chains (α-thal. Current medical practice for management of these patients in Pakistan, is multiple blood transfusions followed by, Iron chelation therapies, as excess iron produces redox species which damages heart, liver and endocrine system, Induction of fetal hemoglobin production, bone marrow transplant, and in a selected sub-set splenectomy is performed. In research centers abroad new therapies such as molecular pharmacological agents, gene therapy and Artificial blood products are becoming mainstay of the treatment. Splenectomy as an option for selected sub-set of thalassemia patients is a safe option, resulting in decreased maintenance transfusions, with vast comparative improvement in quality of life. Children with hypersplenism and increased packed RBC's requirement are referred to us for splenectomy

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from our in house pediatric hematology department and multiple pediatric units around the province.

MATERIALS AND METHODS

This was a prospective study encompassing one year of data and patients from January 1st 2018 to 31st December 2018, and from a total of 208 elective splenectomies performed in year 2018, 174 patients out of 208 were of Thalassemia sub-set,113(64.90%) were male, and 61(35.06%) were female. The age ranged from 5-12 years of age with mean age of 08 years. These patients were operated by the General Surgery Unit of Hayatabad Medical Complex, Peshawar, Pakistan.

The Criteria for referral was:

1. Packed RBC transfusion requirement >250-300 ml/kg/year
2. Dyspnea from massive splenomegaly even with lesser transfusion requirement, that is, >200 ml/kg/year.
3. Symptomatic hypersplenism

Inclusion criteria was children aged 5 -16, Diagnosed case of B-Thalassemia Major, Increased Packed RBC's Requirement > 4 per month, and symptomatic hypersplenism. All other Chronic Hemolytic Anemia Disorders were excluded from the study.

On initial presentation / referral to our unit complete base line workup was done for every patient. The workup included:

a. Hematological investigations: Hb, complete blood count, mean corpuscular hemoglobin (MCH), mean corpuscular volume (MCV), MCHC; blood grouping; complete liver function tests, renal function tests, bleeding time, clotting time, prothrombin time, ApTT, INR etc.

b. Serological investigations: Anti- HIV, HBsAg, Anti-HCV.

c. Serum ferritin, calcium and phosphate (PO4-)

d. Radiological investigations: Ultrasonography of abdomen, andechocardiogram (ECHO).

e. Work-up for tuberculosis: Chest X-ray, mantoux test, erythrocyte sedimentation rate, sputum examination AFB.

Vaccination of (polyvalent pneumococcal, meningococcal and hemophilus influenzae) was completed 2-3 weeks preceding the operative date and the complete workup was again repeated. The parents were counseled regarding the operative procedure, operative complications, post-operative-complications and what benefits will splenectomy provide to the patient and to categorically state that the procedure is not curative but would definitely help with the severity of disease and subsequent quality of life, and informed consent taken.

The splenectomy was performed though Left Sub-Costal Incision; the standard open splenectomy was performed with the following steps:

i. Left sub-costal incision was made to open the abdomen

ii. Peritoneum was opened in the line of incision and splenic artery and vein were identified and ligated.

iii. The spleen was retracted to ligate splenocolic, lienorenal and splenophrenic ligaments between ligatures.

iv. Stomach was retracted, short gastric arteries identified and ligated at gastrosplenic ligament, followed by gatrosplenic ligament, cutting between ligatures.

v. Spleen removed and hemostasis confirmed.

Patients were evaluated post-op in the general surgery ward during their hospital stay for any complications, and put on Penidure (I/M Injection Benzathine Penicillin) at a prophylactic dose of 3-5 lac units at 3 week intervals to be continued for a total of 5 years' prophylaxis.

The children were then put on a regular follow up of once a month to the in-hospital thalassemia unit, which provided us with any long term adverse events over the course of the year. The children parents were informed about the frail immunocompromised status of their child and what to look for and what preventive measures needed to be taken at home or school.

RESULTS[1]

Out of 208 patients 174 underwent splenectomy for thalassemia major induced complications. Out of these 174, 113(64.9%) were male, and 61 (35.1%) were female, with ages ranging from 5 – 12 years of age, with mean age of 09 years. 08 of these patients were HbsAg positive, 05 Anti-HCV positive and 03 HIV positive and 02 both HbsAg and Anti-HCV positive. All of them underwent open splenectomy through left sub-costal incision. All surgeries were uneventful. Post operatively (Table1.1): (01) patient had an internal bleed, patient was re-explored bleed identified and hemostasis secured. (14 / 8.04%) patients had post-operative surgical site infection, for which cultures were sent and antibiotics changed and patients put on double regimen antibiotics. (01) patient had a post-op sub phrenic abscess, which was first identified by ultrasound and followed by CT-Scan, Antibiotics were changed, Urine / Blood Cultures sent and patient referred to Interventional Radiology for Guided aspiration. (05 / 2.9 %) of the patients has a post-operative Ileus due to electrolyte imbalance namely hypokalemia, which was characterized by abdominal distension and vomiting, NG was passed and Electrolytes corrected. Among the Late Complications or Long Term Adverse (Table 1.2) events the commonest was Malaria (09 / 5.2%), followed

