Clinical and hematologic outcomes after splenectomy for congenital hemolytic anemia

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Introduction
Spleen is an essential part of the reticuloendothelial system that is considered as the mononuclear phagocyte system. Phagocytosis of damaged cells, recycling of iron, erythropoiesis, and immunologic response are the main functions of the spleen.

Aim
The aim was to delineate clinical and hematological outcomes of splenectomy in congenital hemolytic anemia patients.

Patients and methods
It was a retrospective descriptive study in the Pediatric Hematology Ward involving patients aged 4–18 years from 2010 to 2016. Data were collected using a structured questionnaire and analyzed using the Statistical Package for the Social Sciences, Version 20.

Results
The study was performed on 104 patients, 60 males and 44 females, age range 4–18 years. The mean age was 9.19 ± 3.33. Postoperative complications developed in 26% of patients, mostly wound infection, hematological parameters, especially hemoglobin level, are elevated after splenectomy and is equal to 6.74 ± 1.27 g% in most patients. Splenectomy decreases blood transfusion needs to 50% of the presplenectomy stage and increases the interval in between blood transfusion after splenectomy to the double.

Conclusion
Splenectomy to the children who suffered from congenital hemolytic anemia such as beta thalassemia major, sickle cell anemia and spherocytosis improved hematological parameters, especially hemoglobin level, so the number of blood transfusions and hospital admissions decreased that improved the quality of life. On the other side, there are early and late postoperative complications which can be avoided by proper perioperative vaccination and taking postoperative 2-weekly long-acting penicillin.

Rationale
Identify the clinical and hematological outcomes of splenectomy in children due to hematological disorders, especially β-thalassemia major. In the locality splenectomy is still one of the most important modalities used in the partial treatment of chronic hemolytic anemia.

Keywords:
anemia, autoimmune disease, β-thalassemia major, chronic idiopathic thrombocytopenic purpura, congenital hemolytic anemia, hemoglobinopathies, membrane defects, spherocytosis, splenectomy, thrombocytopenia

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Introduction

Spleen is a very essential part of the reticuloendothelial system that is considered as the mononuclear phagocyte system. Spleen has a lot of functions such as filtering (culling, pitting, and remodeling), reservoir functions (hematopoiesis), and immunological functions such as phagocytosis of microorganisms and antibody-coated cells, antibody synthesis, cellular immunity, generation of lymphocytes, production of tuftsin in addition to its role in alternate pathway of complement. Other functions include: effects on factor VIII, serum angiotensin-converting enzyme activity, and iron metabolism [1].

If the spleen stops working (surgically removed), the body's immune system can compensate, but significant risk of sepsis is still present [2].

Splenectomy is an operation in which the spleen is removed. The spleen protects the body against bacterial infections. The splenic site is in the uppermost area of the left side of the abdomen, just under the diaphragm.

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Immunization is taken before splenectomy to protect against infections that may occur to patients post-splenectomy. Prior to removing the spleen; immunization is more effective in protecting against infections.

Children undergoing splenectomy should adopt perioperative management

Perioperative management included clinical evaluation and intravenous fluids should be given before surgery and continues postsplenectomy till they have adequate oral intake. Patients also should take pneumococcal, meningococcal, and *Hemophilus influenza* vaccines at least 2 weeks preoperatively. This is given postoperatively in emergency operations only. Preoperative packed red blood cells should be given to increase hemoglobin (Hb) to 10 g/dl; hypoxia, acidosis, hypothermia, and hypercarbia should be avoided at the time of surgery. Finally postsurgery analgesia should be given; chest physiotherapy and early mobilization should be done [3].

Postsplenectomy care

All patients that have undergone splenectomy should take pneumococcal immunization. Meningococcal C and *H. influenzae* type B vaccine must be given to nonimmunized patients. Influenza immunization should be taken every year. Patients also should take prophylactic antibiotics at least for the first 2 years after splenectomy but better if continued for the rest of life. Patients should also receive systemic antibiotics or even admitted to a hospital if infection is suspected [4].

Complications of splenectomy

Hemorrhage, thromboembolism, subphrenic abscess, pneumonia, and fulminant sepsis following splenectomy [overwhelming postsplenectomy infection (OPSI)].

