Original Article

Percutaneous Transluminal Angioplasty of Transplant Renal Artery Stenosis

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Abstract

Introduction: This study aimed to assess the outcome of percutaneous transluminal angioplasty (PTA) as the primary treatment for transplant renal artery stenosis (TxRAS). Materials and Methods: A retrospective review of PTA of TxRAS from April 1999 to December 2008 was performed. Twenty-seven patients (17 males (M):10 females (F)) with the mean age of 49.5 years underwent PTA of TxRAS in the review period. Indications for PTA were suboptimal control of hypertension (n = 12), impaired renal function (n = 6) and both suboptimal control of hypertension and impaired renal function (n = 9). All patients had doppler ultrasound scans prior to their PTA. In addition, 5 of these patients had computed tomography angiography (CTA) and another 7 had magnetic resonance angiography (MRA) evaluation. Mean follow-up period was 57.0 months (range, 7 to 108 months). Results: The stenotic lesions were located proximal to the anastomosis (n = 2), at the anastomosis (n = 15), and distal to the anastomosis (n = 14). Technical success rate was 96.3%. One case was complicated by extensive dissection during PTA, resulting in subsequent graft failure. The overall clinical success rate was 76.9%. Seven out of 26 patients had restenoses (26.9% of cases). These were detected at a mean of 14.3 months post angioplasty (range, 5 to 38 months). All 7 patients underwent a second PTA successfully. Three of these patients required more than 1 repeat PTA. Conclusion: PTA is safe and effective in the management of symptomatic TxRAS and should be the primary treatment of choice. Close surveillance for restenosis is required and when diagnosed, re-angioplasty can be performed.

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Key words: Post transplant hypertension, Kidney transplantation, Transplanted kidney failure

Introduction

Renal transplantation has become a successful means of treatment for patients with end-stage renal failure. However, in patients with kidney transplants, graft dysfunction can occur as a result of transplant renal artery stenosis (TxRAS). This can present with raised creatinine levels or as refractory hypertension resulting in increased use of anti-hypertensive drugs.[1] The incidence of renal artery stenosis in transplant kidneys is quoted as between 1% and 23%.[2] The prevalence of arterial stenosis affecting renal grafts has increased in recent years due to the use of marginal donors and older recipients. TxRAS usually occurs between 3 months and 2 years after transplantation, but earlier or later presentations are not uncommon.[1] Colour doppler ultrasound is used as a screening tool for TxRAS, but angiography remains the gold standard for diagnosis.[3]

Over time, with lesion progression, TxRAS may lead to allograft loss. Early detection of TxRAS is therefore essential in ensuring long-term graft survival. Percutaneous transluminal angioplasty (PTA) has become established as the primary treatment of choice in TxRAS over the last 2 to 3 decades since initial reports in the late 1970s.[4] The objective of this study is to report on our local experience by assessing the outcome of patients that have undergone PTA of TxRAS at our institution over a 9-year period.

Materials and Methods

This retrospective study was performed with the approval of our institutional review board. All patients who underwent PTA of TxRAS between April 1999 and December 2008 at our institution were identified. We collected data from 27 patients (17 males and 10 females) by reviewing their

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medical records. Their ages ranged from 29 to 63 years old with a mean of 49.5 years. All patients received the allograft kidney from a cadaveric donor except for 1 patient who had a living-related transplant. The underlying cause of renal failure was chronic glomerulonephritis in 20 patients; adult polycystic kidney disease in 3 patients; hypertensive nephrosclerosis in 1 patient; diabetic nephropathy in 1 patient; and unknown in 2 patients. With regard to vascular risk factors, dyslipidemia was present in 14/27; diabetes mellitus in 9/27; ischaemic heart disease in 3/27; and hypertension in 25/27 patients. All were cytomegalovirus (CMV) positive. Six patients had a history of acute rejection —5 of these had 1 episode of acute rejection each; the remaining patient had several episodes of acute rejection. The average time of presentation of TxRAS from transplant varied from 1 to 188 months (mean 51.1 months). A trial of conservative treatment would typically be implemented following the initial diagnosis. A decision was made for PTA if there was failure of conservative treatment. The average time from diagnosis to PTA ranged from 0.2 to 35 months (mean 5.8 months).