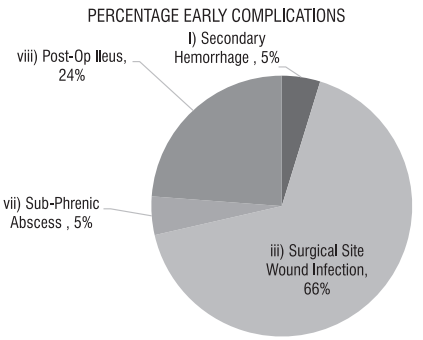

Figure 1: Percentage Early Complications

Table: (1.1) Age, Gender and Hospital Stay (n=174)

Demographics	Number of Patients	Percentage
Gender		
Male	113	64.90 %
Female	61	35.06 %
Age - Range	05 to 12	
Mean Age	9	
Hospital Stay - Range	02 to 08	
Hospital Stay - Average	02 days (154)	88.51%
Morbidity	21	12.10%
Mortality	0	0

by Upper Respiratory Tract Infection (07 / 4.02%), (02) cases of Pulmonary Tuberculosis, (02) cases of Influenza, (02) cases of Minor Abscesses, and (01) case of Para-Influenza. There were no deaths recorded or reported among the patients during the course of this study.

DISCUSSION

With the thalassemia incidence of 5000-9000 per year[3] an autosomal recessive hemoglobinopathy, is one of the commonest genetically transmitted disorders throughout the world. Collective measures including carrier identification, genetic counseling and prenatal diagnosis are required for preventing β-thalassemia. To achieve this objective, Identification of the spectrum of genetic mutations, especially for various ethnic backgrounds in Pakistan is necessary. Therefore, we designed a cross sectional prospective study to identify the frequency of various gene mutations in different ethnic groups of Pakistan. Over a 5-year period, DNA from 648 blood samples [including specimens of chorionic villus sampling (CVS, it has become a major healthcare burden, and with its estimated carrier rate of 5-7 %, with 9.8 million carriers in the population[5]. Thalassemia spectrum of chronic hemolytic anemias

Table: (1.2) Post-Operative Complications

Early Complications	No. / #	%
i) Secondary Hemorrhage	1	0.57
ii) Tube / Drain Complication	0	0
iii) Surgical Site Wound Infection	14	8.05
iv) Deep Vein Thrombosis	0	0
v) Portal Vein Thrombosis	0	0
vi) Pulmonary Atelectasis	0	0
vii) Sub-Phrenic Abscess	1	0.57
viii) Post-Op Ileus	5	2.87
xi) Pancreatic Injury	0	0
Total	21	12.07
Late Complications		0
Post Splenectomy Sepsis	0	0
Upper Respiratory Tract Infections	7	4.02
Influenza	2	1.15
Para-influenza	1	0.57
Tuberculosis	2	1.15
Malaria	9	5.17
Incisional Hernia	0	0
Minor Abscess	2	1.15
Total	23	13.21

is characterized by defective globin chain resulting in hemolysis, premature destruction of RBC's in the bone marrow, and shortened life span of less than 120 days. The disease results in decreased Hb concentrations requiring multiple transfusions sometimes more than 04 transfusions per month. This results in increased iron accumulation in the body, and iron in itself forms Redox species, namely free radicals and its subsequent deposition and accumulation of iron in Heart, liver and endocrine system can result in damage to those organs over time. For iron overload iron chelating agents are used to counteract the iron overload in the patients and ameliorate the subsequent damage over time. The destruction of RBC's in the spleen results in increase in splenic volume which compared to a normal person is 50 to 100 g while in a thalassemic patient it may be as high as 500-1000 g. Multiple therapies are now in existence to decrease the dependency on transfusions of a thalassemia patient, but some of these are limited to more developed countries and in countries like Pakistan which are mostly resource deficient some of these modalities if available are out of reach for the majority of the population. These modalities include, Allogenic Bone Marrow Transplantation, Peripheral Blood Stem Cells Transfusions, Umbilical Stem Cells based Transfusions, Alternate Blood Products, Fetal Hemoglobin Induction, Therapies Targeting Dys-erythropoiesis, Gene Therapy.

