

Long-term Results of Endoscopic Deflux[®] Injection for Vesicoureteral Reflux in Children

Hwanik Kim, M.D.¹
Byung Soo Kim, M.D.¹
Hae Il Cheong, M.D.^{2,3}
Byoung Soo Cho, M.D.⁴
Kwang Myeong Kim, M.D.¹

Department of Urology¹, Seoul National University College of Medicine, Seoul, Department of Pediatrics², Seoul National University Children's Hospital, Seoul, Kidney Research Institute, Medical Research Center³, Seoul National University College of Medicine, Seoul, Department of Pediatrics⁴, School of Medicine, Kyung Hee University, Seoul, Korea

Corresponding author:

Kwang Myeong Kim, M.D.
Department of Urology, Seoul National University Hospital, Seoul National University College of Medicine, 101 Daehak-ro, Jongno-gu, Seoul 110-744, Korea
Tel: +82-2-2072-2407
Fax: +82-2-747-9824
E-mail: kwang@plaza.snu.ac.kr

Received: 31 March 2015
Revised: 20 April 2015
Accepted: 25 April 2015

This is an open-access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/bync/3.0/>) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

Purpose: We evaluated the long-term results of endoscopic Deflux[®] injection for treating vesicoureteral reflux (VUR) in children.

Methods: Between September 2004 and September 2014, 243 children (137 boys and 106 girls) with a mean age of 53 months underwent Deflux[®] injection. Our clinical protocol included radionuclide voiding cystography (RNC) at postoperative 3 months, 1 year and 3 years to assess the VUR resolution.

Results: The cure rates at 3 months, 1 year, and 3 years by patients were 70.8%, 64.3%, and 65.6% for the total patients and 79.2%, 75.2%, and 76.4%, for the ureters, respectively. The recurrence rate of postoperative febrile urinary tract infection (UTI) was 20% in patients without VUR at postoperative 1 year. Twenty patients undergoing ureteroneocystostomy (UNC) significantly had younger age ($P=0.003$), higher VUR grade ($P<0.001$), and lower success rates of Deflux[®] injection ($P<0.05$). On univariate analysis, older age ($P=0.014$) and lower grade of VUR ($P=0.031$) were the significant predictors of a successful outcome. But there was none on multivariate analysis. Younger age, especially age of 0-12 month-old, was the only significant predictor of postoperative febrile UTI recurrence on both univariate and multivariate analysis.

Conclusion: Deflux[®] injection is efficacious with a low complication rate for the anti-reflux procedure in children. There is low recurrence rate of UTI though VUR persists, and high probability of no VUR at 3 years if no VUR at 1 year. It is recommendable not to perform follow-up RNC at 3 years routinely if no VUR at 1 year.

Key words: Vesicoureteral reflux, Deflux[®], Endoscopic treatment, Children, Urinary tract infection

Introduction

Vesicoureteral reflux (VUR) is known to occur in 1% of children and is one of the major causes of urinary tract infection (UTI) and chronic renal failure^{1,2}. The purpose of diagnosing and treating VUR is to prevent these complications. In the past, if medical treatment represented by prophylactic low-dose antibiotics failed, ureteroneocystostomy (UNC) was the only alternative. However, a subureteral injection technique has been in the limelight as a surgical method to replace UNC after Matouscheck first reported on this technique using a cystoscope in 1981 and O'Donnell reported the first clinical examples in 1984^{3,4}. Teflon[®], bovine collagen, Macroplastique[®] and other

materials have been used as injection substances, but there are still many limitations in their efficacy and safety in the pediatric area⁵⁻⁷). Since Stenberg and Läckgren reported the first clinical application of Dextranomer/hyaluronic acid (DX/HA) copolymer (Deflux[®], Q-Med Scandinavia, Uppsala, Sweden) in 1995⁸), Deflux[®] injection therapy has been recognized as an alternative treatment for VUR in the pediatric area. The overall success rate of Deflux[®] injection therapy has been reported as 68-92% and is known to be affected mainly by the grade of VUR^{6,9-11}). Deflux[®] injection therapy also has the clinical advantages of fewer complications and a shorter hospital stay. Since research on the success rate of Deflux[®] injection therapy for VUR in children was first reported in Korea¹²), there have not been enough reports on its long-term prognosis, including the amount of pyelonephritis occurrence and the recurrence of VUR. Thus, this study analyzed the long-term results in children who underwent Deflux[®] injection and evaluated the prognosis of Deflux[®] injection therapy.

