Surgical and anaesthetic outcomes of paediatric splenectomies at a tertiary care institution in South India – A retrospective cohort

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Abstract

Purpose

Splenectomies though well-established in the successful management of several resistant haemoglobinopathies, have not been studied in detail in the paediatric population to assess the outcomes. We conducted this review to primarily assess the surgical and anaesthetic outcomes of paediatric splenectomies and secondarily highlight factors predictive for a high-risk splenectomy.

Methods

A 5 year retrospective chart review was made, and patient follow-up was done jointly using the hospital electronic medical records and telephonic calls. A p value of <0.05 was considered significant.

Results

Among the 69 splenectomised children, 61% were male and the overall mean age was 10.2 years. The cohort consisted of thalassemia's(46%), ITP's(30%), haemolytic anemias(19%) and 1 child each with lymphoma, splenic cyst and Kassabach Meritt syndrome. Most(96%) were electively operated and 23% were performed laparoscopically. 61% received intravenous analgesia and the mean volume of fluid administered intra-operatively was 21ml/kg. There was no documented OPSI, and there was one mortality. The mean follow-up period was 43 months.

Conclusion

Splenectomy was associated with a promising overall outcome with a survival rate of 98.5%. A greater pre-operative transfusion requirement, a larger sized spleen and increased fluid administration intra-operatively, were associated with a worse outcome.

Introduction

Splenectomy has long been recognized as a therapeutic approach to manage patients severely affected with thalassemias (transfusion dependant (TD) and non-transfusion dependant (NTDT)), haemolytic anemias (HA), Immune thrombocytopenic purpuras (ITP) and other miscellaneous haematological conditions based on the evidence that eliminating the splenic macrophage system will ease the disease burden.

Despite the well-established therapeutic potential, concerns remain regarding short and long-term infectious and thrombotic complications [1,2]. The permanent immune impairment rendered by asplenia and susceptibility to severe bacterial infections, along with the increased risk of thromboembolic phenomena, make splenectomy a challenging decision to make especially in the paediatric population.

Copious amounts of literature exist on haematological outcomes of a splenectomy, however data on surgical and anaesthetic concerns in the paediatric population are sparse. With the unavoidable ongoing debate on the risks versus benefits of paediatric splenectomies, we deemed it worthwhile to review the outcomes of the paediatric splenectomies performed at our institution.

Our primary aim was to assess the surgical and anaesthetic outcomes of paediatric splenectomies which included duration of hospital stay, identification of peri-operative events/complications, morbidity and mortality. The secondary aim was to identify factors to predict high risk splenectomies.

Materials And Methods

After obtaining Institutional review board approval (Number- 11826, approved on 30.01.2019), a retrospective chart review was done to retrieve data on paediatric splenectomies performed at our institution over a 5-year period (January 2013-December 2018). The study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. The study was granted exemption from requiring ethics approval, by the Institutional review board as it was retrospective in nature. We derived our study cohort from the hospital medical record system, and data collected included demography, the indications, co-morbid conditions, pre and post-operative investigations, peri-operative surgical and anaesthetic events, and survival of the patients.

The co-morbid conditions were classified into major and minor based on whether medical intervention was required or not. The duration of hospital stay was sub-classified as short stay (3-4 days), regular stay (5-6 days) and long stay (more than or equal to 7 days). For meaningful analysis, the final outcome was divided into the following groups: alive without transfusion, alive with transfusion, expired, or, lost to follow up. Overall survival (OS) was defined as the number of months from the day of splenectomy to the last day of follow-up or death.

Data was computed using Numbers software and descriptive statistics were reported using Mean+/- standard deviation for continuous variables. Frequency, percentages and median were used for categorical variables. Comparison of mean between two groups was done using Mann Whitney's U test, and more than two groups were reported using Kruskall Wallis test. Correlation between the variables was reported using Pearson's Correlation. Association was reported using Chi-square/Fisher’s exact test. Time to event analysis was carried out using Kaplan and Meier Curves. A p value of <0.05 was considered statistically significant. SPSS 21.0 (IBM,Bangalore) was used for the analysis.