The indications for PTA included suboptimal control of hypertension only (n = 12), impaired renal function only (n = 6), and both suboptimal control of hypertension and impaired renal function (n = 9). Impaired renal function was defined as a persistent rise in serum creatinine by 20% or more. Suboptimal control of hypertension was based upon the assessment of the referring nephrologist. All patients had doppler ultrasound scans performed prior to their PTA. In addition, 5 of these patients had computed tomography angiograms (CTA) and another 7 had magnetic resonance angiography (MRA) evaluation following the initial Doppler ultrasound.

Informed consent was obtained from all patients prior to intervention. Diagnostic renal arteriography was performed via a femoral arterial approach; an ipsilateral or contralateral approach was chosen based on the type of surgical anastomosis of the transplant renal artery (end-to-side with use of the external iliac artery or end-to-end with use of the internal iliac artery) and the angle of the anastomosis. Eighteen patients had an end-to-side anastomosis with the external iliac artery (66.7%). The other 9 patients had end-to-end anastomosis with the internal iliac artery (33.3%). If there was concern for contrast material-induced nephrotoxicity, alternative contrast agents (e.g. carbon dioxide and gadolinium) were used for preliminary angiography in selected patients. Carbon dioxide was utilised in 5 procedures and gadolinium in 5 procedures to reduce the volume of iodinated contrast administered. Of these, 2 of the procedures where gadolinium was utilised were performed in the same patient. Gadolinium was utilised prior to the discovery of nephrogenic systemic fibrosis (NSF) as a possible complication in renal impaired patients.[5] On follow-up of a mean of 59.5 months (range, 19 to 78 months), none of the 4 patients have since developed NSF. We now no longer use gadolinium contrast medium in renal impaired patients.

The volumes of iodinated contrast material were kept to a minimum to reduce the risk of nephrotoxicity. After appropriate calibration of the images, measurement of stenosis was made by measuring the ratio between the diameter of the stenosed segment of the artery and the diameter of a normal segment of renal artery. A stenosis was considered to be haemodynamically significant when there was 50% or more narrowing of the luminal diameter on angiography or greater than 10% peak systolic pressure gradient across the lesion. When a decision was made to proceed with PTA, an appropriate guiding sheath was inserted and heparin sodium was administered intra-arterially (2000 to 3000 International Units). The stenosis/stenoses were traversed with a guidewire, followed by the use of 4 French catheters to obtain pressure measurements across the lesion. A range of guidewires was utilised depending on the anatomy of the lesion, and included 0.035", 0.018" and 0.014" wires. Nitroglycerin (100 to 200 ug intra-arterially into the transplant renal artery) was administered to prevent vasospasm on an operator preference basis. The size of the balloon was chosen to oversize the measured diameter of the normal segment of the renal artery by no more than 1 mm. The balloon was inflated across the lesion at nominal pressure for approximately 1 minute. A post PTA angiogram was performed to check for residual stenosis (Fig. 1). Technical success was defined as residual stenosis of less than 30% after PTA and with no flow-limiting intimal flap. Following the procedure, the patients were started on oral aspirin therapy (100 mg daily).

The blood pressure (BP), number of anti-hypertensive drugs and serum creatinine were closely monitored after PTA. Clinical adverse events post-procedure were recorded to assess the complication rate. The patients had a baseline Doppler ultrasound 2 weeks post PTA followed by 6-monthly, then 12-monthly surveillance scans thereafter.

For patients treated for suboptimal control of hypertension, clinical success was defined as normalisation of BP or a reduction in diastolic BP by more than 15 mm Hg and/or reduction in the number or dosage of anti-hypertensive drugs. For patients treated for impaired renal function, clinical success was defined as a serum creatinine reduction of 15% or a less than 15% change from baseline serum creatinine.[6]

Results

The stenotic lesions treated were located proximal to the anastomosis in 2 patients; at the anastomosis in 15 patients; and distal to the anastomosis in 14 patients. Four patients had