Materials and methods

This study retrospectively examined and analyzed the 419 ureters of 243 patients who underwent Deflux[®] injection therapy with a cystoscope performed by a single operator in the Children's Hospital of Seoul National University Hospital between September 2004 and September 2014. All patients were diagnosed with VUR through voiding cystourethrography (VCUG) during urination and underwent Deflux[®] injection.

All procedures were performed under general anesthesia, and an 8Fr Pediatric Cystoscope (Wolf[®], Storz[®]) was used. Before Deflux[®] injection, the location and type of both ureteral orifices and the condition of the bladder were evaluated. Subureteral or intraureteral Deflux[®] injection therapy was carried out by the hydrodistention implantation technique. A postoperative RNC test was conducted three times, at postoperative 3 months, 1 year, and 3 years, and the presence or absence of acute pyelonephritis, the urine's white blood cell count and a Dimercaptosuccinic acid (DMSA) renal scan were also examined.

We adopted the definition of febrile UTI used in the Randomized Intervention for Children with Vesicoure-

teral Reflux (RIVUR) study: a fever of more than 38°C, pyuria findings in a urine test (≥ 10 white blood cells (WBC) per mm^3 (uncentrifuged specimen) or ≥ 5 WBCs per high power field (centrifuged specimen) or a trace or more leukocyte esterase on a dipstick) and more than 100,000 colony-forming units of bacteria per mL in a urine culture test of a clean urine specimen²⁴). The indications for Deflux[®] injection therapy were the following: a deterioration in the affected renal function due to febrile UTI; Persistence of VUR despite relatively old age; severe VUR of grade IV-V; and patients whose caregivers were reluctant to antibiotics prophylaxis. The therapy was carried out preventively when there were abnormal findings in the ureteral orifice shape on the opposite side of the affected area in a cystoscopy conducted during surgery (3 ureters were done for this indication). Postoperatively, VUR Grade I was considered to be a successful procedure (preoperative Grade I based on the success rate of the ureter was judged as a successful surgery when the postoperative grade was 0), and a continuous postoperative VUR of more than Grade II or a recurrence was judged as a failure. If VUR was present during the RNC test conducted after the procedure, prophylactic oral antibiotics were given, or Deflux[®] injection was performed again, or UNC were performed on patient who required definite surgical procedure.

Voiding dysfunction is defined as urination pattern that is abnormal for the child's age. We considered child has voiding dysfunction if child has any of these symptoms; incontinence (urine leakage) during the day and/or night, increase in urinary frequency, urgency (the need to void immediately), urinary hesitancy, dribbling, intermittent urine flow, straining at urination, and/or pain in the back, flank or abdomen. Constipation is defined as defecation less than twice a week according to ROME III criteria. Trabeculation of bladder is graded by formation of muscle bundle and depth of mucosal layer on cystoscopic exam (none, mild, moderate, and severe). Cortical defect on DMSA scan is decided by nuclear radiologists and defined as single or multiple, focal or diffuse areas of decreased or completely absent activity in the renal cortex; (2) diffuse or sharp indentation in contour with thinning of renal cortex; and (3) loss of renal cortex volume.

The statistical analysis was carried out by using IBM SPSS Statistics 18.0 (SPSS Inc., IBM Company, Chicago, IL,

USA) to determine the success rate of the Deflux® injection therapy, the many factors that may affect the success rate, several preoperative factors that may affect UTI recurrence, and a sub-group analysis for the patient group that underwent UNC (Paired T-test, chi-square test, and binary logistic regression analysis for univariate analysis and multivariate analysis was used.). A *P*-value of less than 0.05 was considered statistically significant.

