Endoscopic application of dextranomer/hyaluronic acid copolymer in the treatment of vesico-ureteric reflux after renal transplantation

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OBJECTIVE

• To evaluate the success of endoscopic dextranomer/hyaluronic acid copolymer (DHAC) application in the treatment of patients with recurrent urinary tract infections (UTIs) and vesico-uretere reflux (VUR) into the transplanted graft after renal transplantation.

PATIENTS AND METHODS

• Between January 2008 and April 2009, 19 patients with recurrent UTIs presented VUR proven by voiding cystourethrography.
• To correct VUR of the transplanted ureter, DHAC was injected endoscopically using hydrodistention technique.
• Pre- and postoperative serum creatinine levels, the number of pre- and postoperative UTIs, postoperative complications and reflux resolution rate were recorded. The mean follow-up was 6.5 months.

RESULTS

• The average number of UTIs was reduced significantly from 4.89 (range 2–14) to 1.31 (range 0–4) on pre- and postoperative follow-up, respectively, of 6 months (P < 0.001). The success rate increased from 57.9% after the first injection to 78.9% after the second injection.
• The remaining four patients with residual VUR received long-term low dose antibiotic prophylaxis. In total, two (10.5%) patients developed increasing creatinine levels postoperatively as a result of distal ureteral obstruction, and temporary urinary drainage was necessary in both patients.

CONCLUSIONS

• DHAC appears to be an efficient and minimal invasive method for treating VUR after renal transplantation with respect to short-term success.
• Further investigation with a larger group of patients and longer follow-up is needed to evaluate the prolonged effect, as well as any potential side effects.

KEYWORDS

dextranomer and hyaluronic acid copolymer, renal transplantation, urinary tract infections, ureteral obstruction, vesico-ureteric reflux

INTRODUCTION

VUR into the ureteral graft is considered to be one possible cause of complicated UTIs in renal transplant patients with an associated risk of progressive graft damage. Renal parenchymal defects may be congenital and are usually associated with VUR (e.g. congenital reflux nephropathy) or they may occur in previously normal kidneys caused by recurrent episodes of pyelonephritis with intrarenal reflux as a consequence of symptomatic VUR [1]. In patients after renal transplantation, recurrent UTIs are more common in females and in the presence of VUR into the transplanted ureter [2]. VUR can occur in up to 86% of all kidney transplant patients depending on the implantation technique used [3]. UTIs are a common problem, with an incidence of up to 62%, particularly during the first postoperative months after transplantation. Persistent UTIs are common in patients with bladder dysfunction and an absent antireflux mechanism of the uretero. VUR into the kidney transplant in association with recurrent episodes of pyelonephritis represents a serious risk for the loss of transplant function, which can lead to a reduced long-term survival in immuno-suppressed patients [4]. Thus, VUR and UTIs during adulthood can cause progressive deterioration of kidney function if not treated sufficiently within a particular time interval [5].

All transplant patients therefore appear to be subjected to regular urine monitoring and postoperative voiding cystourethrography (VCUG) aiming to recognize VUR [6]. A negative influence of asymptomatic VUR on the short-term graft survival has not been confirmed previously [7]. Non-recurrent UTIs with low grade reflux have little to no effect on the long-term survival of the transplant.
[8]. Recurrent UTIs associated with VUR, on the other hand, yield renal scar formations. Parenchymal scars can occur in patients without demonstrable VUR; however, it must be noted that the rate of false-negative results on standard VCUG can be as high as 20% compared to cyclic VCUGs [9].

The clinical significance of a demonstrable VUR with respect to any impact on parenchymal kidney function and graft survival remains controversial. Nevertheless, in symptomatic patients with recurrent UTIs, therapy of reflux appears to be mandatory [4].

This is the second study to date aiming to investigate the therapeutic success of dextranomer/hyaluronic acid copolymer (DHAC) in adult kidney transplant patients with symptomatic VUR.

**PATIENTS AND METHODS**

Between January 2008 and April 2008, after renal transplantation, 19 patients (16 females and 3 males) with a mean (range) age of 48 (19–78) years were treated for VUR of the implanted ureter with endoscopic application of DHAC by the hydrodistension injection technique. All patients had a sterile urine culture before endoscopic treatment and received antibiotic therapy for 5 days postoperatively. Fully informed written consent was obtained preoperatively from all patients. A positive approval from ethical committee was obtained (study number UN3748; 280/4.19) to perform the retrospective analysis. Antirefluxive ureteral implantation during transplantation was performed in all patients. Leadbetter Politano method in 11 (57.9%) patients and Lich–Gregoir implantation in 8 (42.1%) cases. VUR into the transplanted graft was identified by VCUG in all patients suffering from recurrent symptomatic UTIs as confirmed by catheter urine cultures at least three times per year. The term ‘UTI’ is defined as positive urine culture showing a quantitative count ≥10⁵ CFU/mL of a typical urinary tract organism. Patients were verified by urodynamics and flow electromyography to exclude dysfunctional voiding and other reasons for functional obstruction retrospectively.

