ORIGINAL ARTICLE

Retrospective Evaluation of the Outcomes of Splenectomy in Patients with β-Thalassemia: Insights from a Tertiary Care Center in Bahawalpur

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ABSTRACT

Objective: To evaluate outcomes of splenectomy in patients with β-thalassemia major.
Study Design: A retrospective study.
Place and Duration of Study: The study was conducted at the Department of Hematology, Bahawal Victoria Hospital Bahawalpur, Pakistan, from June 2022 to June 2023.
Methods: A total of 80 patients with β-thalassemia were included. Participants were divided into Group A (n=40), including patients who had undergone splenectomy, and Group B (n=40), including patients with no splenectomy. The medical records of all participants were reviewed. Complete blood count, serum ferritin, and liver function tests were recorded. Flow cytometry was used to assess lymphocyte populations. Patients in Group A were evaluated 2 years after the splenectomy.
Results: Mean platelet and white blood cell count after splenectomy were 645.70/mm^3 and 16.480/mm3 respectively. Splenectomy resulted in a significant increase in RBC indices, hematocrit, RBC count, and mean hemoglobin level. However, splenectomy did not decrease iron burden, and more patients required iron chelation. Group B had significantly higher total and indirect bilirubin compared to Group A. Splenectomy resulted in a significant increase in total and B lymphocytes. However, Group A had lower IgM Memory B lymphocytes than Group B. CD4 helper T lymphocytes, in total T lymphocytes, CD4+/CD8+ ratio and CD8 cytotoxic T lymphocytes did not differ significantly between both groups.
Conclusion: Splenectomy is associated with the risk of thrombocytosis in the long term. It improves anemia but does not impact blood transfusion requirement or iron burden. Preoperative vaccination can reduce the risk of overwhelming post splenectomy infections.

Keywords: *Blood Transfusion, Red Blood Cells, Splenomegaly, Splenectomy*.

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Introduction

Thalassemia is a disorder of red blood cell (RBC) protein and hemoglobin, which carries oxygen in blood. It is an autosomal hematological disorder affecting the the synthesis of α or β globin chain of hemoglobin. Based on the type of globin chain affected, it can be classified into alpha or beta-thalassemia. Clinical abnormalities are due to premature destruction of fragile RBCs and erythroblasts and ineffective erythropoiesis, which leads to anemia.[1] β-thalassemia is a prevalent disorder caused by a genetic mutation on chromosome 11, which disrupts the production of the β-globin chain.[2] It is a common

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genetic disorder, having an incidence of 10 to 15% in Southeast Asia and the Mediterranean.[3] Clinical spectrum of β-thalassemia consists of thalassemia minor, thalassemia intermedia and thalassemia major. Thalassemia minor and intermedia lead to mild anemia, which does not require blood transfusions. On the contrary, thalassemia major results in severe anemia, and patients need regular blood transfusions since childhood. Thalassemia major is mainly managed through iron chelation and blood transfusion. Thalidomide and combination therapies have also recently emerged as the treatment for beta-thalassemia that significantly reduces the need for blood transfusion.[4] Splenomegaly results due to extra medullary hematopoiesis and excessive destruction of RBCs, which results in increase transfusion requirement. A splenectomy is performed to avoid this complication.[5] Major indications for splenectomy are massive spleen enlargement, increased transfusion and hypersplenism.[6,7] Patients with thalassemia who receive proper blood transfusion and iron chelation are at reduced risk of complications and splenomegaly. These complications are more common in patients of low-income countries that are provided suboptimal care.[8] Splenectomy can be full or partial. Splenectomy is a complicated procedure usually performed in infants to preserve any splenic function. Full splenectomy is performed by laparoscopy, but marked splenomegaly necessitates open surgery.[9] Splenectomy is associated with complications such as infection, thromboembolism, and hypercoagulability. Anemia may recur due to enlargement of splennuculi following splenectomy. Thus, it is important to remove any accessory spleen during surgery. A major complication of splenectomy is overwhelming post splenectomy infections (OPSI), caused by Haemophilus Influenzae, Neisseria Meningititus and Strep Pneumococcus, resulting in hypotension or shock. Various studies have been conducted to assess short and long term outcomes of splenectomy in patients with β-thalassemia major.[10,11] However, there is limited data on the local population. Thus, the aim of this study is to evaluate the long-term outcomes of splen-ectomy in patients with β-thalassemia major.