Results

The mean age of the 243 patients included in this study was 53 (1-270) months at the time of surgery; there were 137 boys and 106 girls. The follow-up period of pediatric urology outpatient was 32 (1-113) months. Five patients complained of preoperative dysuria, such as straining or hesitancy, and 12 people complained of constipation. In a preoperative voiding cystourethrogram (VCUG), VUR was observed in 416 ureter units and the frequency of each VUR grade was 67 for grade I, 96 for grade II, 118 for grade III, 97 for grade IV and 38 for grade V. Postoperative complications were observed in one case that gross hematuria occurred after leaving the hospital, but was treated with conservative treatments such as oral fluid intake, etc. There were no cases of urinary tract infection caused by the surgery (Table 1). All 243 patients underwent an RNC test at postoperative 3 months, and 172 patients (70.8%) had no VUR. At postoperative 1 year, 171 patients underwent an RNC test and 110 patients (64.3%) had no VUR. At postoperative 3 years, 90 patients underwent an RNC test and 59 patients (65.6%) had no VUR. In ureteral numbers, an RNC test was evaluated for 419 ureters at postoperative 3 months and 333 ureters showed no VUR (79.5 %); at postoperative 1 year, 212 ureters out of 282 ureters (75.2%) and at postoperative 3 years, 97 ureters out of 127 ureters (76.4 %) showed no VUR.

Based on VUR grade, the cure rates at postoperative 3 months were 92.5%, 84.4%, 72.9%, 75.3% and 73.7% for grade I, grade II, grade III, grade IV and grade V, respectively. At postoperative 1 year, the cure rates were 84.2%, 74.3%, 81.6%, 72.4% and 48.2%, respectively, and at postoperative 3 years, 81.3%, 70.6%, 81.1%, 78.6% and 63.6%, respectively. The cure rates by grade at postoperative 3

months and 1 year showed a statistically significant difference ($P=0.015$, $P=0.010$). Based on age, the cure rates at postoperative 3 months, 1 year and 3 years were 58.1%, 51.1 % and 66.7% for 0-12 months; 75.5%, 50.0% and 65.0% for 13-36 months; 76.2%, 75.8% and 68.8% for 37-60 months; and 74.4%, 74.6% and 63.6% in more than 60 months. The cure rates by age at postoperative 1 year showed a statistically significant difference ($P=0.012$) (Fig. 1).

Of the ureters that underwent RNC tests at both postoperative 1 year and 3 years, reflux was observed in 22 ureters (55.0%) after 3 years out of 40 ureters that showed reflux in an RNC test at 1 year. In contrast, reflux was observed in only 8 ureters (10.3%) after 3 years out of 78 ureters that did not show reflux at 1 year and there was a statistically significant difference ($P<0.001$).

After the first Deflux® injection, another Deflux® injection was carried out for 33 patients. Among them, 5 patients

Table 1. Patient Characteristics

Parameter	
Age at operation (Months)	53±47
Gender	
Male	137 (56.4%)
Female	106 (43.6%)
Number of patient by preoperative laterality	
Right	31 (12.8%)
Left	47 (19.3%)
Bilateral	165 (67.9%)
Number of ureters by VUR grade	
No VUR	3 (0.5%)
I	67 (11.3%)
II	96 (16.1%)
III	118 (19.8%)
IV	97 (16.3%)
V	38 (6.4%)
Total	
Number of patient who had febrile UTI	229 (94.2%)
Number of kidneys with preoperative DMSA cortical defect	
No defect	61
Right	55
Left	31
Bilateral	19

Values were expressed as mean±SD (age at operation) or number (%) (gender, number of patient by preoperative laterality, number of ureters by VUR grade, number of patient who had febrile UTI, number of kidneys with preoperative DMSA cortical defect).

Abbreviations: VUR, vesicoureteral reflux; UTI, urinary tract infection; DMSA, dimercaptosuccinic acid.

