Subureteric injection for the treatment of vesicoureteral reflux in transplant kidneys

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ABSTRACT

Introduction: Treatment of de novo vesicoureteral reflux (VUR) into the transplanted kidney constitutes a clinical challenge. Herein, we present our data on patients who underwent endoscopic subureteric injection for the treatment of VUR following renal transplantation (RT) in our center.

Methods: The patients who underwent endoscopic subureteric injection for VUR into the transplanted kidney after RT in our department between 2008 and 2023 were reviewed retrospectively. Indication for subureteric injection, age, gender, laterality, number of injections, amount of material used, renal failure etiology, auxiliary procedures, and treatment success were noted. All interventions were performed by pediatric urologists who also perform RT.

Results: During a median followup of 27.5 (4–160) months, 22 patients (17 women, 77.2%) and 23 transplanted ureters (13 right, eight left, one bilateral) were treated with subureteric injections. In all patients, the indications for subureteric injection were recurrent febrile urinary tract infection (UTI), and the grades of VUR varied between I and IV. Patients received a median of 1.65 cc (0.7–2.7) dextranomer-hyaluronic acid copolymer. In total, 10 RTs (eight from living donors, two from cadaveric donors) were performed in another center, whereas 13 RTs were carried out in our center (eight from cadaveric donors and five from living donors). Among the patients who were transplanted in our center, the rate of subureteric injections due to de novo symptomatic VUR after RT was 2.2% (13/593 patients). After subureteric injections, five patients required a second injection due to the recurrence of VUR. Ureteroureterostomy (to the native ureter) was performed in two patients who had further UTIs after the second endoscopic treatment. Eventually, 19/21 patients (90.4%)

benefited clinically from the endoscopic treatment and none of the patients underwent re-do ureteroneocystostomy. It is noteworthy that the etiology of renal failure was VUR nephropathy in seven (31.8%) patients.
Conclusions: Subureteric injection provides a high clinical success for the treatment of de novo VUR after RT.

INTRODUCTION

Urinary tract infections (UTIs) are the most common bacterial infections after renal transplantation (RT) that can present in the forms of pyelonephritis, cystitis, and asymptomatic bacteriuria [1]. UTI after RT has been associated with graft loss and even mortality [2]. Therefore, the diagnosis and treatment of UTIs after RT is crucial. On the other hand, vesicoureteral reflux (VUR) is a well-known risk factor for UTI. Besides, the incidence of VUR after RT has been reported to be as high as 50-86% in some studies [3]. Usually, VUR following RT is a consequence of surgical technique since the bladder rehabilitation prior to RT is carried out in many centers, especially for those from living donors. During RT surgery, avoiding a ureterovesical stricture is often pursued, which might end up with VUR [4].

Antibiotic prophylaxis is the first-line treatment option in patients who develop recurrent UTIs due to VUR after RT. Surgical intervention is required in patients who have breakthrough infections under prophylaxis. Since surgery for a re-do ureteroneocystostomy is a challenging procedure, it is almost always reserved after subureteric injection for the transplanted ureter. Thus, endoscopic subureteric injection, which is a less invasive treatment, is frequently used in the treatment of VUR into the transplanted kidney. The goal of subureteric injection is to obtain the proper coaptation of the neo-ureteric orifice and cease VUR. Historically, many agents including polytetrafluoroethylene, bovine collagen, polyacrylate-polyalcohol copolymer, polydimethylsiloxane, calcium hydroxyapatite and dextranomer/hyaluronic acid (Dx/HA) have been used to date for this purpose [5]. Among those, Dx/HA is the most commonly used agent in the treatment of VUR after RT as well as in pediatric urology. Previous reports have indicated success rates of 53-86% with Dx/HA [6, 7].

In this study, we aimed to analyze our outcomes on the endoscopic subureteric injection of *de novo* VUR into the transplanted kidney following RT and to observe if it is a viable option for treatment.

METHODS

Patients

After approval of the research protocol by an Institutional Reviewer Board (6-14/6/2021) files of the patients who underwent endoscopic treatment for VUR into the transplanted kidney after RT in our department between 2008 and 2023 were retrospectively evaluated. Indication for subureteric injections, age, gender, laterality, center of RT, number of

injections, pre operative VUR grade, duration between RT and subureteric injection, VUR status in native ureters, amount of Dx/HA material used, renal failure etiologies and additional treatments, if required were noted.

