

Is Statistical Significance Sufficient? Importance of Interaction and Confounding in Hypospadias Analysis

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Abbreviations and Acronyms

TIP = tubularized incised plate

UCF = urethrocutaneous fistula

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Purpose: We hypothesized that a stratified analysis, where measures of association between dartos flap coverage and fistula formation were adjusted by segregation into 2 strata according to stent insertion, would help better define the dartos flap-urethrocutaneous fistula association.

Materials and Methods: We retrospectively reviewed 153 consecutive boys with distal hypospadias who underwent tubularized incised plate repair by a single pediatric urologist between 2000 and 2005. Fistula rate was analyzed separately according to patient age, stenting and dartos flap coverage using univariate and multivariable analyses, and checking for effect modification/interaction.

Results: Mean \pm SD age at surgery was 16.5 ± 12.8 months and followup was 17.0 ± 11.6 months. Nonstented tubularized incised plate repair was performed in 88 patients (58%) and dartos flap coverage in 118 (77%). Urethrocutaneous fistula developed in 19 patients (12%). Nonstented repair ($p = 0.003$) and absence of dartos flap coverage ($p < 0.001$) were significantly associated with higher fistula rates. In children without stent a significant increase in fistula rate was observed when dartos flap coverage was not used (9% vs 37%, $p = 0.002$; OR 0.16, 95% CI 0.05–0.51). In boys who underwent stent placement the fistula rate also increased in the absence of dartos flaps, from 2% to 25% ($p = 0.12$; OR 0.05, 95% CI 0.002–1.0).

Conclusions: Dartos flap coverage emerges as an important, clinically identifiable and modifiable risk factor associated with fistula reduction following tubularized incised plate repair for distal hypospadias after adjusting for placement of a urethral stent. Furthermore, stenting is an effect modifier in the association between dartos flap coverage and urethrocutaneous fistula.

Key Words: confounding factors (epidemiology), hypospadias, stents, surgical flaps, urinary fistula

URETHROCUTANEOUS fistula is one of the most common complications reported following distal hypospadias repair in children. According to a recent review on tubularized incised plate urethroplasty, the fistula rate for distal defects ranges from 1% to 35%.¹ Younger age at operation, placement of a urethral stent at repair and coverage of the urethroplasty with a dartos flap have been reported as clinically protective factors

associated with reduction of fistula rates following hypospadias surgery.^{2–6} Although these studies have attempted to demonstrate a relationship between risk factors and UCF, their results may be debated based on lack of adjustment for effect modification and confounding.

Designs of hypospadias analyses have mostly been observational in nature, although such analyses may have shown a statistically significant

association between exposure (for example dartos flap coverage) and outcome (UCF). The described relationship may have been distorted due to imbalance of other potentially important factors (stenting, age, surgical technique) manifesting within the groups studied. Statistical tools exist to control for such imbalances and to determine whether effect modification and/or confounding may have a role in the causal pathway of a given exposure-outcome relationship. As such, any clinical study that fails to identify and account for the presence of effect modification and confounding renders even a statistically significant finding, whether by univariate or multivariable analysis, invalid because it will lead to spurious results.

Techniques aimed at adjusting for effect modification/interaction and confounding can help clarify the role of different factors in the risk of UCF when analyzing hypospadias. In this study we hypothesized that a stratified analysis, where measures of association between dartos flap coverage and fistula formation are adjusted for by segregation into 2 strata according to stent insertion or no stent insertion, would better define the dartos flap-UCF association. We reviewed the experience of a single surgeon with TIP repair for distal hypospadias, focusing exclusively on the relationship between stent placement and dartos flap coverage to determine how these factors interact with each other and to clarify their effect on fistula formation.

MATERIALS AND METHODS

After obtaining approval from our institutional research ethics board we retrospectively reviewed 220 consecutive boys with hypospadias who underwent TIP repair by a single pediatric urologist between 2000 and 2005. We excluded 67 children due to proximal or mid shaft defects (32 patients), reoperation (27), loss to followup (7) and incomplete operative notes (1). As a result, our study sample included 153 patients with distal hypospadias.

TIP repair was performed according to previously published surgical technique with slight variations introduced through time.⁷⁻⁹ The temporal 6-year evolution of this single surgeon series (no dartos flap from 2000 to 2001, 1-layer dartos from 2002 to 2003 and 2-layer dartos from 2004 to 2005; no stent from 2000 to 2002 and routine stenting from 2003 to 2005) makes it possible to analyze more reliably the discrete relationship between dartos coverage and stenting, and their potentially interacting roles contributing to UCF prevention.

Patients were seen at stent removal (approximately 1 week postoperatively), and then at 6 and 12 months postoperatively. After that yearly followup was organized with uroflowmetry in toilet trained children.¹⁰ For the purpose of this study we considered as complications (adverse outcome) only UCF cases.

Univariate analysis was performed to evaluate the significance of a priori identified risk factors for UCF. Thus,

fistula rate was analyzed separately for the variables patient age, stenting and dartos flap coverage. We then used the Mantel-Haenszel test to perform a comparative analysis between dartos flap coverage in regard to fistula formation, taking into consideration the placement (or not) of a urethral stent. Following the Mantel-Haenszel method the adjusted ORs of stented and nonstented cases with dartos flap coverage were compared to determine if an effect modification or interaction was indeed taking place between those 2 variables.

Age was analyzed as a continuous and as a categorical (younger or older than 12 months) variable in the univariate model. The dependent variable (outcome) was dichotomous and defined as presence or absence of fistula. These 3 potential risk factors, age, stent and dartos (independent variables), were selected based on prior knowledge from the literature.^{2,4} On subsequent multivariable analysis age was included as a continuous variable, stenting was coded as no stent or placement of a stent and dartos flap coverage was divided into 3 categories—single layer, double layer and no dartos.

All covariates with a *p* value of less than 0.05 on univariate analysis as well as those with a priori established clinical relevance were entered into a multivariable logistic regression model. Collinearity—condition occurring when 2 or more of the independent variables in a regression equation are correlated—between stenting and dartos flap coverage was assessed and not determined to be statistically significant. We tested 4 logistic regression models and found that the model including stenting, dartos coverage and stenting*dartos (checking for interaction) was the most accurate and fitted data the best. Results were analyzed in terms of β coefficient and Exp- β (OR) with lower and upper 95% confidence intervals.¹¹

Descriptive statistics and binary logistic regression were done with the assistance of commercially available statistics software (SPSS®, version 15.0). Student's *t* test and Pearson chi-square test were used for comparative univariate analyses for continuous and categorical variables, respectively. All tests were 2 sided and *p* < 0.05 was considered statistically significant.

RESULTS

Mean \pm SD (median) age at surgery was 16.5 \pm 12.8 (13) months (range 6 to 96). Mean \pm SD (median) followup was 17.0 \pm 11.6 (13) months (range 12 to 60). Of 153 patients only 3 (2%) had ventral curvature. Meatal position was glanular in 5 patients (3%), coronal in 108 (71%) and distal penile in 40 (26%). Nonstented TIP repair was performed in 88 patients (58%) and dartos flap coverage was provided in 118 (77%). Of the patients 63 (53%) underwent single layer dartos and 55 (47%) double layer. A total of 35 boys (23%) had no dartos coverage. Overall, 19 patients (12%) subsequently had UCF and only 2 had meatal stenosis (1%). More than 90% of the fistulas were detected within the first year postoperatively.

Median patient age at fistula detection was 26 months. We performed 3 separate a priori defined

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