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Dextranomer-Hyaluronic Acid Copolymer Injection into Transplant Ureterovesical Junction for Vesicoureteral Reflux

Hari Tunuguntla*, Kushan Radadia, Nicholas Farber, Christopher J Koprowski

Division of Urology, Robert Wood Johnson University, Hospital, New Brunswick, New Jersey, USA

***Corresponding author:** Hari Tunuguntla, Associate Professor of Urology & Director, Robert Wood Johnson Place, MEB 584, New Brunswick, NJ 08901, USA. Tel: +17322358853; Fax: +17322358018; Email: tunuguha@rwjms.rutgers.edu

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Abstract

Background: Vesicoureteral reflux due to a non-anatomic ureterovesical anastomosis is commonly seen in kidney transplant patients after surgery. The current gold standard treatment of patients with high-grade vesicoureteral reflux and resulting recurrent urinary tract infections is revision of the ureterovesical anastomosis. Non-animal dextranomer-hyaluronic acid copolymer (Dx-HA) is used to treat vesicoureteral reflux in pediatric patients. Limited studies of Dx-HA injection in transplanted kidneys exist.

Objective: The objective of this study is to determine if Dx-HA injection is an effective treatment option for vesicoureteral reflux in kidney transplant patients.

Methods: Four patients were identified to have symptomatic vesicoureteral reflux after renal transplantation. Each patient received Dx-HA injection into the transplant ureterovesical junction. Baseline patient characteristics and treatment characteristics were recorded. Outcomes were assessed with regular patient follow-up.

Results: Median vesicoureteral reflux grade prior to intervention was 3. Three out of four patients were found to have improvement in symptoms including resolution of recurrent urinary tract infections. One patient developed obstruction of the ureter requiring nephrostomy tube placement for drainage of the kidney. One patient required repeat Dx-HA intervention after having symptomatic recurrent urinary tract infections 6 months after initial injection.

Conclusion: Dx-HA injection for vesicoureteral reflux in transplanted ureters can be an alternative treatment choice. Three out of four patients had clinical improvement after Dx-HA injection with one patient requiring repeat intervention. Further prospective trials with a larger patient population need to be performed to determine clinical efficacy of Dx-HA intervention for vesicoureteral reflux in transplanted ureters.

Keywords: Cystoscopy; Dextranomer-hyaluronic acid copolymer; Transplant; Ureter; Vesico-Ureteral Reflux

Abbreviations:

VUR	:	Vesicoureteral Reflux
UTI	:	Urinary Tract Infection
Dx-HA	:	Dextranomer-Hyaluronic Acid Copolymer

Introduction

Vesicoureteral Reflux (VUR) is the abnormal retrograde flow of urine from the bladder into the ureters and kidneys. VUR is a common finding after renal transplantation and has been reported in 3% to 50% of transplanted kidneys [1]. Patients with VUR often complain of lower urinary tract symptoms including pyrexia, dysuria, and frequent urination. Moreover, VUR is a risk factor for recurrent Urinary Tract Infections (UTI), reflex nephropathy and subsequent diminished renal function [2].

Distinct from primary VUR typically seen in pediatric patients, the secondary VUR seen in transplant patients is a result of a non-anatomic uretero-vesical anastomosis at the time of transplant surgery. Fearing possible obstructive complications with a narrow

anastomosis, there is a tendency among transplant surgeons to create a wide ureterovesical anastomosis [3]. The definitive treatment of patients with high-grade VUR and its sequelae is revision of the ureterovesical anastomosis. This is a complex and difficult surgery with significant costs and risks. Common complications of this salvage procedure are ureteral stenosis, fistula, or loss of the transplant kidney [2]. Non-animal dextranomer-hyaluronic acid copolymer (abbreviated Dx-HA, Deflux®, Salix Pharmaceuticals, Inc, Raleigh, NC) injection is often used for VUR in children. It is injected endoscopically at the ureteral orifice to create a functional one-way valve and prevent reflux of urine from the bladder to the kidney. Unlike its predecessor bulking agent polytetrafluoroethylene, unwanted migration of dextranomer particles has not been described [4]. Limited studies of Dx-HA injection in transplanted kidneys exist. The first such case report was published in 2003 and concluded that Dx-HA injection is a reasonable minimally invasive therapy despite the risk of severe complications [5].

Given the limited published data of Dx-HA injections in kidney transplant patients with VUR, we seek to investigate the characteristics of patients with kidney transplants and VUR who were treated with Dx-HA. Specifically, we aim to characterize the clinical and demographic features of patients who underwent successful and unsuccessful Dx-HA treatment. Such information can help providers stratify patients pre-procedurally and avoid Dx-HA injections in patients in whom the intervention is unlikely to be successful. In addition, patients who are found to be good candidates for Dx-HA injection can be offered a minimally invasive treatment modality prior to a more extensive open revision surgery.

