The Swedish Reflux Trial in Children: III. Urinary Tract Infection Pattern

Per Brandström, Elisabeth Esbjörner, Maria Herthelius, Svante Swerkersson, Ulf Jodal and Sverker Hansson*

From the Pediatric Uro-Nephrologic Center, Queen Silvia Children's Hospital, University of Gothenburg (PB, SS, UJ, SH) Göteborg, Department of Pediatrics, Örebro University Hospital (EE), Örebro and Department of Clinical Science, Intervention and Technology, Division of Pediatrics, Karolinska University Hospital (MH), Huddinge, Sweden

Abbreviations and Acronyms

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

RCT = randomized, controlled trial

UTI = urinary tract infection

VCU = voiding cystourethrography

VUR = vesicoureteral reflux

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* Correspondence: Pediatric Uro-Nephrologic Center, Queen Silvia Children's Hospital, SE-416 85 Göteborg, Sweden (e-mail: sverker.hansson@gu.se).

Purpose: We evaluated the difference in the febrile urinary tract infection rate in small children with dilating vesicoureteral reflux randomly allocated to 3 management alternatives, including antibiotic prophylaxis, endoscopic treatment or surveillance only as the control.

Materials and Methods: At 23 centers a total of 203 children were included in the study, including 128 girls and 75 boys 1 to younger than 2 years. Vesicoureteral reflux grade III in 126 cases and IV in 77 was detected after a febrile urinary tract infection (194) after prenatal screening (9). Voiding cystourethrography and dimercapto-succinic acid scintigraphy were done before randomization and after 2 years. The febrile urinary tract infection rate was analyzed by the intent to treat principle.

Results: We noted a total of 67 febrile recurrences in 42 girls and a total of 8 in 7 boys ($p = 0.0001$). There was a difference in the recurrence rate among treatment groups in girls with febrile infection in 8 of 43 (19%) on prophylaxis, 10 of 43 (23%) with endoscopic therapy and 24 of 42 (57%) on surveillance ($p = 0.0002$). In girls the recurrence rate was associated with persistent reflux after 2 years ($p = 0.0095$). However, reflux severity (grade III or IV) at study entry did not predict recurrence.

Conclusions: In this randomized, controlled trial there was a high rate of recurrent febrile urinary tract infection in girls older than 1 year with dilating vesicoureteral reflux at study entry but not in boys. Antibiotic prophylaxis and endoscopic treatment decreased the infection rate.

Key Words: kidney, urinary tract infections, vesico-ureteral reflux, cicatrix, antibiotic prophylaxis

The rationale for treating VUR has been to decrease the risk of new UTI and the development or progress of renal damage.[1,2] Traditional management options are antibiotic prophylaxis or antireflux surgery. The International Reflux Study[3] and the Birmingham Study[4] showed that neither modality is superior to decrease renal scarring or recurrent UTI, although there were more febrile recurrences in the medical group in the former study. Since that time, the endoscopic technique has become established and widely spread as an alternative to open reflux surgery.[5,6] Some groups even advocate it as the primary option for VUR in children.[7–9] The short-term elimination of VUR is well described but there are few reports of long-term results and only a handful focusing on the post-injec-

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tion UTI pattern, of which none are prospective.[10–14]

Active treatment to prevent UTI and renal damage has been considered so obvious that for ethical reasons a control group without preventive measures has not been included in studies until the last decade. With challenges to the efficacy of antibiotic prophylaxis and increasing problems with resistant bacteria including an untreated control group has now become acceptable and necessary.[15,16]

There is a need for controlled studies to evaluate treatment in small children with dilating VUR. The Swedish Reflux trial was set up as a RCT to compare 3 treatment alternatives, including antibiotic prophylaxis, endoscopic therapy and surveillance as the control group, in regard to recurrent febrile UTIs, renal damage and VUR status after 2 years. We analyzed the UTI pattern in the 3 treatment groups.

