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Splenic function is not maintained long-term after partial splenectomy in children with sickle cell disease☆

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ABSTRACT

Background: Partial splenectomy (PS) may allow preservation of splenic function in cases where splenectomy is indicated for hematologic diseases; however, the long-term outcomes are uncertain. We investigated the long-term outcomes of PS in patients with sickle cell disease (SCD).
Methods: A single-institution retrospective chart review was performed for children with SCD who underwent PS from 1997 to 2017. For comparison, we reviewed outcomes for patients who underwent PS for hereditary spherocytosis (HS). The primary endpoint was viability of the splenic remnant as inferred by the presence of remnant perfusion on ultrasound and/or liver spleen scan.
Results: Nine patients with SCD and 26 patients with HS underwent PS at a median age of 11 (IQR, 9–14) and 7.5 (IQR, 6–13) years, respectively. All underwent laparoscopic PS with three (7.9%) conversions to open. Two SCD patients were lost to long-term follow-up. The remaining seven SCD patients had initial postoperative splenic remnant perfusion demonstrated by ultrasonography. By 42 months postoperatively, however, none had a functioning splenic remnant. The median time to loss of splenic remnant was 12.6 (IQR 9.2–28.5) months. In contrast, all HS patients demonstrated robust splenic remnant blood flow with a median follow-up of 46 (IQR 37–82) months.
Conclusion: No patient with SCD who underwent PS had viable splenic tissue for more than 42 months, likely due to continued autoinfarction typical of patients with this disease. Therefore, we believe that PS to preserve splenic function is not indicated in patients with SCD.
Level of evidence: III.

Children with sickle cell disease (SCD) often undergo splenectomy for the prevention of recurrent splenic sequestration crises or chronic hypersplenism. Splenectomy is associated with a small, but potentially life-threatening, risk of overwhelming post-splenectomy infection and, therefore, requires preoperative vaccination against encapsulated bacterial organisms and chronic, daily penicillin prophylaxis in the pediatric population [1, 2]. Partial splenectomy (PS) is a technique in which a portion (10–20%) of the spleen is preserved during surgery to allow for postoperative retention of splenic immune function. Partial splenectomy has been shown to adequately prevent recurrent sequestration crises and reduce the need for transfusion in patients with SCD [3, 4]. Additionally, PS has justified discontinuation of prophylactic antibiotics because of presumed retention of splenic immune function. However, PS is associated with increased intraoperative and perioperative complications when compared to total splenectomy, including conversion from laparoscopic to open surgery, longer operative time, longer hospital stay, splenic remnant regrowth and greater intraoperative blood loss [4, 5]. Despite these risks, PS is sometimes chosen in patients with SCD due to the potential benefits mentioned above [5].

The success of PS is dependent on an adequately perfused splenic remnant. Although previous studies have demonstrated that PS is safe for SCD patients and achieves intended short-term hematologic benefits, the long-term status of the remnant spleen in SCD patients has not been evaluated. In this study, we aimed to determine the natural history of the splenic remnant in SCD patients who undergo PS.

1. Methods

Following local Institutional Review Board approval and waiver of informed consent, we performed a single-institution, retrospective chart review for children with SCD who underwent PS from 1997 to

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2017 at St. Jude Children's Research Hospital. For comparison, we reviewed outcomes for patients who underwent PS for hereditary spherocytosis (HS) during that same time period. The primary endpoint of this study was viability of the splenic remnant as inferred by the presence of remnant perfusion on ultrasound and/or radiocolloid uptake on liver-spleen scan. Variables ascertained included age, gender, SCD genotype (HbSS, HbSC, or HbSβ-thalassemia), indication for splenectomy, surgical method (open versus laparoscopic PS), upper versus lower pole preservation, preoperative splenic volume, intraoperative blood loss, need for conversion from a laparoscopic to an open procedure, preoperative and postoperative hemoglobin levels, hydroxyurea utilization, length of follow-up, total time off antibiotic therapy during long-term follow-up, splenic perfusion assessed by duplex ultrasound, and splenic viability as assessed by liver-spleen scan. All patients underwent serial screening with abdominal duplex ultrasound to assess for splenic perfusion. When splenic perfusion was absent by duplex ultrasound, absence of function was confirmed by nuclear medicine liver-spleen scan.

