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 months (4–160), 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 1–4. 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) and 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] and therefore, the diagnosis and treatment of UTIs after RT is crucial.

Vesicoureteral reflux (VUR) is a well-known risk factor for UTI and the incidence of VUR after RT has been reported to be as high as 50–86% in some studies.[3] VUR following RT can be a consequence of surgical technique, as many centers carry out bladder rehabilitation prior to RT, especially for living donor transplants. VUR may occur while attempting to avoid ureterovesical junction stenosis, which is a more difficult condition to treat during RT surgery.[4]

Antibiotic prophylaxis is the first-line 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 re-do ureteroneocystostomy is a challenging procedure, endoscopic subureteric injection for the transplanted kidney ureter, which is a less invasive treatment, is frequently used in the treatment of VUR. The goal of subureteric injection is to obtain the proper coaptation of the neoureteric 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 for this purpose.[5] Among those, Dx/HA is the most 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 outcomes of endoscopic subureteric injection on de novo VUR into the transplanted kidney following RT and to observe if it is a viable treatment option.

METHODS

Patients

After approval of the research protocol by an institutional review 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, preoperative 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 (modified Lich-Gregoire technique) is performed. Further, a double J stent is placed in all RT surgeries. The patients are followed 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 an antibiotic prophylaxis regimen. 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 faculty members who are pediatric urologists and are also on 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 is to identify the transplant ureter orifice, which is 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 are times when the ureteric orifice is not easily distinguished, particularly in patients with a previous diagnosis of bladder dysfunction (neurogenic or non-neurogenic). In those cases, a ureteral catheter is inserted into the transplant ureter to help identify the ureteric orifice, as well as to facilitate the injection. In each case, the goal is 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 is initially applied to the superior side of the ureter (whenever possible),[8] which is proceeded by the injection of the bulking material circumferentially to maintain optimal coaptation (Supplementary Figure 1; available in the Appendix at *cuaj.ca*). 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 is advanced to the neo-orifice with a full saline flow and the ureteral coaptation is tested before concluding the session. After the injection, the bladder is emptied, and no urethral or ureteral catheter is left in situ. 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 UTI despite antibiotic prophylaxis in all patients. Grades of VUR varied from 1–4, whereas dilating VUR (grade 3–4) was detected in 20 of 23 renal units; three had non-dilating VUR (grade 1–2). Patients received a median of 1.65 cc (range 0.7–2.7) of Dx/HA (Table 1).

In our cohort, 10 patients (eight from living donors, two from cadaveric donors) had undergone RT in

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	Unknown	43
12	M	Unknown	39
13	F	Unknown	26
14	F	Incidental	41
15	F	VUR	28
16	F	VUR	32
17	F	HT	36
18	M	FSGS	35
19	F	Unknown	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; VUR: vesicoureteral reflux.

another center. Alternatively, only 13 transplants of 593 (2.2%) that were performed in our center needed subureteric injections (13 transplants, eight from cadaveric donors and five from living donors). The median age of the whole cohort was 30 years (range 5–57) at the time of RT and the median time between transplantation and endoscopic treatment was 93 months (4–216). The median followup duration was 27.5 months (4–160). Two patients passed away during the followup due to COVID-19-related pneumonia.

After the subureteric injection, UTI recurred and a control VCUG was requested in six patients (indicating a 72.7% initial success rate). All these patients showed radiologic recurrence of VUR and underwent a second subureteric injection. The median time between first and second endoscopic treatment was 4.5 months (3–36). Of these, four had dilating VUR (grade 3–4) and the others had non-dilating VUR (grade 2) before the first injection.

Ureteroureterostomy (to the native ureter, which was non-refluxing) was performed in two patients who 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 one 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 seven (31.8%) patients (Table 2).

DISCUSSION

Vesicoureteral reflux into the transplant kidney following RT is considered a problem when complicated by recurrent febrile UTIs that may compromise graft function in the long-term. Thus, diagnosis and treatment of clinically problematic VUR is of utmost importance in patients with RT. It should be noted that VUR in RT patients ranges from 1–86%, indicating that asymptomatic VUR is also common.[9] Even though the sole impact of VUR on graft function is still debated, it requires treatment once it is accompanied by recurrent febrile UTIs, requires hospitalizations, and causes graft failure. In the literature, symptomatic VUR incidence rate was reported to be 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 typically used as a primary approach. Other treatment options can be surgical or endoscopic. Surgical treatments include re-do ureteroneocystostomy, ureteropyelostomy, cutaneous ureterostomy, and ureteroureterostomy whereas endoscopic treatment includes subureteric injection. In VUR after RT, endoscopic treatment is usually the initial choice due to its non-invasiveness.

Subureteric injection has been done using various bulking agents, including polytetrafluoroethylene, bovine collagen copolymer, polydimethylsiloxane, calcium hydroxyapatite, polyacrylate-polyalcohol, and Dx/HA, with success rates ranging from 30–85.7%.[13,14] In a direct comparison, Akiki et al found that the clinical success rate was significantly higher in the Dx/HA group

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/HA l 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.

than in the polydimethylsiloxane group (65% vs. 33.3%, p=0.035).[15] In another study, the radiologic resolution rate was shown to be as low as 23.5% when using collagen for subureteric injection.[16] Subureteric injection using carbon-coated beads has also shown promising results (a success rate of 75%) in the treatment of eight 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 and double HIT, 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 RT, 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 used in our department since late 1990s. Our recent results in a pediatric series revealed >90% success.[19] Even though subureteric injection for a transplant ureter is a challenging procedure, our results indicate that significant clinical success can be achieved in experienced hands.

In VUR cases detected after RT, success rates of 59.1% and 67.3% have been reported after the first and second injections of Dx/HA, respectively.[20] The mean time between RT and endoscopic treatment is 59.6 months (5–132) months, which is similar to our finding.

There is, however, discrepancy among centers in terms of treatment success definition. Some centers prefer to obtain an early or three-month post-procedure VCUG, while others rely on clinical followup, 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 as such, we do not perform routine postoperative VCUGs.

Alternative surgical options to 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 morbidity rates as high as 16–53%.[23,24] Only two of our patients required open surgery — in the form of ureteroureterostomy — following endoscopic injection treatment failure, after which their UTIs ceased.

Limitations

The current study is not without limitations. First, we had all the restrictions of a retrospective study. Second, the number of patients was limited; however, we have a longer followup period compared to the literature, with a median followup of 27.5 months (4–160). Third, we had no objective radiologic success rates due to the lack of postoperative routine VCUG data. Instead, we based our followup on clinical success described by cessation of febrile UTIs.

CONCLUSIONS

Recurrent febrile UTI is a critical factor for patients with graft failure in the long-term followup of RT. A high suspicion of VUR should be kept in mind in recurrent UTIs, especially when the primary cause of kidney failure is reflux nephropathy. Subureteric injection with Dx/HA is a safe and effective treatment option for VUR in transplant ureters.

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This paper has been peer reviewed.

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