The mean (range) follow-up after DHAC injection was 6.5 (2–19) months. On average, 2.3 mL (range 1–5 mL; mean ± SD 2 ± 1.14 mL) was injected endoscopically into the transplanted neo-orifice. To achieve an obliteration of the ureteral orifice, a hydrodistension technique was used enabling an intrareteric injection of the bulking agent until the reflexive aspect was resolved [10] (Figs 1–5). The preoperative grade of VUR, the number of UTIs at 6 months pre- and postoperatively, postoperative hydronephrosis, postoperative and intraoperative complications, as well as serum creatinine levels pre- and postoperatively were analyzed retrospectively. To monitor the success rates during short-term follow-up, VCU was performed 3 and 6 months after the endoscopic application of DHAC. Successful reflux correction was defined as absent reflux on follow-up VCU. Statistically, we used descriptive analysis (frequency distribution, location parameter...
using mean ± SD, median) and a paired two-tailed t-test. P < 0.05 was considered statistically significant. All statistical analyses were performed using SPSS software (SPSS Inc., Chicago, IL, USA).

RESULTS

Preoperative reflux grade evaluation showed VUR grade II, III and IV with 26.3% (5 patients), 63.1% (12 patients) and 10.6% (2 patients), retrospectively. In all patients (84.2% female and 15.8% male) intraoperative coaptation of the ureteral walls with a circular shingling of DHAC and obturation of the ureteral orifice during an aperistaltic interval was observed. No intraoperative complications occurred throughout the endoscopic procedure. In total, two of 19 (10.5%) patients showed a known dysfunctional voiding on preoperative evaluation, which was treated with standard urological therapy, including regular voiding habits, avoiding holding manoeuvres and biofeedback therapy.

The average creatinine level 1 day pre- and postoperatively was 1.66 (range 0.92–2.42; mean ± SD 1.68 ± 0.43) mg/dL and 1.60 (range 0.91–2.44, mean ± SD 1.62 ± 0.38) mg/dL. On mean (range) postoperative follow-up of 10 (1–24) months, the average serum creatinine remained stable at 1.76 (range 1.07–4.68, mean ± SD 1.64 ± 0.78) mg/dL.

The average number of UTIs in all patients decreased from 4.89 (range 2–14, mean ± SD 3.00 ± 3.41) to 1.31 (range 0–4, mean ± SD 1.00 ± 1.10) on pre- and postoperative follow-up of 6 months (P < 0.0001). On the patient collective with reflux resolution after only one injection of DHAC, the average number of UTIs was reduced significantly from 4.63 (range 2–13) to 0.81 (range 0–2) pre- and postoperatively (P = 0.004).

In the group of patients with reflux correction after two applications of DHAC, no significant reduction of postoperative UTIs on follow-up was noted (P = 0.15), although it should be noted that evaluated postoperative UTIs occurred in the period between first and second injection, where the VUR was not resolved and still persistent.

For patients with persistent reflux after one injection and who refused second application, a significant decrease of UTIs from 4.25 (range 3–5) to 1.5 (range 1–3) was established (P = 0.01) using low dose antibiotic prophylaxis. Urine cultures on pre- and postoperative UTIs included bacteria such as Escherichia coli, Enterococcus, Klebsiella, Staphylococcus saprophyticus, Enterobacter and Proteus mirabilis, but not Candida.

The outcome characteristics of patients are shown in Table 1. In 11 (57.9%) patients, a negative VCUG after the first application of DHAC with a mean follow-up of 6.3 (range 2–16) months was found. Persistent VUR was found in eight (42.1%) patients after one application, with a mean follow-up of 6.9 (range 1–18) months. A second endoscopic therapy was performed after 7, 2, 4 and 16 months after the first application in four of eight patients. After the second DHAC injection, in all four patients, reflux resolution on subsequent follow-up of 2.5 months was found. The success rate after the second endoscopic therapy increased from 57.9% to 78.9%. The other four patients with persistent
VUR after the first DHAC injection preferred long-term antibiotic prophylaxis to prevent UTIs.