Continuous variables were compared using the two-tailed Student's t-test. Categorical variables were compared using the nonparametric Fisher exact test. Kaplan–Meier analysis was utilized to compare rates of splenic perfusion between patients with SCD and HS after PS. A significance threshold of $p < 0.05$ was utilized for all tests. Statistical analysis was performed using GraphPad Prism version 7.0, GraphPad Software (La Jolla, CA, USA) and SAS 9.4 (Cary, NC, USA).

2. Results

A total of 38 patients underwent PS over a 20-year period, of whom 26 (68.4%) had HS, nine (23.7%) had SCD, two (5.3%) had pyruvate kinase deficiency with hypersplenism and one (2.6%) had an inflammatory myofibroblastic tumor. SCD genotype subtypes included five patients with compound heterozygous hemoglobin (Hb SC), three with homozygous hemoglobin SS (Hb SS) disease, and one with β + thalassemia (Hb SB+). The median age at surgery was 8 (IQR, 6–13) years of age (Table 1). A minimally invasive approach for splenectomy was employed for all patients with three conversions to open which all occurred during the early part of the study period. All patients had the upper pole of the spleen preserved during PS. There were no significant differences when comparing HS and SCD patients in age, gender, preoperative splenic volume, and estimated blood loss at surgery (Table 1). The median postoperative splenic volume in HS patients was 333 (IQR, 198–455) mL which was compared to the median preoperative splenic volume of 754 (IQR, 461–1182) mL, $p = 0.03$. (Table 1).

Two of nine SCD patients were lost to long-term follow-up. One of these two patients was transitioned to adult care 5.4 months after surgery and the other was lost to follow-up after 14.2 months. The remaining seven SCD patients had initial postoperative splenic remnant perfusion confirmed in the first 3 months postoperatively. By 42 months postoperatively, however, none had a functional splenic remnant based on the technetium-99 m-sulfur colloid liver-spleen nuclear medicine scan and/or abdominal ultrasound demonstrating lack of blood flow (Fig. 1). The median time to loss of splenic remnant perfusion was 12.6 (IQR 9.2–28.5) months. In contrast, all HS patients demonstrated robust splenic remnant blood flow with a median follow-up of 46 (IQR 37–82) months (Fig. 1).

Five patients were receiving hydroxyurea treatment preoperatively which was continued in the postoperative period, one patient started hydroxyurea 2 years after PS, and three patients did not receive hydroxyurea at all. Ultimately, none of the SCD patients were taken off oral penicillin prophylaxis because of the lack of splenic remnant function. Some were initially taken off antibiotics but were restarted when it became apparent that they no longer had a functioning splenic remnant. In contrast, all HS patients who had been on antibiotic prophylaxis had this discontinued by 24 months (Fig. 2).

At 42 months follow-up, children with HS had a significant increase in hemoglobin level from their preoperative mean of 10.4 ± 1.5 g/dl to a postoperative mean of 12.9 ± 1.5 g/dl, $p < 0.0001$, and decreased reticulocytes from a preoperative mean of 12.4 ± 3.4% to a postoperative mean of 7.1 ± 2.7%, $p < 0.0001$.

In children with SCD, there was no significant change in hemoglobin at 42 months follow-up from a preoperative pretransfusion baseline mean of 11.8 ± 1.4 g/dl to a postoperative mean of 11.4 ± 1.9 g/dl, $p = 0.5$, or in reticulocyte counts from a preoperative mean of 3.9 ± 0.9% to a postoperative mean of 2.9 ± 1.1%, $p = 0.09$.

