Renal Transplant Outcome After Endoscopic Treatment of Vesicoureteral Reflux Using the Subureteric Injection of Calcium Hydroxyapatite

Ayhan Dirim,[1] Huseyin Celik,[1] Eray Hasirci,[1] Cem Aygun,[1] Tahsin Turunc,[1] Hakan Ozkardes,[1] Mehmet Haberal[2]

Abstract

***Objectives*: To evaluate the results of end-stage renal failure in transplanted cases due to vesicoureteral reflux after a subureteric injection of calcium hydroxyapatite (Coaptite).**

***Materials and Methods:* Twenty-three patients (39 renal units) with end-stage renal failure secondary to vesicoureteral reflux were included. Reflux was bilateral in 16 cases and unilateral in 7 of the cases. There were 3 degrees of reflux according to the distribution of renal units. They were low-grade reflux (grades 1 and 2; n=10); medium-grade reflux (grade 3; n=23); and high-grade reflux (grades 4 and 5; n=6).**

***Results:* Reflux resolved completely in 17 patients (28 renal units; 71.8%). There was a regression to grade 1 in 3 patients (5 renal units; 12.8%). Twenty-one patients underwent renal transplant; however, 2 of the patients were excluded from the study as it was not possible to monitor them after transplant. Within an approximately 18.6 month follow-up (range, 3-36 months), 1 of the cases had acute, and 3 of the cases had chronic rejection.**

***Conclusions:* Successful results can be achieved in reflux treatment by an injection of subureteric calcium hydroxyapatite before transplant in patients with end-stage renal failure that developed secondary to vesicoureteral reflux.**

Key words: *Calcium hydroxyapatite; Endoscopic treatment; Renal transplant; Vesicoureteral reflux*

From the Departments of [1]Urology, and [2]General Surgery and Transplantation, Baskent University School of Medicine, Ankara, Turkey

***Address reprint requests to:** Ayhan Dirim, MD, Baskent University School of Medicine Department of Urology, 5. Sokak, No: 48, Bahcelievler, 06490, Ankara, Turkey*

***Phone:** +90 312 2120630 **Fax:** +90 312 2154283 **E-mail:** drayhan_dirim@yahoo.com*

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Introduction

Endoscopic treatment of vesicoureteral reflux has been a popular, minimally invasive treatment procedure for the last 20 to 25 years. The most important reason for this is its relative ease of implementation and the low complication rate. There are several substances used for endoscopic therapy. The applied substances should not be carcinogenic or allergic, but should be nonabsorbable and have a low potential for fibrous formation. They should also be inexpensive and easily accessible (1, 2). Today, the most-common substances used for this purpose are polytetrafluoroethylene (Teflon), collagen, chondrocyte, polydimethylsiloxane (Macroplastique), dextranomer /hyaluronic acid copolymer, and calcium hydroxyapatite (Coaptite).

In this study, the data from transplanted end-stage renal failure patients with vesicoureteral reflux were evaluated. Patients included in this study were treated with subureteric injection of calcium hydroxyapatite before transplant between 2006 and 2009.

Methods

Data were evaluated retrospectively in 23 patients with an average age of 22.5 years (range, 9-46 years). All patients were considered as primary reflux, which is suggested by the pattern of urination and signs of voiding cystourethrography (bladder capacity and configuration). Subureteric injection of calcium hydroxyapatite was administered to a total of 39 renal units (16 bilateral and 7 unilateral cases). The female/male ratio was 12/11. The renal unit number of vesicoureteral reflux with low grade was 10 (grades 1 and 2), medium grade was 23 (grade 3), and high grade was 6 (grades 4 and 5). Five patients

had recurrent urinary tract infection before subureteral injection treatment. Anuria occurred in 15 cases. All patients provided informed written consent. The study was conducted according to the guidelines of the Declaration of Helsinki, and the study protocol was approved before the beginning of the study by the Ethics Committee of Baskent University.

