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Transurethral injection therapy with carbon-coated beads (Durasphere®) for treatment of recurrent pyelonephritis in kidney transplant patients with vesico-ureteral reflux to the allograft

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Abstract: Introduction and objectives: Recurrent transplant pyelonephritis (RTP) secondary to vesico-ureteral reflux (VUR) to the transplant kidney (KTx) remains a significant cause of infectious complications with impact on patient and graft outcomes. Our objective was to verify the safety and efficacy of transurethral injection of Durasphere® to relieve RTP secondary to VUR after renal transplantation.

Patients and methods: Between June 2004 and July 2008, eight patients with RTP (defined as two or more episodes of pyelonephritis after transplantation) and VUR to the KTx were treated with subureteral injections of Durasphere®. The mean age at surgery was 38.8 ± 13.8 yr (23–65). The patients were followed regularly every six months. The mean interval between the KTx and the treatment was 76 ± 74.1 (10–238 months). The mean follow-up was 22.3 ± 16.1 months (8–57 months).

Results: Six patients (75%) were free of pyelonephritis during a mean period of follow-up of 23.2 ± 17.1 months (8–57 months). Two of them had no VUR and four cases presented with G II VUR (pre-operative G IV three cases and one case G III). In one case, symptomatic recurrent cystitis made a second treatment necessary. This patient remained free of infections for three yr after the first treatment and for 18 months after the second treatment. Of the remaining two patients, one had six episodes of RTP before treatment in a period of three yr and only two episodes after treatment in two yr of follow-up. The last case had a new episode of pyelonephritis five months after treatment.

Conclusions: Transurethral injection therapy with Durasphere® is a safe and effective minimally invasive treatment option for KTx patients with recurrent RTP. A second treatment seems to be necessary in some cases.

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Recurrent transplant pyelonephritis (RTP) secondary to vesico-ureteral reflux (VUR) to the transplant kidney (KTx) remains a significant cause of infectious complications with impact on patient and graft outcomes (1, 2). The standard treatment of this condition is the reimplantation of the KTx ureter, which is a considerably challenging procedure that carries the risk of damage to the allograft. A less invasive alternative would be desirable if it proves to be easier and cost-effective. There are only a few reports of endoscopic treatment of VUR to the KTx in the literature with mixed results. Our objective was to verify the safety and efficacy of transurethral injection of

Durasphere® (Carbon Medical Technologies Inc., St. Paul, MN, USA) to relieve RTP secondary to VUR after renal transplantation.