3. Discussion

Partial splenectomy has the theoretical advantage of reducing the threat of overwhelming septicemia by maintaining some immunocompetence (splenic function) compared to total splenectomy [3, 4, 6, 7]. Partial splenectomy continues to be performed in pediatric sickle cell disease patients because only short-term outcomes have been evaluated. A systematic review by Costi et al. revealed that SCD represented 22.6% of all hematological indications for PS in the literature [8]. However, our study shows that splenic viability is not maintained long-term after partial splenectomy for sickle cell disease patients. The median time to loss of the splenic remnant in this population was 12.6 months. In contrast, all patients with hereditary spherocytosis demonstrated splenic remnant blood flow with a median follow-up of 46 months. The persistent splenic perfusion in hereditary spherocytosis patients (who had the same surgeons using identical techniques as SCD patients) but not in SCD patients demonstrates that cessation of perfusion is due to the underlying disease process rather than the surgical technique or approach. The difference in splenic perfusion also resulted in the willingness to discontinue oral penicillin prophylaxis in HS patients, but not in SCD patients.

Both total and partial splenectomy have been demonstrated to be safe in SCD patients and to achieve hematologic benefits including reduction in sequestration crises and the need for transfusion [5]. Our results demonstrate that the hematological parameters improved after PS in HS patients, but not in SCD. This is consistent with other previous reports [5, 7–10]. However, PS has been associated with a higher rate of intraoperative and perioperative complications, including intraoperative blood loss and the need to convert to an open procedure [5, 8, 11]. In a systematic review, the overall rate of conversion to open during laparoscopic PS in the literature was 6.4%. The rate of conversion specifically in children was 5.2% [8]. This is comparable with our conversion rate of 7.9%; three conversions occurring within the first four cases reflected the learning curve for laparoscopic PS. Rice et al. reported that out of 12 children who underwent laparoscopic PS, 50% were converted to open [7].

Table 1
Patient demographics and surgery factors.

	Total n = 38	SCD n = 9	HS n = 26	p-value
Age at surgery, median years (IQR)	8 (6–13)	11 (9–14)	7.5 (6–13)	p = 0.23
Male-to-female	16 M: 22 F	5 M: 4 F	10 M: 16 F	p = 0.80
Preoperative splenic volume, median mL (IQR)	754 (460–1068)	633 (505–1182)	754 (461–1182)	p = 0.64
EBL, median mL (IQR)	200 (137.5–300)	200 (100–300)	200 (150–300)	p = 0.54

SCD: sickle cell disease; HS: hereditary spherocytosis; EBL: estimated blood loss; IQR: interquartile range; M: male; F: female.

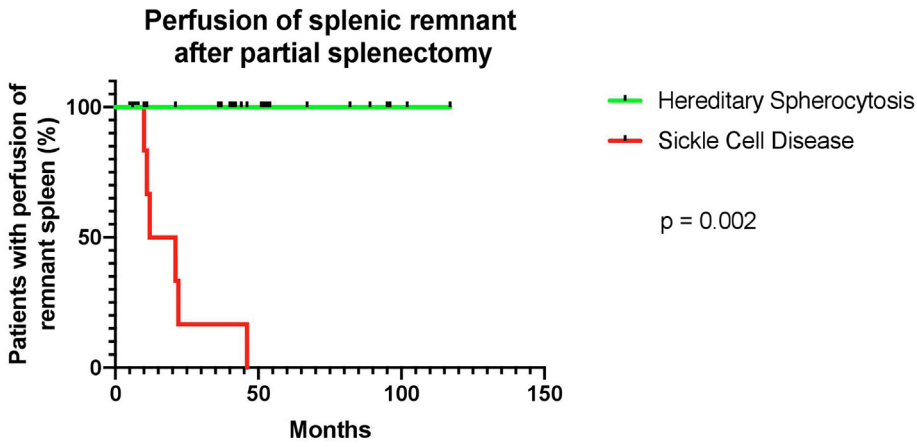

Fig. 1. Kaplan–Meier curve analysis demonstrating perfusion of splenic remnant after partial splenectomy in hereditary spherocytosis and sickle cell disease patients.