It also increases the risk of venous (splenoportal system) or arterial thrombosis due to the increase in the number of platelets postoperatively; hence, the recommendation is not to neglect preoperativeand postoperative anticoagulation. In sickle-cell anemia, pulmonary hypertension has been described as a serious complication.

Bacterial infection is a common complication of splenectomized individuals, and splenectomy leaves the patients vulnerable to encapsulated germs (*Streptococcus pneumoniae*, *H. influenzae*, and *Neisseria meningitidis*); so, it is recommended that patients over 2 years of age and those with functional hyposplenism be vaccinated against pneumococcus, *H. influenzae* type B, and meningococcus at least 2 weeks before splenectomy. In cases of emergency splenectomy, immunization should be performed postoperatively. They should also undergo antimicrobial chemoprophylaxis lifelong. The risk of OPSI is more common and closer to the date of splenectomy and characterized by rapid evolution, hypotension, altered consciousness, or cardiocirculatory shock.

Morbidity and mortality postsplenectomy are mainly due to hemorrhage, infections, and indication for myeloproliferative diseases, such as myelofibrosis and chronic granulocytic leukemia [5].

Guidelines and recommendations for splenectomy

Recommendation for surgery in case of hereditary spherocytosis

The laparoscopic approach is the best. If partial splenectomy is needed, follow-up studies should be done. Ideal splenectomy should be done after the age of 5 years.

In children undergoing splenectomy, if there are symptomatic gallstones, cholecystectomy should be done concomitantly. Extended thrombosis prophylaxis after splenectomy in patients with HS is not indicated [6].

Recommendations for splenectomy in case of hemoglobinopathies (sickle cell and thalassemia)

Frequent blood transfusion, hypersplenism, and splenic abscess [7].

Recommendations for splenectomy in case of autimmune hemolytic anemia

Splenectomy is reserved for patients whom steroid is contraindicated or ineffective [8].

Hematopathology of chronic hemolytic anemias

Hemolytic anemia is a disorder in which red blood cells are destroyed faster than they can be made. The destruction of red blood cells is called hemolysis. Red blood cells carry oxygen to all parts of your body. If there is a lower than normal amount of red blood cells, anemia occurs where blood cannot bring enough oxygen to all body tissues and organs. Without enough oxygen, body cannot work as well as it should. Two common causes of hemolytic anemias are sickle cell anemia and thalassemia. These conditions produce red blood cells that do not live as long as normal red blood cells.

Hypersplenism is complication in children with congenital hemolytic diseases. Hypersplenism is an

overactive spleen. When spleen is overactive, it removes too many blood cells, including healthy ones. Without enough healthy, mature blood cells, the body has a harder time fighting infections and the person may become anemic or even pancytopenic. Anemia occurs when blood does not have the proper amount of oxygen, due to a low number of red blood cells. Diagnosis is generally made based on a physical examination to check an enlarged spleen, blood tests to examine concentration of red and white blood cells and imaging tests, such as an ultrasound, to visualize the spleen. Hypersplenism is a main cause for splenectomy in thalassemia major. By splenectomy, the overdestruction to blood elements caused by the overactive spleen ends thereby improving the Hb level and platelet count, thus decreasing blood transfusion times, frequencies, and risks, thus improving the quality of life [9].

Aim

The aim was to study hematological outcomes of splenectomy for hemolytic anemia with special emphasis on causes, complications, preoperative care, splenectomy technique, and postoperative care.

Patients and methods

This is a retrospective descriptive study.

Study setting: pediatric hematology ward.

Study subjects

(1) Inclusion criteria: children aged between 4 and 18 years, to whom splenectomy was done for chronic hemolytic anemia
(2) Exclusion criteria: other causes of splenectomy, for example, accidental injury, abscess, trauma
(3) Sample size calculation: all patients (104) with splenectomy admitted to the Assiut University Children Hospital from 2010 to 2016 and those fulfilling the inclusion criteria.

Study tools: questionnaires and review of the patient' records.

The descriptive sheet (questionnaire) of the study include:

Statistical analysis

The data were tested for normality using the Anderson–Darling test and for homogeneity variances prior to further statistical analysis. Categorical variables were described by number and percentage, where continuous variables described by mean and SD. χ^2-Test was used to compare between categorical variables where comparison between continuous variables was done by paired *t*-test. A two-tailed *P* less than 0.05 was considered statistically significant. All analyses were performed with the IBM SPSS 20.0 software (IBM Corp., Armonk, New York).