Materials and methods

Between June 2004 and July 2008, a prospective protocol was designed to study the safety and efficacy of carbon-coated beads (Durasphere®, EXP Injectable Bulking Agent from Carbon Medical Technologies Inc.) to treat RTP. The definition of RTP was the diagnosis of two or more episodes of infection after transplantation secondary to VUR in the kidney transplant. The endpoints of the study were to compare the frequency of infections prior and after treatment and to verify the reflux cure after the subureteral endoscopic injection. During the study, eight patients developed 26 confirmed episodes of pyelonephritis attributable to VUR. No patients had voiding dysfunction (evaluated with a pre-operative questionnaire and patient history). Of the eight patients, only two had urological causes that led to chronic kidney disease: one had a contracted bladder secondary to posterior urethral valve that has been previously submitted to an auto-augmentation cystoplasty and the other had reflux nephropathy. In the remaining patients, two had severe hypertension, three had chronic glomerulonephritis, and one had polycystic kidney disease. All KTxs were positioned retroperitoneally through an extended inguinal incision. Vascular reconstruction was performed at the iliac external vessels. The urinary tract was reconstructed using the non-stented Gregoir technique. The ureteral implantation was carried out at the lateral aspect of the vesical dome in all cases. Immunosuppression was achieved with the triple-drug regimen of cyclosporine, azathioprine or mycophenolate mofetil, and prednisone. Patients who underwent repeat transplantation received induction therapy in a sequential immunosuppressive regimen. The details of immunosuppression therapy have been previously published (3, 4). The mean interval between the KTx and the treatment was 76 ± 74.1 months (10–238 months). No patient had other surgical treatment modality for VUR prior to the surgery. The presence of an infectious episode was based on clinical and microbiological data or when clinical data suggested an infection without microbiological isolation that resolved completely with antimicrobial treatment. All patients were initially managed with long-term prophylaxis either with macrodantine or with trimethoprim-sulfamethoxazole. Video cystourethrogram (VCUG) was indicated when, despite antibiotic prophylaxis, the patients continued to present with RTP. In discussing Durasphere® injection, patients were advised regarding the potential need for reinjection, continued long-term antibiotic use, and surveillance VCUGs. Pre-operatively, all patients were checked to be sure they had negative urine cultures. They received 2 g of intravenous ceftriaxone as antibiotic prophylaxis. General anesthesia was administered by a laryngeal mask airway. VUR was reconfirmed intraoperatively by cystography (80 mg of gentamicine was added to the contrast). To perform the procedure, a standard 21 Fr cystoscope was used. The bladder was filled to three fourths volume to permit visualization of the ureter and avoid tension within the submucosal layer of the ureter secondary to overdistention. We preferred to direct a stream of irrigation fluid into the ureter (hydro distension) to open the ureteral neomeatus and better define the injection site. The visual aspect of the refluxive neomeatus was usually of a large round or elliptic hole in the lateral aspect of the bladder dome. The visualization of the neomeatus was not difficult, and most of the time it can be directly accessed with the bladder partially filled. Sometimes it is necessary to manually compress the suprapubic region to facilitate the neomeatus visualization. The 19 gauge needle that comes with the Durasphere® kit was placed within the submucosa of the ureter at the 6 o'clock position, and a small volume (0.1 mL) was injected to confirm implant location. The needle was advanced to a depth of 5–8 mm. The cystoscope was pulled back to visualize subsequent injection (ineffective caudal tracking of the implant may escape notice if only the ureteral orifice is inspected during injection). Durasphere® was then slowly injected to form a submucosal mound, with the coapted ureteral orifice at its apex. If this formation was not seen, the needle was repositioned, and the process repeated. Improper initial placement and subsequent repeat injection occasionally resulted in bilobed or trilobed mounds. The ureter should appear to be completely coapted with proper injection. Attempts at ureteral hydro distention following injection serve to ensure proper technique as the ureter will remain coapted with irrigation. In some occasions, the needle could not be adequately visualized at the bladder dome. This situation was dealt with by slightly bending the needle tip to improve visualization, which easily solved the problem. A mean of 1.6 ± 0.7 mL of Durasphere® (1–3 mL) was used. The injection was easy without clogging of the needle. After injection, a new cystography was performed to confirm the VUR absence in all patients. If

VUR persisted after the first injection, a second one was made to achieve VUR cure. With the bladder partially filled with contrast, the patient was given 40 mg furosemide to confirm that no ureteral obstruction was inadvertently caused. The density difference between the fluid urine and the contrast created an unequivocal image of turbulence proving absence of obstruction. An indwelling Foley catheter was placed until the next day. The patients were allowed to eat, immunosuppression was resumed at the same day, and no postoperative analgesia was needed. The follow-up consisted of physical examination, urinary cultures and VCUG every six months. No antibiotics were given after the procedure. The mean follow-up was 22.3 ± 16.1 months (8–57 months). Operative technique and treatment outcomes are discussed.

