Single Center Experience with Endoscopic Subureteral Dextranomer/Hyaluronic Acid Injection as First Line Treatment in 1,551 Children with Intermediate and High Grade Vesicoureteral Reflux

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Purpose: In recent years the endoscopic injection of dextranomer/hyaluronic acid has become an established alternative to long-term antibiotic prophylaxis and the surgical management of vesicoureteral reflux. We determined the safety and effectiveness of the endoscopic injection of dextranomer/hyaluronic acid as first line treatment for high grade vesicoureteral reflux.

Materials and Methods: Between 2001 and 2010, 1,551 children (496 male, 1,055 female, median age 1.6 years) underwent endoscopic correction of intermediate and high grade vesicoureteral reflux using dextranomer/hyaluronic acid soon after the diagnosis of vesicoureteral reflux on initial voiding cystourethrogram. Vesicoureteral reflux was unilateral in 761 children and bilateral in 790. Renal scarring was detected in 369 (26.7%) of the 1,384 patients who underwent dimercapto-succinic acid imaging. Reflux grade in the 2,341 ureters was II in 98 (4.2%), III in 1,340 (57.3%), IV in 818 (34.9%) and V in 85 (3.6%). Followup ultrasound and voiding cystourethrogram were performed 3 months after the outpatient procedure, and renal ultrasound was performed annually thereafter. Patients were followed for 3 months to 10 years (median 5.6 years).

Results: Vesicoureteral reflux resolved after the first, second and third endoscopic injection of dextranomer/hyaluronic acid in 2,039 (87.1%), 264 (11.3%) and 38 (1.6%) ureters, respectively. Febrile urinary tract infections developed during followup in 69 (4.6%) patients. None of the patients in the series needed reimplantation of ureters or experienced any significant complications.

Conclusions: Our results confirm the safety and efficacy of the endoscopic injection of dextranomer/hyaluronic acid in the eradication of high grade vesicoureteral reflux. We recommend this 15-minute outpatient procedure as the first line of treatment for high grade vesicoureteral reflux.

Key Words: vesico-ureteral reflux, dextranomer, endoscopy, kidney, cicatrix

Abbreviations and Acronyms

DMSA = dimercapto-succinic acid

Dx/HA = dextranomer/hyaluronic acid

UTI = urinary tract infection

VCUG = voiding cystourethrography

VUR = vesicoureteral reflux

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VESICOURETERAL reflux is the most common urological anomaly in children and has been reported in 30% to 40% of those who present with urinary tract infection. The association of VUR, UTI and renal parenchymal damage is well recognized. Reflux nephropathy is a major cause of childhood hypertension, growth impairment and renal insufficiency.[1] The goals of treating the child with VUR are 1) to prevent recurring febrile UTIs, 2) to prevent renal injury, and 3) to minimize the morbidity of treatment and followup. The various options currently available for the management of VUR are 1) long-term antibiotic prophylaxis, 2) open surgical treatment,

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3) observation or intermittent therapy with management of bladder/bowel dysfunction and treatment of UTIs as they occur, and 4) minimally invasive endoscopic treatment. Since Dx/HA was approved by the United States Food and Drug Administration in 2001 as an acceptable tissue augmenting substance, we have used endoscopic Dx/HA injection as the first line of treatment in the management of intermediate and high grade VUR. In this study we determined the effectiveness and safety of this treatment for VUR.

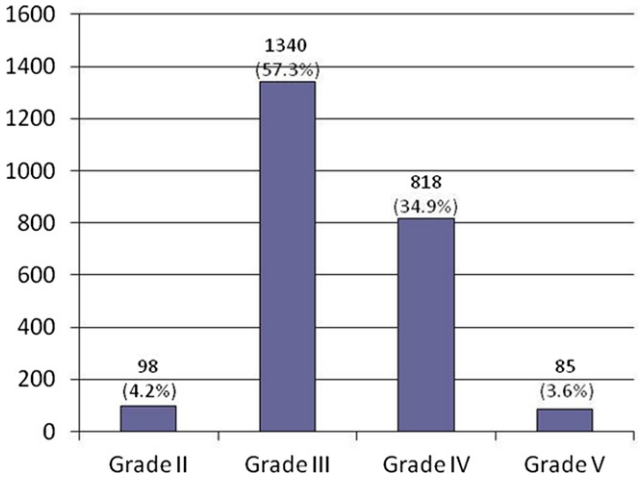
MATERIALS AND METHODS

Between 2001 and 2010, 1,551 children underwent endoscopic correction of high grade VUR using Dx/HA. VUR was diagnosed in all children by VCUG and graded according to the International Classification System.[2] Patients with VUR secondary to neuropathic bladder, posterior urethral valves and ureteroceles were excluded from study.

