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ORIGINAL ARTICLE

Endoscopic treatment of symptomatic VUR disease after the renal transplantation: analysis of 49 cases

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Abstract

Background To evaluate the outcome of endoscopic treatment for symptomatic vesicoureteral reflux (VUR) disease in renal transplantation patients and to determine the factors that were associated with the success rate of the treatment.

Methods A total of 121 symptomatic VUR diseases diagnosed between 2014 and 2018 in 3560 renal transplant patients. The results of 49 VUR cases that presented with febrile urinary tract infection (UTI) and were hospitalized for antibiotic treatment were included in the study. Reflux was detected by voiding cystourethrogram and treatment was performed by endoscopic Deflux® injection. The result of endoscopic treatment was evaluated clinically by 3 months periods.

Results The mean time between transplantation and endoscopic treatment was 59.6 (5–132) months, and the mean follow-up period after the endoscopic treatment was 14 (6–48) months, respectively. The success rate after the first injection was 59.1% ($n=29$) and 67.3% ($n=33$) after the second injection. One patient developed anuria, one patient febrile UTI and four patients developed minimal macroscopic hematuria after the procedure.

Conclusions Endoscopic treatment of symptomatic VUR in transplanted kidney is a safe and feasible procedure. The amount of bulking agent or duration between the transplantation and diagnosis of VUR does not have any impact on the success of the treatment. However, the younger age of the patients and the female gender seem to have a positive effect on the outcome of the procedure.

Keywords Endoscopic treatment · Renal transplantation · Vesicoureteral reflux

Introduction

Vesicoureteral reflux (VUR) is a common condition in renal transplant patients. It is diagnosed with voiding cystourethrography (VCUG) in a range of 10% and 80% in the transplant patients [1, 2]. This clinical situation is usually asymptomatic; however, 3% of VUR can lead to pyelonephritis and/or graft deterioration symptoms in renal transplant patients. Therefore, recurrent urinary tract infections due to VUR in the transplanted kidney are associated with significantly decreased graft survival [3].

The gold standard treatment for VUR is the surgical re-implantation of the ureter to the bladder wall. However, this approach carries some risk for these patients. Immunosuppression drugs that are used for protection of the graft from the immune system can cause severe fibrosis around the transplanted kidney. It is reported previously, that secondary surgery for re-implantation of the graft ureter is related with a morbidity rate of 16–53% [4, 5]. Therefore, most of the centers for kidney transplantation prefer to follow-up VUR cases in transplanted patients instead of surgical operation.

Minimally invasive approach with endoscopic treatment of the VUR has a success rate of 60–80% and a morbidity rate lower than 10% [6, 7]. In this study, we aimed to evaluate the outcome of endoscopic treatment for pyelonephritis secondary to VUR disease of the transplanted kidney and to determine the factors that were associated with the success rate of the treatment.

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Patients and methods

A total of 121 symptomatic cases of VUR were diagnosed in a cohort of 3560 renal transplant patients between January 2014 and December 2018. Symptomatic VUR was defined as febrile urinary tract infection or deterioration of the graft function. Only the results of 49 VUR cases that presented with febrile UTI and were hospitalized for antibiotic treatment were included in the study. The study was approved by the Ethics Advisory Committee of Medicana International Hospital (Approval No. 2019365). Written and verbal consent was obtained from each patient.

Patients who have neurogenic bladder dysfunction ($n=15$) or synchronous multiple ureteral refluxes ($n=12$) in the native ureters were excluded. Patients diagnosed with VUR disease and had elevated serum creatinine levels without febrile UTI were also excluded ($n=45$).

All renal transplant patients were under a three-month follow-up protocol by a senior nephrologist from 2007 to 2018. The patients received trimethoprim-sulfamethoxazole prophylaxis for pneumocystis pneumonia during this period. After these three months, patients did not get any kind of antibiotic prophylaxis. The renal transplants were performed by two different surgical teams, whereas patients with symptomatic VUR were evaluated by the same urologist (MB) who is experienced in the management of urological complications in renal transplanted patients.

The ureterovesical anastomosis was created using a modified Lich-Gregoir technique. The neo-orifice was positioned just laterally to the location of the original ipsilateral ureteral orifice. A double-J stent was routinely placed in the ureter to protect the anastomosis and was removed after ten days, endoscopically. In transplanted patients with febrile UTI and/or deterioration of the graft function which could not be explained by any other reasons rather than VUR, a VCUG was performed. VCUG planned after the urine culture was sterile with proper antibiotherapy. VUR grade was classified according to the international classification [8].