Study technique

Prophylactic antibiotic treatment was administered to all cases before surgery. The procedure was performed on all the patients under general anesthesia in the dorsal lithotomy position by the same surgeon. The position of the ureteral orifice was identified by cystoscopy using 17-French or 20-French cystoscopes. The material was injected at the 6-hour level in the subureteric region, to completely occlude the ureteral orifice, and create a subureteral tunnel. An average of 1.22 mL (range, 0.5-2.5 mL) of calcium hydroxyapatite was used for each renal unit. The mean duration of the procedure was 22 minutes (range, 18-35 minutes). A urethral catheter was inserted in all the patients after the procedure. The catheter was removed 24 hours after the operation, and the patients were discharged. Treatment success was evaluated by voiding cystourethrography approximately 3 months after the operation. Absence of reflux, or regression of the reflux, to grade 1 was considered a success.

Results

The reflux resolved completely in 17 of 23 cases (28 of 39 renal units; 71.8%). In 3 patients (5 renal units; 12.8%), reflux regressed to grade 1. No changes were observed in the reflux of 3 patients (6 renal units; 15.4%) (Table 1). Bilateral nephroureterectomy was performed in 2 of the 3 cases before renal transplant, and the cases were excluded from the study. The other case had bilateral calcium hydroxyapatite injection for the second time and a successful result was achieved. The procedure was accepted as successful in 21 patients (35 renal units; 89.7), with the addition of 1 patient (2 renal units; 5.1%). Twenty-one patients underwent renal transplant following subureteric calcium hydroxyapatite injection, at an average of 6.5 months (range, 4-24 months). Two patients were excluded from the study, as it was impossible to monitor them after transplant. During a mean of 18.6 months' follow-up of 19 patients (range, 3-36 months), 1 case had acute, and 3 of the cases had chronic rejection. The mean serum creatinine level of 19 patients was 7.45 mg/dL (range, 3.8-10.9 mg/dL) before renal transplant and 1.31 mg/dL (range, 0.8-2.5 mg/dL) on the postoperative seventh day. The mean creatinine level was 1.35 mg/dL during follow-up (range, 0.9-1.9 mg/dL).

Acute rejection occurred on the postoperative seventh day in a patient owing to bleeding. One

Table 1. Patient characteristics and outcome.

Case	Age (y)	Sex	Grade of reflux		Urine volume (mL)	Material volume (mL)		Postoperative reflux		Follow-up (mo)	Problem
			Right	Left		Right	Left	Right	Left		
1#	24	M	4	0	Anuria	1	0	0	-	10	No problem
2	25	F	3	2	Oliguria	1	1	0	0	7 (day)	Acute rejection
3	11	M	5	5	Anuria	1.5	1.5	5	5	NUx	-
4	33	M	0	3	Oliguria	-	1.5	-	0	17	No problem
5	21	F	3	3	Oliguria	1	1	0	0	24	No problem
6	24	M	3	3	Oliguria	0.7	0.7	0	0	20	No problem
7	29	F	3	2	Anuria	1	1	3 (0)*	2 (0)*	18	No problem
8	21	M	2	2	Oliguria	2	2	0	0	16	No problem
9	15	F	1	3	Oliguria	0.5	1.5	0	0	31	Urinary infection
10	18	F	3	0	Anuria	1	-	0	-	Excluded from follow-up	-
11#	36	M	2	2	Anuria	1	1	1	1	15	No problem
12#	17	M	3	3	Anuria	1	1	0	0	22	No problem
13	9	F	3	0	Anuria	1	-	0	-	16	Chronic rejection
14	18	F	3	3	Anuria	1	1	0	0	Excluded from follow-up	-
15	36	M	2	2	Anuria	1	1	1	1	23	No problem
16	17	M	3	3	Anuria	1	1	0	0	11	No problem
17	9	F	3	0	Anuria	1	-	0	-	23	No problem
18#	18	F	3	1	Oliguria	1	0.5	0	0	17	Urinary infection
19	36	M	3	3	Anuria	1	1	0	0	3	No problem
20	16	F	4	4	Anuria	1	1	0	0	10	Chronic rejection
21	46	M	4	0	Anuria	2.5	-	1	-	26	No problem
22	20	F	0	3	Anuria	-	2.5	-	0	33	Chronic rejection
23#	19	F	3	3	Oliguria	2.5	2.5	3	3	NUx	-
Mean	22.5					1.17	1.26			18.6	

#The patients had recurrent UTI before injection. *Subureteric calcium hydroxyapatite injection was administered in this case for the second time.
Abbreviations: NUx, nephroureterectomy; UTI, urinary tract infection.

patient with chronic rejection underwent graft nephrectomy because of uncontrolled bleeding following renal biopsy. Chronic rejection occurred on the 16th and 33th months in the other 2 patients (Table 1). None of the patients with rejection had any urinary tract infection symptoms or hints of vesicoureteral reflux. Two females with non-complicated, lower, urinary tract infection were treated successfully, without requiring voiding cystourethrography.