Results

During the 5 year period, there were a total of 69 children who underwent splenectomy, with a mean of age of 10.2 years (Range 3-16). Of these, 42 were boys and 27 were girls. With the exception of 4 patients

from outside the country, the remaining hailed from various states within India including 34 from South India, 27 from East India, and 2 each from Northern and Western Indian states (Table 1).

Table 1: Group wise distribution of patient demography

Parameters	Thalassemia	ITP	Haemolytic anemias	Others *
Number of patients	32	21	13	3
Gender				
- Male	19	11	10	2
- Female	13	10	3	1
Age (years)				
- Median	11	9	8	13
- IQR**	9-13.8	8-12	5.5-13	-
Native place				
- North India	4	1	1	1
- South India	12	11	9	2
- East India	14	7	2	0
- West India	0	1	1	0
- Outside India	2	1	0	0
Duration of hospital stay (days)				
- Median	6	5	4	5
- IQR**	4-7	4-6.5	3-5.5	-
Year of surgery				
- 2015	5	9	5	1
- 2016	12	5	1	1
- 2017	7	5	4	1
- 2018	8	2	3	0

- Not applicable/could not be calculated. Native place: North India (Uttar Pradesh, Tripura, Assam, Madhya pradesh, Meghalaya), South India (Tamilnadu, Andhra Pradesh, Kerala), East India (Bihar, Jharkand, Odisha, West Bengal), West India (Maharashtra), Outside India (Bangladesh).

* Splenic cyst, Lymphoma, Kassabach Meritt syndrome, ** IQR-Interquartile range (Lower quartile-Upper quartile)

Children with a wide range of haematological conditions composed the splenectomy cohort which consisted of patients with mainly thalassemia (n=32, 46%), ITP(n=21, 30%) and HA(n=13, 19%). There was one child each with lymphoma, Kassabach Meritt syndrome and a splenic cyst and these were excluded from the disease specific analysis.

Of all surgeries, 96% were elective and 4% were emergencies. All patients were vaccinated against capsulated organisms according to the recommended institutional protocol within 2 weeks prior to surgery when elective, and 2 weeks following surgery when operated as an emergency. When indicated, pre-operative transfusions and/or oral chelation were given (Deferasirox was preferred over Deferiprone). Open splenectomies (71%) were more common than laparoscopic (23%) and laparoscopy converted to open (6%) splenectomies comprised the rest. The mean operating times in each of these groups were 132, 212 and 199 minutes respectively. No accessory spleens or splenunculi were recorded in any of the patients. All surgeries were performed under general anaesthesia with 61% receiving intravenous analgesics in the form of morphine or patient controlled analgesia. The remaining 39% had analgesia administered by means of epidural catheters. The volume of fluid administered intra-operatively was documented in 81% and averaged at 21ml/kg with a median of 17.7ml/kg. The entire cohort received post-operative antibiotic prophylaxis and education about overwhelming post splenectomy infections (OPSI). In 5% of patients we observed infections during the follow-up period, however none of them fulfilled the criteria for OPSI. The median duration of hospital stay was 5.4 days.

Overall, there was found to be no correlation between the duration of hospital stay and any of the demographic factors, type of disease, indication for surgery, co-morbidities, or modality of analgesia used. There was a negative correlation between the duration of hospital stay and pre-operative values of haemoglobin and platelets, however this was not statistically significant.

There was a statistically significant correlation ($p=0.007$) between the requirement of pre-operative blood transfusions and the duration of hospital stay, ie those requiring more pre-operative transfusions had a significantly longer stay. Likewise, there was a statistically significant correlation between intra-operative fluid administered and duration of hospital stay ($p=0.013$). A longer duration of hospital stay was associated with increased administration of intra-operative fluid which was found to be statistically significant at a 6% confidence interval. There was a highly significant ($p<0.01$) correlation between duration of hospital stay and spleen size, a larger spleen having a longer duration of stay.

By means of a one way Anova test it was found that there was no difference between pre-operative haemoglobin and duration of stay in any of the groups. By the Kruskal Wallis test, it was found that in the in the HA group alone there was a significant difference between pre-operative ferritin and duration of stay (longer) which was significant at a 6% confidence interval. Amongst the other two groups, ferritin values did not have any bearing on the duration of stay.