Endoscopic technique

The patients were positioned in supine lithotomy position under general anesthesia. Cystoscopy was performed to identify the new ureteral orifice location with a 30° lens endoscope. In cases where the neo-orifice could not be located, suprapubic pressure was applied, and the bladder was evaluated at different levels of fullness with a 70° lens cystoscope to obtain more visual area with a greater angle (Fig. 1). In cases where the guidewire could not be inserted into the neo-ureteral orifice due to difficulties in angling the guidewire or due to difficulty in finding

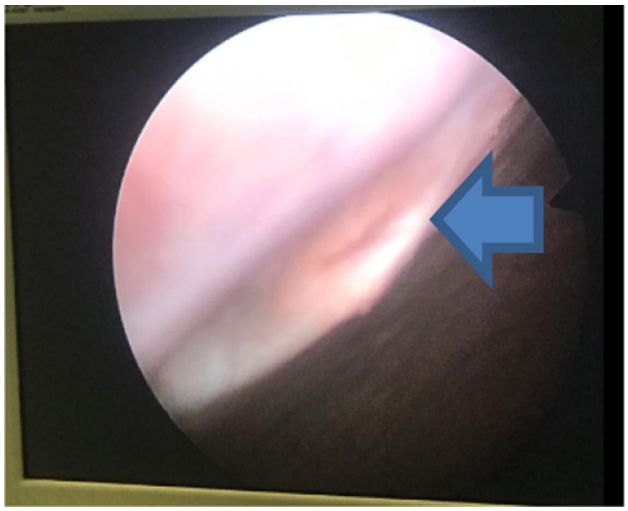

Fig. 1 Localization of neo-orifice at bladder dome. Blue arrow indicates the neo-orifice

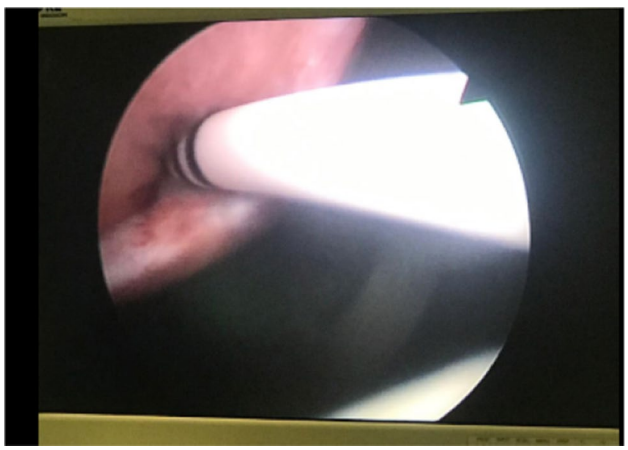

Fig. 2 Insertion of ureteral double-J stent to the ureter over the guidewire

the neo-orifice, a 9.5–10 Fr semirigid URS was used to find the orifice and to facilitate the insertion of the guidewire. We used a Roadrunner hydrophilic PC guide wire (0.038″/145 cm) (Cook Surgical, Indianapolis, IN, USA) to overcome the sharp angle of the neo-orifice more easily. In cases where the sharp angle between the axis of the scope and the axis of the ureter can't be overcome, A five Fr urology torque catheter (0.038 in/65 cm) (Boston Scientific, Natick, MA, USA) was used to redirect the guidewire. Fluoroscopy was used routinely during the insertion of the guidewire into the ureter and during insertion the Double-J (16 cm—4.8 F) catheter over the guidewire through the cystoscope (Figs. 2, 3). The DX-HA (Dexel®) was used as a bulking agent in all cases and injected via endoscopy by the bereaved rigid metal needle (Fig. 4).