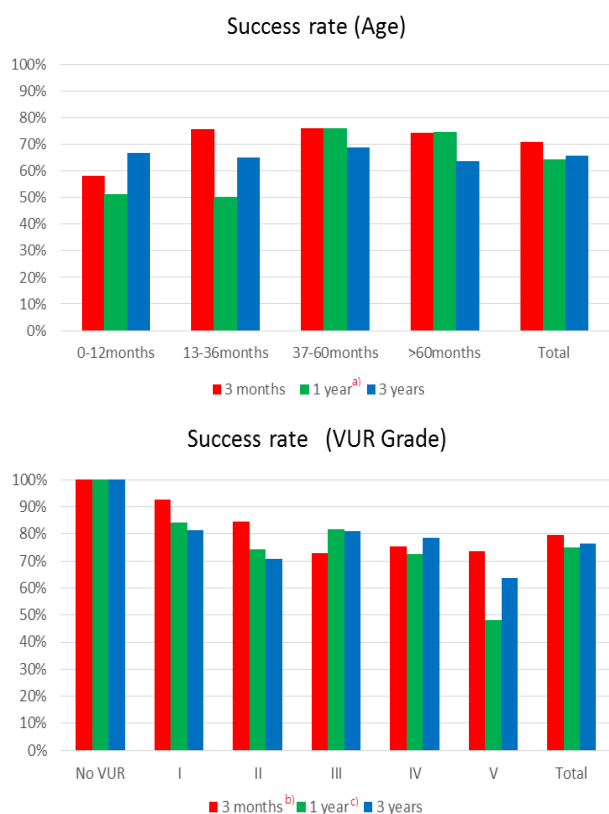


Fig. 1. Success rate at postoperative 3 months, 1 year, and 3 years according to age and VUR grade. *The cure rates by age at postoperative 1 year^{a)} and VUR grade at postoperative 3 months^{b)} and 1 year^{c)} showed statistically significant differences ($P=0.012$, $P=0.015$, $P=0.010$, respectively). Abbreviation: VUR, vesicoureteral reflux.

with VUR received UNC due to febrile urinary tract infection (3 cases) or consultation with caregivers (2 cases). UNC were carried out for 15 patients without conducting Deflux[®] injections again. The UNC were carried out due to febrile UTI after Deflux[®] injection in 7 cases, the presence of VUR even though there was no febrile UTI in 12 cases, and the occurrence of ureterovesical junction obstruction after Deflux[®] injection in 1 case. As for the UNC techniques, there were 14 cases of transtrigonal technique, 4 cases of detrusorrhaphy technique, 1 case of Politano-Leadbetter technique and 1 case of modified Paquin technique. There were no febrile UTIs requiring hospital treatment after UNC in all 20 patients. The patients who underwent UNC were significantly younger than those who did not (22.1 months vs. 55.7 months, $P=0.003$), their VUR grades were significantly higher (4.3 vs. 3.2, $P<0.001$), and the success rate of Deflux[®] injection by period was significantly lower (35.0% vs. 74.0%, $P<0.001$; 31.3% vs. 67.7%, $P=0.004$; and

33.3% vs. 69.1%, $P=0.032$ at 3 months, 1 year and 3 years, respectively).

Postoperative febrile UTIs occurred in 44 patients (18.1%) out of total 243 patients. With regard to the VUR grades of these 44 people, 0 were in grade I (0/2, 0%), 9 in grade II (9/54, 16.7%), 11 in grade III (11/81, 13.6%), 14 in grade IV (14/76, 18.4%) and 10 in grade V (10/30, 33.3%). There were no significant differences in the incidence between grades ($P=0.176$). Patients with febrile UTIs were younger, their VUR grades were higher, and their Deflux[®] injection cure rates were lower compared to patients without UTIs, but these were not statistically significant ($P>0.05$). After 1 year, febrile UTIs occurred after Deflux[®] injection in 20 out of 110 patients without VUR (22.2%), but the presence or absence of VUR after 1 year showed no statistically significant correlation with febrile UTI occurring after surgery ($P=0.141$). All these 20 patients received conservative treatment in the hospital, such as the administration of intravenous antibiotics in the early days. However, UNC were carried out on 8 of them (40%) to prevent recurrence. Febrile UTIs after the procedure showed no statistically significant correlation with preoperative VUR grade and age at surgery ($P>0.05$), but did show a correlation with whether to conduct a Deflux[®] injection again (31.8% vs. 9.6%, $P<0.001$) or whether to conduct a UNC (18.2% vs. 6.0%, $P=0.008$). Of the predictors of postoperative UTI recurrence, the age of 0-12 months was the only statistically significant factor in both the univariate analysis and multivariate analysis (univariate analysis: odds ratio (OR)=2.87, 95% confidence interval (CI)=[1.27-6.48], $P=0.038$; multivariate analysis: OR=7.62, 95% CI=[1.84-31.54], $P=0.028$). Of the several factors that may affect the success rate of Deflux[®] injection therapy, such as sex, age at surgery, degree of VUR, presence or absence of voiding dysfunction, presence or absence of constipation, degree of trabeculation in the bladder, etc., age at surgery and degree of VUR were the factors that may affect the success rate at postoperative 1 year according to the univariate analysis, and in the multivariate analysis, it was found that no factors had a statistically significant correlation ($P>0.05$). There was no statistically significant factor that may affect the success rate at postoperative 3 months and postoperative 3 years (Table 2).

