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Long-term incidence of febrile UTI after DxHA treatment of VUR

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KEYWORDS

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Abstract *Purpose:* To assess the long-term incidence of febrile urinary tract infection (fUTI) in children treated by endoscopic injection of dextranomer/hyaluronic acid (DxHA) for vesicoureteral reflux (VUR).

Materials and methods: Prospective study from January 2002 to December 2009 in children treated at our institution for VUR by endoscopic injection of DxHA. All children underwent clinical and renal/bladder ultrasound follow up at 3 months after procedure, then annually. Post-operative voiding cystourethrogram (VCUG) control was performed only for patients with recurrent fUTI.

Results: 227 children (177 female) were included. Mean patient age at inclusion was 4.7 years. The mean duration of follow-up was 51.6 months. During follow-up, 18.9% had one or several fUTIs, of whom 48.8% had VUR at VCUG. No recurrence of fUTI was observed after 4 years of follow-up. We identified three risk factors for fUTI recurrence: cystitis cystica at the time of injection ($p = 0.007$), preoperative renal scarring ($p = 0.018$), and the disappearance of the implant at 3-month follow-up ultrasound ($p = 0.037$).

Conclusions: The long-term incidence of recurrent fUTI after endoscopic treatment of VUR is low. Our data show that the clinical results of endoscopic treatment should be interpreted with a follow up of at least 4 years.

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Introduction

Since the publication of the International Reflux Study in Children in 1992 [1], it is established that eliminating vesicoureteral reflux (VUR) has little impact on the prognosis of renal function, which is determined by the prior

existence of renal dysplasia. However, correcting VUR significantly reduces the incidence of subsequent febrile urinary tract infection (fUTI), which represents considerable morbidity for patients and their families.

In 2010 and 2012, the American Urology Association and the European Urology Association [2,3] respectively issued

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guidelines for the management of VUR in children, aimed at reducing the risk of fUTI and renal scarring. The results of VUR treatment are evaluated according to three main criteria:

- Radiologic result, evaluated by a negative voiding cystourethrogram (VCUG)
- Renal prognosis, assessed by evolution of renal scars on dimercaptosuccinic acid (DMSA) scan
- Clinical outcome, evaluated by the cessation of recurrent fUTI (low economic cost and best quality of life for patients and their families).

Most of the published studies determine the success rate of endoscopic treatment by the disappearance of reflux on VCUG (around 70–80% at initial injection for all grades) [4]. However, the clinical outcome has not been extensively assessed in the literature.

The recurrence rate of fUTI ranges from 12% to 36% after antibiotic prophylaxis [5–7], from 4.6% to 24% after surgical reimplantation [8,9] and from 0.75% to 27% [10,11] after endoscopic treatment.

Over the past 2 decades, endoscopic treatment has become the first-line therapy for VUR. DxHA (Deflux[®], Q-Med, Uppsala, Sweden), approved by the FDA in 2001, is now the most widely used bulking agent for this indication.

The purpose of this prospective study was to evaluate the long-term clinical outcome after endoscopic DxHA injection for VUR in children with a special focus on the recurrence rate of fUTI. The secondary aim was to identify possible risk factors for fUTI recurrence in this population.

Materials and methods

Patient population

This prospective cohort study was performed from January 2002 to December 2009, in a paediatric population recruited in our university hospital. Children were included after one or several episodes of fUTI. In all children, the diagnosis of VUR was confirmed by VCUG, performed after fUTIs. VUR was graded according to the international grading system established by the International Reflux Study in Children [1].

In addition to VCUG, all children underwent renal ultrasound and DMSA scan before intervention.

Exclusion criteria

We excluded patients with VUR associated with posterior urethral valve, neurogenic bladder, pyelo-ureteral duplication, and bladder diverticula. Furthermore we excluded children with a history of ureteral reimplantation, or endoscopic injection.

Technique

Endoscopic therapy consisted of a subureteral injection of DxHA according to the classical STING procedure [12]. Intervention was performed under general anaesthesia

using a cystoscope (Storz[®]) with offset lens 9.5 Charriere and/or a direct vision 11 Charriere.

A dose of antibiotics (amoxicillin/clavulanic acid) was systematically administered at the start of the anaesthesia. After discharge, antimicrobial prophylaxis (trimethoprim–sulfamethoxazole or Cefixime) was prescribed for a limited period of 8 days.

Follow-up

All children underwent urinary tract ultrasound 3 months after the procedure.

We decided not to perform systematic postoperative VCUG, except in children with high-grade VUR.

If any anomaly was detected on pre-operative DMSA scan, repeat DMSA scan was systematically performed 3 years later. Abnormal DMSA scan was defined as the presence of scarring, single or multiple focal defects, and contribution of one kidney to total renal function <45% on DMSA Scan.

An annual visit was scheduled at our surgical unit or with the family practitioner.

The occurrence of each post injection fUTI was checked with the family doctor and/or parents by phone or regular mailing, and defined as fever above 38.5 °C, and blood C-reactive protein (CRP) level of >4 mg/L, and positive dipstick test (nitrite and leukocytes), and monomicrobial positive urine culture results at >100 000 colony-forming units/mL and leukocyturia >10 000/mL. Urine sample was collected with an external collector in children with uncontrolled voiding.

The exhaustiveness and accuracy of the recorded data was verified by a questionnaire sent to parents at the end of the study (December 2009). In the case of non-response despite reminders, the family physician was contacted by phone to verify the accuracy of recorded data.

Statistical analysis

Quantitative data are presented as mean \pm standard deviation (SD) and categorical data as number and percentage. Categorical variables were compared using the Chi square test and quantitative variables using the Student *t* test, as appropriate.

Children were classified according to presence or absence of at least one episode of fUTI at follow up.

We evaluated the risk of recurrence of fUTI based on prognostic variables identified by bivariate analysis. Variables with a *p* value of <0.20 were retained for inclusion in the Cox regression multivariate analysis. We plotted the risk of recurrent fUTI using the Kaplan–Meier method.

All analyses were performed using SAS version 9.2. (SAS Institute, Cary, NC, USA).

Results

Patient population

From January 2002 to December 2009, 259 patients were treated in our centre for VUR by endoscopic injection of

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