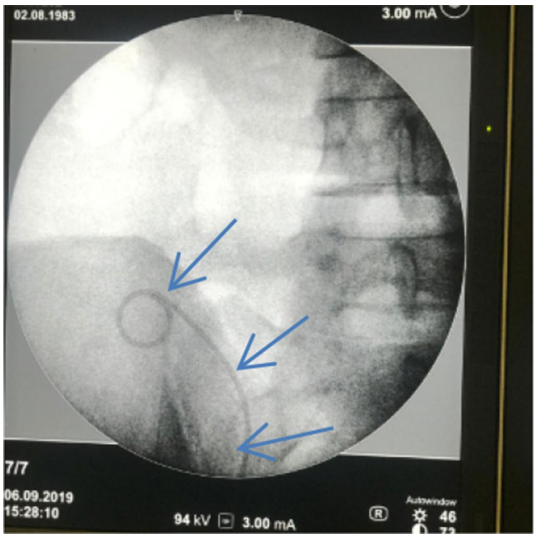

Fig. 3 Appearance of double-J stent on fluoroscopy. Blue arrows indicate the ureteral double-J stent

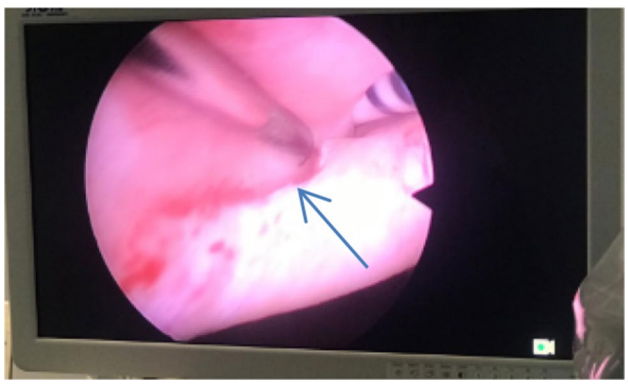

Fig. 4 Injection of the bulking agent with the bereaved rigid metal needle. Blue arrow indicates the tip of the metal needle

The injection was applied at the level of ureteral neo-orifice at six o-clock position around the double-J stent until the orifice was completely obliterated (Fig. 5). However, if the double-J stent could not be inserted, the bulking material injected more carefully to prevent total obstruction.

At the end of the procedure, a ureteral catheter was inserted to observe the urine output for 24 h. The serum creatinine level was checked before the discharge of the patient, and the double-J stent was removed after ten days. The successful treatment was defined as no febrile UTI during the follow-up period. In clinically failed cases, open ureteral re-implantation surgery was performed.

The follow-up of the patients was done according to clinical symptoms. In patients in whom recurrent febrile UTI persisted, a VCUG was planned. Continuous variables were reported as mean ± standard deviation (SD) or median.

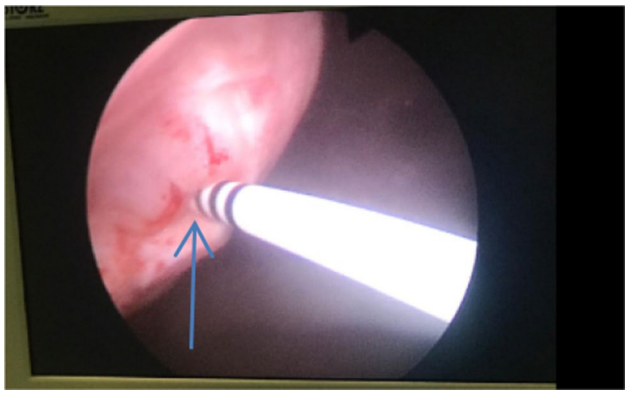

Fig. 5 The final appearance of the neo-orifice after injection. Blue arrow indicates completely obliterated neo-orifice around the double-J stent

Table 1 The demographic and preoperative data of the patients

Patients	49
Median age (range) years	47 (26–76)
Gender	
Male	21
Female	28
Symptoms-Febrile UTI attacks before treatment	
1–2	28
3–4	21
Medical history	
DM	5
Ureteral re-implantation	1
Renal transplantation	
First tansplantation	46
Second transplantation	3

DM diabetes mellitus

Categorical variables were reported as number and percentage. The independent *t* test or Mann–Whitney test was used to compare continuous variables, while Pearson's Chi-square test was used to compare categorical variables. Statistical analysis was performed with SPSS version 22.

Results

The outcome of 49 patients with recurrent febrile UTI and VUR into the graft ureter was evaluated in this study. The demographic and preoperative data of the patients are presented in Table 1.

The mean time between transplantation and endoscopic treatment was 59.6 (5–132) months, and the mean follow-up period after the endoscopic treatment was 14 (6–48)

months. The clinical and perioperative data are summarized in Table 2.