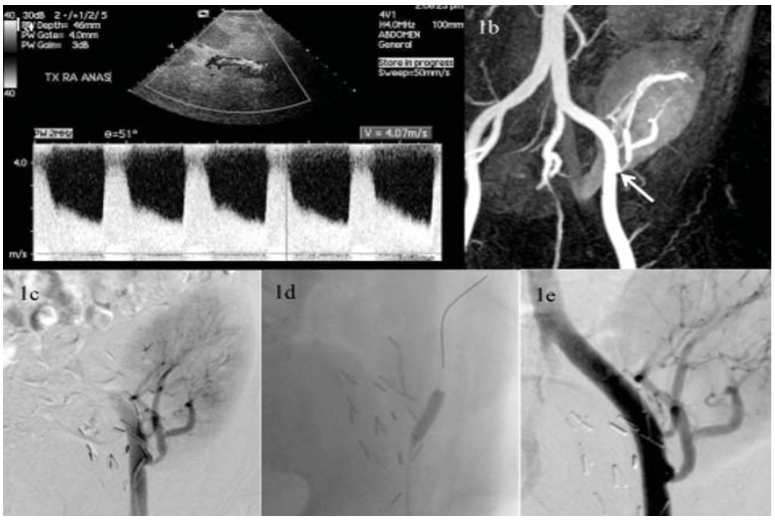

Fig. 1. Case of a 50-year-old male with a 1-year-old transplant allograft. (A) Ultrasound doppler showed peak systolic velocity (PSV) of more than 4 m/second of the transplant renal artery. (B) Contrast enhanced MRA confirmed TxRAS at the anastomotic site (arrow). (C) Angiogram via the ipsilateral femoral approach confirmed a 75% TxRAS. (D) PTA performed with 5 mm x 20 mm angioplasty balloon. (E) Post PTA angiogram demonstrated a good result with 20% residual stenosis.

more than one segment of stenosis. We used an ipsilateral approach in 9 patients and a contralateral approach in the remaining 18 patients. The sizes of the angioplasty balloons utilised ranged from 3 mm to 8 mm in diameter.

Immediate technical success was achieved in 96.3% of the cases (26 out of 27 patients). The only technical failure was in a patient with a 15-year-old graft, where the procedure was complicated by extensive dissection and surgical exploration had to be performed immediately on the patient (Fig. 2). At surgery, the extensive dissection was confirmed, but it was also noted that the recipient left internal iliac artery and the allograft arteries were diffusedly diseased due to atherosclerosis. A surgical bypass was created across the dissected segment but in spite of that, the allograft could not be salvaged and the patient had to resume haemodialysis.

One patient had a moderate dissection post PTA that was treated by stenting (Fig. 3). Another patient had a moderate groin haematoma that resolved with conservative treatment.

In the 26 patients who had successful PTA, the mean follow-up was 57.0 months (range, 7 to 108 months). Post PTA, there was a significant reduction in BP in 12 patients. The BP remained stable in 13 patients, while there was worsening of BP in the remaining patient. The number of anti-hypertensive medications decreased in 10 patients and remained unchanged in 14 patients (5 of these patients had the dosage of the existing number of drugs reduced). In the remaining 2 patients, the number of anti-hypertensive medications increased. In 1 of the 2 patients, the BP remained stable following the increase in number of medications by 1 additional drug and no repeat procedure was undertaken. In the second patient, the BP continued to worsen following PTA due to re-stenosis, thus increasing the requirement for anti-hypertensive drugs from 3 to 4. However, the patient was not keen for a repeat PTA and was thus managed conservatively.

At 6 months after PTA, the serum creatinine improved by more than 15% in 6 patients (23.1%), remained stable in 19 patients (73.1%) and worsened by more than 15% in 1 patient (3.8%). Twenty-two of 26 patients had follow-up of 1 year or more. At 1 year following PTA, the serum creatinine improved by more than 15% in 8 patients (36.4%) and remained unchanged in 9 patients (40.9%); the serum creatinine worsened by more than 15% in 5 patients (22.7%). The overall clinical success rate was therefore 76.9% (20 out of 26 patients). Of the poor clinical success patients, 2 initially presented with hypertension; 2 with elevated

