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Original study

Outcome following splenectomy in young thalassemic patients aged five to eighteen years. A single centre observational study.

Genç talasemi hastalarında (5-18 yaşları arası) yapılan splenektomi sonrası izlem sonuçları. Tek merkezli gözlemsel bir çalışma.

Paul Dibyashree, Arkaprovo Roy, Shuchismita Chakraborty, Alamgir Hossain

Medical College, Kolkata, India
Corresponding address: Dr. Paul Dibyashree, **drdpaul25@gmail.com**
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ABSTRACT

Excessive destruction of abnormal red blood cells and resultant extra-medullary haematopoiesis in beta thalassemia major leads to splenomegaly, hypersplenism and increased requirement of blood transfusion, which often necessitate splenectomy.

To evaluate the outcome of splenectomy among patients with beta thalassemia major

A retrospective cross-sectional study was conducted on 26 beta thalassemia major patients, in the age group of 5 to18 years, who underwent elective splenectomy in a tertiary hospital between April, 2016 and May, 2018. Their pre-operative, peri-operative and post-operative follow up data were collected from a prospectively maintained database and analysed.

Out of 26 patients, 8 (30.8%) were female and 18 (69.2%) male. Mean age of our study population was 9.3 years. Mean haemoglobin at the time of admission was 5.76 +/- 0.49 g/dl and mean pre-operative blood transfusion requirement was 31.77 +/- 9.34 units/yr. Median length of post-operative hospital stay was 6 days. Immediate post-operative complications included haemorrhage in 1 (3.8%) patient, sepsis in 1 (3.8%), pulmonary complication in 1 (3.8%), wound infection in 2 (7.7%) and death of 2 (7.7%) patients. 19 (73.1%) patients did not encounter any post-operative complication. The mean blood transfusion requirement after splenectomy, as assessed in median follow-up over 26 months, was 13.00+/-7.15 units/yr.

In conclusion, for patients with beta thalassemia major being managed in resource limited set-up, splenectomy can be considered as an effective procedure for reducing the blood transfusion requirement and hence, prevent its associated adverse effects.

Keywords: Thalassemia; splenectomy; outcome.

ÖZET

Anormal kırmızı kan hücrelerinin aşırı yıkımı ve bunun sonucunda beta talasemi majörde ekstra-medüller hematopoez, splenomegaliye, hipersplenizme ve sıklıkla splenektomi gerektiren kan transfüzyonu gereksiniminin artmasına neden olur.

Amacımız beta talasemi majörlü çocuk hastalarda splenektomi sonuçlarını değerlendirmektir.

Üçüncü basamak bir hastanede Nisan 2016 ve Mayıs 2018 tarihleri arasında elektif splenektomi uygulanan 5-18 yaş grubundaki 26 beta talasemi majör hastası üzerinde retrospektif kesitsel bir çalışma yapılmıştır. Ameliyat sonrası takip verileri ileriye dönük olarak tutulan bir veri tabanından toplandı ve analiz edildi.

26 hastanın 8'i (%30,8) kadın, 18'i (%69,2) erkekti. Çalışma grubumuzun ortalama yaşı 9,3 idi. Başvuru anındaki ortalama hemoglobin 5,76 +/- 0,49 g/dl ve ameliyat öncesi ortalama kan transfüzyon ihtiyacı 31,77 +/- 9,34 ünite/yıl idi. Ameliyat sonrası hastanede kalış süresi ortalama 6 gündü. Postoperatif ani komplikasyonlar 1

(%3,8) hastada kanama, 1 (%3,8) hastada sepsis, 1 (%3,8) hastada pulmoner komplikasyon, 2 (%7,7) hastada yara enfeksiyonu ve 2 (%7,7) hastada ölüm şeklindeydi. 19 (%73,1) hastada postoperatif herhangi bir komplikasyonla karşılaşmadı. 26 aylık medyan takipte, splenektomi sonrası ortalama kan transfüzyonu gereksinimi 13.00+/-7.15 ünite/yıl idi.

Sonuç olarak, sınırlı kaynaklarla tedavi edilen beta talasemi majör hastalarında splenektomi, kan transfüzyonu gereksinimini azaltmak ve dolayısıyla ilişkili olumsuz etkileri önlemek için etkili bir prosedür olarak kabul edilebilir.

Anahtar kelimeler: Talasemi; splenektomi, takip.

INTRODUCTION

Thalassemia is a Greek word derived from thalassa meaning ‘sea’ and emia meaning ‘related to blood’. The disease is more common in Southeast Asia and Africa (1). It is the most common genetic disorder in the world, with an incidence of 10-15 % in the Mediterranean and Southeast Asia (2). In this autosomal recessive inherited haematological disorder, the synthesis of the alpha or the beta globin chain of haemoglobin is either decreased or absent. Depending on the type of globin gene affected, thalassemia can be classified as alpha or beta, the latter being more common. Clinical abnormalities are attributable to ineffective erythropoiesis and premature destruction of erythroblasts and fragile red blood cells (RBC) leading to anaemia.