The success rate after the first injection was 59.1% ($n=29$) and 67.3% ($n=33$) after the second injection.

In 16 renal transplant cases, febrile urinary tract infections persisted. These cases were defined as failed endoscopic treatment. Postoperative VCUG in these patients revealed VUR with decreased grade compared to the previous VCUG findings. Three of the patients with failed endoscopic treatment underwent an open surgical ureteral re-implantation. The remaining 13 patients with failed treatment were scheduled for continuous antibiotic prophylaxis. The mean follow-up period of the 13 patients who did not achieve clinical success after endoscopic treatment was 13.6 (12–17) months. The mean creatinine level measured before endoscopic treatment was 1.56 ± 0.6 mg/dl, whereas the mean of the last measured creatinine levels during the follow-up period after unsuccessful endoscopic treatment was 1.99 ± 0.63 mg/dl. The difference between the creatinine levels was statistically significant ($p<0.01$). All patients had at least two attacks of pyelonephritis during their follow-up [mean 3.23 ± 1.09 (2–5)].

The patients in whom endoscopic treatment failed had statistically higher numbers of pyelonephritis attacks and an increase of serum creatinine levels than the patients who had succeeded from endoscopic treatments ($p<0.01$ and $p<0.01$).

We did not find any statistically significant association between the success rate and the period of renal transplantation to the diagnosis of VUR ($p=0.327$). The grade of reflux was not associated with the success of the procedure ($p=0.173$). The success rate was also not related to the amount of the bulking agent material ($p=0.840$) that was used. Age was associated with the success rate of the treatment. The mean age of the patients in whom the treatment was defined as clinically successful was statistically lower in younger patients (age 43.20 ± 11.32 vs 52.72 ± 12.56; p 0.013) (Table 3). Another parameter that was related to the success of the treatment was gender. Clinical success was achieved in 82.1% of the female patients, whereas this rate was 47.6% for male patients ($p=0.013$) (Table 3).

In the follow-up period, one patient developed anuria after the operation; therefore, this patient was reoperated for insertion of a double-J stent (This case was the first case of the series). Four patients developed macroscopic hematuria that resolved within 12 h. One patient developed febrile UTI

Table 2 The operative data of the patients

Median time (months) transplantation-endoscopy (range)	38 (5–132)
Median follow-up, months (range)	14 (6–48)
Mean mmol/l pretreatment creatinine (range)	1.27 (0.6–3.6)
No. of VUR grade (%)	
1	1 (2)
2	24 (49)
3	22 (44.9)
4	2 (4.1)
Amount of bulking agent, cc (mean)(range)	2.75 (1–4)
Ureteral cathaterization	
Inserted	41
Can not inserted	8
Number of endoscopic injection	
1	49
2	20
Complication	
Anuria	1
Miminal hematuria	4
Urinary infection	1
Clinical success	
No febrile UTI (%) buralar hatalı	33 (67.3%)
1 febrile UTI	2 (4.3%)
$x>1$ febrile UTI	14 (28.5%)
Failed cases	
Ureteral re-implantation, *n*	3
Follow-up, *n*	13

VUR vesicoureteral reflux, *UTI* urinary tract infection

Table 3 Univariate analysis of factors predicting clinical success or failure

Variable	Clinical success	Clinical failure	*p* value
Gender			0.013
Male	10	11	
Female	23	5	
Age (mean ± SD), years	43.20 ± 11.32	52.72 ± 12.56	0.013
Injected bulking agent(mean ± SD), ml	2.74 ± 0.66	2.78 ± 0.69	0.84
Grade			0.173
Less than grade 3	20	5	
Greater than grade 3	15	9	
Time[a] (mean ± SD), months	62.89 ± 36.12	51.43 ± 37.71	0.327

[a]Time: duration between transplantation and first symtoms

3 days after the endoscopic management and was treated with parenteral antibiotics according to the urine culture.

Discussion

VUR is a common condition that can be detected after renal transplantation. Molenaar et al. suggested that in most cases, this condition doesn't have any impact on early bacteriuria, renal function and graft function [9]. However, if VUR starts to become symptomatic (acute pyelonephritis or/and deterioration of the graft function), appropriate treatment should be planned.

The symptomatic VUR rate was reported to be between 0.3 and 5.8% in the literature [10–12]. In our renal transplant population, this rate was 3.3%; this rate was comparable with the literature.