Methods

The retrospective study was conducted at the Department of Hematology Bahawal Victoria Hospital Bahawalpur, Pakistan from June 2022 to June 2023. Patients with β-thalassemia were included in the study by consecutive sampling. The sample size was calculated by 95% CI, 5% error rate, and 80% power of the study. Patients who were recently diagnosed with β-thalassemia and did not receive a blood transfusion or those with diabetes, infection, inflammation, renal, cardiac, and pulmonary disease were excluded. Informed consent of the participants was taken. The ethical Review Board of the hospital approved the study on dated: 5th May 2022 vide letter no: 12-04, and the identity of patients was kept anonymous.

A total of 80 patients were included. Participants were divided into Group A (n=40), including patients who had undergone splenectomy, and Group B (n=40), including patients with no splenectomy. Indications for splenectomy were pancytopenia, severely enlarged spleen (>20 cm and >2.2 pounds), and blood transfusion requirement > 250 ml/kg/year. Patients who underwent splenectomy were vaccinated against Haemophilus influenza type B, Neisseria meningitis, and Streptococcus pneumonia 2 to 4 weeks before surgery. Patients with platelet count > 1000 000/mm^3 were given antiplatelets (75 mg aspirin).

Medical records of all participants were reviewed. Complete blood count, serum ferritin and liver function tests were recorded. Flow cytometry was used for assessing lymphocyte populations. Patients in Group A were assessed 2 years after the splenectomy. Percentages of $CD8^+$ (T-cytotoxic cells), $CD4^+$ (T-helper cells), $CD3^+$ (T lymphocytes), $CD19^+$ $CD27^+$ IgM^- (switched memory B cells),

Table-1: Baseline characteristics of study groups

Variables	Group A (n=40)	Group B (n=40)	*t Statistics*	*P*-value
Age	11.83± 2.35	6.46 ± 2.97	7.20	0.0
Sex			1.33	0.19
Male	27 (67.5%)	22 (55%)		
Female	13 (32.5%)	18 (45%)		
BMI	16.03 ± 2.09	14.76 ± 2.30	2.42	0.020
Age at 1st transfusion (months)	8.98 ± 4.16	9.75 ± 6.44	0.42	0.678
Patients requiring regular chelation	27 (67.5%)	17 (42.5%)	2.28	0.028
Frequency of transfusion (days)	33.32 ± 7.10	30.58 ± 12.87	1.01	0.320
Liver size (cmBCM)	6.97 ± 3.18	4.28 ± 2.07	6.35	0.0

$CD19^+$ $CD27^+$ IgM^+ (IgM memory B cells), $CD19^+$ $CD27^+$ (total memory B cells), $CD19^+$ $CD27^-$ (naive B cells) and $CD19^+$ (total B lymphocytes). Findings of the flow cytometer were presented on the histogram (Figure.1).

SPSS version 27.0 was used for data analysis. Continuous variables were presented as mean ± SD, and categorical variables as percentages. Continuous variables were analyzed using an independent sample *t*-test and categorical variables through the χ^2-test. *P* value < 0.05 was considered statistically significant.

Results

Mean age of patients at the time of splenectomy was 6.78 ± 2.44 years. The mean post-operative follow-up period was 6.36 ± 3.02 years. Mean platelet and white blood cell count was 645.700/mm^3 and 16.480/mm^3 respectively. (Table-1).

Splenectomy resulted in a significant increase in RBC indices, hematocrit, RBC count, and mean hemoglobin level. However, splenectomy did not decrease iron burden and more patients required iron chelation. Group B had significantly higher total and indirect bilirubin compared to Group A. (Table-2).

Splenectomy resulted in a significant increase in total and B lymphocytes. However, Group A had significantly lower IgM Memory B lymphocytes compared to Group B. CD4 helper T lymphocytes, total T lymphocytes, the CD4+/CD8+ ratio, and CD8 cytotoxic T lymphocytes did not differ significantly between both groups. (Table-3).