Regarding the ureterovesical anastomosis technique in our center, an extravesical anterolateral ureteroneocystostomy technique (modified Lich-Gregoire technique) is performed in our center. Further, a DJ stent is placed in all RT surgeries. The patients are followed up by the Division of Nephrology, as per their clinical protocol. Voiding cystourethrography (VCUG) is requested in the setting of recurrent febrile UTIs. All patients with confirmed VUR are initiated on antibiotic prophylaxis regimen. Then, they are referred to Urology for treatment as soon as they had breakthrough infections under antibiotic prophylaxis. Subureteric injection is the primary treatment modality in our center for patients with *de novo* VUR after RT. Following the procedure, all patients are investigated via urinary ultrasonography at the first month to detect any *de novo* hydronephrosis indicating post-injection ureteral obstruction. Further, success of the procedure is determined clinically (No VCUG if UTIs ceased).

Subureteric injection procedure

All subureteric injections were performed by the faculty members of our department that are pediatric urologists who also are in the renal transplantation team. After obtaining negative urine culture within one week prior to the operation, all patients underwent intervention in the lithotomy position under general anesthesia using a pediatric cystoscope, due to its superior maneuverability. Dx/HA was used as the bulking agent in all patients using a plastic/metal needle. In the surgical technique, the first step was to identify the transplant ureter orifice, which was sometimes easily seen on the anterolateral side (right or left) of the bladder. Moreover, in some cases with higher VUR grade, the ureter could even be scoped with the pediatric cystoscope. Nevertheless, there were times that the ureteric orifice was not easily distinguished, particularly in patients with a previous diagnosis of bladder dysfunction (neurogenic or non-neurogenic). In those cases, a ureteral catheter was inserted into the transplant ureter in order to help identify the ureteric orifice as well as to facilitate the injection. In each case, the main idea was to achieve an optimal coaptation of the ureteric orifice. Considering the alteration of the anatomy in a modified Lich-Gregoir ureteroneocystostomy, the superior aspect of the ureter is backed by muscular layer (detrusor) as opposed to the inferior aspect in orthotopic position, during cystoscopy. Since the intention is to use this musculature as a backing support for the injection material, the Double HIT injection technique was initially applied to the superior side of the ureter (whenever possible) [8], which was proceeded by the injection of the bulking material circumferentially in order to maintain optimal coaptation (Supplementary video 1). This might explain the higher volumes used in this series when compared to the low volumes used for children. After completion of the circumferential injection, the tip of the cystoscope was advanced to the neo-orifice with a full saline flow and the ureteral coaptation was tested before concluding the session. After the injection, the bladder is emptied and no urethral or ureteral catheter is left in situ. The patients are discharged 2-4 hours after the procedure.

RESULTS

Between 2008 and 2023, 22 patients (17 women, 77.2%) underwent subureteric injections for 23 transplanted ureters (13 right, 8 left, 1 bilateral). The indication for subureteric injection was recurrent febrile UTIs despite antibiotic prophylaxis in all patients. Grades of VUR varied between I and IV whereas dilating VUR (Grade III-V) was detected in 20 of 23 renal units and 3 had non dilating VUR (grade I-II). Patients received a median of 1.65 cc (range 0.7-2.7) of Dx/HA.

In our cohort, 10 patients (8 from living donors, 2 from cadaveric donors) have undergone RT in another center. Contrarily, 13 transplants out of 593 (2.2%) that were transplanted in our center needed subureteric injections (13 transplants, 8 from cadaveric donors and 5 from living donors). The median age of the whole cohort was 30 (ranging from 5 to 57) at the time of RT and the median time between transplantation and endoscopic treatment was 93 (4–216) months. The median follow-up duration was 27.5 (4-160) months. Two patients passed away during the follow-up due to COVID-19 pneumonia.

After the subureteric injection, UTI recurred and a control VCUG was requested in 6 patients (indicating a 72.7% initial success rate). All these patients showed radiological recurrence of VUR and underwent a second subureteric injection. The median time between first and second endoscopic treatment was 4.5 (3-36) months. Of these, 4 had dilating VUR (Grade III-IV) and the others had non-dilating VUR (Grade II) before the first injection. Ureteroureterostomy (to the native ureter which was non-refluxing) was performed in two patients whom had further UTIs after the second endoscopic injection. Eventually, 19 of 21 patients benefited from the endoscopic treatment clinically. Further, none of the patients underwent re-do ureteroneocystostomy. The risk of developing postoperative ureteral obstruction after subureteric injection was monitored using serum creatinine levels and urinary ultrasonography within 1 month post intervention. No post-injection ureteral obstruction was detected in the cohort. Also, it is noteworthy that the etiology of renal failure was VUR nephropathy in 7 (31.8%) patients.

