

# Clinical Value of Persistent but Downgraded Vesicoureteral Reflux after Dextranomer/Hyaluronic Acid Injection in Children

Minki Baek,<sup>1</sup> Min Young Kang,<sup>2</sup>  
Hahn-Ey Lee,<sup>2</sup> Kwanjin Park,<sup>2</sup>  
and Hwang Choi<sup>3</sup>

<sup>1</sup>Department of Urology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul; <sup>2</sup>Department of Urology, Seoul National University College of Medicine, Seoul National University Hospital, Seoul; <sup>3</sup>Department of Urology, Armed Forces Capital Hospital, Seongnam, Korea

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Address for Correspondence:

Hwang Choi, MD

Department of Urology, Armed Forces Capital Hospital, 66 Yuldong-2-gil, Bundang-gu, Seongnam 463-040, Korea  
Tel: +82.31-725-6247, Fax: +82.31-706-0987  
E-mail: hchoimd@gmail.com

We aimed to investigate the clinical value of persistent but downgraded vesicoureteral reflux (VUR) after dextranomer/hyaluronic acid (Dx/HA) injection in children. The medical records of 128 children (195 ureters) who underwent Dx/HA injections for VUR were reviewed. The incidences of pre- and post-operative febrile urinary tract infections (UTIs) were analyzed in children with or without persistent VUR on voiding cystourethrography (VCUG) 3 months postoperatively. The surgical results of VUR persistent children who underwent a single additional injection were assessed. The VUR resolved completely in 100 ureters (51.3%), was persistent in 95 ureters, and newly developed in 2 ureters. The incidence of pre/post-operative febrile UTIs were  $0.35 \pm 0.39$  per year and  $0.07 \pm 0.32$  per year in VUR resolved children ( $P < 0.001$ ), and  $0.76 \pm 1.18$  per year and  $0.20 \pm 0.61$  per year in VUR persistent children ( $P < 0.001$ ). A single additional Dx/HA injection (44 ureters) resolved VUR in 29 ureters (65.9%), and also reduced the VUR to grade I in 7 ureters (15.9%), II in 4 (9.1%), and III in 4 (9.1%). Even in children with persistent VUR after Dx/HA injection, the incidence of febrile UTIs decreased markedly. The VUR grade significantly decreases after single additional Dx/HA injection.

**Key Words:** Vesico-Ureteral Reflux; Endoscopy; Pyelonephritis; Pediatrics

## INTRODUCTION

Since the approval of dextranomer/hyaluronic acid (Dx/HA) by the U.S. Food and Drug Administration in 2001, injection therapy for vesicoureteral reflux (VUR) using Dx/HA has become increasingly popular in many parts of the world. An increased probability of resolution of VUR with the hydrodilatation implantation technique has been reported (1), and several authors have reported high success rates with injection therapy that are comparable to those of open ureteroneocystostomy (1, 2). However, it should be remembered that these excellent results were attained by expert surgeons and that universally, there is a certain period of time required to overcome the high learning curve necessary to perform these procedures (3, 4). The average success rates of injection therapy for primary VUR in children according to the reflux grade have been reported to be 79% for grade II VUR, 72% for grade III, 63% for grade IV, and 51% for grade V by meta-analysis (5). It should, therefore, be recognized that every child who undergoes Dx/HA injection for primary VUR is at risk of persistent reflux after the procedure. Thus, it is important to elucidate the clinical meaning of persistent post-injection reflux in the process of applying injection therapy for VUR in children. Moreover, since the primary goals of managing VUR are the prevention of acute pyelonephritis and renal

damage, it is important that the probabilities of febrile urinary tract infection (UTI) that may cause renal damage be evaluated.

In this study, we sought to investigate the clinical value of persistent but downgraded VUR after Dx/HA injection by analyzing the incidence of pre- and post-operative febrile UTI. Also, we tried to investigate the surgical results of an additional single Dx/HA injection in children with persistent post-injection reflux.

