Multivariate Comparison of the Efficacy of Intraureteral Versus Subtrigonal Techniques of Dextranomer/Hyaluronic Acid Injection

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Purpose: Numerous factors have been postulated to increase success rates for dextranomer/hyaluronic acid injection for vesicoureteral reflux. Ureteral hydrodistention combined with intraureteral injection reportedly improves injection success rates. We combined the results of 5 pediatric urologists to evaluate the efficacy of this technique compared to that of subtrigonal-only injection in relation to other factors.

Materials and Methods: Patients with primary vesicoureteral reflux undergoing dextranomer/hyaluronic acid injection from April 2002 to December 2005 at 2 institutions were eligible. Only patients with primary vesicoureteral reflux were included in the study. Injection success was defined as the complete absence of reflux on followup voiding cystourethrogram or radionuclide cystogram. Predictors of a successful outcome were analyzed statistically with logistic regression. Factors included in our analysis were gender, age, vesicoureteral reflux grade, dysfunctional voiding, amount of injected dextranomer/hyaluronic acid, injection technique (intraureteral vs subureteral) and surgeon.

Results: A total of 301 patients (453 ureters) with a median age of 5.5 years met inclusion criteria, of whom 199 (66%) were cured at 3 months of followup. Of the patients 145 (48%) underwent subureteral injection and 156 (52%) underwent ureteral hydrodistention combined with intraureteral injection. On multivariate analysis only vesicoureteral reflux grade ($p < 0.001$) and surgeon ($p = 0.01$) were significantly predictive of injection success. There was a trend toward significance with ureteral hydrodistention combined with intraureteral injection ($p = 0.056$).

Conclusions: In our multivariate model only vesicoureteral reflux grade and surgeon were independently predictive of injection success in patients with primary, uncomplicated vesicoureteral reflux. There was a trend toward improved results with ureteral hydrodistention combined with intraureteral injection, although this did not achieve statistical significance.

Key Words: ureter, bladder, vesico-ureteral reflux, hyaluronic acid, injections

Vesicoureteral reflux is a common and controversial problem in pediatric urology, affecting approximately 1% of children in the United States.[1] Since its introduction to the United States in September 2001, the use of Dx/HA copolymer (Deflux®) for endoscopic correction of VUR has increased greatly. The minimal morbidity of Dx/HA injection prompted some investigators to recommend its use as a first line alternative to traditional therapeutic standards of antibiotic prophylaxis or open ureteroneocystostomy.[2] However, the reported efficacy of Dx/HA injection is variable with case series showing a success rate of 64% to 100%.[3–7] It is difficult to directly compare these series because they were performed in heterogeneous patient populations using different injection techniques and varying definitions of success and failure.

Kirsch et al recently advocated the use of the HIT technique, which increased their success rates.[8] To our knowledge these results have not been validated at other institutions. We present a multi-institutional cohort study of Dx/HA injection for the treatment of children with VUR, in which we evaluated the importance of injection technique as a predictor of treatment success.

MATERIALS AND METHODS

Patient Selection and Clinical Features

After obtaining approval from the appropriate Institutional Review Boards we identified 467 patients who underwent Dx/HA injection at the 2 study institutions between April 2002 and December 2005. All patients were determined to have VUR by VCUG or RNC. Patients and families were presented with a detailed explanation of currently accepted management options for VUR, including: antibiotic prophylaxis, Dx/HA injection and open ureteroneocystostomy. Patients electing Dx/HA injection were tracked in a database maintained by study nurses and 1 of us (JCR). Only the first Dx/HA injection in a patient was considered in this analysis. Radiological followup consisted of cyclic voiding studies (VCUG or RNC) and renal ultrasound performed 3 months postoperatively. Treatment success was defined as the absence of VUR and obstruction on these imaging modalities.

Exclusion criteria included paraureteral diverticula in 20 patients, ureteral duplication in 42, prior bladder surgery in 17, neurogenic bladder in 14 and lack of adequate radiographic followup at 3 months in 73. Only ureters with pre-

Study received approval from the institutional review boards.

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† Financial interest and/or other relationship with Qmed.

DOI:10.1016/j.juro.2007.03.174

operative radiographically proven VUR were analyzed. Contralateral ureters that were not initially injected but later developed de novo VUR were not included in our analysis.

Injection Technique

The method of injection technique was determined by the attending surgeon. We defined the HIT and subureteral injection techniques in accordance with published descriptions.[8,9] The figure shows these techniques.

Statistical Methods

Univariate logistic regression models were constructed to predict treatment success at 3 months. Covariates analyzed were gender, age, VUR grade, dysfunctional voiding, amount of injected Dx/HA, injection technique and surgeon. All covariates with univariate $p < 0.2$ were included in a multivariate logistic regression model. Model residuals revealed no violation of regression assumptions. Statistical analyses were performed using SPSS®, version 14.0. All tests were 2-sided and $p \leq 0.05$ was considered statistically significant.