Table 2. Correlation between postoperative 1 year success rate of endoscopic Deflux® injection and other factors.

Factor	Number (%)	Univariate analysis			Univariate analysis		
		OR	95% CI	P value	OR	95% CI	P value
Sex							
Female	73 (42.7)	1(ref)		0.510	1(ref)		0.721
Male	98 (57.3)	0.80	0.43-1.53		1.14	0.57-2.28	
Age							
0-12 months	45 (26.3)	1(ref)		0.014	1(ref)		0.093
13-36 months	30 (17.5)	0.96	0.38-2.41		0.84	0.32-2.25	
37-60 months	33 (19.3)	2.99	1.11-8.03		2.54	0.88-7.31	
>60 months	63 (36.8)	2.81	1.24-6.35		2.17	0.85-5.54	
Preoperative VUR grade							
V	24 (14.0)	1(ref)		0.031	1(ref)		0.143
IV	45 (26.3)	2.75	0.99-7.63		2.00	0.67-5.95	
III	63 (36.8)	5.33	1.94-14.64		3.88	1.31-11.49	
II	38 (22.2)	2.86	0.99-8.22		1.86	0.56-6.16	
I	1 (0.6)	2692458107.16	>0		1487622898.63	>0	
Voiding dysfunction							
No	167 (97.7)	1(ref)		0.138			
Yes	4 (2.3)	0.18	0.02-1.74				
Constipation							
No	160 (93.6)	1(ref)		0.550			
Yes	11 (6.4)	1.52	0.39-5.94				
Trabeculation							
None	109 (63.7)	1(ref)		0.802			
Mild	50 (29.2)	0.91	0.46-1.82				
Moderate	6 (3.5)	1.11	0.20-6.36				
Severe	6 (3.5)	2.79	0.31-24.7				
Cortical Defect on DMSA scan							
None	44 (37.0)	1(ref)		0.636			
Right	37 (31.1)	1.44	0.58-3.60				
Left	24 (20.2)	1.39	0.49-3.92				
Bilateral	14 (11.8)	0.69	0.21-2.32				

Age at surgery and degree of VUR were the factors that may affect significantly the success rate in the univariate analysis.

Abbreviations: OR, Odds ratio for success; 95 % CI, 95 % confidence interval; VUR, vesicoureteral reflux; DMSA scan, Dimercaptosuccinic acid scan; ref, reference value.

Discussion

In the treatment of VUR, the concept of subureteral injection therapy under a cystoscope has developed considerably since it was introduced in the 1980s^{3,4}. This treatment is thought to resolve VUR by forming solid support behind the intravesical ureter and increasing the submucosal length of the ureter³. Many studies have reported the efficacy and safety of endoscopic treatment as a first-line treatment for VUR¹³⁻¹⁶. Since first reported by Stenberg and Läckgren in 1995, Dextranomer/hyaluronic acid (DX/

HA), out of a number of injection substances⁸, is the most commonly used in VUR injection treatment in pediatrics and the only healing substance approved by the Food and Drug Administration for its safety.

