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ORIGINAL ARTICLE

Retrospective study of endoscopic treatment in children with primary vesicoureteral reflux and multivariate analysis of factors for failure

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Abstract

Objective. The aim of this study was to investigate endoscopic treatment in children with primary vesicoureteral reflux (VUR) and conduct a multivariate analysis of factors for failure. *Material and methods.* Between August 2006 and January 2012, 216 children (32 boys and 184 girls) with primary VUR (grades I–IV) who underwent endoscopic treatment were analysed. Patients with grade V VUR were excluded. Hydrodistension tests and intraureteral injection techniques were performed, if applicable. Urinary ultrasound and voiding cystourethrography were studied 3–6 months after surgery. Univariate and multivariate logistic regression were used for statistical analyses. *Results.* In total, 172 children (21 boys and 151 girls) were enrolled, and 280 ureters were treated (108 bilateral, 64 unilateral; three with grade I, 34 with grade II, 214 with grade III and 29 with grade IV VUR). The median (± SD) age was 7.8 ± 3.1 years (boys 7 ± 3.1 years, girls 7.9 ± 3.1 years). The mean (± SD) follow-up was 24.4 ± 4.1 months (boys 28.2 ± 8.1 months, girls 21.4 ± 4.1 months). Mean injected volume per ureter was 1.8 ± 0.5 ml. A single injection resolved the reflux in 79.6% and a second injection resolved it in 90.4% of ureters. Eight children (4.6%) had postoperative febrile urinary tract infections (fUTIs). Postoperative fUTIs were significantly associated with failures in injection ($p < 0.001$). Renal scars were significantly associated with postoperative fUTI ($p = 0.006$). Haematuria occurred in three children (minor complication); a non-functional kidney was observed in one child (major complication) and a laparoscopic nephrectomy was performed. Fourteen children underwent ureteroneocystostomy owing to unsuccessful VUR treatment. *Conclusions.* Endoscopic injection of small-diameter microsphere (80–120 μm) non-animal dextranomer–hyaluronic acid copolymer seems to be an effective treatment for VUR. Only postoperative fUTI and the presence of a renal scar were correlated with failed endoscopic treatment of VUR.

Key Words: *antibiotic prophylaxis, dextranomer–hyaluronic acid copolymer, paediatrics, urinary tract infection, vesicoureteral reflux*

Introduction

Vesicoureteral reflux (VUR), which may lead to different clinical properties in children, has been defined as reflux of urine from the bladder to the ureter and/or renal pelvis.

VUR affects around 1% of all children, making it the most common paediatric abnormality of the urinary tract [1,2]. It is also associated with urinary tract infections (UTIs), which may lead to pyelonephritis, renal scarring and chronic renal insufficiency [1,2]. Moreover, febrile urinary tract infection (fUTI) is the most prominent symptom for abnormalities of the urinary tract as well as in primary VUR, during infancy or childhood. Around one-third of children with UTIs have VUR [2,3]. However, VUR may be asymptomatic in some children and it may cause serious clinical problems such as irreversible renal

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damage [2–4]. Therefore, it is essential to follow children with VUR both clinically and with different modalities of kidney function, so that they can be treated if their renal function or clinical status deteriorates.

Over the past 20 years, treatment options for VUR have changed in parallel with developments in technology and endoscopic surgery. Injection of non-animal dextranomer–hyaluronic acid (NA Dx/HA) has become the most commonly used endoscopic treatment option for VUR [4]. Although the safety and efficiency of NA Dx/HA in the endoscopic treatment of VUR have been shown in the literature, the precise factors affecting success rates have not yet been clearly determined [5,6].

As well as endoscopic treatment, follow-up is very important. During follow-up, voiding cystography (VCUG) is essential. However, VCUG is an X-ray-based radiological examination usually used for determining success on VUR resolution, and it may be traumatic for children [7,8].

The objective of the present study was to investigate the rate of resolution of primary VUR after endoscopic injection of NA Dx/HA and reasons for failure, using parameters such as age, gender, laterality, dysfunctional voiding, renal scarring and continuation of fUTI.

Material and methods

This retrospective study was approved by the institutional review board. The children's parents signed the institutional consent forms. The children had been referred to the paediatric urology outpatient clinic from the paediatrics outpatient clinic. Exclusion criteria were missing data, irregular follow-up and grade V VUR, which was treated surgically.

Between August 2006 and January 2012, 216 children (32 boys and 184 girls) were operated on for VUR with injection of small-diameter microspheres (80–120 μm) of Dx/HA. Patients' files were reviewed from hospital records. In total, 172 children (21 boys and 151 girls) who attended the outpatient clinic for regular control with postoperative VCUG were enrolled.