The cause of VUR after renal transplantation may be related to the ureteral re-implantation technique. Farr et al. suggested that, in the Lich-Gregoir re-implantation technique, tunnel length, vesical wall quality, use of stents and experience of the surgical team can influence the occurrence of VUR [13]. In our cases, the Lich-Gregoir technique with a submucosal tunnel at least three cm was performed in all cases by two experienced renal transplant surgical teams. To the best our opinion the submucosal tunnel is the most important issue for the occurrence of VUR, The EAU (European Association of Urology) guidelines also recommend that the antireflux tunnel for the ureterovesical anastomosis should be 3–4 cm long [14].

Surgical re-implantation of the ureter is the gold standard treatment of VUR with a success rate of more than 80%. However, ureteral re-implantation surgery is associated with relatively high morbidity rates (16–53%) [5, 12]. Overall morbidity and success rates of endoscopic treatment modalities were reported to be 10% and 60–86, respectively by Akiki et al. The endoscopic treatment was preferred to benefit from lower morbidity rates from this study [12]. We also prefer the endoscopic approach as the first-line treatment for VUR in transplant patients for the same reasons.

The success rates of different kinds of bulking agents for the treatment of VUR various in previous studies. The success rate of collagen was reported to be around 50–67%, and for polytetrafluoroethylene, it was reported to be 30–53% [15, 16]. DX-HA is the most recent bulking agent that is used. DX/HA is formed of cross-linked dextranomer microspheres (80–250 µm in diameter) suspended in a carrier gel of stabilized sodium hyaluronate. DX/HA is biodegradable, the carrier gel is reabsorbed, and the dextranomer microspheres capsulated by fibroblast migration and collagen ingrowth [17] Sparks et al. demonstrated that in case of injection outside of the bladder of DX-HA does not cause any important problem during ureteral re-implantation after failed ureteral injection; material is encapsulated with limited inflammatory reaction without distant migration [18]. The clinical success rate of DX-HA was reported to be higher than other bulking agents [19].

Akiki et al. reported a clinical success rate of 42.1% after the first injection and 56.1% after the second injection in 58 patients with VUR who underwent endoscopic injection treatment. They used DX-HA and polydimethylsiloxane as bulking agents [12]. Pichler et al. reported a study including 19 renal transplant recipients in which they performed submucosal injection during hydrodistension of the bladder using DX-HA. The success rate after the first and second injection was 57.9% and 78.9%, respectively. However, early ureteral obstruction with hydronephrosis and increased serum creatinine levels were noted in 10.5% of patients [6]. In a recent study, Wang et al. reported the success rate of injection treatment with DX-HA as 75% in 16 patients [19].

In our study, we used only DX-HA as a bulking agent for all cases. The success rate after the first and second injection was 59.1% and 67.3%, respectively. Our success rate was higher than the success rate of the Aikiki et al. study (67.3% vs 56%). This difference may be explained by the fact that only DX-HA was used as injection material instead of two different bulking agents that were used in the Akiki study. Further, the procedures were performed by the same surgeon in our study instead of multiple surgeons. In addition, our mean follow-up period was shorter than the follow-up period of Akiki et al. (14 months vs 38 months).

Our success rate is lower than the studies by Wang et al. and by Pichler et al. (67.3% vs 78.9–75%). This discrepancy can be explained by the higher patient number of our study (49 vs 16–19).

Some studies stated that VUR grade is a factor that affects the clinical success of injection treatment. High-grade VUR (3 and 4) was related to lower success rates after injection treatment in these studies [16, 20]. In contrast, another study noted that preoperative VUR grade does not influence the success of the injection treatment [12]. In our study, we did not find any relation between preoperative VUR grade and the success of the injection treatment (p 0.21). Interestingly, the rate of clinical success was considerably higher in females than in males (85.7% vs 52.4%). In contrast, Akiki et al. achieved higher clinical success rates for male patients than for females. We were not able to make a reasonable explanation for this difference between the genders.

In the current study, the duration between the diagnosis of VUR and kidney transplantation did not correlate with the success of endoscopic treatment. Further, the amount of bulking material did not have any impact on the success of the treatment (p 0.87 and p 0.84). However, the success rate of the treatment was higher in younger patients (p 0.021).