DISCUSSION

Vesicoureteral reflux into the transplant kidney following RT is considered a problem when complicated by recurrent febrile UTIs that may high likely compromise graft function in the long-term. Thus, diagnosis and treatment of clinically problematic VUR has utmost importance in patients with RT. It should be noted that VUR in RT patients ranges from 1% to 86% indicating that asymptomatic VUR is also common [9]. Even though the sole impact of VUR on graft function is still debated, it needs treatment once it is along with recurrent febrile UTIs, require hospitalizations and cause graft failure. In the literature, symptomatic VUR rate was reported between 0.3-3%, which is in accordance with our results [10-12].

Since RT patients are not subjected to the maturation of the ureterovesical junction as in children, antibiotic prophylaxis is usually used as a primary approach in order to ensure if the VUR is absolutely problematic. Thus leaves two main treatment strategies for VUR into the transplanted kidney; surgical or endoscopic. Surgical treatment options are re-do ureteroneocystostomy, ureteropyelostomy, cutaneous ureterostomy, and ureteroureterostomy whereas endoscopic treatment is subureteric injection. In VUR after RT, endoscopic

treatment is usually the initial choice due to its non-invasiveness as well as the bothersome nature of re-do surgery.

The treatment of VUR has surpassed a long way in the search of an optimal bulking agent beginning with polytetrafluoroethylene, and followed by bovine collagen copolymer, polydimethylsiloxane, calcium hydroxyapatite, polyacrylate-polyalcohol and Dx/HA. Previous series have reported various success rates ranging from 30% to 85.7% with various materials in subureteric injection due to VUR after RT [13, 14]. Akiki et al. found that the clinical success rate was significantly higher in the Dx/HA group than in the polydimethylsiloxane group (65% vs 33.3%, p= 0.035) [15]. On the other hand, radiological resolution rate was shown as low as 23.5% in another study that looked into use of collagen for subureteric injection, which already have been shown low success rates in children [16]. Furthermore, subureteric injection using carbon-coated beads has also been reported to show promising results (a success rate of 75%) in the treatment of 8 transplant patients with recurrent pyelonephritis secondary to VUR [17], whereas an overall success rate of 53.8% was reported in 26 kidney recipients who underwent subureteric injection using Dx/HA [7] .

In pediatric urology practice, subureteric injection is widely used in the treatment of VUR, and new surgical techniques such as hydrodistension implantation technique and double HIT techniques have recently been developed. Implementation of these techniques have improved success rates of this procedure up to 92% in children with native ureteral orifice [18]. As our team consists of pediatric urologists who also deal with renal transplantation, it is undisputable to expect a reflection of their expertise on the endoscopic treatment of VUR following RT. Although control VCUG was not routinely performed in our cohort for various reasons (UTI risk, repeated radiation exposure, etc.), we attribute the high clinical success in our series to this surgical experience.

The endoscopic treatment of VUR has been utilized in our department since late 1990s, shortly after this technique was promoted. Furthermore, we have recently showed our results in pediatric series that revealed >90% success even for experienced pediatric urology fellows [19]. Even though subureteric injection for transplanted ureter is a challenging procedure, our results indicated that significant clinical success can be achieved in experienced hands, as 90% of the patients in our study showed clinical benefit.

In VUR cases detected after RT, success rates of 59.1% and 67.3% were reported after the first and second injections of Dx/HA, respectively [20]. The mean time between RT and endoscopic treatment was 59.6 (5-132) months, which was similar to our findings. This finding underlines that VUR might not only be a surgical complication both also an unidentified phenomenon specific to RT patients.

On the other hand, there is discrepancy among centers in terms of treatment success definition. Some centers prefer to obtain an early VCUG or three months after the procedure, while others rely on clinical follow-up, defined by the cessation of febrile UTIs, without performing routine VCUG. We think that symptomatic response can be considered sufficient as the ultimate aim is to cease further pyelonephritis, and we do not perform routine post operative VCUGs due to previously mentioned reasons.

Other surgical options instead of endoscopic subureteral injection are re-do ureteroneocystostomy, or pyeloureterostomy/ureteroureterostomy into the native ureter. A success rate of 83-100% can be achieved by anastomosing the transplanted ureter to the native ureter [21, 22]. However, these open surgical procedures are not used as the first treatment option due to high morbidity rates as high as 16-53% [23, 24]. In this context, only two of our patients required open surgery following endoscopic injection treatment failure, in the form of ureteroureterostomy after which their UTIs ceased.