Age, gender, presenting symptoms, dysfunctional voiding, VUR side, comorbid diseases, grade of VUR (evaluated using the International Reflux Study Committee scale) [2,7], former operation history, preoperative VCUG, preoperative renal ultrasonography and preoperative renal scarring in renal scintigraphy were recorded as demographic data. Operation outcomes including injected volume of NA Dx/HA, and postoperative parameters including postoperative VCUG, renal ultrasonography, fUTI, additional injections and additional open surgeries were recorded. All children underwent VCUG and ultrasonography 3 and 6 months after surgery.

fUTI despite antibiotic prophylaxis, persistent VUR and/or parental preference for injection over antibiotic prophylaxis were indications for injection. Detailed questioning was used to diagnose the urge syndrome, infrequent voiding and/or constipation with therapy, including timed voiding, anticholinergics and/or laxatives as indicated, initiated before injection. In addition, grade I reflux was endoscopically treated when associated with contralateral reflux of a higher grade.

The operative technique described by Peters et al. [7] was used. All operations were performed by a single experienced surgeon (SY). In brief, all children underwent cystoscopy under general anaesthesia in the lithotomy position. During cystoscopy, the location of the orifice was visualized with the bladder nearly empty. Hydrodistension tests and intraureteral injection techniques were performed, if applicable. The needle was placed directly into the orifice and advanced into the subureteral space. Then, NA Dx/HA was injected to create a mound, elevating and coapting the orifice. In cases where the creation of a mound in the orifice was unsuccessful, additional NA Dx/HA was injected to achieve the desired appearance. Successful coaptation was confirmed visually by directing the saline irrigation stream towards the orifice after treatment was completed. All children had an indwelling urethral catheter after the operation and the catheter was removed before the patient was discharged from hospital. In addition, the children who underwent injection for VUR continued antibiotics for prophylaxis after injection until treatment success was confirmed by postoperative VCUG. Success of treatment was defined as complete resolution of reflux when no VUR was demonstrated in VCUG. Follow-up visits were stopped in the outpatient clinic for successfully treated children. Children who had persistent VUR were recommended reinjections.

In the case of bilateral VUR, a higher grade was used for analysis. Reflux grade and injected volume of NA Dx/HA were analysed as continuous and categorical variables.

In statistical analysis univariate and multivariate linear logistic regression analyses were used to determine the predictive factors for failure of injections. Continuous variables were compared using the *t* test. Categorical variables were compared by chi-squared or Fisher's exact test. Statistical analysis was performed using SPSS version 12.0 software. A p value less than 0.05 was accepted for statistical significance.

Table I. Demographic data of the children.

Parameter	Boys	Girls	Total patients
Age, mean ± SD (years)	7 ± 3.1	7.9 ± 3.1	7.8 ± 3.1
Gender	21	151	172
Grade of VUR			
I	–	2	2
II	5	15	20
III	12	116	128
IV	4	18	22
Bowel symptoms	5	28	33
Voiding symptoms	6	41	47
Other	2 PUV, 1 VSD	1 renal agenesis, 1 growth and developmental retardation, 1 Fanconi anaemia	Not assessed

VUR = vesicoureteral reflux; PUV = posterior urethral valve; VSD = ventral septal defect.

Results

There were 172 children (21 boys and 151 girls) enrolled in the study. The mean (± SD) age of the children was 7.8 ± 3.1 years (boys 7 ± 3.1 years, girls 7.9 ± 3.1 years). Mean follow-up was 24.4 ± 4.1 months (boys 28.2 ± 8.1 months, girls 21.4 ± 4.1 months). Reflux was observed in 108 bilateral and 64 unilateral ureters. Reflux was grade I in three ureters, grade II in 34 ureters, grade III in 214 ureters and grade IV in 29 ureters. The VUR corrections were performed in 28 right, 36 left and 108 bilateral ureters (280 ureters in total). The mean injected volume per ureter was 1.8 ± 0.5 ml (median 2 ml). The demographic data are summarized in Table I.

A single injection resolved reflux in 133 children (77.3%) (in 223 ureters; 79.6%). Twenty-three children underwent reoperation and one child needed a third session. After reinjections, reflux was treated in 157 children (91.2%) (in 253 ureters; 90.4%) (Table II).

Eight children (4.6%) had fUTIs following endoscopic correction. Multivariate analysis showed that gender, age, VUR grade, dysfunctional voiding, renal scarring and injected volume did not affect the success rate, but only postoperative fUTI was significantly associated with failure ($p < 0.001$) (Table III). There were 25 children with renal scars on scintigraphy. In addition, renal scars were significantly associated with postoperative fUTI in multivariate analyses ($p = 0.006$) (Table III).