The clinical spectrum of beta thalassemia includes thalassemia minor or thalassemia trait, thalassemia intermedia and thalassemia major. Patients with thalassemia minor and intermedia have mild to moderate anemia and usually do not require regular blood transfusions. However, patients with thalassemia major have severe anaemia and become transfusion dependent from childhood. Nowadays, thalassemic patients are classified into transfusion dependent thalassemia (TDT) or non-transfusion dependent thalassemia (NTDT) depending on the requirement of regular blood transfusions.

The unbalanced alpha and beta globin chain synthesis leads to accumulation of unpaired alpha chains in cytoplasm which form toxic inclusion bodies that kill the developing erythroblasts. The surviving RBCs containing inclusion bodies are trapped and destroyed in the spleen, leading to splenomegaly and profound haemolytic anaemia. This stimulates erythropoietin release resulting in compensatory erythroid hyperplasia and extra-medullary haematopoiesis, and a vicious cycle ensues. Extra-medullary haematopoiesis and haemolytic anaemia lead to gross hepatosplenomegaly, growth retardation, gall stones, leg ulcers and high output congestive heart failure (2).

On the other hand, repeated blood transfusions at short intervals lead to accumulation of iron in liver, heart, pancreas, testis, thyroid and the central nervous system. Consequently, cardiomyopathy, cirrhosis of liver, diabetes mellitus, hypopituitarism, hypogonadism and infertility ensue.

The rationale of splenectomy in TDT patients is to reduce transfusion requirement and thereby decrease iron overload (3).

MATERIAL and METHOD

Study design

We conducted a retrospective cross-sectional descriptive study, using a prospectively collected database, in the Department of General Surgery at a tertiary care hospital.

Study population

Twenty-six patients with beta thalassemia major, aged 5 to 18 years, who had undergone elective splenectomy in this institution between April, 2016 and May, 2018 were included in the study. Written informed consent was obtained from each participant. Data regarding clinical examination findings, pre and post-operative blood transfusion requirement, hospital course, post-operative complications and any infection were collected from the patients’ record books. The procedures followed were in accordance with the ethical standards of the Institutional Ethics Committee and the Helsinki Declaration of 1975, revised 2013.

Inclusion criterias

i. Beta thalassemia major patients undergoing elective splenectomy between April, 2016 and May, 2018.

ii. Patients aged 5 yrs to 18 yrs.

iii. Patients who provided written informed consent to participate in the study.

Exclusion criteria

i. Patients undergoing splenectomy for other causes.

ii. Patients below 5 yrs or above 18 yrs of age.

iii. Patients who did not provide written informed consent.

Pre-operative preparation

A standardised protocol was followed for pre-operative preparation. All patients were vaccinated with Pneumococcal, Meningococcal and Haemophilus influenza type b (Hib) vaccines at least 14 days before operation. Pre-operative haemoglobin cut-off was taken as 5 gm/dl. Pre-operative blood transfusion was done in patients with lower haemoglobin (Hb) level in order to raise it to 5gm/dl or more. Pre-operative blood investigations included complete haemogram, serum electrolytes, PT/INR, APTT, liver and kidney function tests and viral markers. Chest X-ray and electrocardiogram were done for

anaesthetic check-up. Abdominal ultrasonography or contrast enhanced computed tomography was done to assess size of the spleen.

Operative technique

Open splenectomy was carried out under general anaesthesia on an elective basis in all cases.

Post-operative care

Antibiotic was given routinely at the induction of anaesthesia and continued for 5-6 days post-operatively depending on patient's condition. Monitoring of pulse, blood pressure, temperature, intake and output was done during post-operative hospital stay. Patients were allowed orally from post-operative day 1.

Follow up

All patients were followed up at the out-patients' clinic for at least one year.

Operational definitions

i. 1 unit of PRBC was taken as 250ml.

ii. Hypersplenism was defined as anaemia, neutropenia or thrombocytopenia with or without splenomegaly.

iii. Abdominal discomfort due to splenomegaly was defined as massive splenomegaly (crossing the umbilicus) leading to huge abdominal distension and interfering with daily routine activities.

Statistical analysis

The short term outcomes analysed were intra-operative blood transfusion requirement, length of hospital stay, post-operative complications and mortality occurring within one month of operation. The long-term outcomes analysed was blood transfusion requirement (in ml/kg/yr) after splenectomy. Data were analysed with SPSS software for Windows. Quantitative data were presented as mean +/- standard deviation and compared using Student's t test. Qualitative data were presented as number and percentage. Results were considered statistically significant if P value <0.05.

RESULTS

Patient characteristics

The mean age of the patients was 9.3 years (range: 5 to 18 yrs). There were 18 (69.2%) male and 8 (30.8%) female subjects. Most common indications of splenectomy was hypersplenism in 16 (61.5%) patients followed by increased transfusion requirement in 6 (23.1%) and massive splenomegaly (crossing the umbilicus) causing abdominal discomfort in 4 (15.4%) (Table1). Pre-operatively, the mean blood transfusion requirement was 31.77+/-9.34 units of PRBC/year. Mean haemoglobin at the time of admission was 5.76 +/- 0.49 g/dl.