PATIENTS AND METHODS

The study design was described previously.[17] Briefly, this open, multicenter RCT included 128 girls and 75 boys 1 to younger than 2 years with grade III–IV VUR. Nine and 194 cases were identified after prenatal screening and symptomatic UTI, respectively. 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). Before randomization the children were investigated by ultrasound, VCU and DMSA scintigraphy. At 2-year followup VCU and DMSA scan were done at a median age of 3.8 years. Children were randomly assigned to prophylaxis (69), endoscopic treatment (66) or surveillance (68) by computer, matching for gender, previous UTI, VUR grade, DMSA uptake defect, bladder size, duplication and center using minimization procedures.[18]

Regular visits and telephone contacts were scheduled at 3-month intervals when information on episodes of fever, intercurrent illnesses and antibiotic consumption since the previous contact was recorded. Families were encouraged to present for extra visits when symptoms suggested UTI, especially high fever. UTI between randomization and followup DMSA scan was reported and evaluated by the same pediatric nephrologist (UJ).

A UTI diagnosis was defined as bacteriuria 100,000 cfu/ml or greater in urine obtained by the midstream or bag technique, or any number of bacteria after suprapubic bladder aspiration. To exclude asymptomatic bacteriuria and contaminated urine only infections with symptoms consistent with UTI and supporting laboratory results (increased C-reactive protein, positive nitrite test and pyuria on dipstick) were approved with febrile infection defined as body temperature 38.5C or greater. After careful consideration a total of 10 febrile episodes in 9 girls were included as febrile UTI, although culture results did not meet preset criteria. One, 1 and 7 girls were in the prophylaxis, endoscopic and surveillance arms, respectively. Six of the latter girls had additional febrile recurrences with 100,000 cfu/ml or greater. Children with recurrence were promptly treated with antibiotics for 10 days.

Children randomized to prophylaxis were prescribed 0.5 to 1 mg/kg trimethoprim (58), 1 mg/kg nitrofurantoin (6) or 5 mg/kg cefadroxil (5) once daily. Questions on adherence to prophylaxis were asked at each contact but compliance was not otherwise tested. For endoscopic injection we used Deflux®. Prophylaxis was continued until a new VCU showed resolution or downgrading of VUR to grade I–II. In the surveillance group no specific preventive measures were done. Main end point variables were recurrent febrile UTI, VUR status and renal damage on DMSA scintigraphy at 2 years. The latter 2 variables were reported previously.[19,20]

Analysis was done according to allocated treatment on the intent to treat principle. For comparison between groups the chi-square exact test was used for nonordered categorical variables and the Kruskal-Wallis test was used for continuous variables. For pairwise comparison between groups Fisher's exact test was used for dichotomous variables, the Mantel-Haenszel chi-square exact test was used for ordered categorical variables and the Mann-Whitney U test was used for continuous variables. Kaplan-Meier life table analysis was done to compare time to first recurrence between the groups. Survival curves were plotted using Kaplan-Meyer estimates and formally tested by the log rank test 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

Overall 53 of the 203 patients, including 45 girls and 8 boys, experienced a total of 91 new symptomatic UTIs during the median 2.05-year followup. In 98% of patients followup was more than 1.8 years. Of these cases 16 were nonfebrile UTI, including 11 with temperature less than 38.0C and 5 with a fever of 38.0C to 38.4C. Subsequently only febrile recurrences (38.5C or greater) were considered. We noted a total of 67 febrile recurrences in 42 girls and a total of 8 in 7 boys (table 1). The difference between girls and boys was significant ($p = 0.0002$). At recurrence in these 49 patients the sampling technique was bag in 18 (3 on prophylaxis, 5 with endoscopic therapy and 10 on surveillance), midstream in 26 (6 on prophylaxis, 6 with endoscopic therapy and 14 on surveillance), catheter and bladder aspiration in 1 each (endoscopic therapy) and an unspecified technique in 3 (1 per group).

In the prophylaxis group febrile recurrence was seen in 8 of 43 girls (19%) with trimethoprim resistant bacteria in 7 (table 1). In the endoscopic group 10 of 43 girls (23%) had recurrence, including 5 with resistance to trimethoprim. In the surveillance group 24 of 42 girls (57%) had recurrence with tri-

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