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Single-stage versus multi-stage pull-through for Hirschsprung's disease: Practice trends and outcomes in infants

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ABSTRACT

Purpose: The aim of this study was to evaluate surgical treatments and outcomes in a multi-institutional cohort of neonates with Hirschsprung's disease (HD).
Methods: Using the Pediatric Health Information System (PHIS) from 1999 to 2009, neonates diagnosed with HD were identified and classified as having a single stage pull-through (SSPT) or multi-stage pull-through (MSPT). Diagnosis and classification algorithms and clinical variables and outcomes were validated by multi-institutional chart review. Groups were compared using logistic regression modeling and propensity-score matched analysis to account for baseline differences between groups.
Results: 1555 neonates with HD were identified; 77.2% underwent SSPT and 22.8% underwent MSPT. Misclassification of disease or surgical treatment was <2%. Rates of SSPT increased over time ($p = 0.03$). Compared to SSPT, patients undergoing MSPT had significantly lower birth weights and higher rates of prematurity, non-HD gastrointestinal anomalies, enterocolitis, and preoperative mechanical ventilation. Patients undergoing MSPT had significantly higher rates of readmissions (58.5 vs. 37.9%) and additional operations (38.7 vs. 26%). Results were consistent in the propensity-score matched analysis.
Conclusion: Most neonates with HD undergo SSPT. In patients with similar observed baseline characteristics, MSPT was associated with worse outcomes suggesting that some infants currently selected to undergo MSPT may have better outcomes with SSPT. However, there remains a subgroup of MSPT patients who were too ill to be adequately compared to SSPT patients; for this subgroup of severely ill infants with HD, MSPT may be the best option.

Surgical management of neonatal Hirschsprung's disease (HD) is typically performed with either a single stage pull-through (SSPT) consisting of an early primary colo-anal reconstruction in the neonatal period, or a multi-stage pull-through (MSPT) characterized by a leveling colostomy followed by delayed colo-anal reconstruction later in infancy. Over time, SSTPs have been performed more frequently with SSPTs now the most commonly performed procedures [1]. This transition to predominantly performing SSTP has occurred without evidence from prospective trials comparing SSPT and MSPT. Most reports have been retrospective reviews at one or several centers [2–10]. At this point, the widespread adoption of SSPT in clinical practice precludes the development of a rigorously designed multi-center prospective trial to directly compare these two options [11]. Furthermore, the rarity of Hirschsprung's disease coupled with its treatment at a large number of centers further challenges the feasibility and utility of a prospective clinical trial.

Administrative datasets represent a source for developing large multi-institutional cohorts of patients with rare diseases [12,13]. However, reliance on administrative data alone raises concerns about the accuracy of those data and whether treatment recommendations should be based on such studies. To address this, comparative effectiveness studies may be performed by combining the administrative data with multi-institutional chart validation of key variables and outcomes [13–16]. Several groups have used this approach with data from the Pediatric Health Information System (PHIS) database [13,17–19]. The objective of this study was to use the PHIS and multi-institutional chart validation to compare outcomes between SSPT and MSPT in a multicenter cohort of infants with Hirschsprung's disease. We hypothesized that (1) rates of SSPT are increasing; (2) patients selected to undergo MSPT are more severely ill; and (3) in patients with similar severity of illness, SSTP may lead to more long term morbidity.

1. Methods

1.1. Study design

We performed a retrospective multi-institutional cohort study to evaluate surgical treatment patterns and compare outcomes of SSTP and MSTP in infants with Hirschsprung's disease (HD). Our primary

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outcomes were readmission rate and rate of additional operations within 2 years after pull-through. Secondary outcomes were rates of post-operative enterocolitis, surgical site infections (SSI), small bowel obstruction (SBO), anastomotic leak, and hospital charges and costs. Charges were calculated as the total billed charges for inpatient care from the index admission through 2 years after the pull-through procedure. These charges were converted to costs by using the hospital-specific ratios of cost to charge (RCC) estimates for the total cost of each inpatient stay. These ratios are reported to the Center for Medicare and Medicaid Services (CMS) and used to convert reported charges to estimates of their true economic costs. Cost data for each hospital were further adjusted for the regional wage index as reported by the CMS. Neither the charges nor costs described in this study include physician charges.

1.2. Cohort identification and validation

This study utilized the PHIS which includes comprehensive administrative data from 44 free-standing children's hospitals, including demographics, diagnoses and procedures using *International Classification of Diseases 9, Clinical Modification* codes (*ICD-9-CM*) [20]. Date-stamped billing data for imaging, procedures, laboratory tests, medications, and supplies are also included, and encrypted medical record numbers enable longitudinal tracking of individual patients across hospital encounters.