## MATERIALS AND METHODS

The medical records of children who underwent Dx/HA injection for primary VUR performed by a single surgeon from November 2004 to January 2009 were retrospectively reviewed. Preoperative patient characteristics, such as age, gender, laterality, and preoperative VUR grade, were reviewed. Each child included in this study underwent a preoperative voiding cystourethrography (VCUG). Lower urinary tract function was investigated in toilet trained children ( $n = 110$ ). Concerning the voiding symptoms and bowel movement, we used a structured questionnaire of 'the dysfunctional voiding scoring system' (6). The presence of bladder and bowel dysfunction (BBD) was determined from voiding symptoms focusing on frequency, urgency, incontinence, characteristics of urine stream, and bowel movement. Subjects with other urologic anomalies, such as uretero-

pelvic junction obstruction, ureteral duplication, ureterocele, cystic kidney disease, or neuropathic bladder, were excluded. Three months postoperatively, VUR grade was assessed in all patients using VCUG. The VUR grade was determined according to the International Reflux Study Classification (7). If the persistent VUR was bilateral, the higher of the two VUR grades was used.

The episodes of pre- and post-operative febrile UTIs (episodes per year) were compared in patients with or without persistent VUR on voiding cystourethrography (VCUG) 3 months postoperatively. Febrile UTI was defined as documented urine cultures of 100,000 colony-forming units (CFUs) per milliliter or greater on a clean urine specimen with fever (38°C or higher) that necessitated hospital admission and administration of intravenous antibiotics (8). The postoperative follow-up period for children with postoperative persistent reflux was defined as the period of time from the day of the first operation to the day of the second operation. Continuous antibiotic prophylaxis was not routinely performed postoperatively, however low-dose prophylactic antibiotics (trimethoprim 2 mg/sulfamethoxazole 10 mg per kg, once a day) were administered in selected cases. These were in children with persistent high grade VUR (higher than grade IV) on VCUG 3 months postoperatively, with a clinical history of frequent preoperative febrile UTI episodes.

Also, the surgical outcome after an additional single injection was also investigated in patients who underwent more than one Dx/HA injection treatment.

Statistical analysis was performed using SPSS 17.0 for Windows (SPSS for Windows, SPSS Inc, Chicago, IL, USA). A paired t-test was used to compare the pre- and post-operative VUR grades or febrile UTI episodes. A *P* value less than 0.05 was considered to be statistically significant.

### Ethics statement

The study protocol was approved by the institutional review board of Seoul National University Hospital (IRB number: 0807-078-251). Under the board's approval, written informed consent was exempted from all study participants.

## RESULTS

Our study population comprised of 128 children (72 boys and 56 girls) who underwent initial Dx/HA injection for primary VUR, with a mean age of  $61.7 \pm 42.0$  months. Bilateral VUR was present in 67 patients (53.9%), and was unilateral in 61 patients, in a total of 195 ureters. Preoperative reflux grades were I in 12 ureters (6.2%), II in 49 (25.1%), III in 82 (42.1%), IV in 45 (23.1%), and V in 7 (3.6%). Of the 110 toilet trained children, 42 (38.1%) had BBD and the remained 68 (61.9%) had not BBD. Three months postoperatively, among the 195 ureters that were treated with Dx/HA injection, VCUG demonstrated that reflux re-

solved completely in 100 ureters, was persistent in 95 ureters (75 patients), and was newly developed in 2 ureters (the VUR grade was I in one ureter and II in another ureter) that had no preoperative reflux. Among the 97 ureters that had persistent or newly developed reflux, 44 were treated with an additional Dx/HA injection and 2 (both grade V) underwent open ureteroneocystostomy using Cohen's method. The mean duration of postoperative follow-up was  $16.2 \pm 10.1$  months. Postoperative reflux grades of the 195 ureters were 0 in 100 ureters (51.3%), I in 21 ureters (10.8%), II in 41 (21.0%), III in 22 (11.3%), IV in 9 (4.6%), and V in 2 (1.0%). Table 1 lists the subjects' demographic characteristics and the pre- and post-operative VUR grade data. When ureters with persistent or newly developed reflux were analyzed ( $n = 97$ ), preoperative reflux grades were 0 in 2 ureter (2.1%), I in 4 (4.1%), II in 15 (15.5%), III in 36 (37.1%), IV in 34 (35.1%), and V in 6 (6.2%), and postoperative reflux grades were I in 22 ureters (22.7%), II in 42 (43.3%), III in 22 (22.7%), IV in 9 (9.3%), and V in 2 (2.1%) (Fig. 1). Among the patients with persistent VUR after Dx/HA injection, 4 patients (3 patients with grade IV and 1 patient with grade V) received continuous antibiotics prophylaxis. The success rate in the presence and absence of BBD was 38.1% (16 of 42) and 54.4% (37 of 68), respectively ( $P = 0.87$ , two-sided Fisher's exact test).