Results

Eight patients were diagnosed with RTP secondary to VUR. The mean number of RTP was 3.25 ± 1.6 (1–6 episodes). Microbiological isolation was confirmed in 21 episodes (80.8%). The pre-operative characteristics and pathological data are summarized in Table 1. The procedure was well tolerated by all patients. There were no cases of urinary retention or hematuria. The mean age at surgery was 38.8 ± 13.8 yr (23-65). One patient (case 1) had, additionally, bilateral VUR to the primitive kidneys (grade 2 at the right side and grade 4 at the left), which was simultaneously and successfully treated in the same fashion by injection of 1 mL of Durasphere® at each side. No deterioration of graft function was observed in any case. All patients were followed and the mean follow-up was 22.3 ± 16.1 months (8–57 months). Six patients (75%) were free of pyelonephritis during a mean follow-up of 23.2 ± 17.1 months (8–57 months). Two of them had no VUR and four cases presented with G II VUR (pre-operative G IV three cases and one case G III). In one of them, symptomatic recurrent cystitis made a second treatment necessary. This patient remained free of infections for three yr after the first treatment and for 14 months after the second treatment. One of the remaining two patients had six episodes of RTP before treatment in a period of three yr and only two episodes after treatment in two yr of follow-up. The other patient presented with a new episode of pyelonephritis after five months of follow-up. Case number 3 had a duplex KTx from a pediatric cadaveric donor and VUR occurred to both renal units. The treatment technique was identical to the other cases. No patient developed ureteral obstruction after the procedure. The clinical success rate (patients free of infections during the follow-up period) in this series was 75%. The overall success rate (patients rendered free of infections plus the case in which the frequency of RTP was considerably reduced) was 87.5%.

Table 1. Treatment details and outcomes

Patient	1	2	3	4	5	6	7	8
Donor	LRD	CD	CD	CD	CD	LRD	LNRD	LRD
Race	W	B	A	W	B		W	W
Sex	F	M	F	M	F	M	F	F
Pre-operative VUR grade	3	3	4	4	2	3	3	4
Injected volume	1	1	2	3	1	2	2	1
Post-operative VUR grade	1	2	2	2	0	0	0	0
Follow-up	5	13	13	13	28	15	3	52

KTx, kidney transplant; VUR, reflux; CD, cadaveric; LR, living related; LNR, living non-related.

Discussion

Urinary tract infection remains a significant cause of infectious complications in KTx recipients, occurring at least once in 25% of them. Although 77% of cases are composed of uncomplicated acute bacterial cystitis, acute pyelonephritis happens in 23% of cases (1).

Secondary VUR after KTx is observed in up to 86% of KTxs (5). Currently, VUR can be managed by observation with suppressive antibiotics, endoscopic injection of bulking agents, and ureteral reimplantation. Open surgery in the non-transplanted population is a simple and effective procedure with a success rate of 95–99% (6, 7). However, the correction of VUR by conventional surgical reimplantation of the allograft ureter is a challenging procedure that can lead to complications such as stenosis, fistula, or even loss of the kidney. Therefore, a minimally invasive therapy would be extremely valuable for these patients. Endoscopic treatment of VUR has been attempted with different substances. They need to be inert, easily injectable, and stable with time so that volume is not lost and must not extrude or migrate. It should also be non-toxic, non-carcinogenic and devoid of allergenic potential and, therefore, fully biocompatible, causing minimal local inflammation. The basic principle is to buttress beneath the ureteral orifice, thereby allowing ureteral mucosa coaptation during bladder filling. As a result, a flap valve mechanism and even a hydrostatic and nipple valve mechanism are created. Polytetrafluoroethylene has been the material most commonly used, with a success rate of up to 85% (8). In some cases, polytetrafluoroethylene particles have been shown to migrate to the brain and lungs, eliciting a granulomatous reaction (9).

Subureteral injection of collagen has also been reported, with a success rate up to 83% (10, 11). Difficulties with collagen therapy include the need for skin testing, as the foreign bovine protein can be allergenic. Biodegradation and contraction of the injected collagen lead to VUR recurrence, despite initial successful treatment. Autologous injectable materials include fat, collagen, chondrocytes, and bladder muscle cells. Again, difficulties with biodegradation and contraction as well as poor success rates limit their usefulness (12). The silicone elastomer polydimethylsiloxane was recently introduced for the endoscopic treatment of VUR with success rates up to 81.8% (13, 14). Dextranomer/hyaluronic acid is another compound made up of cross-linked dextran polysaccharide molecules. It forms microspheres that are 80–120 μm in diameter. Its use can lead to a success rate of 72% (15).

