The Swedish Reflux Trial in Children: I. Study Design and Study Population Characteristics

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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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Purpose: We compared the rates of febrile urinary tract infection, kidney damage and reflux resolution in children with vesicoureteral reflux treated in 3 ways, including antibiotic prophylaxis, endoscopic therapy and surveillance with antibiotics only for symptomatic urinary tract infection.

Materials and Methods: Children 1 to younger than 2 years with grade III–IV reflux were recruited into this prospective, open, randomized, controlled, multicenter study and followed for 2 years after randomization. The main study end points were recurrent febrile urinary tract infection, renal status on dimercapto-succinic acid scintigraphy and reflux status. Outcomes were analyzed by the intent to treat principle.

Results: During a 6-year period 128 girls and 75 boys entered the study. In 96% of cases reflux was detected after urinary tract infection. The randomization procedure was successful and resulted in 3 groups matched for relevant factors. Recruitment was slower than anticipated but after patients were entered adherence to the protocol was good. Of the children 93% were followed for the intended 2 years without a treatment arm change. All except 2 patients completed 2-year followup scintigraphy.

Conclusions: Recruitment was difficult but a substantial number of children were entered and randomly assigned to 3 groups with similar basic characteristics. Good adherence to the protocol made it possible to address the central study questions.

Key Words: kidney, vesico-ureteral reflux, urinary tract infection, disease recurrence, disease progression

The VUR literature is extensive but there are widely divergent opinions on how children with this condition should be treated. In a critical review in 1994 Winberg questioned whether current routines for VUR in children took full account of recent scientific results.[1] On his initiative a Swedish state-of-the-art conference was arranged.[2] The basis of the recommended new guidelines was a critical review of the literature as well as clinical experience since several issues had not been adequately studied. The aim was to design guidelines that limited renal damage and future complications with minimal discomfort to the child. The new strategy focused on renal development and function rather than on VUR, a shorter time on antibi-

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otic prophylaxis and increased attention to bladder dysfunction. Thus, children with febrile UTI who were 2 years old or older were not recommended to undergo routine VCU and children with grade I–II VUR would not be followed further unless there was evidence of renal damage.[3]

Another aim of the state-of-the-art conference was to define future research projects to answer clinically important questions. A randomized, multicenter study with or without antibiotic prophylaxis in children with grade III–IV VUR was proposed. Active treatment to prevent renal damage development or progression was previously considered so obvious and important that for ethical reasons a control group without active treatment had hardly been considered until the last decade, when the lack of controlled studies of antibiotic prophylaxis was brought to attention.[4,5] As antibiotic prophylaxis efficacy was challenged, including an untreated surveillance group became acceptable and necessary.

Another issue to investigate was endoscopic treatment for VUR. This technique had become an alternative to long-term antibiotic prophylaxis and open surgery. However, interest focused on eliminating VUR with little attention to the subsequent pyelonephritis rate or to long-term kidney development. The endoscopic technique had to be tested in a randomized study that preferably included an untreated control group.[6]

Thus, the protocol of the Swedish Reflux Trial was based on random allocation to 3 treatment alternatives, including antibiotic prophylaxis, endoscopic therapy or surveillance without specific preventive measures. The study aim was to compare the rates of febrile UTIs, kidney damage and reflux status after 2 years in the 3 groups. Secondary outcomes were complications, and the impact of factors such as VUR grade, gender and bladder dysfunction. This first article describes the study design, study population characteristics and adherence to the study protocol.

STUDY DESIGN

A total of 23 pediatric centers extending from county hospital to university level participated in this multicenter RCT, of which 22 covered 80% of the Swedish population of 9 million and 1 was in Oslo, Norway. Figure 1 shows the overall protocol design. Investigations done before study inclusion were urinary tract ultrasound, VCU, DMSA scintigraphy and excretory urography. Optional bladder function assessment was done by a 4-hour micturition observation.[7]

For study inclusion patients had grade III–IV VUR at ages 1 to less than 2 years. Children diagnosed with dilating VUR before age 1 year received prophylaxis and were eligible for study if repeat VCU between ages 1 and 2 years showed grade III–IV VUR. Study exclusion criteria were previous urogenital surgery, malformation (except duplication), known neurological disease, stone disease, glomerular filtration rate below 70 ml per minute per 1.73 m^2, split renal function below 15% or suspected noncompliance (inability to understand Swedish or previous noncompliance).

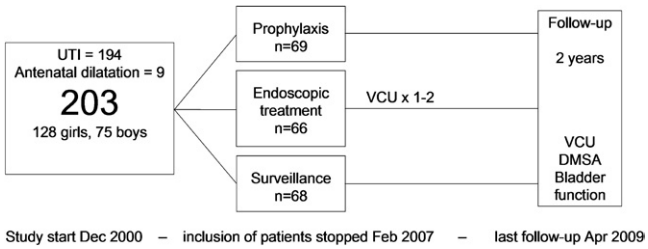

Figure 1. Overall protocol design

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.[8] To have an equal number of patients per group with at least 80% power for all pairwise comparisons using Fisher's exact test and assuming a 0.10, 0.40 and 0.60 febrile UTI recurrence rate in the endoscopic, prophylactic and surveillance groups, respectively, 97 evaluable patients were needed per group. To allow for a 10% dropout rate 330 patients would be randomized. With a calculated recruitment rate of 100 patients per year and a followup of 2 years the total study time was assumed to be 5 to 6 years.

Followup was scheduled at 3-month intervals, consisting of visits every 6 months and telephone interviews between visits. The protocol included questions on fever episodes, intercurrent illness and antibiotic consumption since the previous contact. Weight, height, blood pressure and urinalysis were recorded at all visits. Families were instructed to make extra visits to their pediatric outpatient clinic if symptoms suggesting UTI appeared, especially high fever. A special protocol was used when UTI recurrence was suspected with monitoring of urine dipstick results, urine culture, temperature and C-reactive protein.

At the end of the 2-year study period DMSA scintigraphy and VCU were repeated. Bladder function was evaluated by uroflow, ultrasound determination of post-void residual urine and a comprehensive history of bladder and bowel habits. End points were febrile UTI during followup, progression of DMSA uptake defects present on initial examination or new