Febrile UTIs occurred in 3 (5.7%) of the 53 subjects who had no reflux on VCUG 3 months postoperatively. The incidence of febrile UTI was  $0.35 \pm 0.39$  per year before injection, and decreased significantly to  $0.07 \pm 0.32$  per year after injection in all the 53 children without reflux on VCUG 3 months postopera-

**Table 1.** Pre- and post-operative characteristics in all children

Parameters	Preoperative	Postoperative	<i>P</i> value
Age at operation (months)	$61.7 \pm 42.0$		NA
Gender			NA
Boys	72 (56.3%)		
Girls	56 (43.7%)		
Number of ureters by preoperative laterality			NA
Right	32		
Left	29		
Bilateral	134		
Number of ureters by VUR grade			NA
No reflux	100 (50.8%)		
I	12 (6.2%)	22 (11.2%)	
II	49 (25.1%)	42 (21.3%)	
III	82 (42.1%)	22 (11.2%)	
IV	45 (23.1%)	9 (4.6%)	
V	7 (3.6%)	2 (1.0%)	
Total	195	197*	
Number of patient who had febrile UTI	120 (93.8%)	15 (11.7%)	< 0.001 <sup>†</sup>
Number of kidneys with preoperative DMSA cortical defect	94 (47.7%)		NA

Values were expressed as mean  $\pm$  SD (age at operation) or number (%) (gender, number of ureters by preoperative laterality, number of ureters by VUR grade, number of patient who had febrile UTI, number of kidneys with preoperative DMSA cortical defect). \*Two ureters with contralateral de novo refluxes were added; <sup>†</sup>Chi-square test. NA, not applicable; VUR, vesicoureteral reflux; UTI, urinary tract infection; DMSA, dimercaptosuccinic acid.

tively ( $P < 0.001$ ). In all of the three patients with febrile UTIs who underwent VCUGs during the follow-up period, VUR was detected in one patient and there was no VUR in the two others.

Febrile UTIs occurred in 12 (16%) of the 75 subjects who had persistent reflux. The incidence of febrile UTI was  $0.76 \pm 1.18$  per year before injection, decreasing significantly to  $0.20 \pm 0.61$  per year after injection in the children with persistent reflux ( $P < 0.001$ ) (Fig. 2). The postoperative VUR grade distribution of those who experienced postoperative febrile UTIs was as follows: I in one ureter (8.3%), II in four (33.3%), III in five (41.7%), IV in one (8.3%), and V in one (8.3%). All patients had experienced preoperative febrile UTIs, and 11 had experienced more than 2.

The preoperative VUR grade of the 44 ureters (32 children) that were treated with a single additional Dx/HA injection were I in 5 ureters (11.4%), II in 21 (47.7%), III in 12 (27.3%), IV in 6 (13.6%), and postoperative reflux grades were 0 in 29 ureter (65.9%), I in 7 (15.9%), II in 4 (9.1%), III in 4 (9.1%) (Fig. 3).