Table 1: Indications of splenectomy (n=26).

Indications	n	Percentage (%)
Hypersplenism	16	61.5
Increased transfusion requirement	6	23.1
Abdominal discomfort	4	15.4

Peri-operative outcome

Mean intra-operative transfusion requirement was 1.12+/-0.32 units of PRBC. Post-operative complications occurred in 7 patients and included wound infection in 2 (7.7%) patients, sepsis in 1 (3.8%), haemorrhage in 1 (3.8%), pulmonary complications in 1 (3.8%) and death of 2 (7.7%) patients. 19 (73.1%) patients did not encounter any post-operative complication. Median length of post-operative hospital stay was 6 days.

Follow up

Follow-up was done for a median period of 26 months. Mean transfusion requirement post-splenectomy decreased to 13.0+/-7.15 units of PRBC/year and the difference from the mean pre-operative transfusion requirement (31.77+/-9.34 units of PRBC/year) was statistically significant (p value <0.001, 95% confidence interval) (Table2). Long-term complications observed were recurrent infections in 3 (12.5%), thrombosis in 1 (4.2%) and sub acute intestinal obstruction in 1 (4.2%) patient, all of which were managed conservatively.

Table 2: Difference between pre and post-splenectomy transfusion requirements (units/year).

	Paired Differences					T score	Df	Significance (2-tailed) P value
	Mean	Standard deviation	Standard error of mean	Lower limit of 95% CI	Upper limit of 95% CI			
Pre and post-splenectomy blood transfusion requirement (units/year)	18.75	4.56	0.93	16.82	20.67	20.13	23	<0.001

Df – Degree of freedom, CI-Confidence interval

DISCUSSION

Splenomegaly in thalassemia is primarily a consequence of inadequate transfusion therapy. In order to suppress extra-medullary erythropoiesis, the pre-transfusion hemoglobin (Hb) should be maintained above 9–10.5 g/dL (4,5). Maintenance of a suboptimal haemoglobin level over an extended period of time, as is the situation in resource poor set-ups, promotes the development of splenomegaly and resultant hypersplenism. Consequently, a vicious cycle of low Hb and increased transfusion requirement ensues.

In these individuals, splenomegaly may be reversible with adequate transfusion for prolonged periods (6). However, this is seldom the option for us as we are challenged with restricted blood supply, limited medical and financial resources and lack of awareness among patients and guardians who mostly seek medical help only when symptomatic. Hence, we often have to resort to splenectomy to curb the increasing transfusion needs and reduce iron overload.

The spleen is involved in both innate and acquired immunity. Splenectomised patients are susceptible to infection by a variety of pathogens, especially encapsulated organisms like Streptococcus pneumoniae , Neisseria meningitides or Haemophilus influenzae type b and Gram negative organisms like Escherichia coli and Pseudomonas species, which may cause overwhelming post-splenectomy infection (OPSI). OPSI is defined as a syndrome of fulminant sepsis that may initially present as generalized non-specific viral symptoms but very quickly deteriorates into a charade of multiple organ failure within 24–48 hours (7). Vaccination against S. pneumoniae, N. meningitidis, and H. influenzae type b (Hib) can help prevent OPSI and these vaccines should preferably be administered either 14 days prior to planned splenectomy or 14 days after an urgent splenectomy to ensure an adequate response (7). In our study, all patients were vaccinated with these vaccines 14 days before elective surgery.

The usual indications for splenectomy in patients with thalassemia include hypersplenism, increased blood transfusion requirements and symptomatic splenomegaly (6), out of which most common is hypersplenism (8,9). Similar picture is observed in our study where hypersplenism was the indication in majority (61.5%) of cases. Splenectomy is advised when blood transfusion requirement becomes more than 250ml/kg per year or interval between blood transfusions becomes less than 2 weeks (10). In our study group, the mean annual preoperative blood transfusion requirement was 31.77+/-9.34 units of PRBC.

Reduction in transfusion requirement after splenectomy has been well documented in a number of studies (9-12). Similar result has been found in our patients as well.

Median post-operative hospital stay (6 days) of our patients was less than that reported in the study conducted by Konstadoulakis (6.5 days) (13).

Infections and thromboembolic events are common complications after splenectomy(14).The incidence rate of OPSI among splenectomised individuals is 0.13 per 100 person years and is associated with significant morbidity as well as up to 50–70% mortality (15,16). We encountered 12.5% recurrent infections and 4.2% thrombotic events in our splenectomised patients. However, none of our patients suffered from OPSI.

The limitations of this study include – data ragarding the iron load of the patients before and after splenectomy was not obtained, it was a retrospective study and had limited follow-up period. A prospective study with longer follow-up and analysis of quality of life is required to confirm the parameters evaluated in this study.

Conclusion

Splenectomy can be viewed as a necessary evil for suboptimally transfused beta thalassemia major patients. Although it reduces transfusion requirement, there remains a concern for the risk of recurrent infections and thrombotic events. Prophylactic vaccination is recommended to reduce the risk of OPSI.

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