Furthermore, all children were divided into three subgroups to analyse the learning curve, looking at the success rate chronologically. There were 58 children in group 1, 57 in group 2 and 57 in group 3. Three children in group 3, 15 in group 1 and 12 in group 2 needed reinjections. In addition, two children in group 3 had undergone ureteroneocystostomy, while five children in group 1 and six in group 2 had undergone open surgery. The numbers of reinjections and open surgeries were significantly lower in group 3 than in the other groups ($p < 0.001$).

Two boys had undergone previous operations for posterior urethral valves, one girl had Fanconi anaemia, one boy had a ventricular septal defect, and one girl had growth and developmental delay. Acute haematuria occurred in three children after injection. A Foley catheter was reinserted in these children.

Table II. Resolution of vesicoureteral reflux in endoscopically treated ureters with small-diameter microsphere (80–120 μm) non-animal dextranomer–hyaluronic acid copolymer.

Parameter	1st injection[a]		Reinjection[a]		3rd injection[a]		Failure[b]	
	Boys	Girls	Boys	Girls	Boys	Girls	Boys	Girls
Grade I	–	3/3 (100)	–	–	–	–	–	–
Grade II	8/8 (100)	21/26 (80.7)	–	5/5 (100)	–	–	–	–
Grade III	16/20 (80)	157/194 (80.9)	6/6 (100)	11/35 (31.4)	–	1/1 (100)	3	20
Grade IV	2/2 (100)	18/27 (66.6)	–	8/11 (72.7)	–	–	–	3
Total	223/280 (79.6)		30/57 (52.6)		1/1 (100)		26	

[a]Number of successfully treated ureters/Total number of ureters (%); [b]number of ureters.

Table III. Factors affecting postoperative failure and febrile urinary tract infections (fUTIs) after endoscopic injection for vesicoureteral reflux (VUR), in multivariate analyses.

Parameter	Factors affecting postoperative failure	Factors affecting postoperative fUTIs
Gender	0.65	0.71
Age	0.72	0.33
VUR grade	0.55	0.34
Dysfunctional voiding	0.57	0.52
Renal scar	0.07	0.006*
Injected volume	0.06	0.06
fUTI	<0.001*	N/A

N/A = not applicable.
*Significant association ($p < 0.05$).

After a short period, the haematuria disappeared and the children were discharged. There was a major complication of an atrophic right kidney in one child in the follow-up period, and a laparoscopic simple nephrectomy was performed. One girl needed ureteroneocystostomy due to ureteral obstruction after injection. Fourteen ureteroneocystostomies were performed in children with failed injections.

Discussion

The present retrospective, non-randomized study reviewed the institutional VUR database. According to the results, the first NA Dx/HA injection was successful in 133 children (77.3%) (in 223 ureters; 79.6%). After reinjections, the endoscopic VUR treatments were successful in 157 children (91.2%) (in 253 ureters; 90.4%). The results of this study show that having fUTI was associated with failure. Nevertheless, the present series had few complications. Since endoscopic injection of NA Dx/HA has become the most commonly used endoscopic treatment option for VUR in children, its success rate has come into question [4]. Despite the reported high success rates with injection of NA Dx/HA, there may be some factors which cause failure of treatment.

The outcomes and success rate of the first injections in this study were in parallel with the results of Lee et al. [9]. In addition, Kirsch et al. reported their experience as being 72% successful after a single injection [10]. The success rate was also increased with additional injections in the present series. The overall success rate was 90.4% of the ureters in this series was higher than the results of Elder et al. [11]. In their meta-analysis, the success rate was 54% of children and 68% of ureters by reinjections [11]. The higher success rate in the current series may related to the paediatric surgeon (SY), who had experience from a long-term fellowship programme. Moreover, the success rate was increasing, and the requirement for reinjections and ureteroneocystostomies was decreasing over time, according to this series. The impact of the learning curve is apparent in the results of the present study.

The present results and surgical techniques were similar to those of Higham-Kessler et al. [5]. An intraureteral injection technique was used, if applicable. They reported that most failures of endoscopic correction were associated with mound shifting [5]. In the present study, mound shifting was determined in nine children and additional injections were needed. Moreover, all of the nine children had dysfunctional voiding. The outcomes of this series showed that additional injections were needed if children had dysfunctional voiding. Therefore, clinical evaluation of patients is essential before VUR treatment for comorbidities, specifically voiding dysfunction.