Preventive strategies to prevent overwhelming postsplenectomy infection are education, immunoprophylaxis, and chemoprophylaxis

(1) Education:
Patients should understand the time course of progression and the potential seriousness of OPSI. They should notify their doctor in the event of any acute febrile illness, rigors, or systemic symptoms and should inform any new physician or dentists of their asplenic or hyposplenic status to have adequate antibiotic cover.
(2) Immunoprophylaxis:
This is defined for
   (a) *S. pneumoniae:* pneumococcal vaccine is a polysaccharide vaccine that contains 23 bacterial types
   (b) *H. influenzae* type B immunization
   (c) Meningococcal immunization.
   It covers types A, C, W135, and Y.
(3) Chemoprophylaxis:
Penicillin or amoxicillin must be taken once daily [10].

Research outcome measures

(1) Primary (main): studying the hematological outcomes of splenectomy for hemolytic anemia
(2) Secondary (subsidiary): study of the causes, complications, postoperative care, splenectomy technique, and postoperative care.

Results

Our study was performed on 104 patients at the Hematology Department of Pediatric Hospital Assiut University. The duration of the study was from 2010 to 2016; there are 60 males and 44 females with the age range of 4–18 years. The mean age of the group was 9.19 + 3.33. Most of the patients came from rural areas (62 patients, 56.3%) and 42 (43.7%) patients came from urban areas.

Discussion

Spleen constitutes an important part of the reticuloendothelial system, also known as the mononuclear phagocyte system. The spleen plays a

History		
Name		
Age		
Sex		
Residence		
Weight		
Height		
Questionnaire		
	Yes or no	Another answer
Are you from rural or urban ?		
When were you diagnosed as		
Thalassemia		
Spherocytosis		
Sickle cell anemia		
How much do you suffer mechanical discomfort?		
How many times do you take blood per month?		
Did you find blood for transfusion easily? 'frequency'		
Did you find healthy donors easily?		
Did you find your blood group for blood transfusion easily?		
Have your ever experienced reaction or hypersensitivity from blood transfusion?		
Is compatible blood available or not?		
What is your average hemoglobin at which you receive blood?		
What about your activities, social life, and psychology before splenectomy?		
What about your school attendance and schooling before splenectomy?		
How your parents suffer before you did splenectomy?		
At which age you did splenectomy ?		
Have you received vaccinations '*Pneumococcus* vaccine, *Meningococcus* vaccine, *Haemophilus influenza*' type B 'before or after splenectomy?'		
For those who received vaccinations after splenectomy…why?		
For those who didn't receive vaccinations at all …why?		
Do you take prophylactic antibiotic after splenectomy, e.g., long-acting penicillin?		
For those who are not compliant to antibiotics … why?		
What complications have you developed postoperatively, for example, fever, hemorrhage, sepsis, thromboemboli, or nothing at all?		
Does mechanical discomfort improved after splenectomy?		
What about frequency of blood transfusion per month after splenectomy? Did it increase or decrease?		
Do intervals between blood transfusions increased or decreased?		
What is your average hemoglobin after splenectomy? Did it increased or decreased?		
What is your average hemoglobin at which you receive blood after splenectomy?		
What about your activities, social life, and psychology after splenectomy?		
What about your school attendance and schooling after splenectomy?		
Does your quality of life improved after splenectomy or not?		
Are you more happy totally after or before splenectomy?		
What is your parents' impression after splenectomy?		
Examination		
Vital signs		
Pulse		
Blood pressure		
Temperature		
Respiratory rate		
Pallor		
Jaundice		
Cyanosis		
Head and neck examination		
Thalassemic facies		
Upper and lower limb examination		
Organomegally		
Lymphadenopathy		
Skin rash (purpura, ecchymosis)		
Other system affection		

Contd...

Contd...
Investigation
Complete blood count
Hemoglobin
Mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, hematocrit
White blood cells
Platelets

role in immunity against bacterial infections and it has many other functions.

β-Thalassemia is a great health problem all over the world; excessive hemolysis and extramedullary hematopoiesis lead to splenomegaly which increase the need for blood transfusion that may need splenectomy.

In our locality still blood transfusion and splenectomy are of important strategies used in the management of chronic hemolytic anemia especially β-thalassemia as children have an excellent hematologic response after splenectomy.