Materials and Methods

All patients over 18 years of age with a kidney transplant who were diagnosed with symptomatic VUR at a single institution and treated with Dx-HA between 2006 and 2015 were eligible for inclusion in this study. Patients were excluded if they had an allergy to Dx-HA, were ineligible to receive the injection, or if they had a history of cystectomy. Four patients were identified to fit these criteria. Baseline patient characteristics were recorded and included patient age, gender, transplant type, time between transplantation and VUR diagnosis, reflux grade (International Reflux Classification) via voiding cystourethrography, and initial VUR symptoms. Each patient was offered Dx-HA injection as a novel treatment modality to address symptomatic VUR, with an appropriate discussion of possible benefits and risks of the procedure. Treatment characteristics were recorded and included time between transplantation and VUR diagnosis and Dx-HA injection, number of Dx-HA injections, pre-procedure and post-procedure (3 months) creatinine measurements, procedure complications, recurrence of symptoms and follow-up time post-injection. Outcomes were assessed with regular patient follow-up. Our institutional review board has approved this study and our study conforms to the provisions of the Declaration of Helsinki.

Results

Three male patients and one female patient were identified to have symptomatic vesicoureteral reflux after renal transplantation. The median age of patients receiving Dx-HA injection was 61.5 years (range: 26-68 years). Two patients had deceased donor renal transplants, one patient had a live donor transplant, and one patient rejected a deceased donor transplant, which was subsequently explanted and replaced with a live donor transplant. Median time between transplantation and VUR diagnosis was 33 months (range: 10-39 months), and median VUR grade amongst our patients was 3 (range: 1-5). VUR was diagnosed by retrograde cystography. All patients had symptomatic recurrent Urinary Tract Infections (UTIs) prior to presentation. Each patient received Dx-HA injection into the symptomatic transplant UVJ. Median follow-up time since Dx-HA treatment was 12 months (range: 7-18 months) for detailed patient characteristics see (Table 1).

Patient	Age	Gender	Transplant type	Time between transplantation and VUR† diagnosis (months)	Time between VUR† diagnosis and injection (months)	Reflux grade via VCUG‡	Initial presentation
A	66	M	Deceased donor (2013)	10	3	1	Increased frequency, recurrent UTI§
B	68	M	Deceased donor (2011)	33	5	3	Recurrent UTI§, mild hydronephrosis
C	57	M	Live donor (2011)	38	1	3	Recurrent UTI§
D	26	F	Deceased donor (2000), Live donor (2007)	39	51	5	Recurrent UTI§
† VUR, vesicoureteral reflux; ‡ VCUG, voiding cystourethrography; §UTI, urinary tract infection							

Table 1: Patient Characteristics.

Overall, three out of four patients (75%) were found to have improvement in symptoms including resolution of recurrent UTIs.

Of note, one of these three patients (patient A) had symptomatic recurrent UTIs 5 months after Dx-HA injection. This patient required a repeat injection of Dx-HA at the UVJ of the transplanted ureter, which resolved the infections. That patient had an increase of 0.3mg/dL in their serum creatinine 3 months post of each Dx-HA injection. The two other patients (patients B and C) had a decrease in serum creatinine measurement 3 months post injection, with an average decrease of 0.6mg/Dl for detailed treatment information see (Table 2).

Patient	Total number of Dx-HA† injections	Serum Cr pre/post (3 months) Dx-HA† (mmol/L)	Recurrent UTI‡ after treatment?	Complications	Follow-up since Dx-HA† injection (months)
A	2	1.2/1.5	1st treatment - Yes	Recurrent UTI‡ 5 months after initial tx	18
		1.5/1.8	2nd treatment - No		
B	1	3.6/2.8	No	None	13
C	1	2.0/1.6	No	None	11
D	1	1.7/3.5	Yes	Obstruction, needed nephrostomy tube	7
† Dx-HA, Dextranomer-hyaluronic acid copolymer; ‡ UTI, urinary tract infection					

Table 2: Treatment Details.

The patient who did not achieve resolution of her UTIs encountered a complication from the procedure and suffered from obstruction of the symptomatic ureter. This patient - who had a history of transplant rejection necessitating a second transplant - was found to have an uptrending creatinine from 1.7 mg/dL to 3.5 mg/dL one-month post-injection, which decreased to 1.5mg/dL at 3 months after nephrostomy tube placement. No serious complications were reported in other patients.

