The Role of Splenectomy in The Treatment of β-Thalassemia Major Patients: A Literature Review

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Abstract

Thalassemia is a group of inherited blood disorders due to the reduction or absence of globin chain synthesis which can cause hemolytic anemia. β-thalassemia major is a severe type of thalassemia, in which patients require lifelong transfusions for survival. Extravascular hemolysis on the spleen results in splenomegaly, meanwhile, extramedullary hematopoiesis causing hypersplenism to develop in beta-thalassemia major patients. Hypersplenism, symptomatic splenomegaly, and increased annual need for blood transfusion in thalassemia patients are indicators of splenectomy. However, aside from the benefit of splenectomy which may reduce the need for transfusion in people with thalassemia with the goal of reducing iron overload, it may also be linked to several major negative effects that may outweigh any benefits, such as postoperative infections with high mortality rate and thrombotic events.

Keywords : Splenectomy; β-Thalassemia Major; Infection; Iron overload

1. Introduction

Thalassemia is a group of inherited blood disorders due to the reduction or absence of globin chain synthesis which can cause hemolytic anemia. β-thalassemia major is a severe type of thalassemia characterized by a genetic deficiency in beta-globin chain synthesis, in which patients require lifelong transfusions and may have a shorter life span than other types [1].

The excess of free α chains in beta-thalassemia patients causes hemolysis of red blood cells due to extravascular shape changes [2]. Red blood cell hemolysis can be classified as intravascular or extravascular. Extravascular hemolysis occurs in the reticuloendothelial system, one of which is in the spleen. This process will cause splenic hypertrophy resulting in splenomegaly which can be identified based on complaints of an enlarged abdomen in thalassemia patients [3].

The majority of β-thalassemia major patients rely on regular blood transfusions combined with iron chelation therapy to survive [4]. If the bone marrow is inadequate to inhibit the anemia, extramedullary hematopoiesis may persist to facilitate the bone marrow in correcting for the hemolysis, resulting in hypersplenism in beta-thalassemia major patients [5].

Splenectomy in thalassemia major is indicated in cases of increased annual need for blood transfusion in patients with thalassemia, hypersplenism, and symptomatic splenomegaly due to severe hemolysis [5] However, aside from its benefits for transfusion-dependent patients, it also has its own complications such as postoperative infections and thromboembolic events [6].

2. Splenectomy

Thalassemia major typically presents splenomegaly and hypersplenism in its clinical manifestations. The suggested method of treatment is splenectomy to reduce increased blood intake and the associated severe iron overload [33]. As the annual transfusion requirements exceed 200 ml/kg/year of pure red cells, splenectomy may be suggested as one of the numerous ways to lower blood transfusion requirements [5]. There are two ways a splenectomy can be performed, open surgery and laparoscopic. The laparoscopic method appears to be the most beneficial when performing splenectomy [5]; where patients may have less pain after surgery, shorter hospital stay, an earlier return to regular activities with shorter recovery time, fewer incidences of incisional hernia and fewer immediate complications than open surgery [7]. Meanwhile, partial splenectomy is effective in lowering blood transfusion requirements, and it is advised for children who are less than 5 years of age due to a higher risk of fulminant post-splenectomy sepsis [5, 32].

3. Risk of Complications

3.1. Infection

Splenectomy is seen as acceptable therapy in transfusion-dependent thalassemia patients and may lessen the requirement for blood transfusions [5]. However, it may also be associated with a variety of negative outcomes. Patients with thalassemia as an indication for splenectomy may have a higher future risk of sepsis or overwhelming post-splenectomy infection, in which post-splenectomy infections are potentially severe [6]. The spleen serves as a filter for bacteria and senescent blood cells, making it a crucial component of the reticuloendothelial system. Its function in preventing infections is aided by its capacity to stimulate both innate and adaptive immune responses to pathogens, including encapsulated bacteria [8]. Because splenic macrophages that filter and phagocytose bacteria and other bloodborne pathogens are removed during splenectomy, this may result in severe systemic infection, known as overwhelming post-splenectomy infection (OPSI) [9]. OPSI is a permanent life-long condition with a mortality rate is around 50 to 70% and the majority of deaths occur within the first 24 hours. With prompt diagnosis and patients are given treatment immediately, it can reduce mortality [5].

According to a study, even more than ten years after splenectomy, the risk of infectious illnesses and the risk of mortality from infections remained noticeably increased [7]. *Streptococcus pneumoniae*, *Haemophilus influenzae* type B, and *Neisseria meningitidis* are the most common organisms that cause infections in splenectomized patients, and they can lead to fulminant sepsis and mortality. Patients with asplenia are also at risk for less common infections owing to *Capnocytophaga*, *Babesia*, and malaria [8]. A cohort study in German stated that Pneumococcal infections continue to be the leading cause of severe sepsis and septic shock after splenectomy [10]. A study in Minnesota stated that there were 36% of patients developed a post-splenectomy infection, the most common infection included pneumonia [11]; being responsible for over 50% of cases of OPSI. Besides pneumonia, the risk of meningitis and septicemia were also increased significantly in splenectomized patients [7].

Splenectomized patients were more susceptible to infections and had a considerably higher risk of infections, such as pneumococcal pneumonia and septicemia. Despite extensive supportive interventions, the

mortality rate for such infections is approximately 50% [5]. Therefore, early intervention based on clinical suspicion is important. Meanwhile, those who did not obtain full complete immunization had the highest risk of infection following splenectomy. Lack of complete immunization was related to decreased time to infection and higher risks of bloodstream infections at 5 years. Vaccination protocols for all reasons, excluding cancer, will improve and lower the risk of infectious complications. [12]. According to the Guideline of Thalassemia International Federation, vaccines and prophylaxis antibiotics are recommended to be given 2 weeks prior surgery and postoperatively [5]. Additionally, patients should also be offered annual influenza vaccination which it has been shown to reduce mortality [13].

