The Swedish Reflux Trial in Children: II. Vesicoureteral Reflux Outcome

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Abbreviations and Acronyms

DMSA = ^{99m}technetium dimercapto-succinic acid

Dx/HA = dextranomer/hyaluronic acid copolymer

UTI = urinary tract infection

VCU = voiding cystourethrography

VUR = vesicoureteral reflux

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Purpose: We compared reflux status in children with dilating vesicoureteral reflux treated in 3 groups, including low dose antibiotic prophylaxis, endoscopic therapy and a surveillance group on antibiotic treatment only for febrile urinary tract infection.

Materials and Methods: A total of 203 children 1 to younger than 2 years with grade III–IV reflux were recruited into this open, randomized, controlled trial. Endoscopic treatment was done with dextranomer/hyaluronic acid copolymer. The main end point was reflux status after 2 years. Data were analyzed by the intent to treat principle.

Results: Reflux status improved in all 3 treatment arms. Of patients in the prophylaxis, endoscopic and surveillance groups 39%, 71% and 47%, respectively, had reflux resolution or downgrading to grade I–II after 2 years. This was significantly more common in the endoscopic than in the prophylaxis and surveillance groups ($p = 0.0002$ and 0.0030, respectively). After 1 or 2 injections 86% of patients in the endoscopic group had no or grade I–II reflux but recurrent dilating reflux was seen in 20% after 2 years.

Conclusions: Endoscopic treatment resulted in dilating reflux resolution or downgrading in most treated children. After 2 years endoscopic treatment results were significantly better than the spontaneous resolution rate or downgrading in the prophylaxis and surveillance groups. However, of concern is the common reappearance of dilating reflux after 2 years.

Key Words: kidney, urinary tract infections, vesico-ureteral reflux, deflux, endoscopy

TREATMENT options in children with dilating VUR consist mainly of conservative management with antibiotic prophylaxis and surgical correction for VUR. However, management is controversial with few randomized studies on which treatment recommendations can be based.[1] Open surgery has to a large extent been replaced by laparoscopic and endoscopic techniques. The endoscopic treatment introduced in 1981[2] was initially presented as an alternative to reimplantation but later suggested as first line treatment.[3–5]

Today the most commonly used bulking agent for endoscopic treatment is Dx/HA. Many studies have focused on the short-term elimination of VUR but a few on long-term results.[6,7] The high rate of VUR spontaneous resolution or downgrading requires randomized studies with age matched controls to evaluate treat-

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ment efficacy. Little attention has been given to the subsequent rate of renal infection and damage. To our knowledge only 1 randomized study compared the efficacy and safety of Dx/HA treatment.[8]

Thus, in 2000 we started a prospective trial in which children 1 to younger than 2 years with dilating VUR were randomly assigned to 3 treatment alternatives, including antibiotic prophylaxis, endoscopic therapy or surveillance. In this randomized, controlled trial we compared the rate of febrile UTI, kidney damage and VUR status after 2 years. Secondary outcomes were complications and the impact of factors such as VUR grade, gender and bladder dysfunction. We present VUR outcomes with special attention given to the endoscopic treatment group.

PATIENTS AND METHODS

In this randomized, controlled trial we included 128 girls and 75 boys with grade III–IV VUR on VCU at ages 1 to less than 2 years. The study design was previously described in detail.[9] Patients were randomly allocated to low dose antibiotic prophylaxis, endoscopic treatment or surveillance. Nine and 194 cases were detected after prenatal screening and symptomatic UTI, respectively. Children diagnosed with dilating VUR before age 1 year were given prophylaxis and, if repeat VCU between ages 1 and 2 years revealed grade III–IV VUR, the patient was eligible for study. Initial VCU was done before age 1 year in 132 patients (65%), in whom repeat VCU during year 2 of life was the basis for study inclusion. Followup was 2 years.