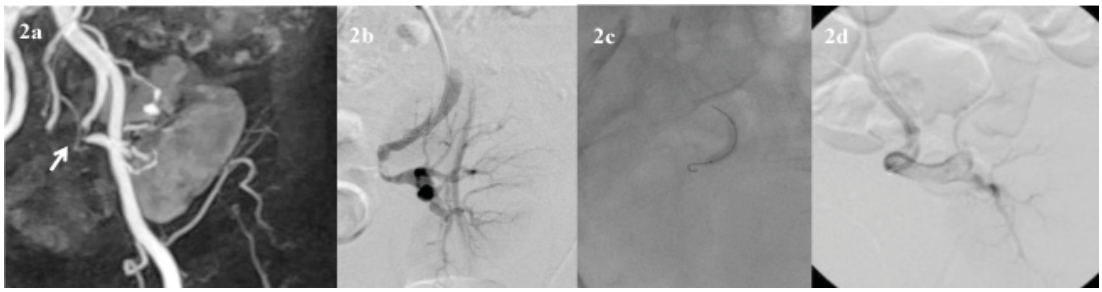

Fig. 2. Case of a 57-year-old woman with a 15-year-old allograft. (A) MRA showed a severe stenosis at the transplant artery anastomosis (arrow). (B) Pre PTA angiogram confirmed a severe 95% TxRAS with intrarenal arterial disease. (C) PTA performed with a 4 mm x 20 mm angioplasty balloon. (D) Post PTA angiogram showed severe flow limiting dissection that could not be salvaged.

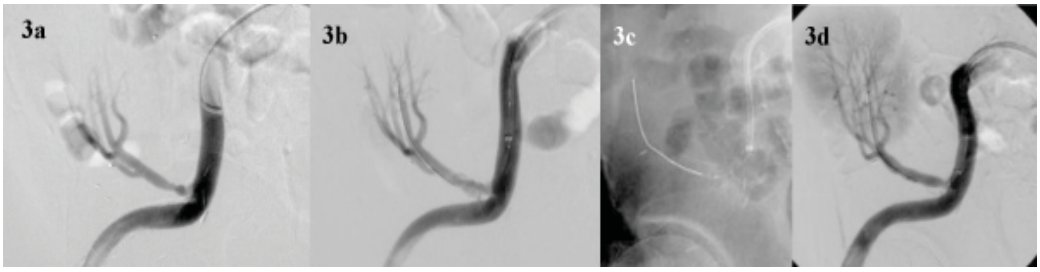

Fig. 3. Case of a 55-year-old man with a 2-year-old allograft. (A) Angiogram showed a 70% focal stenosis of the proximal transplant renal artery. (B) Post PTA angiogram demonstrated a moderate dissection that was resistant to redilatation. (C) A 6 mm x 18 mm balloon expandable stent was deployed across the lesion. (D) Post stenting angiogram shows successful treatment of the dissection with no residual stenosis.

creatinine and 2 with both hypertension and elevated creatinine. However, 4 out of the 6 poor clinical success cases had a history of acute rejection.

Seven out of 26 patients (26.9%) had restenoses of the TxRAS on follow-up. These were detected at a mean of 14.3 months post PTA (range, 5 to 38 months). Two patients had an end-to-side anastomosis; the rest had an end-to-end anastomosis. All cases of restenosis occurred in cadaveric allografts. None of the restenosis patients had episodes of acute rejection. None of the patients with poor clinical success presented with restenosis on follow-up.

All 7 were successfully treated with a repeat PTA. Two patients had stents inserted during the repeat PTA due to early restenosis. Three of the patients who had restenosis required more than 1 repeat procedure. Two patients required 2 repeat PTAs while the remaining patient had 3 procedures. A total of 38 procedures were performed in 27 patients. All the patients who underwent repeat PTA had stable renal function except 1. She eventually lost the function of her allograft 42 months after the second repeat PTA due to chronic rejection. One patient died from pneumonia 8 months after the second repeat PTA.

Discussion

TxRAS is not uncommon after renal transplantation, and it should be considered in patients who have worsening hypertension and/or renal dysfunction. The most common causes of stenosis are 'technical' where the stenosis occurs due to surgical technique, usually located at the anastomosis and especially at the end-to-end anastomosis. This may be due to trauma during kidney harvesting and transplantation, or less commonly, as a result of the anastomosis being too tight. Kinking or angulation of the artery is another possibility.[7]

CMV infection can also contribute to the development of TxRAS by causing proliferation of vascular cells, including endothelial cells, neointimal cells and smooth muscle. This effect may in part be due to inhibition of p53 by viral gene products.[8] Recipients who were CMV negative and then became CMV positive after transplantation had a significantly higher prevalence of TxRAS versus those who remained seronegative.[9]

Immunological injury has also been proposed as a possible cause, especially in diffuse and multiple stenoses. Intimal proliferation was associated with chronic rejection prior to the introduction of cyclosporine, but no consistent correlation has been found between acute rejection and TxRAS.[10] In our study, 6 patients were complicated by acute rejection (22.2%) but only 2 of them had more than 1 segment of stenosis. In addition, this may be confounded by positive CMV serology in all 6 patients.