There have been many reports on the early success rate of Deflux® injection therapy and the overall success rate is relatively good, 68-92%^{6,9-11}. In 2004, Kirsch reported that the early success rates of Deflux® injection using the hydrodistention implantation technique are similar to those of UNC⁶. In our study as well, the case that VUR was cured in an RNC test in the 3rd month after Deflux® injection

(based on the ureter) was found to be 74.6%. However, there are few reports on the long-term results of Deflux[®] injection therapy. In 2001, Läckgren reported on the long-term follow-up results of 7.5 years after Deflux[®] injection and reported a good success rate: the success rate was 84% in the first VCUG, but dropped slightly to 74% in the long-term follow-up¹⁷. However, there is a problem in interpreting these results, because long-term VCUG was only carried out for 45 ureters (13.4%) out of 334 treated ureters and there was a high drop-out rate. On the other hand, unlike Läckgren's report, Lee and Gatti reported¹⁸ rather disappointing long-term follow-up results in 2009. The success rate in the first postoperative VCUG was 73%, but recurrence was identified in 39 (26%) out of 150 ureters in the postoperative 1 year VCUG and the overall cumulative failure rate was 54% (130/241 ureters). In our study, the success rate in the first RNC test conducted at 3 months after Deflux[®] injection was 79.5% (333/419 ureters) and relatively good long-term follow-up results were shown with a success rate of 75.2% (212/282 ureters) at the 1 year follow-up and 76.4% (97/127 ureters) at the 3 year follow-up. However, only 127 out of 419 ureters (30.3%) were tracked through the 3 years, which can be said to lack numeric significance.

Previous studies have analyzed the factors that can predict the success rate of Deflux[®] injection therapy. In the paper published in our center in 2007, the degree of VUR ($P=0.035$) and the presence or absence of voiding dysfunction ($P=0.001$) were the factors that could predict the success rate¹². In 2013, Kajbafzadeh analyzed 372 patients who underwent Deflux[®] injection therapy and the success rate was 86.6%. The degree of preoperative VUR, treatment techniques, and whether to form a mound, hyper/isoechogenic oval protuberance around the ureterovesical junction in an ultrasound performed after the procedure were factors that can predict the success rate in the univariate analysis. The degree of preoperative VUR and whether to form a mound were statistically significantly related to the success rate in the multivariate analysis²¹. In our study, the degree of preoperative VUR ($P=0.031$) was a factor that can predict the success rate, but another predictor could be identified if more extensive research is performed.

There is no definite answer regarding how long follow-up should be carried out after Deflux[®] injection therapy. According to a multicenter prospective trial that reported

long-term follow-up results in recent years¹⁹, the early success rate was 68% (based on ureters, postoperative 6 months) in 284 patients (424 ureters). It was also reported that 46% of the entire patient group was followed up at postoperative 3 years and 21% of recurrence was identified between 6 months and 3 years in the ureters among them. Thus, the authors argued that even if successful injection therapy was conducted, the presence or absence of VUR needs to be tracked for at least 3 years. In this study, the recurrence rate was 20.0% based on the ureters at postoperative 3 years, showing a similar level of recurrence rate. Given that the presence or absence of VUR recurrence is not statistically correlated with postoperative febrile UTI occurrence in the reflux test carried out at postoperative 1 year, there is a need for long-term follow-up of at least 1 year or more after Deflux[®] injection therapy. According to the long-term results of the endoscopic treatment of VUR with a bulking agent in a study published by Stredele et al. in 2013, the success rate at 3 months after Deflux[®] injection was 81.5% and the success rate after 37 months was 78.5%. Approximately 20% may experience recurrence at postoperative 2-3 years, so a 3-year follow-up was recommended after successful endoscopic treatment²². However, from the result that VUR was observed in 55.0% after 3 years of ureters that showed VUR in RNC test at 1 year, while VUR was observed in 10.3% after 3 years of ureters without VUR at 1 year, we can draw conclusion that it is recommendable not to perform follow-up RNC at 3 years routinely if no VUR at 1 year due to low recurrence rate of UTI though VUR persists and high probability of no VUR at 3 years if no VUR at 1 year.