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3.2. Vascular Risk

Portal vein thrombosis is a well-known complication following splenectomy in beta-thalassemia major. Reduced coagulation inhibitor levels in women, thrombocytosis, and large splenomegaly are risk factors for developing portal vein thrombosis [14]. A study in Egypt reported a case of an 8-year-old female TM patient with a preoperative platelet count of 410 000/mm^3 who developed her PVT one year after her splenectomy [15]. After splenectomy, Doppler ultrasonography is advised in order to examine for portal vein thrombosis in all patients [14].

Splenectomized patients have a higher risk of venous thromboembolism [16]. Thalassemic patients have commonly reported thromboembolic (TE) events in addition to risk factors such diabetes, cardiac dysfunction, abnormal liver function, and post-splenectomy thrombocytosis. Although thromboembolic events are common in thalassemia intermedia patients, the incidence of TEs has been reported in thalassemia major patients in some studies [15, 17]. These events may be triggered by some factors, including anemia, changes in platelet aggregation, coagulation contact phase factors, and inhibitors, all of which contribute to a hypercoagulable condition, as well as the substantial rise in hematocrit following blood transfusion [17]. In conclusion, even before splenectomy, all thalassemia patients should be considered for prophylactic antiplatelet and antithrombotic medication. [14].

3.3. Cancer

Several studies have suggested an increased long-term cancer incidence in splenectomy patients. Splenectomy may reduce long-term immune function, making the patient more susceptible to infection. Even if patients with a history of autoimmune disease were excluded, the risk of malignancy remained significantly elevated [13]. The risk of most cancers was highest in the first 2-5 years following splenectomy and lasted for more than 10 years. Patients who underwent splenectomy had an increased risk of death from any cancer, especially from cancer of the liver [7].

4. Hematological Outcome

In transfusion-dependent thalassemia, splenectomy is used to alleviate iron overload by reducing blood intake and the requirement for transfusions. The frequency of blood transfusions per year in splenectomized patients decreased significantly after splenectomy [18-21]. A study found a decrease in the frequency of blood transfusion to about 50% of the pre-splenectomy stage, from pre-splenectomy mean of 24 times per to post-splenectomy mean of 12 times per year [22]. Meanwhile, splenectomy improves anemia by increased hemoglobin levels [22-25]. However, some studies found the maintenance of adequate Hb levels in splenectomized patients [20-21, 26].

In patients with hematological disorders, especially thalassemia, there is also an increase in platelets

[22, 26-27]; and WBC [22, 27]. Splenectomized patients were more susceptible to infection and had a higher risk of septic complications associated with higher mortality than non-splenectomized patients, which explains the increase in WBC after splenectomy. Meanwhile, the high PLT count may have contributed to the severe episodes of pulmonary embolism and deep vein thrombosis which occurred after splenectomy in some beta major thalassemia patients [27].

5. The Effect of Splenectomy on Iron Balance

The main management of patients diagnosed with β thalassemia major is life-long blood transfusions for survival. Regular blood transfusions, combined with increased intestinal iron absorption due to ineffective erythropoiesis, result in iron overload [5]. Iron overload is thalassemia major patients' primary cause of morbidity and mortality, which can be determined by serum ferritin measurement [28]. Several studies found that serum ferritin appears to increase after splenectomy [20-21, 26]. Splenectomy does not lessen the iron burden in thalassemia patients since the ferritin levels remained high after the procedure, and many patients were found to be receiving regular iron chelation [23]. A study also reported splenectomized patients had a higher incidence of myocardial siderosis than those with an intact spleen [29]. However, other study have shown that splenectomy has a positive effect on iron balance since it considerably lowers blood consumption, iron uptake, serum ferritin, and ALT levels. Although, serum ferritin and ALT levels remained elevated [23]; and showed at a very slow decreasing trend after splenectomy, despite an immediate decline in iron intake in splenectomized patients compared with non-splenectomy patients [30]. This leads to the conclusion that it remains unclear how splenectomy will affect iron overload.

6. Patient's Quality of Life

Splenectomy improve the quality of life of thalassemia patients, approximately 90.4% felt a definitive improvement in the quality of life after splenectomy [31]. Due to the decrease in the requirement for blood transfusions, patients and their families had greater quality of life, more physical activity, and fewer hospital visits as a result of maintaining sufficient Hb% [22]. In addition, the frequency of blood transfusions lowers significantly with a decrease in physical, psychological, and financial burden on patients and their family [25]. Splenectomy also promotes physical activities with improved school attendance and academics [25, 31]. After a splenectomy, patients' and their families' overall quality of life improves, thus the procedure shouldn't be postponed if necessary.

7. Conclusion

Splenectomy is widely considered an appropriate option in β-thalassemia major, but it also carries an increased risk of many post-splenectomy-related morbidities, including overwhelming post-splenectomy infection (OPSI). Vaccines and prophylaxis antibiotics are recommended to be given prior surgery and postoperatively to reduce the risk of infectious complications. Moreover, splenectomy benefits in decrease frequency of blood transfusions and excellent hematological outcome with improved quality of life, but the effect of splenectomy on iron overload remains unclear.

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