Discussion

The incidence of urinary tract infection in patients undergoing renal transplant remains high (2, 3). Vesicoureteral reflux is one of the most significant causes of urinary system infections that can emerge after transplant (4). Nephroureterectomy is an invasive procedure used for vesicoureteral reflux treatment in transplant candidates. It causes the disappearance of endocrine functions, particularly when performed bilaterally (5).

In recent years, endoscopic treatment methods have been used as an alternative to open surgery, as they are easy to perform, have a low morbidity, a short hospitalization period, and a high success rate (6). Since the 1980s, several autologous and nonautologous injection materials have been used for the endoscopic treatment of vesicoureteral reflux. However, there is still an argument about an ideal injection material (7).

The first material used in endoscopic treatment is polytetrafluoroethylene (Teflon) (8). The long-term safety of polytetrafluoroethylene is unclear. Moreover, the formation of local and metastatic granulomas following polytetrafluoroethylene injection have been reported (9). Collagen has been used as an alternative to polytetrafluoroethylene, because it does not migrate, is easy to apply, and demonstrates a minimal local reaction (10). However, it may lead to reflux recurrence in the long-term owing to volume loss (11). Although there are not enough studies, the autologous fat and chondrocyte use in the endoscopic treatment of vesicoureteral reflux also have been investigated (12). Poly-dimethylsiloxane is an alternative injection material with a high success rate reported for a single injection. Choo and associates (13) reported an 86% success rate in a study conducted with 30 women. However, immune reaction formation, granuloma development, and migration were considered drawbacks (13, 14). One of the most popular injection materials that has been used in recent years is dextranomer/hyaluronic acid copolymer. Because its particle size is larger than 80 μm, it reduces the chance of migration. It is not immunologic. Therefore, it is considered to be more advantageous compared with previous injection materials (15, 16). Long-term monitored studies with extensive series do not exist in the literature.

Calcium hydroxyapatite was first used in urology for the endoscopic therapy of urinary incontinence (17). It is a new agent used for the endoscopic management of vesicoureteral reflux. It can be safely used owing to its nonimmunologic nature, and the absence of systemic toxicity and allergic reactions. Its mean particle size is 100 μm, reducing the chance of migration. It is easy to use and does not require any special equipment apart from cystoscopy (1). One of the most important features of calcium hydroxyapatite is its radio-opaque nature. Therefore, it is easy to evaluate its migration and volume loss by x-ray visualization (1, 6, 17).

Despite the existence of many studies in the literature concerning the endoscopic management of vesicoureteral reflux, there are not enough studies regarding transplanted cases after endoscopic treatment. Jackson and associates recorded an 80% success rate with polytetrafluoroethylene injection to 9 renal units in 5 renal transplant candidates (18). Aygün and associates (3) reported an 87.5% success rate by using siloxane and collagen on 32 renal units in 17 transplant candidates. Özok and associates (16) reported an 82.7% success rate following dextranomer/hyaluronic acid copolymer injection on 21 renal units in 29 transplant candidates. In this study, the success rate with calcium hydroxyapatite injection was 89.7%. After the first injection, a success rate of 90% was recorded for low-grade reflux (grades 1 and 2; n=9/10), 86.9% for medium-grade reflux (grade 3; n=20/23), and 66% for high-grade reflux (grades 4 and 5; n=4/6). In studies conducted with calcium hydroxyapatite in children with primary reflux, a 52.1% to 85% success rate was demonstrated (1, 7, 19, 20, 21). In this study, no complications in association with the procedure were reported in any of the cases. However, in another study, 23% of the patients complained about transient, mild, lumbar and hypogastric discomfort, limited to the first operative day (21).

The results of this study suggest that calcium hydroxyapatite is an alternative injection material that can be used before transplant in end-stage renal patients with vesicoureteral reflux.

Conclusions

Calcium hydroxyapatite is a material that can safely be used in the endoscopic management of vesicoureteral reflux owing to its relative ease of implementation, low incidence of adverse effects, nonimmunologic and nonallergic nature, and its limited chances of migration.

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