In two (10.5%) patients, hydronephrosis grade IV, based on distal ureteral obstruction, evolved 3 and 6 days post DHAC injection. Deterioration of kidney function with an acute increase of serum creatinine levels of 8.92 mg/dL and 4.01 mg/dL, respectively, and associated pain in the lower abdomen required desobstruction by a temporary ureteral stent in one case and a percutaneous nephrostomy in the second patient. Endoscopically, the lumen of the ureteral orifice was obstructed by a vast swelling around the injection site, which appeared as an inflammatory postoperative reaction. Power Doppler ultrasound of the urinary bladder showed an increased vascularity of this injection site; no urinary jet was observed. One week after kidney drainage, antegrade as well as retrograde pyelography displayed immediate drainage without any signs of further ureteral obstruction.

DISCUSSION

An incidence of secondary VUR in transplanted kidneys of up to 79% is reported in recent studies [11,12]. The association between VUR, UTI and reflux nephropathy has been established for many years, both for native kidneys as well as for renal transplants [13,14]. Compared with the conception that kidneys overcome the risk of acquiring new pyelonephritic scarring after infancy, Coulthard and Keir [15] reported that the same scarring risk applied to kidney transplants from older donors subjected to UTIs and VUR.

The prevention of reflux nephropathy and the successive development of multiple scars, which may result in a significant loss of renal function, is highly recommended. Whenever VUR is suspected in patients with transplanted kidneys, the corresponding ureters should be tested for VUR and treated minimally invasively with low-dose nighttime antibiotic prophylaxis or by endoscopic correction. VUR after kidney transplantation occurs for different reasons. Many surgeons perform an open refluxing ureteroneocystostomy avoiding potential ureteral stenosis, which could negatively affect graft outcome. Furthermore, bladder dysfunction with secondary bladder wall alteration not only aggravates antirefluxive surgery, but also impairs the degree of reflux.

In children, endoscopic application of DHAC in the native ureter for the correction of VUR yields a resolution rate of up to 90% after one injection [10]. In patients with secondary reflux, the success rate is slightly less (71%) after the first application [16]. There are only few reports on endoscopic bulking agent therapy for VUR after renal transplantation. During a mean follow-up period of 17.3 months, four of nine ureters showed resolution of VUR and one ureter showed improvement to grade I VUR in paediatric renal transplant patients after one DHAC injection [17].

The transurethral injection of Deflux® (dextranomer/hyaluronic acid copolymer, Qmed Scandinavia, Uppsala, Sweden) in adult kidney transplant patients eliminating the symptomatic reflux was described in 2007 in four patients by Seifert et al. [18], where three of four patients, after 36 months of follow-up, showed no VUR on VCUG with a significant reduction of UTIs. Transurethral application of DHAC therefore appears to represent an efficient and minimally invasive treatment option in addition to antibiotic long-term prophylaxis and ureteral reimplantation surgery for the treatment of secondary VUR after renal transplantation [18].

In previously untreated adult patients with primary VUR and recurrent episodes of pyelonephritis, the endoscopic therapy of VUR with DHAC is a simple and efficient technique, with low comorbidity and a success rate of 69% after the first endoscopic injection and 81% after the second one [19]. The preliminary results reported in the present study give a success rate of 57.9% after one endoscopic injection of Deflux® and 78.9% after secondary application. Further investigations with a larger cohort of patients and longer-term follow-up studies are necessary to evaluate the prolonged therapeutic effect of DHAC as a treatment option in renal transplant patients with symptomatic VUR.

Compared to the high success rates after endoscopic therapy with DHAC in primary VUR patients, there are significant technical differences with respect to the endoscopic therapy of refluxive allograft ureters. Scarring of the implantation site as well as the non-orthotopic position of the ureteral orifice at the sidewall or dome of the bladder with difficult accessibility for the endoscopic needle appear to comprise reasons for the lower success rates. Pushing down the dome of the bladder through the impression of the lower abdomen as well as the use of a flexible guidewire may compensate for these difficulties [18]. An additional factor explaining the decreased success rates as well as postoperative recurrent UTIs comprises an inadequately treated coexisting bladder dysfunction [20]. The presence of a bladder dysfunction with dysfunctional voiding and intermittent increased bladder pressure can also trigger the occurrence of recurrent UTIs and secondary VUR. Aear et al. [21], in a study of 30 children with VUR and voiding dysfunction, reported a correlation with an increased detrusor pressure and the degree of VUR. Patients with high detrusor pressure should be evaluated for the presence of VUR and renal scars [21]. Dysfunctional voiding can also be observed in kidney transplant patients, which is frequently reflected in the form of a nocturia, and, with an occurrence rate of 60%, can be considered as being frequent. In addition to the danger of a secondary VUR through the increased intravesical pressure, bladder dysfunction represents a risk of impairment to transplant function and appears to influence negatively the success rate of endoscopic therapy [22,23].