The OS for the entire splenectomy cohort was 98.5% with a mean duration of survival of 43 months. Among the individual groups, the calculated OS rates were 96.9%, 100% and 100% in thalassemia, ITP, and HA groups respectively.

For clarity of results, we separately analysed the patient data under the following disease specific sub-categories. Table 2 summarises these results.

Table 2: Group wise distribution of the study results

PARAMETERS	Thalassemia (n=32)	ITP (n=21)	Haemolytic anemias (n=13)
Indications for surgery			
- Medical management failure	0	20	1
- Transfusion dependent	24	1	8
- Hypersplenism	3	0	1
- Transfusion dependent + Hypersplenism	5	0	3
Co-morbidities (more than 1 possible)			
- Major ^^	10	3	2
- Minor ^^^	2	2	1
- None	26	16	10
Duration of hospital stay (days)			
- 3-4	9	10	8
- 5-6	13	6	3
- >/= 7	9	5	2
Median/Mean haemoglobin levels (g/dl)			
- Preoperative	7.6/7.7	12.1/11.6	8/8.3
- Postoperative	10.9/10.8	10.9/10.9	9.8/10/8
Median/Mean platelet count (lakh)			
- Preoperative	1.3/1.5	0.13/0.19	1.7/2.3
- Postoperative	2.2/3.1	0.56/0.80	3.5/3.8
Median/ Mean ferritin levels (ng/ml)			
- Preoperative	1565/2270.4	-	749/985.5
- At last follow-up	2846/3286.6	-	2569/2569 (n=2)

PARAMETERS	Thalassemia (n=32)	ITP (n=21)	Haemolytic anemias (n=13)
Pre-operative disease specific medication			
- Desferrioxamine	19	0	2
- Hydroxyurea	10	0	0
- Ecospirin	2	0	1
- Steroid	0	21	1
- Azathioprine	0	21	1
- Dapsone	0	20	0
- Intravenous Immunoglobulins	0	7	0
- Danazol	0	3	0
- Tacrolimus	0	1	0
- Mycophenolate Mofetil	0	1	0
- Rituximab	0	0	1
Median/Mean number of transfusions prior to making the surgical decision			
- Platelet concentrate	0	5/12.3	0
- Packed red cells	78/91	-	14/29
Requirement of pre-operative optimisation			
- None	8	14	7
- Packed red cells	24	0	6
- Platelet concentrate	0	7	0
Ultrasonography findings			
- Median/Mean Spleen size (cms)	18/18.7	8.6/9.3	13.7/14.2
- Gallstones present	6	0	4
- Portal vein enlarged	3	0	0
- Splenic vein enlarged	2	0	0
- Hepatomegaly	17	0	4

PARAMETERS	Thalassemia (n=32)	ITP (n=21)	Haemolytic anemias (n=13)
Approach to splenectomy			8
- Open	32	6	3
- Laparoscopic	0	13	2
- Laparoscopy converted to open	0	2	
Median/ Mean surgical duration (minutes)			
- Open	120/129	120/130	120/121
- Laparoscopic	-	210/215	180/200
- Laparoscopy converted to open	-	188/188	210/210
Intra-operative analgesia			
- Intra-venous including Patient controlled analgesia	17	4	6
- Epidural	15	17	7
Intra-operative parameters			
- Haemoglobin (g/dL)	8.7 *** (n=1)	-	-
- Potassium (mg/dL)	2.9 *** (n=1)	-	-
- IV Fluid administered (ml/kg)	17.3/18.2	18/24.5	17.8/21.3
- Urine output (ml/kg/hour)	5/5 (n=2)	-	2/1.7 (n=3)
Intraoperative transfusions			
- Packed red cells	15	5	5
- Platelet concentrate	1	13	1
- Cryoprecipitate	0	1	0
- Fresh Frozen Plasma	1	3	0
Reportable events			
- Anaesthetic	1*	0	0
- Surgical	1**	2^	2^
Post-operative ecospirin			
- Yes	13	0	7
- No	19	0	6