However, the perceived benefit of retained splenic immune function and the possibility of stopping prophylactic antibiotics during childhood are attractive features of partial splenectomy that have led to its use in sickle cell disease patients. Retained splenic immune function is dependent on adequate perfusion of the splenic remnant. In this study, we demonstrated that this perfusion is relatively short-lived in SCD patients and does not enable cessation of prophylactic antibiotic therapy for a clinically meaningful amount of time. The standard criterion for assessing splenic function is a technetium-99 m-sulfur colloid liver-spleen scan, since detection of Howell–Jolly bodies does not always reflect splenic function accurately [12, 13].

It is very likely that the initial presence, but eventual cessation of splenic perfusion after PS for SCD patients is due to autoinfarction of the splenic remnant. In contrast, splenic autoinfarction is not a feature of HS, explaining why these patients had sustained splenic perfusion and only required prophylactic antibiotics for a short period of time following surgery. Vaso-occlusion, the primary pathophysiologic process leading to splenic autoinfarction is reduced by hydroxyurea therapy, a myelosuppressive agent that reduces the frequency of painful episodes by raising the fetal hemoglobin level in SCD patients [14]. However, hydroxyurea treatment of some patients in this cohort did not appear to prevent splenic autoinfarction and loss of remnant perfusion.

The informed decision to perform a partial splenectomy is made when the surgeon and patient/family decide that the potential long-term immune benefits outweigh the short-term intraoperative and perioperative risks for the patient. This study suggests such long-term benefits in SCD patients are likely absent due to infarction of the splenic remnant and should inform this discussion in the future.

4. Conclusions

The median time to loss of perfusion of the splenic remnant in patients who underwent PS for SCD was 12.6 (IQR 9.2–28.5) months and no patient with SCD in this study had viable splenic tissue for more than 42 months, likely due to continued autoinfarction typical of patients with this disease. Therefore, we believe that PS to preserve splenic function should not be performed in patients with SCD.

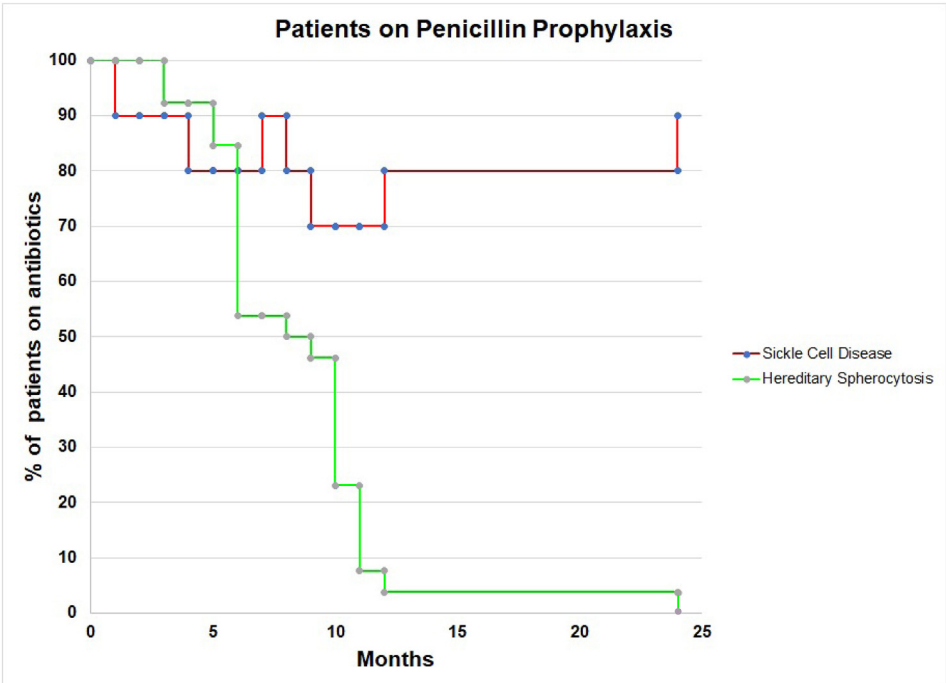

Fig. 2. Long-term follow up of hereditary spherocytosis and sickle cell disease patients on oral penicillin prophylaxis.

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