Before randomization the children were investigated with ultrasound, VCU, DMSA scintigraphy and excretory urography. Study exclusion criteria were previous urogenital surgery, malformation (except duplication), known neurological disease, stone disease, glomerular filtration rate less than 70 ml per minute per 1.73 m^2, split renal function below 15% or suspected noncompliance (inability to understand Swedish or previous noncompliance).

All radiological investigations were reevaluated at the coordinating center by the same radiologist (ES) blinded to other data. VCU was done and VUR was graded according to International Reflux Study in Children standards.[10] The highest VUR grade was used to classify each case. VUR downgrading was defined as a VUR decrease to grade I–II and resolution was defined as no VUR. Urography was used to detect duplex systems. VUR status at randomization was previously reported.[9] VUR was bilateral in 111 patients (55%), and bilateral and dilating in 56 (28%). A total of 35 patients (17%) had duplicated ureters, which was unilateral in 28 and bilateral in 7.

For endoscopic injection we used Dx/HA. In cases of persistent dilating VUR the endoscopic procedure was repeated for a maximum of 3 injections. Ultrasound was done at 1 month and VCU was repeated 3 months after each injection. VCU was not repeated after a third injection to avoid excessive radiation.

The endoscopic procedure was performed at a total of 6 pediatric surgical centers. Treatment was done using general anesthesia on an outpatient basis. Injection was performed according to standard technique.[11,12] Using a standard, low pressure type prefilled syringe and a 25 cm 3.5 Ch steel needle a median volume of 0.8 ml Dx/HA (range 0.2 to 2.0) was injected submucosally in or below the ureteral orifice at the 6 o'clock position to create a prominent bulge and raise the distal ureter and ureteral orifice. In cases of duplication and complete separation of the ureters injection was done under the refluxing ureter and a second injection was usually given laterally under the distal ureter to ensure that the 2 ureters were elevated.[13]

Children randomized to prophylaxis were prescribed trimethoprim as the first choice. In the endoscopic group patients were given prophylaxis until a new VCU showed resolution or downgrading to nondilating VUR. In the surveillance group no specific preventive measures were used. At the end of the 2-year study period DMSA scintigraphy and VCU were repeated.

Children were randomly assigned to prophylaxis, endoscopic treatment or surveillance by computer, matching for gender, previous UTI, VUR grade, DMSA uptake defect, bladder size, duplication and center using minimization procedures.[14]

Analyses were done according to allocated treatment on the intent to treat principle. For ordered categorical variables the Mantel-Haenszel chi-square exact test was used. Spearman's rank correlation coefficient was used for nonparametric correlation analysis with $p < 0.05$ considered significant. The study was approved by the research ethics committees at participating centers. Informed consent was obtained from each participating family.

RESULTS

2-Year VUR Status

Two-year VCU was done in 185 of the 203 patients (91%). It was not performed in 1 of 69 patients (1%) on prophylaxis, 14 of 66 (20%) with endoscopic treatment and 3 of 68 (4%) on surveillance. Reasons for not repeating VCU after 2 years were fear of the investigation in 9 cases, protocol violation in 7, recurrent urine retention after previous catheterizations in 1 and the family moved abroad in 1.

VUR status improved in all 3 treatment groups (table 1 and fig. 1). VUR resolved in 13%, 38% and 15% of patients in the prophylaxis, endoscopic and surveillance groups, and was downgraded to grades I–II in 26%, 33% and 32%, respectively. VUR resolution and downgrading were significantly more common in the endoscopic than in the prophylaxis and surveillance groups ($p = 0.0002$ and 0.0030, respectively). There was no statistical difference in VUR outcome between the prophylaxis and surveillance groups ($p = 0.3906$).

Groups

Prophylaxis and surveillance. Of the 85 girls in the prophylaxis and surveillance groups 82 underwent VCU after 2 years. Grade III VUR at randomization was associated with a significantly better outcome than grade IV ($p = 0.0177$, table 2). In boys no such