The above-mentioned results show that the ideal bulking agent is still to be found, which led us to attempt a new bulking agent to try to improve results. To our knowledge, this is the first report of use of Durasphere® to treat VUR in KTx patients with RTP. As this is not the primary indication for Durasphere®, it should be mentioned that we utilized it as an ''off-label'' use. Durasphere® is composed of pyrolytic carbon-coated zirconium oxide beads in a water-based carrier gel (97% water and 3% beta-glucan). The beads have a dimension between 251 and 300 μm, which minimizes migration because their size is above the 80 μm threshold for particle migration (16). Pyrolytic carbon coating has been used for 30 yr in the heart valve industry and no skin test is necessary. Kitchens et al. have advocated the use of standard technique if the ureteral neomeatus is easily accessible, and a percutaneous technique if there is technical difficulty (17). At least in KTx patients, we found no difficulty in identifying and accessing the neomeatus, probably because all our transplanted patients had the uretero-vesical anastomosis performed in the same manner at the lateral aspect of the bladder dome. Ureteral obstruction is a rare complication of endoscopic therapy for VUR, reported in less than 1% of patients treated with polytetrafluoroethylene paste (18). Dextranomer/hyaluronic acid injection is associated with a small risk of post-operative ureteral obstruction requiring endoscopic intervention, with an overall incidence of less than 0.6% of ureters injected (19). Obstruction risk seems to be higher in complex cases of VUR. Perez-Brayfeld et al. have described a case with bilateral obstruction that was successfully managed with bilateral ureteral stents for two wk (20). Transurethral injection therapy can also cause persistent obstruction by the implant that may need open conventional surgery to correct the problem, particularly in dysmorphic appearing refluxing ureters (21). Although rare, obstruction in a single kidney is a complication that should be avoided at any cost. We preferred to use the minimum possible amount of the bulking agent and check the result with an intraoperative VCUG and verification of urine flow before making additional injections. Even complex cases can be treated endoscopically with a positive response in 63% of duplex ureters (22). One of our patients had a duplex KTx from a pediatric cadaveric donor with VUR to both units. Both ureters were anastomosed together and implanted in the bladder. VUR was corrected using the same technique although two injections were necessary. As ureteral obstruction is a risk to be considered after subureteral injection of bulking agents, we decided to observe our patients until the day after the procedure. There were no complications resulting from the injections in this casuistic. Interestingly, in some cases, the recurrence of VUR did not mean recurrence of infection. This was probably because of the fact that in these patients the VUR recurred to a lower grade. Even in these cases the treatment was considered successful because other treatment and prevention strategies failed. In our casuistic, retreatment was necessary only once, and the second injection was successful so far. We believe that this is a procedure that can be repeated if necessary and we would prefer it instead of indicating an open procedure. As the injected volume of the bulking agent is small, it is unlikely that it would preclude or cause significant difficulties to an open procedure should it be necessary. Although endoscopic treatment has a lower success rate compared to open conventional surgery, it has the advantage of being an outpatient procedure that is minimally invasive with a low morbidity and a lower overall cost (23). This is particularly true in renal transplant patients, as has been demonstrated by Cloix et al. and Mallet et al. (24, 25). We estimated the cost of an open procedure to be U$9263.00 compared to U$1947.00 per treatment for the endoscopic procedure.

Conclusions

Transurethral injection therapy with Durasphere® is a safe and effective minimally invasive treatment option for patients with RTP secondary to VUR to the kidney transplant with an overall success rate of 87.5%. It avoids a major open surgery although a second treatment may be necessary. Ureteral

obstruction was not observed in any case. Endoscopic injection may be an interesting initial approach for the management of VUR in KTx patients before resorting to more difficult open surgical procedures.

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