PARAMETERS	Thalassemia (n=32)	ITP (n=21)	Haemolytic anemias (n=13)
Median/Mean follow-up (months)	12.5/14	23/21	15/14
Final outcome			
- Alive without transfusion	10	17	10
- Alive with transfusion	15	1	2
- Expired	1	0	0
- Lost to follow up	6	3	1

- Not applicable/ Not done

* Elaborated in the discussion section, **Pneumothorax, *** Done on the patient who was brought in for emergency splenectomy in a critical condition, ^ Bleeding, Pancreatic tail injury, ^^ Hypothyroidism, Immunodeficiency, Malignancy, Seizures, Hyperuricemia, Cushings syndrome, Cardiac illness, Chronic liver disease, Posterior Reversible encephalopathy syndrome, ^^^ Choledocholithiasis, Autism, Ceft palate, Porcencephalic cyst, Hypovitaminosis, Hypogonadism.

I) THALASSEMIA

There were 32 thalassemia patients and all underwent elective splenectomies. Of these, 15 had beta thalassemia major (TM), and 17 had NTDT (inclusive of thalassemia intermedia variants). The most common indication for splenectomy was transfusion dependency(75%). The median number of packed cell transfusions received by each child before surgery was 78.

Though most of the children(81%) were otherwise healthy, 10 had major co-morbidities and 2 had minor co-morbidities (Table 2). Nineteen patients (59%) were on pre-operative chelation therapy and their mean ferritin values were 3284.8 ng/ml pre-operatively and 3513.7 ng/ml post-operatively. Seven (39%) of these were documented to have continued the chelation post-operatively. Additionally, 10 children received hydroxyurea (to reduce transfusion requirements) and 2 received anti-platelets (aspirin) prior to surgery.

The routine pre-operative investigations done in this group were haemoglobin(100%), platelet counts(100%), ferritin(100%), creatinine(84%) and potassium(63%). Post-operatively, the same parameters were re-assessed. The mean pre and post-operative haemoglobin values were 7.7g/dl (Range 4-10.8) and 10.8g/dl (Range 7.3-14) respectively.

Twenty four (75%) of the children received packed red cell transfusions pre-operatively. 62% of children with a haemoglobin of more than or equal to 8g/dL were transfused. Thus we concluded that the decision to transfuse packed cells was consultant based rather than based on a target number.

Since thalassemic children had a uniformly large mean sonographic spleen size of 18cms (Range 12.6-32.5), all surgeries were performed via a laparotomy. Other concurrently noted significant sonographic findings were hepatomegaly(56%), portal vein enlargement(9%) and splenic vein enlargement(6%). The mean operating time was 129 minutes (Range 60-270). Cholecystectomy was performed in 19% of the patients through the same incision. One patient had an iatrogenic pneumothorax on table and an intercostal drainage tube was inserted. Subsequent recovery was uneventful.

The mean volume of intra-venous fluid administered was 18.2ml/kg and 47% of the patients needed an intra-operative packed cell transfusion. Peri-operative pain was managed with intravenous opioids in 53% and with epidural analgesics in 47%. Post-operatively anti-platelets were started in 41% of the patients and the mean post -operative platelet count in this group was 3.2 lakhs (Range 0.6-12.2).

Forty-one percent of the thalassemia patients had a regular duration of hospital stay, while 28% each had a short and long duration of stay. At the end of the follow-up period (mean of 14 months), 38% were transfusion independent and 58% required transfusions though less frequently than before.

Six patients (19%) were lost to follow up after surgery and 2 patients (6%) had infections, however none qualified as OPSI. In this sub-group we had a 10 year old girl with thalassemia intermedia who succumbed to the surgery in the immediate post-operative period in the PACU(Post anaesthesia care unit). Excluding her, there was no other mortality.

2) ITP

Twenty-one patients with ITP underwent splenectomy. The indication for splenectomy was failure to respond to medical management in all. All children had received azathioprine and steroids.

The mean pre-operative haemoglobin levels were 11.6 g/dl (Range 8-13.8) and post-operative levels were 10.9 g/dl (Range 7.2-13.2). Albeit not routinely checked, serum creatinine (48%) and potassium (48%) levels whenever done were found to be normal. Comparison of platelet counts prior to and after surgery revealed an increase in the mean count from 0.19 lakh (Range 0.03-0.9) to 0.8 lakh (Range 0.04-2.38).