Splenectomy is indicated in a subset of Thalassemic patients who have increased Packed RBC's demand and Symptomatic Hypersplenism. Splenectomy is a safe procedure with good outcomes in thalassemic patients with decreased transfusion dependence requiring blood transfusion every 3rd to 4th week[6] not all thalassemia patients respond to splenectomy. Moreover, splenectomy may increase many unfavorable consequences. The study about the efficacy and complications after splenectomy is limited and the effect of splenectomy on iron overload is still unclear.\n\nThis study aims to investigate the long-term efficacy of splenectomy, factor predicting a response to splenectomy, the consequences of splenectomy complications, CBC parameter changes and the effect on iron overload parameters after splenectomy.\n\nMethods\n\nAll TDT patients (PRC transfusion ≥3 units/year, the patients who are most likely to benefit from Splenectomy are Type (HbH and B/E), higher Neutrophil Percentage and Older Age at the time of Splenectomy[6] not all thalassemia patients respond to splenectomy. Moreover, splenectomy may increase many unfavorable consequences. The study about the efficacy and complications after splenectomy is limited and the effect of splenectomy on iron overload is still unclear.\n\nThis study aims to investigate the long-term efficacy of splenectomy, factor predicting a response to splenectomy, the consequences of splenectomy complications, CBC parameter changes and the effect on iron overload parameters after splenectomy.\n\nMethods\n\nAll TDT patients (PRC transfusion ≥3 units/year. Splenectomy is performed in patients with varied hematological disorders and is comparatively safe procedure with minimal complications[7-10] Madinah Teaching Hospital, Faisalabad from January 2011 to December 2016. Method: After a good preoperative workup and preparation, 112 patients underwent elective open splenectomy from Jan 2011 to Dec 2016. Early postoperative complications were recorded. P value <0.05 was considered significant. Results: Of 112 patients, 09 patients (8%. The most common complication in long term being Overwhelming Infection Post Splenectomy OSPI[9,10] principally infectious and thromboembolic; the frequency of complications varies with the conditions that led to splenectomy (hematologic splenectomy, trauma, presence of portal hypertension. In the Thalassemia Sub-group there is a chance of developing Tricuspid Valve regurgitation and Subsequent Pulmonary Hypertension[6] not all thalassemia patients respond to splenectomy. Moreover, splenectomy may increase many unfavorable consequences. The study about the efficacy and complications after splenectomy is limited and the effect of splenectomy on iron overload is still unclear.\n\nThis study aims to investigate the long-term efficacy of splenectomy, factor predicting a response to splenectomy, the consequences of splenectomy complications, CBC parameter changes and the effect on iron overload parameters after splenectomy.\n\nMethods\n\nAll TDT patients (PRC transfusion ≥3 units/year. The surgical options for splenectomy are partial splenectomy, total splenectomy and open versus laparoscopic splenectomy, the partial splenectomy is a temporary measure is recommended in age group less than 05 years[8], and laparoscopic being more beneficial than open splenectomy[8].

Regarding post-operative complications Ahmed et al[7] Madinah Teaching Hospital, Faisalabad from January 2011 to December 2016. Method: After a good preoperative workup and preparation, 112 patients underwent elective open splenectomy from Jan 2011 to Dec 2016. Early postoperative complications were recorded. P value <0.05 was considered significant. Results: Of 112 patients, 09 patients (8% had 09 % post-operative complications in 112 patients (Secondary Hemorrhage in 02, while Ileus in 01), while Thai et al[9] in his analysis found post-splenectomy patients to have a high incidence of OSPI compared to the control group (17% Vs 14%), while Salem et al in 36 patients[8] had no post-operative complication in his review of splenectomy of thalassemic children. Compared to our results of early complications being 12.1% and Late Complications being 13.1 % of the total all well within the reported margins, In addition, research on spleen surgery in CHA is challenged by the heterogeneity of diseases, small number of subjects, variations in technique, and inconsistent use of standardized data[11].

We had a higher incidence of surgical site infections among our dataset 8.1%, which was mainly reported within a week of discharge, and required re-admission. The SSI was followed by Malaria 5.2 % as a late complication, the fact being that the reported cases were from malaria endemic region, compared to 18.75% Reported Malaria Infection in Post-Splenectomy patients by Merchant et al[2], though he had reported higher incidence of post-operative complications for splenectomy as high as 50% but add it to the fact that his mean follow-up was five years[2]. The next most common complication was Upper Respiratory Tract Infection at 4.02 %.

Regarding our experience through the year our patients have improved significantly requiring one transfusion at most per month with average Hb of 7 – 10 gm/ ml. The patient subset has not reported any mortalities and have become active with resumption of daily routine as a normal child, the only focus being to be a bit cautious on the preventive aspect as these children are now a bit immunocompromised compared to other children.

