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Hematologic outcomes after total splenectomy and partial splenectomy for congenital hemolytic anemia☆,☆☆

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ABSTRACT

Purpose: The purpose of this study was to define the hematologic response to total splenectomy (TS) or partial splenectomy (PS) in children with hereditary spherocytosis (HS) or sickle cell disease (SCD).
Methods: The Splenectomy in Congenital Hemolytic Anemia (SICHA) consortium registry collected hematologic outcomes of children with CHA undergoing TS or PS to 1 year after surgery. Using random effects mixed modeling, we evaluated the association of operative type with change in hemoglobin, reticulocyte counts, and bilirubin. We also compared laparoscopic to open splenectomy.
Results: The analysis included 130 children, with 62.3% ($n = 81$) undergoing TS. For children with HS, all hematologic measures improved after TS, including a 4.1 g/dl increase in hemoglobin. Hematologic parameters also improved after PS, although the response was less robust (hemoglobin increase 2.4 g/dl, $p < 0.001$). For children with SCD, there was no change in hemoglobin. Laparoscopy was not associated with differences in hematologic outcomes compared to open. TS and laparoscopy were associated with shorter length of stay.
Conclusion: Children with HS have an excellent hematologic response after TS or PS, although the hematologic response is more robust following TS. Children with SCD have smaller changes in their hematologic parameters. These data offer guidance to families and clinicians considering TS or PS.

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Splenectomy can control select clinical symptoms in severely affected children with congenital hemolytic anemias (CHA) such as hereditary spherocytosis (HS) or sickle cell disease (SCD) [1–5]. However, the risks associated with total splenectomy (TS) such as postsplenectomy sepsis and venous thromboembolism remain major concerns for patients and clinicians [6]. Advances with splenectomy for CHA in the last 2 decades have included laparoscopy [4,7–9] and partial splenectomy (PS) [2,3,5,10]. Although the advantages of laparoscopy are becoming more clear, studying the impact of partial splenectomy is limited by small sample size, rare clinical events, lack of comparison groups, narrowly focused patient populations, and use of nonstandardized data [5,11]. To address this gap in understanding of splenectomy, we formed a clinical research consortium entitled Splenectomy in Congenital Hemolytic Anemia (SICHA), composed of pediatric surgeons and hematologists at 16 sites in North America [12].

With no reports focused on a direct comparison of TS vs. PS, the goal of the current study was to examine the differences between these procedures in a head-to-head evaluation. Our consortium has operated an observational, multicenter registry for children with CHA undergoing different types of splenectomy, and has recently demonstrated excellent clinical outcomes and low risk of adverse events in children undergoing TS or PS [3]. However, the low rate of clinical events limits the ability to identify subtle but important differences between procedures given multiple clinical confounders; therefore, the current report uses random effects mixed modeling to account for confounding variables in this heterogeneous population. We hypothesized that TS and PS would not result in significantly different hematologic outcomes in children with HS or SCD, and used a random effects model to compare outcomes of TS and PS in children with HS and SCD. We also examined hematologic responses over time, and compared outcomes between laparoscopic and open procedures.

1. Methods

1.1. SICHA

The SICHA clinical research consortium was established to provide a research infrastructure for high-quality, standardized data collection to support the study of children with CHA. After input from multiple stakeholders, a data dictionary, data collection system, and prospective study protocol were implemented to develop a Web-linked, observational, prospective patient registry collecting high-fidelity outcomes of children with CHA undergoing different types of splenectomy. The details of registry operations have been previously published [3,12].

1.2. Study population

Children aged 2–17 years with HS or SCD undergoing PS or TS from 2005 to 2014 at one of the 16 SICHA sites were reviewed for the study ($n = 130$). Patients with CHA classified as “other thalassemia or “other congenital hemolytic anemia” were excluded. As an observational registry, no care was dictated by this study, and the decision for TS or PS was left to the discretion of the family and primary clinicians. Patients with splenectomy for trauma or idiopathic thrombocytopenia purpura were not enrolled. Institutional Review Board approval was obtained from each site, and informed consent was required.

1.3. Study design

We analyzed demographic and disease characteristics, operative techniques, and hematologic outcomes, with hematologic variables collected at baseline and 4, 24, and 52 weeks after surgery. Our main comparison groups were TS vs. PS. Patients converted from PS to TS as well as from laparoscopic to open approach were analyzed in an intention to treat manner. A sensitivity analysis examining PS converted to TS as TS was also performed. Other variables of interest included gender, race/ethnicity, laparoscopic vs. open technique and diagnosis [2].

1.4. Outcomes

The primary hematologic outcomes were hemoglobin, reticulocyte count, and bilirubin. Secondary outcomes included remnant splenic volume (estimated by surgeon intraoperatively and by follow-up ultrasound), estimated blood loss, length of stay (LOS), postoperative and long-term blood transfusion requirements, postsplenectomy sepsis, and death. All variables have been previously defined [3].

1.5. Statistical analysis

We expressed outcomes using count and percentages for categorical variables and median and interquartile range for continuous variables. To determine significant differences between cohorts, Pearson's chi-squared or Fisher's exact test were used as appropriate for categorical data and the Mann–Whitney U test was used for continuous data.

To account for confounding factors and better understand expected hematologic outcomes following different procedures, a random effects mixed model was applied to hematologic outcomes. This allowed us to use multiple time points for each patient, increasing the power to identify associations between case characteristics and hematologic changes [13]. The random effects mixed model included the following variables: gender, race/ethnicity, laparoscopic vs. open technique, PS vs TS, diagnosis, baseline laboratory measures, and weeks from surgery. In addition to the factors above, the association of the hematologic outcomes with weeks after surgery was examined to evaluate for temporal trends in the hematologic response. Results of the mixed model are described as the point estimate in the difference between 2 groups and the 95% confidence interval (CI) around that estimate. It was determined *a priori* to include an interaction term between diagnosis and response to surgery. If a significant interaction existed, these populations would be analyzed separately. p-Values <0.05 were considered statistically significant, with type I error controlled at the level of comparison. All statistical analyses were performed using R (v. 3.02; R Foundation for Statistical Computing, Vienna, Austria).

2. Results

2.1. Patient characteristics

Of 130 eligible cases in the SICHA registry 120 children (92%) had 4-week follow-up and 81 children (62%) had 1 year follow-up. Most patients in all groups had follow-up through 1 year, with mean follow-up (standard deviation) for each group of interest as follows: total splenectomy, 34 (21) weeks; partial splenectomy, 42 (18) weeks; open splenectomy, 47 (13 weeks); and laparoscopic splenectomy, 33 (21) weeks. The majority of children underwent TS (62%), with the remaining children undergoing PS. SCD made up 53% of children, while 47% had HS (Table 1). The use of PS did not differ by diagnosis; however, patients with splenic sequestration as an indication for surgery were more likely to undergo TS.

2.2. Hematologic outcomes

Unadjusted hematologic outcomes are described in Figs. 1 and 2. Using adjusted mixed modelling analysis, we found differences in the hematologic response to surgery between SCD and HS (interaction $p<0.001$ for all parameters) and analyzed these groups separately. Children with HS experienced increased hemoglobin (4.1 g/dl; 95% CI: 3.1–5.1 g/dl; $p < 0.001$), decreased reticulocytes (8.3%; 5.2%–11.4%; $p < 0.001$), and decreased bilirubin (1.9 mg/dl; 0.5–3.4 mg/dl; $p = 0.01$) after splenectomy (Fig. 3). Children with HS undergoing laparoscopic surgery (TS or PS) trended toward a smaller increase in