Seven patients (33%) were transfused platelets immediately before surgery to optimise their counts. We found that pre-operative platelets were transfused if the count was less than 0.19 lakh.

The mean sonographic spleen size was smaller than that of the thalassemia group -9.3cms (Range 6.8-12.8). None had gallstones, hepatomegaly or an enlarged portal or splenic vein. Most of the surgeries were elective (19/21). The indications for emergency splenectomy in the remaining 2 were major transfusion requirement and an acute intra-cranial bleed. Fifteen spleens (71%) were approached laparoscopically, 2 of which required conversion to laparotomy in view of uncontrollable bleeding. The remaining 6 (29%) were performed open. The mean operating times were 215, 188 and 130 minutes in the laparoscopic arm, converted arm and open arms respectively.

During surgery, 62% of the patients were transfused with platelet concentrates and 24% with packed red cells after ligation of the splenic hilum. The mean volume of intra-venous fluid administered intra-operatively was 24.5ml/kg. Most (81%) of the patients, had an epidural infusion for analgesia, and 19% had intra-venous analgesics administered.

About half the children (48%) had a short stay while 28% had a regular stay and 24% had a long in-patient stay. The mean follow up period was 21 months at the end of which 81% were transfusion independent.

There were no reportable surgical or anaesthetic events or peri-operative mortalities in this group. Three patients were lost to attrition. One patient who required 24 units of packed cells and 37 platelet concentrates had an emergency splenectomy. Though his peri-operative period was difficult, this patient has been transfusion independent for over 44 months.

3) HAEMOLYTIC ANEMIAS

There were 13 patients with HA who underwent splenectomy. This subset included 8 hereditary spherocytosis and elliptocytosis 8(61%), 2 sickle cell anaemias 2(15%), 1 pyruvate kinase deficiency (8%), 1 autoimmune haemolytic anaemia 1(8%), and 1 G6PD (glucose-6-phosphate dehydrogenase) deficiency (8%).

The most common indication for splenectomy (Table 1) among this sub-group was transfusion dependency (61%). In this group 77% did not have any co-morbidities.(Table 2)

The mean pre-operative haemoglobin and platelet levels were 8.3g/dl and 2.3lakh respectively. Packed red cells were transfused pre-operatively and intra-operatively in 46% and 38% respectively. The patient with G6PD deficiency had a low pre-operative platelet count of 13,000 necessitating 2 platelet concentrate transfusions for surgery. The ferritin levels were monitored in 69% and ranged from 325 to 2333 ng/ml. 15% of the patients were on chelation before surgery.

The mean spleen size was 14.2cms (Range 11-18.7cms) and 31% each were found to have gallstones and hepatomegaly. The approach to surgery was made predominantly based on the spleen size. 62% underwent open surgery. Those with cholelithiasis (n=4) underwent concurrent cholecystectomy. 5 patients with spleen size varying between 11.5-13.1cms were planned for laparoscopy. 2 among these had to be converted to laparotomy in view of bleeding and pancreatic tail injury respectively. The mean operating time in the open, laparoscopic and converted arms were 121, 200 and 210 minutes respectively.

The mean intra-venous fluid administered was 21.3ml/kg. Epidural (54%) and intra-venous analgesia (46%) were used with nearly equal frequency in this group. There was no untoward anaesthetic event encountered. In view of a rising platelet count following surgery, 54% were prescribed anti-platelets.

There were no fatalities. 62% had a short stay , 23% had regular stay whereas 15% had a long stay.

The mean follow up period was 14 months (1-41 months). With the exception of 1 patient who was lost to follow up, 83% were transfusion independent and 17% were transfusion dependent (but with a lesser requirements). One patient had posterior reversible encephalopathy syndrome which normalised completely following surgery.