Discussion

The clinical significance of posttransplant VUR remains controversial, as does its management. According to some reports, as many as 4.5% of patients with posttransplant VUR require hospitalization for UTIs [6,7]. While the repair of symptomatic VUR may only be indicated in a fraction of posttransplant patients, the treatment of choice has been reimplantation of the allograft ureter [2]. Thus, endoscopic correction of reimplanted ureters potentially fills an important role in addressing morbidity associated with VUR before more drastic and costly open surgical correction must be performed. Early reports of endoscopic correction of posttransplant VUR centered on subureteric injection of polytetrafluorethylene (Teflon). Cloix et al. reported on 21 patients treated with this technique in 1993, but observed a discouraging 30% success rate [8]. Another series of 15 post-transplant patients with polytetrafluorethylene injection a decade later yielded an overall success rate of 66% [9]. After polytetrafluorethylene started to wane in popularity, some researchers then showed interest in collagen for tissue bulking. However, an initial report observed recurrence of UTIs in all patients (n=7) in one series by Latchamsetty and colleagues [10].

Since the introduction of Dx-HA, some early work was done using the bulking agent on reimplanted ureters. Two studies reported success rates resolving symptomatic VUR ranging from 68%-70% [11,12]. Given the encouraging results of Dx-HA injection treating VUR in cases of ureteral reimplantation, research naturally extended to include posttransplant VUR patients [3]. Seifer at al. performed subureteral injections of Dx-HA in four female posttransplant patients with initial success in all four patients. Two patients developed recurrent symptomatic VUR 3 and 4 months later, which was corrected in both with a second injection of Dx-HA. Unfortunately, one of these patients who received a second Dx-HA injection later developed an obstruction from the periureteral bulking agent, necessitating ureteropyeloplasty. No complications occurred during a follow-up period of 29 months in the other three patients [2]. In 2010, Yucel et al. described a larger series (n=26) of posttransplant patients with symptomatic VUR treated with Dx-HA injections. Here, patients were stratified into nondilating and dilating VUR groups (grade 1-2 vs. grade 3-5, respectively), and success rates of subureteral and intraureteral Dx-HA injection were compared. Ultimately, they observed a success rate of 90% in 10 patients with nondilating VUR, compared to a success rate of only 31.25% in 16 patients with dilating VUR. No statistically significant differences were observed in terms of success rates comparing subureteral and intraureteral injection techniques [3].

One year later, Pichler and colleagues published a series of 19 posttransplant patients with symptomatic VUR treated with dextranomer-hyaluronic acid copolymer injection. In this series, 60% of patients had resolution of their reflux symptoms after one injection, with 79% achieving resolution of symptoms after two injections. Additionally, the average number of UTIs over 6 months was reduced from 4.89 to 1.31 on pre- and post-op follow-up ($P<0.001$). Mean follow-up time was 6.5 months. Two patients suffered from ureteral obstruction on days 3 and 6 post-operatively that necessitated percutaneous nephrostomy and temporary ureteral stenting. There was an observed acute increase of serum creatinine of 8.92mg/dL and 4.01mg/dL in these patients [13]. Our results are

consistent with many of the previously reported cases. Our success rate of 75% falls in line with the reported range of previous reports. We observed recurrent UTIs in one patient that resolved after a second injection of Dx-HA. Given the observation of ureteral obstruction as a complication of reinjection with Dx-HA, clinicians must proceed cautiously in these cases and be cognizant of the volume of Dx-HA used. Our patients received 3 milliliters of Dx-HA on initial injection. The one patient who required a second injection only received 1 milliliter of Dx-HA. We did observe one complication of ureteral obstruction, though it was after one injection. Like the two patients with ureteric obstruction described in the series above, our patient had a doubling of her plasma creatinine from 1.7mg/dL to 3.5mg/dL. No other patients in our series had such a dramatic change in creatinine. Additionally, this patient had the most complex history, considering that she had a grade of 5 and a previously explanted rejected renal transplant in 2006. Based on the aforementioned evidence, a high VUR grade may correlate with lower Dx-HA injection success rates, but more data is needed. In addition, injection is more challenging in patients who have had multiple ureteral reimplantations.

This case series, though limited by the small number of patients studied, contributes additional literature to a promising treatment of a difficult clinical entity whose evidence is as of yet primarily limited to small data sets with relatively short follow-up periods. In the future, a multicenter, randomized control trial comparing endoscopic Dx-HA injection against definitive open VUR repair in posttransplant patients with symptomatic VUR would help clinicians better understand the potential role for this treatment option in this patient population.

Conclusion

Endoscopic Dx-HA injection may be a reasonable early treatment option in lieu of open surgical repair in renal transplant patients with symptomatic VUR. Common complications include non-resolution of recurrent UTIs and ureteral obstruction requiring decompression, with possible loss of transplant function. A second injection of Dx-HA can overcome initial failure of treatment. Patients with a history of previous ureteral reimplantation or who have high grade VUR may be less likely to achieve resolution of VUR symptoms after Dx-HA injection. A randomized control trial would ideally compare open VUR repair against endoscopic Dx-HA injection treatment.

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