There was no report of OPSI. one patient had a liver abscess; aspirated pus showed Klebsiella spp. It was treated with ciprofloxacin. One patient reported post-splenectomy portal vein thrombosis after 1 year of surgery. Patient had a fever and severe abdominal pain. The platelet count was 1000000/mm3. Abdominal ultrasonography was used for diagnosis. Liver function tests, bleeding time, clotting time, partial thromboplastin time, and prothrombin time are within normal range. This patient was managed with antiplatelet and anticoagulant agents.

Discussion

Elective splenectomy is widely used to manage various medical disorders. Thalassemia patients have elevated RBS indices, hematocrit, hemoglobin, and RBCs after splenectomy, and the frequency of transfusions and related complications is reduced.[12,13] In this study, we evaluated the outcomes of splenectomy in patients with beta-thalassemia. The results showed that despite increase the increase in HB level, the requirement for blood transfusion did not reduce significantly as iron overload and red cell dysfunction persisted. Splenectomized patients needed blood transfusion every 35 days. Iron overload remained persistent after

Table-2: Complete blood picture and liver function tests in study population

Variables	Group A	Group B	*t Statistics*	*P*-value
RBCs (10^9/l)	3.6 ± 1.1	3.1 ± 0.55	5.98	0.0
WBCs (10^8/µl)	15.55 ± 10.88	8.52 ± 3.30	7.02	0.0
Hemoglobin (g/dl)	6.64 ± 1.15	5.66 ± 1.01	9.93	0.0
MCV (fl)	72.1 ± 7.2	61.33 ± 7.8	8.56	0.0
HCT (%)	21.60 ± 5.32	17.75 ± 4.2	7.62	0.0
MCH (pg)	20.8 ± 4.1	18.08 ± 2.2	7.77	0.0
MCHC (g/dl)	29.6 ± 1.2	28.4 ± 1.8	7.45	0.0
Platelet count(10^9/l)	643.600 ± 300.3	339.600 ± 159.8	5.98	0.0
Total bilirubin (µmol/l)	22.61 ± 6.64	40.32 ± 41.50	2.66	0.011
Indirect bilirubin(µmol/l)	16.42 ± 5.91	31.77 ± 47.74	2.25	0.030
Albumin (g/dl)	3.47 ± 0.55	4.0 ± 0.49	3.55	0.001
ALT (IU/l)	80.15 ± 26.0	50.05 ± 51.38	3.58	0.001
AST (IU/l)	110.40 ± 65.40	50.90 ± 30.64	6.98	0.0
Serum ferritin (mcg/l)	2900.1 ± 1410	1800.2 ± 1650.6	3.51	0.001

Table-3: Lymphocyte subsets in both groups

Variables	Group A	Group B	*t* Statistics	*P*-value
Total lymphocytes	66.01 ± 11.54	59.13 ± 13.47	2.21	0.030
B lymphocytes	17.16 ± 2.32	14.97 ± 2.13	3.42	0.001
Naive B lymphocytes	77.70 ± 11.78	68.79 ± 12.74	2.09	0.040
Total memory B lymphocytes	24.40 ± 11.80	33.36 ± 12.10	2.15	0.035
IgM memory B lymphocytes	9.79 ± 3.30	18.14 ± 6.37	6.99	0.0
Switched memory B lymphocytes	16.10 ± 8.15	16.88 ± 6.83	0.09	0.930
T lymphocytes	64.95 ± 11.65	61.45 ± 15.60	0.40	0.690
$CD4^+$	43.10 ± 8.20	37.05 ± 9.02	1.72	0.089
$CD8^+$	26.50 ± 7.33	24.36 ± 7.25	0.66	0.510
$CD4^+$ / $CD8^+$ ratio	1.85 ± 0.50	1.70 ± 0.51	0.09	0.930

the operation, thus this risk of organ damage. A study found that splenectomized patients have a higher risk of myocardial siderosis (49%) than the general population (29%).[14] Casale et al. reported contrary results and concluded that there was a significant reduction in ferritin, blood transfusion, and iron intake after splenectomy.[15] Caocci et al. also reported a contradiction with respect to the reduction of results, and Imran et al. concluded the same