Discussion

Paediatric non malignant haemoglobinopathies impose a significant strain on the healthcare system especially in lower middle income countries owing to lifelong transfusion dependency and lack of universal access to safe and cost effective blood products. Transfusion related complications like iron overload and its effects on various organs, risk of blood borne infections and related cost of healthcare only adds to this financial burden. Splenectomy affords symptomatic relief and can reduce transfusion dependency in many [3-7], but is not without its risks, hence is considered as a therapeutic option only when absolutely necessary and the benefits outweigh the risks.

The splenectomies performed at our institution were mostly for thalassemia's, ITP's and haemolytic anemias. These seem to be the universal indications as supported by Yacobovich et al [1]. Our institute being one of the few tertiary referral centres for various paediatric haematological conditions expanded the study cohort to children hailing from pan Indian states and the Indian peninsula.

OUTCOMES

A significant proportion of splenectomised patients achieve long-term control of their disease with minimal morbidity and mortality [1,3,8,9]. In keeping with current literature, our study too yielded impressive overall survival rates with 98%. The follow-up period being inconstant precluded calculation of event free survival rates(morbidity).

Various factors have been implicated and studied in predicting the outcomes of splenectomies. We measured our surgical and anaesthetic outcomes in terms of duration of hospital stay, morbidity and mortality.

Hospital stay

The mean and median duration of hospital stay were 5.4 and 5 days respectively. A greater pre-operative transfusion burden, increased intra-operative fluid requirement and a larger spleen were the three parameters that resulted in a longer duration of hospital stay in this study. We did not find other studies with similar findings. Interestingly, none of the other predicted factors including presence of co-morbidities, modality of surgery, surgical duration, or type of analgesia used, affected the duration of stay. Though laparoscopic splenectomy has been reported to result in shorter length of stay [13,14,21] we did not find any significant difference in the duration of stay between open and laparoscopic surgery.

Rayaz Ahmed et al reported a mean hospital stay of 6 days in 254 ITP patients [8], and Bhatt et al found that intra cranial haemorrhage, gastro intestinal bleed, sepsis, thrombosis, and male sex were associated

with a longer hospital stay [12]. Besides these studies, literature on duration of stay is sparse and as both these studies included only ITP patients, further comparison cannot be made.

Morbidity

The most dreaded complication following splenectomy is undoubtedly OPSI and though infrequent, poses significant morbidity and mortality. Most fatal post splenectomy infections occur within 2 years of surgery [13]. We had one patient with repeated infections during follow up, but no documented OPSI. The overall follow-up duration however, precludes comment on infections that could have developed later. In a similar study on 103 splenectomised children, there was no documented OPSI, but the overall incidence rate of infection per 100 person-years of follow-up was 1·6 for Thalassemia without a central line, spherocytosis and ITP, respectively (p=0·018) [1].

The possible reason for minimal documented infections, fewer ITP relapses and minimal long term complications in our study could be attributed to the varied patient profile and the early termination of follow up. Since several patients hailed from other states many chose to follow up at their hometowns following surgery. This precluded calculation of event free survival rates.

Following splenectomy, there is an increased risk of venous and arterial thromboembolism including acute pulmonary, splenic and portal vein thrombosis [2]. These along with the risk of pulmonary hypertension, leg ulcers, and silent cerebral infarctions are more in the NTDT group due to the greater prevalence of a hyper-coagulable state [4,14,15]. That we did not encounter any episodes of the same could be partially attributed to the initiation of anti-platelets in patients(n=18) who were considered to be at risk. Though there were no pre-defined criteria, the at risk patients included those with pro-thrombotic states, thrombocytosis following surgery, and those who had a longer than usual surgical duration.

Mortality

The incidence of mortality associated with splenectomy in literature varies and most often of the time is due to post splenectomy infectious complications especially OPSI [18]. Peri-operative mortality is rare and is usually associated with hemorrhage**.**

The unexpected peri-operative mortality in our study stimulated us to probe deeper into the possible red flag signs that could aid as precautionary markers for future splenectomies.