Previous studies have reported that the degree of VUR and the degree of voiding dysfunction influence the success rate of injection therapy¹². This may be considered due to the fact that the position of Deflux[®] uplift changes due to high detrusor pressure accompanying voiding dysfunction. According to the recent research of Puri et al.²⁰, 47.3% of patients with voiding dysfunction before surgery have been treated successfully. Our study did not identify a significant correlation between the presence or absence of voiding dysfunction and the surgical success rate. When viewed in light of this information, future research seems to be needed to evaluate relationship between voiding dysfunction and success rate.

In this study, there were few cases of urinary tract infection due to VUR persisting after Deflux® injection therapy (22.2%). Even if the statistical significance is insignificant due to the small number of patients, it can be assumed that the effect of Deflux® injection therapy itself drops the probability of urinary tract infection. The study published by Baek et al. in 2013 explained that the probability of urinary tract infection after Deflux® injection therapy drops because VUR grade decreases and bladder function is improved, depending on the growth of the child²³.

This study has several limitations. The first includes the retrospective study characteristics, the somewhat small number of patients, and the large amount of RNC follow-up loss (especially at 3 years) during the long-term follow-up. The second limitation is that only the presence or absence of VUR was identified, and it was difficult to determine the grade due to the nature of the RNC test. The third limitation is that the analysis of the long-term follow-up results of Deflux® injection therapy was evaluated by the presence or absence of postoperative VUR recurrence and the presence or absence of febrile UTI occurrence, while several other elements, including the degree of renal scarring and renal function etc., should also be considered. Finally, the number of patients who underwent the DMSA scan and renal ultrasound for postoperative follow-up was so small that it was difficult to find out if there was a correlation between the size, shape, parenchymal thickness of the kidney and the postoperative urinary tract infection. Thus, multi-institutional prospective study will be needed to find an answer to the controversy over the long-term follow-up results of Deflux® injection therapy.

Conclusion

This study found that the success rates of Deflux® injection therapy are excellent: 79.5% at postoperative 3 months, 75.2% at postoperative 1 year, and 76.4% at postoperative 3 years. The probability of urinary tract infection is not high, although VUR can occur after Deflux® injection therapy, and if there is no VUR at postoperative 1 year, it is highly likely that there will be no VUR at postoperative 3 years. Therefore, if there is no VUR at postoperative 1 year, it is recommendable that there is no need to follow up with

RNC at 3 years. In the future, the long-term follow-up results of Deflux® injection therapy through multi-institutional prospective research are needed.

Conflict of interest

No conflict of interest exists in relation to submitted manuscript, and there was no source of funding.

References

- Smellie JM, Barratt TM, Chantler C, Gordon I, Prescod NP, Ransley PG, et al. Medical versus surgical treatment in children with severe bilateral vesicoureteral reflux and bilateral nephropathy: a randomised trial. *Lancet* 2001;357:1329-33.
- Jacobson SH, Hansson S, Jakobsson B. Vesico-ureteric reflux: occurrence and long-term risks. *Acta Paediatr suppl* 1999;22-30.
- Matouschek E. Treatment of vesicorenal reflux by transurethral Teflon-injection. *Urologe A* 1981;263-4.
- O'Donnell B, Puri P. Treatment of vesicoureteric reflux by endoscopic injection of Teflon. *J Urol* 2002;167:1808-9; discussion 1810.
- Dodat H, Aubert D, Chavrier Y, Geiss S, Guys JM, Lacombe A, et al., Vesicoureteric reflux in children: long-term results of endoscopic treatment by Macroplastique injection. *Prog Urol* 2004; 14:380-4.
- Kirsch AJ, Perez-Brayfield M, Smith EA, Scherz HC. The modified sting procedure to correct vesicoureteral reflux: improved results with submucosal implantation within the intramural ureter. *J Urol* 2004;171:2413-6.
- van Capelle JW1, de Haan T, El Sayed W, Azmy A. Azmy, The long-term outcome of the endoscopic subureteric implantation of polydimethylsiloxane for treating vesico-ureteric reflux in children: a retrospective analysis of the first 195 consecutive patients in two European centres. *BJU Int* 2004;94:1348-51.
- Stenberg A, Läckgren G. A new bioimplant for the endoscopic treatment of vesicoureteral reflux: experimental and short-term clinical results. *J Urol* 1995;154:800-3.
- Puri P, Chertin B, Muruges V, Dass L, Colhoun E. Treatment of vesicoureteral reflux by endoscopic injection of dextranomer/hyaluronic acid copolymer (Deflux): preliminary results. *J Urol* 2003;170:1541-4.
- Chertin B, Colhoun E, Velayudham M, Puri P. Endoscopic treatment of vesicoureteral reflux: 11 to 17 years of followup. *J Urol* 2002;167:1443-6.
- Routh JC, Vandersteen DR, Pfefferle H, Wolpert JJ, Reinberg Y. Single center experience with endoscopic management of