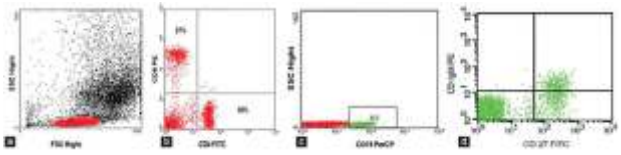

Fig.1: Flow cytometric analysis. A) Lymphocyte population presented in forward and side scatter histogram. B) Expression of $CD8^+$ and $CD4^+$ in T lymphocyte. C) gating of $CD19^+$ cells. D) CD27 and IgM expression in B cells. FITC (fluorescein isothiocyanate), FSC (forward scatter), perCP (peridin chlorophyll protein), PE (phycoerythrin), SCC (side scatter)

results, concluding that splenectomy significantly impacted the frequency of blood transfusions in extremely dependent patients.[17]

The current study's results showed that more splenectomized patients were on chelation due to a significantly elevated ferritin level, indicating the procedure's inadequacy in lowering the iron burden. Ismail et al. reported a significantly high level of ferritin after splenectomy.[18] Serum albumin was lower, and transaminases were higher in splenectomized patients than non-splenectomized patients. A previous study reported that organ damage associated with iron overload was comparable in splenectomized and non-splenectomized patients.[19]

In the current study, splenectomized thalassemic patients had high lymphocyte and leukocyte counts. The increase in lymphocytes suggests the spleen's role in controlling lymphocyte counts and its ability to act as a lymphocyte reservoir. These findings are consistent with the results of previous studies, which reported that splenectomized thalassemia patients have a significant increase in B lymphocytes.[20,21] Nonsplenectomized patients had higher IgM memory B cells than splenectomized patients. IgM memory B cells are produced in the spleen. Macrophages in the liver and spleen can effectively remove opsonized bacteria. However, encapsulated bacteria can only be removed by the spleen as it produces pentameric IgM, which facilitates direct or indirect phagocytosis of the bacteria.[22]

Thalassemia major increases the risk of infection due to altered immunoglobulin levels and complement activation, hemochromatosis, and cardiopulmonary disease. Splenectomy is furthering this risk; OPSI is a major and fatal complication of splenectomy. Preventive measures such as antibiotic prophylaxis, vaccines, patient education and increased awareness can significantly reduce the risk of OPSI. In the current study, patients were properly vaccinated before the operation, and no case of OPSI was reported.[23] Previous studies demonstrate that splenectomy is associated with the risk of thrombosis.[24] Splenectomy causes an increase in microparticles and reactive thrombocytosis, which increases the risk of venous thromboembolism. Incidence of portal vein thrombosis following splenectomy ranges from 0.6 to 9%, patients present with abdominal pain and fever.[25] In current study, 1 patient reported portal vein thrombosis after a year of splenectomy. High suspicion index, timely diagnosis and routine anticoagulation can increase chances of successful outcome.

Thalassemia patients with increased transfusion requirements, marked splenomegaly, and complications like pancytopenia are candidates for splenectomy. It is a major procedure, and a thorough risk-benefit analysis should be undertaken for each patient. Many complications stem from the severity of these rather than splenectomy alone.

The study has a few limitations. First is the discrepancy in age, weight, and height between both groups. Second, only severely thalassemic patients underwent splenectomy, due to which there may be a chance that low serum albumin and high serum ferritin level in splenectomized patients can be due to severe disease before the operation.

Conclusion

Splenectomy is associated with the risk of thrombocytosis in the long term. It improves anemia but has no impact on blood transfusion requirements or iron burden. The risk of overwhelming post-splenectomy infections

(OPSI) can be reduced by preoperative vaccination.

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Authors Contribution

MIK: Idea conception, data collection, manuscript writing and proofreading

FA: Study designing, data analysis, results and interpretation

HM: Idea conception, data collection

NSY: Study designing

AS: Data collection

NM: Data collection, data analysis, results and interpretation

HIK: Idea conception