In conclusion, endoscopic treatment of pyelonephritis secondary to VUR in transplanted kidney is a safe and

effective technique. The amount of bulking agent or duration between the transplantation and diagnosis of VUR doesn't have any impact on the success of the treatment. However, younger age and female gender seem to have a positive effect on the success of the procedure.

Compliance with ethical standards

Conflict of interest The authors have declared that no conflict of interest exists.

Ethics standards The study was approved by the Ethics Advisory Committee of Medicana International Hospital (Approval No. 2019365). This article does not contain any studies with animals performed by any of the authors.

Informed consent Prior to the procedure, a written and verbal consent was obtained from each patient.

References

1. Karam G, Maillet F, Braud G, et al. Surgical complications in kidney transplantation. Ann Urol. 2007;41:261–75.
2. Molina G, Feitosa LC, Martin X, et al. Incidence of vesico-ureteral reflux after allograft renal transplantation. Transplant Proc. 1994;26:292.
3. Ohba K, Matsuo M, Noguchi M, et al. Clinicopathological study of vesicoureteral reflux (VUR)-associated pyelonephritis in renal transplantation. Clin Transplant suppl. 2004;18:34–8.
4. Krishnan A, Swana H, Mathias R, et al. Redo ureteroneocystostomy using an extravesical approach in pediatric renal transplant patients with reflux: a retrospective analysis and description of technique. J Urol. 2006;176:1582–7.
5. Hau HM, Tautenhahn HM, Schmelzle M, et al. Management of urologic complications in renal transplantation: a single-center experience. Transplant Proc. 2014;46:1332–9.
6. Pichler R, Buttazzoni A, Rehder P, et al. Endoscopic application of dextranomer/hyaluronic acid copolymer in the treatment of vesicoureteric reflux after renal transplantation. BJU Int. 2011;107:1967–72.
7. Romero NP, Romo MIG, Vegas AG, et al. Deflux injections for vesicoureteral reflux in transplanted kidneys. Transplant Proc. 2010;42:2892–5.
8. Lebowitz RL, Olbing H, Parkkulainen KV, et al. International system of radiographic grading of vesicoureteric reflux: International Reflux Study in Children. Pediatr Radiol. 1985;15:105–9.
9. Molenaar NM, Minnee RC, Bemelman FJ, Idu MM. Vesicoureteral reflux in kidney transplantation. Prog Transplant. 2017;27(2):196–9.
10. Masahiko H, Kazunari T, Tokumoto T, et al. Comparative study of urosurgical complications in renal transplantation: intravesical versus extravesical ureterocystoneostomy. Transplant Proc. 2000;32:1844–6.
11. Whang M, Yballe M, Geffner S, et al. Urologic complications in more than 2500 kidney transplantations performed at the Saint Barnabas healthcare system. Transplant Proc. 2011;43:1619–22.
12. Akiki A, Boissier R, Delaporte V, et al. Endoscopic treatment of symptomatic vesicoureteral reflux after renal transplantation. J Urol. 2015;193:225–9.
13. Farr A, Györi G, Mühlbacher F, et al. Gender has no influence on VUR rates after renal transplantation. Transpl Int. 2014;27:1152–8.
14. European Association of Urology: Guidelines (2012). Available at https://www.uroweb.org/guidelines/online-guidelines/. Accessed 29 Sep 2012.
15. Joshi P, Jha A. Subureteric collagen injection treatment for vesicoureteral reflux in renal transplantation. Transplantation. 2004;78:250–1.
16. Mallet R, Game X, Mouzin M, et al. Symptomatic vesicoureteral reflux in kidney transplantation: results of endoscopic injections of Teflon and predictive factors for success. Prog Urol. 2003;13:598–601.
17. Stenberg A, Lackgren G. A new bioimplant for the endoscopic treatment of vesicoureteral reflux: experimental and short-term clinical results. J Urol. 1995;154:800–3.
18. Sparks S, Decambre M, Christman M, et al. Salvage ureteral reimplantation after failure of dextranomer/hyaluronic acid injection. J Urol. 2011;186:257–60.
19. Wang HH, Ding WF, Chu SH, et al. Endoscopic Treatment for post-transplant vesicoureteral reflux. Transplant Proc. 2019;51(5):1420–3.
20. Elder JS, Diaz M, Caldamone AA, et al. Endoscopic therapy for vesicoureteral reflux: a meta-analysis. I. Reflux resolution and urinary tract infection. J Urol. 2006;175:716–22.