CONCLUSION

We conclude that splenectomy is a safe procedure for Thalassemia subset select patients with hypersplenism and >4 PRBC's requirement per month, with minimal complications. And with a bit of counseling and education of the parents of the child and proper follow up and prophylaxis most of the long term complications

can be avoided, which may result from this procedure. We further iterate the fact that large multicenter randomized studies need to be conducted on the splenectomy subset of hemolytic anemias patients to ascertain for certain what should be the standard surgical approach towards patients suffering from Congenital Hemolytic Anemias.

REFERENCES

1. VALENTINE WN, NEEL J V. HEMATOLOGIC AND GENETIC STUDY OF THE TRANSMISSION OF THALASSEMIA. Arch Intern Med [Internet]. 1944 Sep 1 [cited 2018 Dec 31];74(3):185. Available from: http://archinte.jamanetwork.com/article.aspx?doi=10.1001/archinte.1944.00210210032005

2. Merchant RH, Shah AR, Ahmad J, Karnik A, Rai N. Post Splenectomy Outcome in β-Thalassemia. Indian J Pediatr [Internet]. 2015 Dec 23 [cited 2018 Dec 31];82(12):1097–100. Available from: http://link.springer.com/10.1007/s12098-015-1792-5

3. Ansari SH, Shamsi TS, Ashraf M, Bohray M, Farzana T, Khan MT, et al. Molecular epidemiology of β-thalassemia in Pakistan: far reaching implications. Int J Mol Epidemiol Genet [Internet]. 2011 [cited 2018 Dec 31];2(4):403–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22200002

4. Fibach E, Rachmilewitz EA. Pathophysiology and treatment of patients with beta-thalassemia - an update. F1000Research [Internet]. 2017 [cited 2018 Dec 31];6:2156. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29333256

5. Ahmed S, Saleem M, Modell B, Petrou M. Screening Extended Families for Genetic Hemoglobin Disorders in Pakistan. N Engl J Med [Internet]. 2002 Oct 10 [cited 2018 Dec 31];347(15):1162–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/12374877

6. Tantiworawit A, Dumnil S, Osataphan N, Rattanathammethee T, Hantrakool S, Chai-Adisaksopha C, et al. The Pros and Cons of Splenectomy in Transfusion Dependent Thalassemia Patient. Blood [Internet]. 2018 Nov 21 [cited 2019 Jan 1];132(Suppl 1):4901–4901. Available from: http://www.bloodjournal.org/content/132/Suppl_1/4901?sso-checked=true

7. Ahmad, Irshad; Saleem, Saira; Anjum, Shakeel; Rehan AG. POSTOPERATIVE SPLENECTOMY COMPLICATIONS. Prof Med J [Internet]. 2017 [cited 2019 Jan 1];24(09):1322–6. Available from: https://web.b.ebscohost.com/abstract?direct=true&profile=ehost&scope=site&authtype=crawler&jrnl=10248919&AN=125911227&h=o2Pu9sR%2BYccx0%2BFPQ2ey6lOixQ%2FACk%2Ffexve%2B8vJ6aIqEile2SzucDPALPXwyYEqhMvxHHoVJJS2kcyjjRZOJg%3D%3D&crl=c&resultNs=AdminWebAuth&resu

8. Al-Salem AH. Splenectomy for Children With Thalassemia. J Pediatr Hematol Oncol [Internet]. 2016 Jan [cited 2019 Jan 1];38(1):1–4. Available from: http://content.wkhealth.com/linkback/openurl?sid=WKPTLP:landingpage&an=00043426-201601000-00001

9. Thai L, Mahevas M, roudot-Thoraval F, Languille L, Dumas G, Khellaf M, et al. Long-Term Complications after Splenectomy in Adult Chronic Immune Thrombocytopenia with a Minimum Follow up of 10 Years. First Results from a Single-Center Case-Control Study in 140 Patients with Primary ITP. Blood [Internet]. 2014 [cited 2019 Jan 1];124(21). Available from: http://www.bloodjournal.org/content/124/21/232?sso-checked=true

10. Buzelé R, Barbier L, Sauvanet A, Fantin B. Medical complications following splenectomy. J Visc Surg [Internet]. 2016 Aug 1 [cited 2019 Jan 1];153(4):277–86. Available from: https://www.sciencedirect.com/science/article/pii/S1878788616300297

11. Rice HE, Crary SE, Langer JC, Kemper AR, Splenectomy in Congenital Hemolytic Anemia Consortium. Comparative effectiveness of different types of splenectomy for children with congenital hemolytic anemias. J Pediatr [Internet]. 2012 Apr 1 [cited 2019 Jan 1];160(4):684–689.e13. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22050869