Following an uneventful anaesthesia and surgery, a 10 year old girl with NTDT had hypotension and arrested in the PACU in the immediate post-operative period. Though the exact cause of death could not be identified (primary haemorrhage was ruled out), she was at a high-risk for venous and arterial thromboembolism being an NTDT patient. Root cause analysis by all the involved disciplines declared a thromboembolic event to be the most probable cause of mortality. This incident reiterates that NTDT patients are at a higher risk of experiencing peri-operative complications. We recommend that NTDT patients undergoing splenectomy be thoroughly investigated prior to surgery, intensively monitored post-operatively and have a low threshold for being initiated on anti-platelets.

FACTORS AFFECTING OUTCOMES

Transfusions

There are clear recommendations for the frequency of transfusions (annual transfusion requirement exceeding 200 ml/kg/year of pure red cells) and target haemoglobin levels in TD TM patients [5]. The decision to perform surgery however, is made when chelation is insufficient to balance the iron overload caused by the increased frequency of transfusions. There was no comparison group of non-splenectomized patients in our study however, to have such a cutoff. The children who underwent splenectomy had an average of 140 packed cell transfusions following which a surgical plan was made. Though there was no correlation between the number of transfusions and the duration of hospital stay in the TM group, an overall longer hospital stay was noted with increasing transfusion requirement when considering the entire splenectomy cohort.

Way back in the 1980's Graziano et al documented a 39% decrease in the annual iron loading in patients requiring greater than 250 ml/kg/year [16] and Cohen et al found that non-splenectomised patients had a 30% higher transfusion requirement [6]. Splenectomy decreases the transfusion requirements and thereby the transfusion dependent iron overloading as evidenced by 31% of our TM patients being transfusion free and 47% requiring less frequent transfusions post splenectomy.

In NTDT however, transfusions are administered judiciously due to concerns regarding iron overload and alloimunization especially in the newly transfused, splenectomised and pregnant patients. In order to thus avoid too many transfusions, splenectomy is resorted to earlier on in this group. This is supported by our study finding of a mean of 47 units of transfusion before surgery is resorted to as opposed to 140 in TM patients.

Chelation

Iron overload in TM is due to frequent blood transfusions as opposed to increased gastrointestinal absorption in NTDT [5], resulting in long term deleterious effects like liver fibrosis, endocrine failure and myocardial damage in the absence of chelation. Assessment of liver iron concentration is the gold standard for quantification of total body iron [4], but is infrequently employed in set ups like ours due to financial constraints of the patients. Spot measurements of serum ferritin as employed in our study, though utilised routinely, have the downside of underestimating the level of iron overload especially in NTDT patients. This limitation precluded making a fixed protocol for the ferritin level that would necessitate the initiation of chelation.

The median levels of serum ferritin in chelated patients differed in the TM (2448 ng/ml) and NTDT (1378ng/ml) groups. Though clearcut guidelines exist on when to initiate and manage chelation for TM [5] and NTDT [4] , it seems reasonable to modify the regimes based on a combination of factors including the diagnosis, transfusion requirements, pre-operative ferritin values and logistics like serum ferritin levels at their first presentation to the haematology department.

Eight percent of the TM patients were on pre-operative chelation as compared with 41% in the NTDT group, supporting the evidence that iron overload in the latter group is a cumulative and more deliberate process [4] necessitating a tighter and earlier control.

As per guidelines in literature [4,5], chelation once started should continue post-operatively but in our study only 7/21(Thalassemia) did so which we felt was possibly due to under documentation at follow-up.

SURGICAL FACTORS

Spleen Size

A massive splenomegaly is known to be associated with longer operating times, more ports and greater rate of conversion to open when laparoscopy is used. Cetin Ali et al in a study on 50 children undergoing laparoscopic splenectomy found that the spleen size did not make a significant difference to the outcome [7]. Conversely, a larger spleen in our study was associated with a worse final outcome ($p<0.01$) irrespective of the operative approach. This was likely because, most of our study spleens being from the thalassemia and haemolytic anemia groups, were on average much larger in size.