**DISCUSSION**

Our data demonstrated that even if a child has persistent reflux after Dx/HA injection, the probability of febrile UTI is markedly decreased. The decrement in the rate of post-injection febrile UTI may be mainly a result of the decrease in the VUR grade, and also due to the functional improvement of the bladder as children grow. It is well known that one of the most important risk factors for febrile UTI in children with VUR is the grade of the reflux (9). Therefore, the clinical significance of downgraded reflux after Dx/HA injection is valuable in light that the primary goal of treatment for VUR in children is to prevent renal damage associated with recurrent febrile UTIs. In our study, 164 (83.1%) of the 197 ureters showed a VUR lower than grade II after single Dx/HA injection. Most of the cases showing persistent high-grade reflux postoperatively were downgraded to grade I or II following a single additional Dx/HA injection.

The incidence of febrile UTI after open ureteral reimplantation has been reported to be 8%-24% in previous studies (10-12)

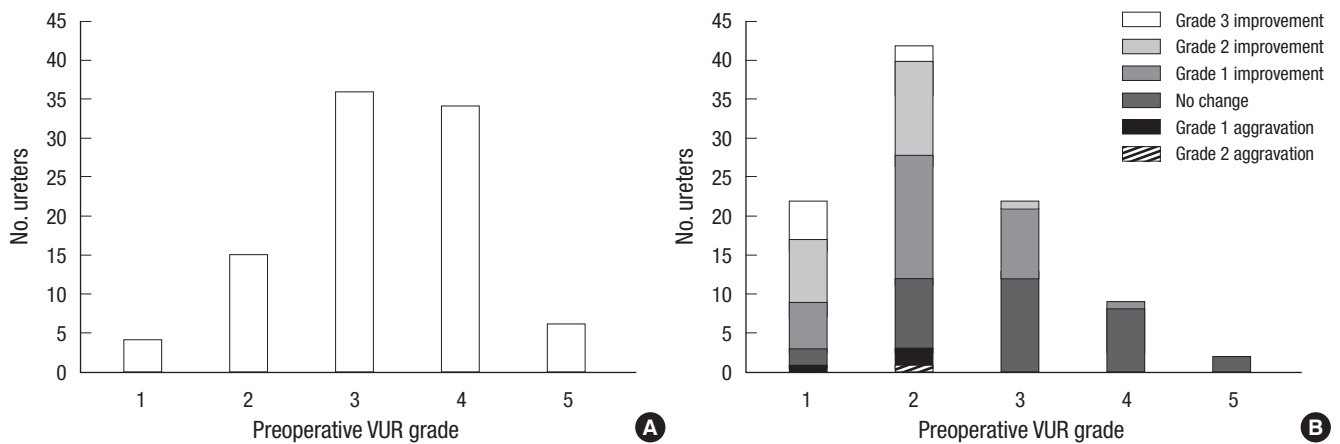


Fig. 1. Pre- and post-operative vesicoureteral reflux grade in children with persistent refluxing ureters. (A) Preoperative vesicoureteral reflux grade (n = 95). (B) Postoperative vesicoureteral reflux grade (n = 97). VUR, vesicoureteral reflux.