- vesicoureteral reflux in children. *J Urol* 2006;175:1889-92.
12. Park Y, Kim G. Dextranomer/hyaluronic acid copolymer (Deflux[®]) injection for vesicoureteral reflux in children: The efficacy and safety. *KJU* 2007;48:620-6.
 13. Capozza N, Caione P. Dextranomer/hyaluronic acid copolymer implantation for vesico-ureteral reflux: a randomized comparison with antibiotic prophylaxis. *J Pediatr* 2002;140:230-4.
 14. Elder JS, Diaz M, Caldamone AA, Cendron M, Greenfield S, Hurwitz R, et al. Endoscopic therapy for vesicoureteral reflux: a meta-analysis. I. Reflux resolution and urinary tract infection. *J Urol* 2006;175:716-22.
 15. Puri P, Chertin B, Velayudham M, Dass L, Colhoun E. Treatment of vesicoureteral reflux by endoscopic injection of dextranomer/hyaluronic acid copolymer: preliminary results. *J Urol* 2003;170:1541-4.
 16. Al-Hunayan AA, Kehinde EO, Elsalam MA, Al-Mukhtar RS. Outcome of endoscopic treatment for vesicoureteral reflux in children using polydimethylsiloxane. *J Urol* 2002;168:2181-3.
 17. Läckgren G, Wählin N, Sköldenberg E, Stenberg A. Long-term followup of children treated with dextranomer/hyaluronic acid copolymer for vesicoureteral reflux. *J Urol* 2001;166:1887-92.
 18. Lee EK, Gatti JM, DeMarco RT, Murphy JP. Long-term followup of dextranomer/hyaluronic acid injection for vesicoureteral reflux: late failure warrants continued follow-up. *J Urol* 2009;181:1869-74.
 19. Schmedding A, Zeeh U, Huebner U, Krause M, Lorenz C. Sx IN-prospective multicenter survey of subureteral injection in children. Presented at International Conference on VUR in Children, Goteborg, Sweden, 4-6 June 2009.
 20. Puri P, Kutasy B, Colhoun E, Hunziker M. Single center experience with endoscopic subureteral dextranomer/hyaluronic Acid injection as first line treatment in 1,551 children with intermediate and high grade vesicoureteral reflux. *J Urol* 2012;188(4 Suppl):1485-9.
 21. Kajbafzadeh A, Tourchi A, Aryan Z. Factors that impact the outcome of endoscopic correction of vesicoureteral reflux : a multivariate analysis. *Int Urol Nephrol* 2013;45:1-9.
 22. Stredle RJF, Dietz HG, Stehr M. Long-term results of endoscopic treatment of vesicoureteral reflux in children : Comparison of different bulking agents. *J Pediatr Urol* 2013;9:71-7.
 23. Baek M, Kang MY, Lee HE, Park K, Choi H. Clinical value of persistent but downgraded vesicoureteral reflux after Dextranomer/Hyaluronic acid injection in children. *J Korean Med Sci* 2013;28:1060-4.
 24. Keren R, Carpenter MA, et al. Rationale and Design Issues of the Randomized Intervention for Children With Vesicoureteral Reflux (RIVUR) Study *Pediatrics* 2008;122:240-50.