RESULTS

A total of 301 patients (453 ureters) with primary VUR were included in our analysis. Median patient age was 5.3 years (95% CI 0.4-11.8). The cohort was predominantly female (262 of 301 or 87%) and 111 ureters (24.5%) had persistent VUR at 3 months of followup. Subureteral injection was performed in 204 ureters (45%) and it was successful in 141 (69%). In contrast, HIT was performed in 249 ureters (55%) and it was successful in 201 (81%). Interestingly there was no significant difference in the time frame of injections between the HIT and STING subgroups, as manifested by median injection dates and the range of injection dates. Success rates decreased with increasing VUR, including 83% (25 of 30 cases), 82% (206 of 250), 66% (106 of 161) and 53% (8 of 15) for grades I to IV/V. The average amount of Dx/HA injected was 0.93 ml (range 0.2 to 3.5).

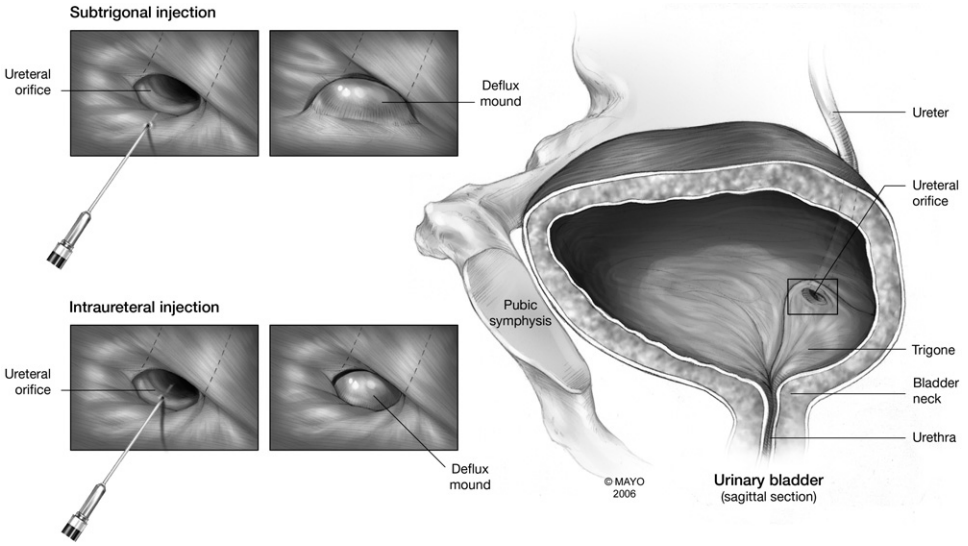
On univariate analysis we found that gender, age, VUR grade, injection technique and surgeon were significant predictors of outcome (see table). On multivariate analysis only VUR grade and surgeon remained significant predictors of outcome, although there was a trend toward significance for injection technique (see table). There was a definite association between surgeon and injection technique ($p < 0.001$), which explained much but not all of the difference in injection failure rates. Similarly there was a significant association between surgeon and VUR grade ($p < 0.001$). Despite adjustment for these differences by multivariate analysis surgeon remained an important predictor of outcome ($p = 0.01$).

DISCUSSION

In 1995 Stenberg and Lackgren introduced their experience with Dx/HA in 75 children, reporting a 68% cure rate at 3 months of followup.[9] Since that time, multiple series have shown highly divergent cure rates of 64% to 100%.[3–7,9] Unfortunately these series are difficult to compare due to their heterogeneous patient populations and differing study end points, eg grade 0 vs grade I VUR. In 2004 Kirsch et al described the use of the modified STING (or HIT) technique in the setting of Dx/HA injection, reporting a per patient cure rate of 89% across all VUR grades.[8] While the use of this modification was encouraging, these results have not been validated or reproduced. Nonetheless, results such as these coupled with the minimally invasive nature of injection therapy led some investigators to conclude that Dx/HA injection may be an acceptable first line modality for the treatment of uncomplicated VUR in some children.[2]

We determined the reproducibility of success reported with the HIT technique. We combined the results of 5 fellowship trained pediatric urologists at 2 tertiary pediatric hospitals, of whom all are experienced with Dx/HA injection therapy. Our study population was limited to only patients with primary VUR who received a single Dx/HA injection. We excluded all patients with an anatomically or functionally complex bladder to avoid potential confounding factors. Multivariate regression was done to adjust for important covariates such as VUR grade, which we would reasonably expect to impact our results.

Our findings are notable for various reasons. We noted a trend toward improved outcome with the HIT injection tech-



Two injection techniques