Fig. 1 outlines the methodology used for cohort identification. The PHIS was queried for patients born between January 1999 and September 2009 who had at least one hospital admission by 60 days of life associated with the *ICD-9-CM* diagnosis code for Hirschsprung's disease (*ICD-9-CM* 751.3). This age criteria ensured that only patients with HD diagnosed in the neonatal period would be included. Any patient without a subsequent *ICD-9-CM* procedure code for colo-anal reconstruction within 1 year of life was excluded under one of two assumptions: [1] without a definitive procedure for HD within 1 year, it was unlikely that the diagnosis code indicated actual presence of disease, or [2] delayed pull-through in these patients may be related to either longer segment Hirschsprung's disease, total colonic aganglionosis, or severe comorbid illnesses. The cohort was then divided into the two treatment groups: SSPT patients were identified as having a colo-anal reconstruction procedure code as their first HD related procedure; MSPT patients were identified as having a stoma creation procedure code as their first procedure followed by a colo-anal reconstruction procedure code on a later date. In order to reflect the decision to perform either an SSPT or an MSPT in infants with similar physiology and risks, this search strategy excluded patients managed with rectal irrigations who underwent a single stage pull-through after 60 days of life because of the potential for overlap between patients undergoing SSPT with MSPT patients coming back for their pull-through procedures.

To ensure the validity of the PHIS data, medical record chart validation of patient characteristics, diagnoses, treatments, and outcomes was performed at 3 Children's Hospital Association member-hospitals. Medical records were reviewed to confirm the data available in PHIS on the diagnosis of HD, type of repair (SSPT or MSPT), and clinical variables and outcomes. The chart review validation study was approved by each participating hospital's Institutional Review Board (Nationwide Children's Hospital, Children's Hospital of Philadelphia, and Monroe Carell Jr. Children's Hospital at Vanderbilt).

1.3. Statistical analysis

Pre-operative and operative variables were compared between treatment groups using two sample t-tests or Wilcoxon rank sum tests for continuous variables and Pearson chi square tests for categorical variables. Marginal logistic regression models accounting for patient clustering within hospitals were used to compare the effect of SSPT versus MSPT on our primary outcomes; marginal linear regression models were used to compare log transformed hospital charges and costs between groups. Additional operations included redo pull-through, ostomy procedures, colectomies, biopsies of the small or large intestine, colonoscopies, and anal procedures including dilation, myomectomy, or sphincterotomy. Because morbidity in the MSPT group includes complications that can occur between the time of stoma creation and definitive colo-anal reconstruction, we compared the groups from the time of initial surgery (either stoma or pull-through) until 2 years after pull-through procedure (excluding the planned pull-through procedure and its associated admission in the MSPT group for our primary outcomes). To assess the impact of having a longer follow-up period in the MSPT group, we performed a sensitivity analysis to compare outcomes looking only at the 2 year time period after pull-through. Since the results of both of these analyses were similar, we only report outcomes for the analysis from time of initial surgery through 2 years after pull-through.

A propensity score matched analysis was performed in order to control for potential differences in pre-operative exposures between the two treatment groups. In order to include variables with missing data, multiple imputation was performed by a Markov Chain Monte Carlo method [21]. Propensity scores were estimated using a separate logistic regression model including all pre-operative variables with $p < 0.20$ in bivariate analyses and first-order interactions with $p < 0.10$ for each of 20 imputed datasets. Propensity scores were then averaged and SSPT and MSPT patients were matched using 1:1 nearest neighbor matching within calipers of width equal to 0.25 times the standard deviation of the logit of the propensity score [22,23]. Patients without an eligible match were excluded. Standardized differences for the pre-operative variables in the matched groups were computed and were all ≤ 0.10 [22,24]. Because of ambiguity in the diagnosis codes and timing of enterocolitis during the initial admission, propensity score matching was performed with and without this variable. Since results were similar, we report the matched cohort that included the enterocolitis variable. Also, in an attempt to minimize potential confounding caused by the presence of a greater number of long segment HD patients in the MSPT group, we carried out a sensitivity analysis designed to exclude the majority of patients with long segment HD that undergo MSPT. Based on reported average ages of 10–14 months at the time of pull-through in patients with long segment HD undergoing MSPT, we performed a similar propensity score matched analysis including only patients who had a pull-through procedure by 6 months of age [25–28].

All analyses were performed using SAS v9.3 (SAS Institute, Cary, NC). The propensity score matching was performed using the "gmatch" SAS macro [29]. All tests were 2-tailed and $p < 0.05$ was considered statistically significant.

2. Results

2.1. Cohort identification and validation

The PHIS search strategy outlined in Fig. 1 identified 1555 infants with Hirschsprung's disease. The diagnosis of HD was confirmed for all patients at all three validating institutions ($n = 133$). As far as treatment group assignment into MSPT or SSPT, all 47 patients were assigned to the correct treatment group at one hospital, while 1 out of 30 and 1 out of 56 were incorrectly assigned at each of the other hospitals. This yielded an overall treatment group misclassification rate of 1.5% (Table 1). With a few exceptions, overall misclassification rates for specific demographic and clinical pre-operative characteristics were low across all 3 validating institutions (Table 1). For example, the proportion of patients across all 3 hospitals with discrepant values was: 0% for gender, 0% for prematurity, 0–4% for the various types of congenital anomalies, and 10% for gestational age; however, the misclassification rate was 20% for birth weight and 14%