Nonetheless, overall morbidity with respect to severity and the number of postoperative UTIs decreased significantly, which correlates with the similar reduction of the incidence of UTIs after endoscopic therapy of primary VUR in children [24].

In the present study, we observed two cases (10.5%) of early ureteral obstruction after DHAC injection into the transplant's ureteral neo-orifice caused by tumescence and an inflammatory process of the surrounding ureteral tissue, accompanied by hydronephrosis and a significant increase in creatinine levels up to 4.01 and 8.92 mg/dL, respectively. The use of a temporary percutaneous nephrostomy and a ureteral stent, respectively, was necessary. A possible cause for ureteral obstruction after endoscopic treatment was reported by Seifert et al. [25] who described a 3-cm long stenotic segment of the distal ureter resulting from an obstructing periureteral bulky mass with histologically verified postoperative
inflammation, particularly periureteral phlebitis and a moderate foreign body reaction. This adult patient was the first case of ureteral obstruction after transurethral injection of DHAC for the treatment of secondary VUR after renal transplantation. The filiform stenosis of the distal ureter was corrected by ureteropyeloplasty with the native ureter [25].

Because of grade II and III reflux and the large corresponding lumen of the neo-ureter, a total quantity of 4 and 5 mL of DHAC, respectively, was injected to achieve complete coaptation of ureteral walls. This high volume of the bulking agent may be one reason for the postoperative ureteral obstruction in these two patients that required temporary double J stent placement. Patients with voiding dysfunction or neurogenic bladder appear to be at increased risk of postoperative ureteral obstruction after DHAC, although the overall incidence of postoperative obstruction in primary reflux treated with endoscopic therapy is less than 0.7% [26]. Our two patients with ureteral obstruction presented with dysfunctional voiding. Both patients were treated with standard urological therapy, including regular voiding habits, avoiding holding manoeuvres and biofeedback therapy.

Therefore, we consider that neurogenic bladder or voiding dysfunction that is a risk factor for obstructive complications after DHAC injection should be excluded preoperatively by videourodynamics investigations.

In children with primary VUR, Deflux® injection is associated with a small risk of postoperative ureteral obstruction, with an overall incidence of less than 0.7% in a cohort of 745 patients. A temporary ureteral stent is technically simple, effective and curative [24]. Serrano et al. [27] reported the complication rates of subureteric endoscopic injection of bulking agents such as Macroplastique® (polymethylsiloxane, Uroplasty, Minnetonka, MN, USA), Deflux® (dextranomer/hyaluronic acid copolymer, Q-med Scandinavia, Uppsala, Sweden) and Polytef® (polytetrafluoroethylene, Coloplast, Minneapolis, MN, USA) in children with VUR. In this overview, five patients (0.6%) presented with a ureteral obstruction inducing ureterohydronephrosis, and only two children required a transient nephrostomy [27]. Steinberg et al. [28] noted no signs of ureteral obstruction or adverse reactions after Deflux® implantation in 75 children with grade III and IV primary VUR [28]. The results obtained in the present study also show that endoscopic therapy had no negative influence on serum creatinine course in renal transplant patients. The mean creatinine level was maintained at 1.64 mg/dL on a postoperative follow-up of 10 (range 1–24) months. Only one female patient doubled her creatinine level to 4.69 mg/dL, 11 months after Deflux® injection based on chronic transplant nephropathy (verified by biopsy), with consecutive chronic rejection of renal transplant graft. The kidney transplantation in this case was performed in April 1987. There was no clinical correlation between endoscopic VUR treatment and creatinine increase, and neither postoperative ureteral obstruction nor UTI was noted at the time of creatinine elevation.

In conclusion, the use of transurethral injected bulking agents such as DHAC appears to comprise a minimally invasive and efficient procedure for treating secondary VUR after renal transplantation in approximately 60% of cases after one injection. Additionally, the endoscopic treatment of VUR in patients with recurrent UTIs after renal transplantation lowers significant severity and number of postoperative UTIs. Early ureteral obstruction with deterioration of graft function requiring temporary drainage represents a related complication. Neurogenic bladder or voiding dysfunction that may predispose to obstructive postoperative complications should be considered before treatment. To evaluate the prolonged effect of DHAC, long-term follow-up with a larger group of patients is necessary.

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CONFLICT OF INTEREST

None declared.

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Abbreviations: DHAC, dextranomer/hyaluronic acid copolymer; VCUG, voiding cystourethrogram.