Of the 1,551 children who underwent endoscopic treatment 496 (32%) were male and 1,055 (68%) were female. Median age at endoscopic injection was 1.6 years (range 1 month to 14.2 years). Reflux was unilateral in 761 children and bilateral in 790, and comprised 2,341 refluxing units. VUR grade at endoscopic treatment was II in 98 (4.2%), III in 1,340 (57.3%), IV in 818 (34.9%) and V in 85 (3.6%) (see figure).

Of the 98 grade II refluxing units 84 ureters were associated with a higher grade (grade III to V) on the contralateral side. There were 8 patients with grade II reflux who had recurrent febrile UTIs and 6 with grade II reflux with renal scarring on DMSA imaging. The indications for VCUG in the 1,551 children were UTI in 1,389 (89.6%), screening for sibling VUR in 98 (6.3%), urinary incontinence without a history of UTI but with pelvicalyceal dilatation on ultrasound in 55 (3.5%) and prenatally diagnosed hydronephrosis in 9 (0.6%).

Endoscopic treatment was done on an outpatient basis according to a previously described technique.[3,4] A 9.5 to 14Fr cystoscope was inserted into the bladder with the child under general anesthesia. A 4Fr Puri disposable catheter (Karl Storz™) was then introduced through the cystoscope. In children with intermediate grade reflux the needle was introduced under direct vision under the bladder mucosa, 2 to 3 mm below the affected ureteral orifice at the 6 o'clock position, and advanced about 4 to 5 mm into the lamina propria of the submucosal portion of the ureter. In children with grade IV and V VUR with a golf hole ureteral orifice the injection was performed by inserting the needle not below but rather directly into the affected ureteral orifice. Dx/HA injection was started slowly and continued until a volcanic bulge of the implant was seen. A correctly placed implant creates the appearance of a nipple, on top of which sits the slit-like ureteral orifice.



VUR grade at treatment by refluxing units

Antibiotic prophylaxis was continued after the procedure until VCUG and renal ultrasound were performed after 3 months. Renal and bladder ultrasound were done again at 1 year, and then every 2 years thereafter to monitor the appearance of the upper urinary tract as well as the site and size of the subureteral Dx/HA copolymer implant. Patients were followed for 3 months to 10 years (median 5.6 years) and occurrence of febrile UTIs was noted. After successful endoscopic correction 39 (2.5%) children were lost to followup. Of the remaining 1,512 patients 1,464 (96.8%) were followed for more than 1 year and 921 (61%) were followed for 5 years or more.

Renal scarring was evaluated by DMSA scintigraphy, and classified into 3 groups of mild (focal defects in uptake between 40% and 45%), moderate (uptake of renal radionuclide between 20% and 40%) and severe (shrunken kidney with relative uptake less than 20%). DMSA scans were performed 4 to 6 months after an initial urinary tract infection.

Factors potentially influencing the outcome including preoperative history of presentation (such as UTI, sibling VUR or bladder/bowel dysfunction), gender, age, VUR grade and renal scarring were analyzed. Detailed information was obtained on children with bladder and bowel dysfunction. We considered a child to have bladder and bowel dysfunction if there was a history of urgency, frequency and/or daytime incontinence, infrequent voiding and constipation. Bladder dysfunction was treated with regular voiding, timed voiding, complete bladder emptying, increased fluid intake during the daytime and reduced fluid intake in the evening. Bowel habits were assessed and when indicated the importance of regular bowel movements was emphasized. Increased fiber intake and laxatives were started before endoscopic injection.

For statistical analysis the chi-square test and Mann-Whitney U test were used when appropriate. Univariate and multivariate logistic regression analysis was performed to identify factors predicting failure of Dx/HA copolymer injection in children. All covariates that were significant on univariate analysis were included in a multivariate regression model with statistical significance considered at $p < 0.05$.

RESULTS

DMSA scan was performed in 1,384 patients (89.2%) and renal scarring was detected in 369 (26.7%).