In our study, β-thalassemia represents 92.4% of all splenectomy cases.

The patients incorporated in our study have undertaken splenectomy operation due to hematological disorders: splenectomy due to hypersplenism caused by thalassemia was done in 54 (52.2%) patients and due to mechanical discomfort in 42 (42.2%) patients which was also caused by thalassemia. Spherocytosis was a cause of splenectomy in five (4.8%) patients in our study. The remaining three (2.8%) patients of our study group complained of sickle cell anemia.

Splenectomy is better done after the age of 5 years to prevent OPSI; in the present study 88 patients were splenectomized after the age of 5 years but only 16 patients before 5 years due to severity of hypersplenism and mechanical discomfort.

Short-term and long-term complications may occur postsplenectomy including increased rate of thrombotic complications and OPSI [11].

Most of the patients studied were vaccinated by *Pneumococcus* vaccine, *Meningococcus* vaccine, and *H. influenza* type B vaccine as illustrated by Tables 1 and 2. Patients compliant to taking long-acting penicillin every 2 weeks were 73% (76 patients) (Table 2). The remaining patients were not complaint to taking long-acting penicillin due to low socioeconmic factors, poverty, painful injection, and shortage of the product.

Hemorrhage developed in three patients only that were reexplored and secured. Acute dilatation of the stomach (3.7%) occurred in two patients and was treated by an a nastrogastric tube. Wound infection occurred in seven patients and one patient only developed incisional hernia (3.7%) as a late complication. Subphrenic abscess developed in two patients and thromboembolic complications developed in two patients. Pancreatic injury and pulmonary atelectasis were not observed in our study. OPSI occurred in 10 patients of the 27 (26%) patients, who suffered from postoperative complications in our study, seven of the 10 were not vaccinated (Table 3). These results are similar to the study performed at Liaquat university in Pakistan which was done by Abdul Salam Memon; the postoperative complication at Memon's study was only 18.5% [8].

Table 1 Indications of splenectomy

	Number of patients who did splenectomy (percentage of patients who did splenectomy)
Thalassemia	
hypersplenism	54 (52.2)
mechanical discomfort	42 (40.2)
Spherocytosis	5 (4.8)
Sickle cell anemia	3 (2.8)

Splenectomy also decreases blood transfusion needs to about 50% of the presplenectomy stage and increases the interval in between blood transfusion after splenectomy to the double. In our study, annual blood transfusion rate decreased from 294.85 ± 22.6 to 138.41 ± 90.38 ml/kg/year and the time interval between transfusions increased from 14 days to about 30 days (Table 4). These results are in agreement with the results which are found by Akhtar *et al*. [11].

In patients with hematological disorder specially thalassemia, there is an increased rate of RBC removal by the spleen; therefore, RBCs, Hb, hematocrit, and RBC indices are elevated after splenectomy as well as WBCs and platelets as illustrated in Tables 5 and 6. These results are similar to results of study at the *Egyptian Journal of Surgery* done by Samir *et al*. [12].

Postsplenectomy, patients and their families had better life quality and their physical activities improved due to decreased abdominal distension, heaviness,

Table 2 Guidelines used for prevention of postsplenectomy infections (state of vaccinations)

Vaccination	Taken before splenectomy [*n* (%)]	Taken after splenectomy [*n* (%)]	Not taken [*n* (%)]	P_1 before vs after	P_2 before vs not taken	P_3 after vs not taken
Pneumococcus vaccine	65 (62.5)	30 (28.8)	9 (8.7)			
Meningococcus vaccine	65 (62.5)	30 (28.8)	9 (8.7)	<0.001**	<0.001**	<0.001**
Hemophilus influenza type B vaccine	65 (62.4)	30 (28.8)	9 (8.7)			
Long-acting penicillin every 2 weeks						
Compliant			76 (73.0)			
Noncompliant			28 (26. 29)			