In the present series, there was only one postoperative fUTI in a child with grade II VUR. The success rate in grade II VUR was 85.2% after the first injection. After reinjection, the overall success rate was 100% and there were no fUTIs in children with grade II VUR. The other fUTIs were in children with grade III–IV VUR, after the first injection. In these children, reinjections were unsuccessful. Furthermore, they underwent ureteroneocystostomy. Postoperative fUTI was significantly associated with failure rates after VUR treatment by injection, in agreement with the results of Stenberg et al. [12]. They reported a fUTI rate of 3.4% in the follow-up period. After injection, the rate of postoperative fUTI was 4.65% in the present study. Puri et al. reported that recurrent VUR was associated with fUTI after injection [13]. In the current study, fUTI was determined by a positive urine culture in symptomatic patients. These findings concurred with an older series in an experienced centre [8]. Preoperative renal scarring was significantly associated with postoperative fUTI. To the authors' knowledge, these findings are unique in the literature. It seems that if there was a preoperative renal scar on the VUR side, there would be fUTI after

treatment, and possible failure of treatment. Moreover, these patients had no comorbidities, constipation or dysfunctional voiding.

The success of treatment was evaluated by VCUG during follow-up 3 and 6 months after injection. Although VCUG has been widely used in the follow-up period, it is an X-ray-based test and it can be traumatic for children. Alternatively, an isotope cystogram may be used for checking VUR after an operation [14]. The isotope cystogram may be more sensitive and emits less radiation than VCUG [14], but this modality can demonstrate only reflux higher than grade II that needs to be treated, and it can be more time consuming and expensive than VCUG. [14]. Therefore, the present authors preferred VCUG for follow-up after VUR treatment. The first injections were successful in 13 children (86.6%) with grades I and II VUR. They had no renal scarring or dysfunctional voiding before injection. VCUG was also performed in these children during the follow-up period. In a comparative study, Elmore et al. reported significantly lower rates of fUTI in patients with VUR treated by endoscopic injection of NA Dx/HA [15]. The outcomes of this study were similar to the reports of Elmore et al. [15]. The first injection was unsuccessful in two children (13.3%) who did not have renal scars before injection, and who did not have dysfunctional voiding, with grade II VUR. In the light of these results, a patient with grade I or II VUR, who had no renal scar before injection and no fUTI in the postoperative period, may not have to undergo VCUG, which is an X-ray-based and traumatic examination.

Some published studies reported higher overall success rates with endoscopic treatment, approaching those seen with open surgery (in the region of 90%), after up to 12 months' follow-up [16–18]. However, there is an apparent learning curve with this treatment procedure. Kirsch et al. reported success rates of 60% for the first 20 of 134 patients, increasing to 80% for the last 20 cases [10]. In the present series, three reinjections and two ureteroneocystostomies were performed in the last 57 patients. This was also significant for the learning curve of NA Dx/HA injection for VUR, as mentioned with regard to the impact of the learning curve in VUR.

Läckgren and coauthors reported that almost all children had been treated endoscopically and they experienced no significant complications or adverse events [19,20]. This was observed in the first clinical study of NA Dx/HA for VUR, and also in the first large-scale study (310 procedures in 228 children with VUR) [20]. Snodgrass [21] and Vandersteen et al. [22] reported isolated cases of ureteral obstruction or hydronephrosis following endoscopic treatment with NA Dx/HA, but the overall incidence of this was estimated as less than 0.7%. In the present series, there were a few complications. Three patients (1.7%) had acute haematuria, one patient (0.58%) had an atrophic kidney and underwent laparoscopic nephrectomy, and one ureteral obstruction (0.58%) was treated by ureteroneocystostomy. However, these were major complications, and Vandersteen et al. reported similar complications to those in this study [22].

There were some limitations in this study. First, this was a retrospective study. Although this clinic was a reference clinic for VUR treatment, the number of patients was low and there was a lack of data in the follow-up groups. Recently, endoscopic treatment of VUR has been performed in peripheral hospitals in the community, and this situation may lead to irregular follow-up.

The results of the present study show that the indicator of unsuccessful treatment of VUR was fUTI, which was associated with preoperative renal scarring. The European guidelines on vesicoureteral reflux in children [2] and the guidelines of the American Urological Association on management of primary vesicoureteral reflux in children [7] suggest endoscopic treatment for VUR. However, accurate reasons for failure of injection are still lacking. To the authors' knowledge, the findings of this study are unique in the literature. In addition, in the light of these results, there may be no need to perform VCUG to evaluate success in the follow-up period in patients with grades I and II VUR, without renal scars or voiding dysfunction.

In conclusion, endoscopic injection of small-diameter microsphere (80–120 μm) NA Dx/HA seems safe and effective in the treatment of VUR, with acceptable complications. In the present study, postoperative fUTI was the only factor correlating with failed endoscopic correction of VUR and/or renal scarring. Further randomized, prospective, multicentre studies are required to confirm the optimal management of VUR and the follow-up period.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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