Limitations

The current study is not without limitations. Firstly, we had all restrictions of a retrospective study. Secondly, the number of patients was limited. However, we have a longer follow-up period compared to the literature, with a median follow-up of 27.5 (4-160) months. Thirdly, we had no objective radiological success rates due to the lack of postoperative routine VCUG data. Instead, we based our follow-up on clinical success described by cessation of febrile UTIs, because VCUG has its own complications including hospital-acquired UTI in this immunocompromised patient group.

CONCLUSIONS

Recurrent febrile UTI is a critical factor for graft failure in the long-term follow-up of RT. A high suspicion of VUR should be kept in mind in the follow-up of recurrent UTIs, especially when the primary cause of kidney failure is reflux nephropathy. Nevertheless, subureteric injection treatment using Dx/HA provides a safe and a highly successful alternative for transplant kidneys with VUR.

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FIGURES AND TABLES

Table 1. Patient characteristics

Patient	Gender	Primary renal disease	Age at transplantation (year)
1	F	VUR	20
2	F	VUR	30
3	M	VUR	7
4	M	VUR	30
5	F	Incidental	20
6	F	RPGN	12
7	F	Chronic pyelonephritis	42
8	F	Diffuse Mesangial Sclerosis	5
9	M	Chronic pyelonephritis	43
10	F	FMF amiloidosis	40
11	F	N/A	43
12	M	N/A	39
13	F	N/A	26
14	F	Incidental	41
15	F	VUR	28
16	F	VUR	32
17	F	HT	36
18	M	FSGS	35
19	F	N/A	29
20	F	VUR	21
21	F	FMF amiloidosis	57
22	F	Neuropathic bladder	19

F: female; FMF: familial Mediterranean fever; FSGS: focal segmental glomerulosclerosis; HT: hypertension; RPGN: rapidly progressive glomerulonephritis; M: male; N/A: not applicable; VUR: vesicoureteral reflu

Table 2. Clinical course and data of the patients									
Patient	**VCUG grade before injection therapy**	**eGFR before injection therapy (ml/min/1.73m^2)**	**Age at injection therapy (year)**	**Period from transplantation to injection (months)**	**Total amount of Dx/HA injection (ml)**	**Febrile UTI after injection therapy**	**2nd procedure**	**Period from the last procedure to timing of final followup (months)**	**eGFR at the final followup exam**
1	4	34	30	120	1.6	-	-	15	N/A
2	4	23	37	84	0.7	-		12	11
3	4	8	18	132	1.4	-		31	12
4	3	58	31	15	1.2	-		8	57
5	2	28.2	36	192	1.7	+	2nd Dx/HA injection 1.5ml (3 years after 1st injection	18	26.6
6	4	N/A	14	15	2	-	-	61	11
7	3	75	50	102	2.4	-	-	26	74
8	3	N/A	11	84	0.9	-	-	160	5
9	3	27.9	46	35	1	+	2nd Dx/HA injection 1.5ml(21 months after 1st injection)	49	13.4
10	4	132	53	180	1	+	2nd Dx/HA injection 0.7ml (3 months after 1st injection)	29	51.5
11	4	92	44	4	1.5	-		94	52.9
12	3	N/A	50	132	1.7	-		142	47
13	4	N/A	44	216	2	-		5	N/A
14	3	N/A	50	111	2.7	-		63	24.5
15	3	N/A	29	16	1.7	-		8	N/A
16	3	85	36	44	1.7	-		75	82.4

17	1	N/A	41	60	2	-		132	40.75
18	3	48	52	204	2	-		60	36
19	3	82	40	132	1.5	+	2nd Dx/HA injection 1.5 ml (4 months after 1st injection)	6	80
20	4	74	35	168	1.3	-		12	79.8
21	3	51	52	61	0.9	+	2nd Dx/HA injection 0.7 ml (5 months after 1st injection) Ureteropyelostomy 4 months after 2nd injection)	4	50.5
22	4	45	20	4	2.4	+	2nd Dx/HAl injection 2.5 ml (3 months after 1st injection) Ureteroureterostomy 5 months after 2nd injection)	8	58

Dx/HA: dextranomer-hyaluronic acid; eGFR: the estimated glomerular filtration rate; N/A: not applicable; UTI: urinary tract infection; VCUG: voiding cystourethrogram.