P_1 compares P value between patients who took the vaccines before splenectomy with those who took after splenctomy; P_2 compares P value between patients who took the vaccines before splenectomy with those who did not take the vaccine; P_3 compares the P value between patients who took the vaccines after splenectomy with those who did not take the vaccine. Statistics test used is one-way analysis of variance test. Dose and duration: patients should take *Pneumococcal*, *Meningococcal*, and *H. influenza* vaccines at least 2 weeks preoperatively; this is given postoperatively in emergency operations only. Postsplenectomy penicillin must be taken once daily every 2–4 weeks for life or at least for the first 3 years after splenectomy (600 000 unit IM in patients <27 kg and1.2 million unit IM in >27 kg). Influenza immunization booster dose should be taken in children that present with life-threatening *H. influenza* infection and booster dose of meningococcus vaccine should be taken after 5 years. Nine patients did not tae the vaccine due to poverty, illiteracy and difficult accessibilty to the vaccines. Patients were not complaint to taking long-acting penicillin due to low socioeconomic factors, poverty, painful injection, and shortage of the product.

Table 3 Postoperative complications

Complications of splenectomy	*n* (%)
Early complications	
Hemorrhage	3 (2.88)
Stomach dilatation	2 (1.9)
Wound infection	7 (6.7)
Pulmonary atelectasis	0
Subphrenic abscess	2 (1.9)
Pancreatic injury	0
Thromboembolic	2 (1.9)
Late complications	
Incisional hernia	1 (0.96)
Postsplenectomy sepsis	10 (7 of them were not vaccinated) (9.6)
Total	27 (26.0)

Table 4 Frequency of transfusion of blood required presplenectomy and postsplenectomy

	Presplenectomy	Postsplenectomy	*P*
Intervals between blood transfusions	2 weeks±4 days	4 weeks±5 days	<0.001**
Annual transfusion rate	294.85±22.6 ml/kg	138.41±90.38 ml/kg	<0.001**
Number of blood transfusions per year	24±2	12±3	<0.001**

Presplenectomy means before splenectomy, postsplenectomy means after splenectomy. Statistics test used is paired sample *t*-test.

Table 5 Laboratory parameters presplenectomy and postsplenectomy

	Presplenectomy	Postsplenectomy	*P*
CBC 'pretransfusion'			
Hb	4.75±1.02	6.73±1.27	<0.001**
RBCs	3.1±0.61	3.80±1.2	<0.001**
MCV (fl)	62.35±8.7	72.2±8.5	<0.001**
MCH (pg)	19.16±2.6	21.6±4.5	<0.001**
MCHC (g/dl)	29.4±2.2	30.4±1.8	<0.001**
HCT (%)	22.60±5.42	18.81±5.3	<0.001**
WBC	7.60±3.40	15.48±11.01	<0.001**
Platelets	140.600±160.9	444.700±298.4	<0.001**

Data are represented as means±SD. HCT, hematocrit; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; RBC, red blood cell; WBC, white blood cell. $P \leq 0.05$ was considered significant. Statistics test is the paired sample *t*-test.

and discomfort. Also decrease in frequency of blood transfusion and hospital visits occurred due to maintenance of adequate Hb%, as well as improve school attendance and participation in outdoor sports. Memon's Pakistanian study agrees also with our study [8].

Table 6 Benefits and improvement of quality of life of splenectomies patients and their families

	Preoperative status	Postoperative status
Blood transfusion frequency	4-5 units per month	1-1.5 units per month $P<0.001^{**}$
Hemoglobin level	4.75±1.02 g%	6.74±1.27 g% $P<0.001^{**}$
Changes and improvement of life	Patient search for 5-6 healthy donors per month	Patient search only for 1-2 healthy donors per month
	Patients suffer more traveling and multiple transfusions	Patient suffer less traveling and single transfusion
	Patient could do no or minimal physical activity only at home	Patient could resume outdoor physical activity
	Patient suffers inability for education or schooling	Patient could start schooling with improving education
	Patients suffer mechanical discomfort	Relieve of mechanical discomfort occurred
Impression of children's parents	More burden on parents	Less burden on parents

Summary and conclusion

Splenectomy to the children who suffered from chronic hemolytic anemias gain improved Hb level, so frequency of blood transfusion and hospital visits decreased, and quality of life improved. In the other side there are early and late postoperative complications specially OPSI which can be avoided by vaccination before splenectomy and taking antibiotics post splenectomy.

Recommendations include: splenectomy should be done only when indicated, splenectomy improves lifestyle and quality of life of patients with chronic hemolytic anemia, OPSI should be avoided by vaccination before splenectomy and taking antibiotics after splenectomy.

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Conflicts of interest

There are no conflicts of interest.

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