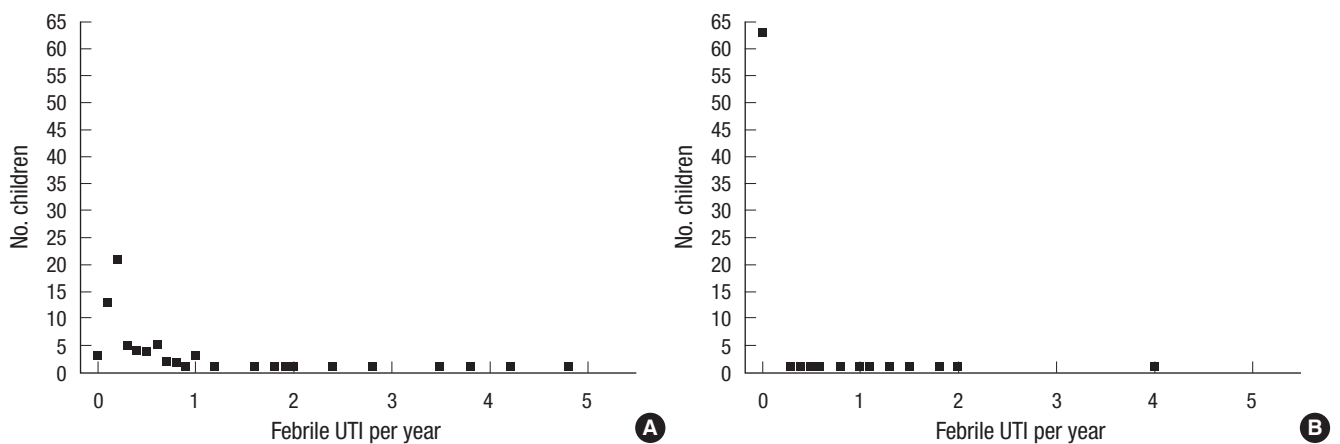
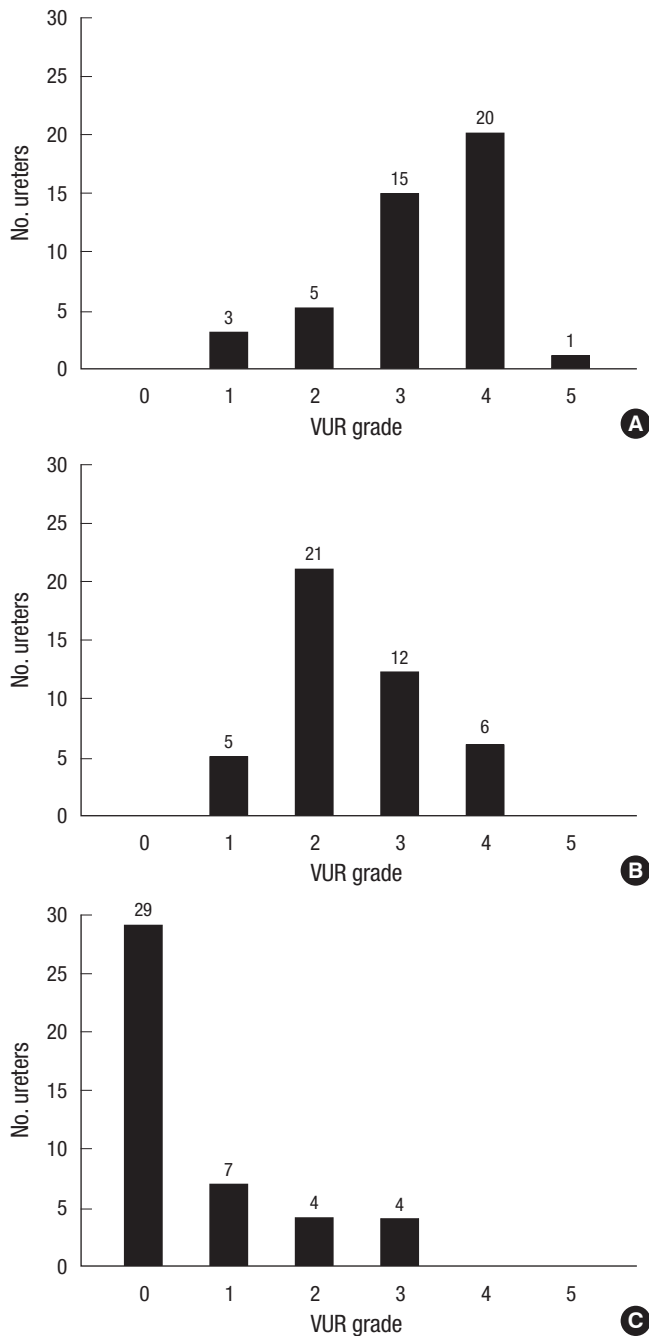


Fig. 2. Incidence of pre- and post-operative febrile urinary tract infection in children with persistent refluxing ureters (n = 75). (A) Incidence of preoperative febrile urinary tract infection. (B) Incidence of postoperative febrile urinary tract infection. UTI, urinary tract infection.



