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Unilateral vesicoureteral reflux: Does endoscopic injection based on the cystoscopic appearance of the ureteral orifice decrease the incidence of *de-novo* contralateral reflux?

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Abstract *Objective:* In patients with unilateral vesicoureteral reflux (VUR), it has been suggested that injection of a non-refluxing but cystoscopically abnormal contralateral ureteral orifice (UO) with dextranomer/hyaluronic acid (Dx/HA) should be performed to prevent the development of *de-novo* contralateral VUR. We evaluate the effectiveness of this practice.
Patients and methods: Patients with primary unilateral VUR undergoing injection of Dx/HA from 2002 to 2005 at two institutions were eligible. Patients with unilateral VUR with cystoscopically abnormal contralateral UOs were injected with Dx/HA, while patients with normal appearing UOs received no treatment. Multivariate logistic regression models were used to estimate the impact of prophylactic injection on the development of *de-novo* contralateral VUR.
Results: In total, 101 patients with unilateral VUR and an abnormal appearing contralateral UO underwent prophylactic injection of Dx/HA while 45 patients with a normal appearing contralateral UO were untreated. In patients receiving prophylactic Dx/HA, 9% (9/101) of the previously non-refluxing ureters developed *de-novo* VUR. Similarly, 13% (6/45) of patients with a normal appearing UO treated by observation alone developed *de-novo* VUR ($P = 0.55$). The overall incidence of 10% (15/146) *de-novo* contralateral VUR matches published results where this protocol was not followed.
Conclusions: Our findings suggest that cystoscopic assessment and prophylactic treatment of an abnormal appearing, non-refluxing contralateral UO with Dx/HA is of little clinical benefit and should be abandoned.

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Introduction

Vesicoureteral reflux (VUR) is found in approximately 40% of children presenting with a urinary tract infection (UTI), with roughly half of those diagnosed initially found to have unilateral VUR [1—4]. Interestingly, with extended follow-up, up to one third of patients initially thought to have unilateral VUR will be found to have bilateral VUR on repeat VCUG [1]. The development of contralateral VUR after an initially negative study is believed to be due to either the lack of sensitivity of the radiographic examination, the presence of intermittent VUR, or a high-grade contralateral refluxing unit serving as a 'pop-off' mechanism for a low-grade ipsilateral refluxing unit [2,5,6].

The development of contralateral VUR is problematic after unilateral surgical intervention, with published studies reporting that 7—20% of patients undergoing either endoscopic injection therapy or ureteroneocystostomy will develop *de-novo* contralateral VUR [6—11]. In an attempt to prevent the development of *de-novo* contralateral VUR after endoscopic intervention for unilateral VUR, Elmore et al. have recently recommended assessment of the contralateral, non-refluxing ureteral orifice (UO) at the time of cystoscopy. In patients with an abnormal appearing contralateral UO, and in select circumstances in patients with a normal UO, these authors recommend that endoscopic injection of that ureter be concurrent with dextranomer/hyaluronic acid (Dx/HA) injection [11]. This recommendation seems to be based on the hypothesis that an abnormal appearing UO is associated with a higher likelihood of developing *de-novo* contralateral VUR, while a normal appearing UO has a decreased risk for *de-novo* reflux. By following this protocol, it is hypothesized that the overall risk of *de-novo* contralateral VUR (currently reported at 7—15% in most studies) that occurs following endoscopic treatment of unilateral VUR could be significantly decreased [10—15] The purpose of this study is to report our results with a policy of prophylactic injection of Dx/HA into a non-refluxing, abnormal appearing UO, and its impact on the onset of *de-novo* contralateral VUR.

Patients and methods

Patient selection and clinical features

After obtaining approval from the relevant institutional review boards, we conducted a retrospective cohort study of all patients undergoing Dx/HA injection for the treatment of VUR at two institutions. The first patient was enrolled in April 2002 and the last in December 2005. Inclusion criteria were a minimum of one multi-cycle VCUG or radionuclide cystogram (RNC). The families of all children radiographically diagnosed with VUR at our institutions are routinely presented with a detailed explanation of all currently accepted management options for VUR, including observation, antibiotic prophylaxis, Dx/HA injection and open surgical ureteroneocystostomy. Only patients with primary, unilateral VUR undergoing their first Dx/HA injection were included in this study. All patients with secondary VUR or anatomic abnormalities such as ureteral duplication and periureteral diverticula were excluded. Injection of the contralateral, non-refluxing ureter was performed based upon the attending surgeon's assessment of the UO. We elected to treat contralateral non-refluxing UOs that had either stadium, horseshoe or golf-hole configurations and that were associated with a grade II or higher appearance of the UO upon hydrodistension. Of note, no patients in this study were found to have a golf-hole appearance to the non-refluxing-contralateral UO [13,16]. The amount of injected Dx/HA was based upon the resulting degree of coaptation of the UO, i.e. the injection was continued until adequate coaptation was achieved. The injection technique used was either subureteral (subureteric transurethral injection, STING) or intraureteral (hydrodistention-implantation technique, HIT). The decision on which technique to use was based on the discretion of the attending surgeon. Routine postoperative radiologic follow-up evaluations were obtained 3 months following the injection and consisted of either a cyclic VCUG or RNC along with a renal ultrasound. Treatment success was defined as the absence of VUR on the 3-month postoperative cyclic radiographic study.

Statistical methods

Univariate logistic regression models were constructed to predict treatment success at 3 months. Covariates analyzed include: gender, age, VUR grade, presence of dysfunctional voiding, amount of injected Dx/HA, injection technique and the operating surgeon. Model residuals revealed no violation of regression assumptions. Multivariate modeling was not possible because an inadequate number of outcomes were observed in our sample—less than 10 per candidate covariate—and the resulting model would have been overfitted. Statistical analyses were performed using SPSS 14.0 (SPSS Inc., Chicago, IL). All tests were two-sided and *P*-values of $\leq$0.05 were considered statistically significant.

Results

One hundred and forty-six patients with unilateral VUR met our inclusion criteria. Tables 1 and 2 summarize the characteristics of the cohort. There is a statistically significant variance between the two study groups regarding mode of presentation. Specifically, patients undergoing prophylactic bilateral Dx/HA injection were more likely to have presented with a UTI, while patients undergoing unilateral injection were more likely to have their VUR diagnosed during an evaluation for sibling reflux or antenatal hydronephrosis. The two study groups were otherwise statistically similar. The median patient age at the time of treatment for both groups was approximately 6 years (range 1 month to 18 years), both cohorts were predominantly female (91%), and the median number of preoperative cyclic radiographic studies was 3 (range 1—6). There were no significant differences between the two cohorts in terms of number of preoperative cyclic VCUGs or RNCs.

In 101 patients (69%) the non-refluxing contralateral ureter had an abnormal appearing UO and was prophylactically injected with Dx/HA, while in 45 patients (31%) the contralateral UO appeared cystoscopically normal and thus no treatment of the non-refluxing ureter was rendered.