OTHER FACTORS

Emergency versus Elective surgery

Non-traumatic splenectomy is an elective procedure requiring pre-operative optimisation, bearing in mind the co-existing patient conditions. Rarely an emergency splenectomy is warranted for indications like intracranial haemorrhage, refractory thrombocytopenia, splenic rupture and splenic abscess. Four percent (n=3) of our splenectomies were emergencies as compared with 21% as stated by Samuk et al[17]. Amongst the three in our study, one was completed laparoscopically (hospital stay 4 days) whereas two were performed open (6 & 20 days). Long duration of stay was complicated by an intra-cranial hemorrhage. The duration of hospital stay patients depends on the underlying disease [17] as well as the precipitating factor that led to surgery. Likewise a similar finding was noted by Samuk et al. Though all these three patients survived and followed up for 16-44 months, further comment on the outcomes of emergency splenectomies cannot be made as the numbers for comparison are small.

Laparoscopy versus laparotomy

Laparoscopic surgery has the downside of possible residual disease due to undetected accessory spleens [10,11], however none of our patients in the laparoscopic cohort manifested signs of recurrent or residual disease during their follow-up period.

Among the entire cohort in our study, only 29% underwent laparoscopic attempted splenectomies. In the ITP group however 71% were attempted laparoscopically as these spleens are known to be generally smaller. In the thalassemia group and most of the haemolytic anaemia patients, the large spleen size

(mean of 19 cms) precluded safe laparoscopic surgery hence laparotomy was resorted to. Our rate of laparoscopy is much lower than the overall global rate [10] owing to poor finances and lack of insurance coverage.

Our conversion rate (20%) was almost at par with Qureshi et al (15%) [10] and our median laparoscopic operating time (205 minutes) was comparable with that of Sandoval et al (180 minutes)[11] and Qureshi et al (213 minutes) [10].

ANAESTHETIC FACTORS

Anaesthetic management of children with haemoglobinopathies is challenging with unanticipated difficult airways, peri-operative high blood pressures, iron overload, endocrinological and cardiac abnormalities, restrictive respiratory patterns and pulmonary hypertension [18] often being associated with the disease processes. The pulmonary hypertension results from chronic hemolysis and disturbed nitric oxide physiology, while maxillary bone enlargement due to extra-medullary hematopoiesis poses challenges to airway management [18]. In our study we did not face any of the above mentioned challenges. Existing literature does not mention any specific effect of fluid management on outcome. We however noticed that worse outcomes were noted with increased administration of intra-operative fluid ($p=0.013$). In our study both intravenous analgesia and regional analgesia (epidural catheter infusion) were effective and we did not find that one was superior to the other probably due to the efficient acute pain care services at our centre.

Greater pre-surgical transfusion requirements, a larger spleen size and increased peri-operative fluid administration were the red flag signs we identified which have not been mentioned elsewhere in literature. Yet, in-order to quantify the same, we would require having a prospective study design with a larger sample size.

LIMITATIONS

The study being retrospective had the disadvantage of confounding and inability to determine causation. The relatively short follow-up period and smaller sample size when compared with other series which precluded identifying patients with late relapses, recurrences and follow-up of certain delayed complications.

Conclusions

In summary, paediatric splenectomy was associated with a promising overall outcome with a survival rate of 98.5% at 43 months. A greater pre-operative transfusion requirement, a larger sized spleen and increased fluid administration intra-operatively, were associated with a worse outcome.

Abbreviations

TD- Transfusion dependent

NTDT- Non transfusion dependent thalassemia

ITP- Immune thrombocytopenic purpura

HA- Haemolytic anemia

TM- Thalassemia major

OS- Overall survival

OPSI- Overwhelming post splenectomy infection

G6PD- Glucose-6- phosphatase deficiency

PACU- Post anaesthesia care unit

Declarations

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Author contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Aureen Ruby DCunha, Ekta Rai, Tarun John K Jacob, Anup Joseph Devasia and Grace Rebekah. The first draft of the manuscript was written by Aureen Ruby DCunha and all authors commented on previous versions of the manuscript. Ekta Rai was the overall guide and mentor. All authors read and approved the final manuscript.

Competing interests

The authors have no relevant financial or non-financial interests to disclose, and have no competing interests to declare that are relevant to the content of this article.

Ethics approval

This retrospective chart review study involving human participants was in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration

and its later amendments. The Institutional Review Board of the Institution approved the study and waived off ethical clearance as the study was retrospective in nature and all the procedures were being performed as part of routine care.

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