**Fig. 3.** Surgical results after additional single injection ( $n = 44$ ). (A) Preoperative vesicoureteral reflux grade. (B) Vesicoureteral reflux grade three months postoperatively. (C) Vesicoureteral reflux grade after additional single injection. VUR, vesicoureteral reflux.

and the incidence of febrile UTI after injection therapy for VUR in children has been reported to be approximately 5% (8, 11, 13, 14). The lower risk for febrile UTI after injection therapy compared to that of open surgery may be due to minimal changes in the bladder dynamics and/or a less favorable environment for bacterial adherence with injection. The proportion of the total 128 patients experiencing a febrile UTI after Dx/HA injection in our study was 11.7% (15 patients), which was slightly higher than

those of previous reports (8, 11, 13, 14). This result may be due to the fact that our study population included a higher proportion of bilateral cases compared with previous studies. One notable finding is that most of the children who experienced postoperative febrile UTI in our study had frequent preoperative febrile UTI episodes, implying that children with a history of frequent preoperative febrile UTIs may be more susceptible to postoperative febrile UTI and should be followed-up carefully.

There were two cases (3.3%) of newly developed contralateral reflux, but these were low grade. Generally, the incidence of concomitant development of contralateral reflux when one side is corrected has been reported to be 5%-18% after open uretero-neocystostomy (15, 16) and 8.3%-13.5% after injection therapy (17-19). It has been suggested that the development of contralateral de novo reflux may be due to the elimination of a pop-off mechanism, surgical distortion of the trigone, or missed reflux on initial VCUG.

We defined febrile UTI using a strict definition, which was culture-positive pyuria with fever of 38°C or higher that necessitated hospital admission for intravenous antibiotics; all of the children were followed-up postoperatively at our hospital; and the postoperative follow-up protocol was standardized and applied to every patient. In our country, a child with a febrile UTI is almost always admitted to a hospital. We applied the same criteria (hospital admission) for recording pre- and post-injection febrile UTI. Thus, differences between the counted and actual numbers of episodes of pre- and post-injection febrile UTIs were unlikely.

In this study, the success rate after Dx/HA injection was lower in children with BBD. A meta-analysis by AUA Vesicoureteral Reflux Guideline Update Committee demonstrated the relationship among BBD, VUR, and febrile UTI as follow; 1) the risk of febrile UTI in children with VUR is greater in those with than without BBD, 2) the rate of cure following injection therapy is less in children with than without BBD, 3) the rate of postoperative UTI is greater in children with than without BBD. Therefore, when a child has an evidence of BBD, treatment of BBD should be indicated. There are insufficient data to recommend a specific treatment regimen for BBD, but possible treatment options include behavioral therapy, biofeedback, anticholinergic medications, or treatment of constipation (20).

We decided to administer low-dose prophylactic antibiotics to patients who had postoperative high grade persistent reflux with a clinical history of many preoperative UTI episodes; therefore, the antibiotics group was mixed with the non-antibiotics group during the postoperative follow-up period. However, among the 75 patients who had postoperative persistent VUR, we prescribed prophylactic antibiotics to only 4 patients. It can be logically concluded that if antibiotics prophylaxis was not administered to any children in the postoperative follow-up period, then the risk of febrile UTI may have been slightly high-



er compared to that observed in the present results. Administration of antibiotics may have affected the incidence of febrile UTI to some degree. Although such prophylaxis is generally recommended in children with VUR to prevent febrile UTIs and subsequent renal damage, there is not sufficient evidence to show that antibiotic prophylaxis has a real and consistent beneficial effect in this regard. A recent and well-designed study (21) revealed that low-dose prophylaxis may reduce the absolute risk of symptomatic UTIs in children with predisposing factors, such as VUR, by approximately 7%. We think that our study data can reflect 'real-life' clinical practice and the protocol for our study does not negatively affect its applicability to a population of children with VUR because most clinicians generally would administer low-dose antibiotics to children with high grade reflux or those who are thought to be susceptible to UTI.

Conclusively, in children with persistent VUR, the number of febrile UTI episodes may be decreased after Dx/HA injection. After children who need a single additional injection receive the injection, the VUR grade may decrease significantly.

## DISCLOSURE

The authors have no conflicts of interest to disclose.

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