Stenosis can also occur due to atherosclerosis of the donor renal arteries or recipient iliac arteries, or both.[10] A haemodynamic mechanism has been suggested in end-to-side anastomosis, with angulation between donor renal artery and the recipient iliac artery leading to turbulent blood flow.[7,9] In our study, 18 out of 27 patients had an end-to-side anastomosis. However several studies have shown no difference in the prevalence of TxRAS between the end-to-side and end-to-end techniques.[9]

A higher incidence of TxRAS is reported in cadaveric transplants (range, 13.2% to 17.7%) compared with live donors (range, 1.3% to 5.8%).[10] Greater cold ischaemia time, which is inevitable in cadaveric transplants, is compounded by the use of pulsatile perfusion systems that may contribute to endothelial damage in the renal artery.[9] The majority of our cases were in patients with cadaveric allografts (26 out of 27). However this may also be a result of cadaveric transplants being more prevalent than living-related transplants in the local setting. Cyclosporine has also been suggested as a cause for TxRAS by inducing endothelial injury leading to the development of a stenosis. However no studies have been conclusive.[10]

Early TxRAS that occurs within a few months of surgery is likely secondary to technical causes or trauma whereas TxRAS developing more than 6 months following surgery cannot be as readily explained and may be associated with the progression of underlying atherosclerosis.[10]

There are 3 main types of TxRAS: (i) stenosis at the

anastomosis; (ii) localised stenosis, proximal or distal to the anastomosis; and (iii) diffuse or multiple stenoses.[7] Preanastomotic arterial stenoses are usually due to atherosclerosis or clamp injuries while stenoses at the anastomosis are usually due to technical problems related to surgery. Stenoses distal to the anastomosis are usually due to immune reactions or haemodynamic turbulence from the anastomosis leading to intimal hyperplasia. Intrarenal distal stenoses, on the other hand, are usually due to chronic rejection. Post anastomotic stenoses tend to be more severe and more frequently associated with end-to-side anastomoses compared to end-to-end anastomoses, which tend to be at the anastomoses.[10]

PTA has been for years considered the initial treatment of choice for TxRAS as it does not preclude subsequent surgical correction. The technical success of PTA for TxRAS has been reported in 70% to 90% of the cases with a low complication rate. Our results of technical and clinical success are comparable to those quoted in the literature.[1,9,11-15] We noted that 4 out of the 6 cases of poor clinical success had a history of acute rejection. This may be a possible cause for our discrepancy between technical success and clinical success rates. Restenosis rate after PTA alone has been quoted as between 16% and 62%.[11] The restenosis rate in our patients (26.9%) falls within this range. PTA is considered to be more favourable compared to surgical intervention, which carries increased risk of graft loss as well as ureteral injury.[10,15] Transplant patients are also poor surgical candidates in general because of their chronic immunosuppressed state.[4]

There are a few limitations in our study. Firstly, as the study is retrospective, the follow-up protocol post PTA may not be strictly standardised. The number of patients in our study is also relatively small, but this can be attributed to the low incidence of this condition among our renal patients. Another limitation is that for the purpose of this study, we utilised serum creatinine as the marker of renal function. A more accurate assessment of renal function would have been the glomerular filtration rate (GFR). GFR was however not a standard utilised in our clinical practice during the earlier part of the study period. It was not possible to obtain the patients' weights at the time points of the serum creatinine results due to the retrospective nature of our study. However, most studies in the literature assessing the success of PTA in TxRAS have utilised serum creatinine as the marker for renal function.[1,9,12,15]

Metallic stents can be inserted for the treatment of recurrent or ostial stenoses. Stenting is associated with high initial technical success and a good patency rate with minimal complications.[10] Many recent reports highlight the role of PTA with stenting in limitation of recurrence, leading some authors to suggest stent implantation at the first angioplastic procedure.[11] However limited studies have been reported to date and there is a lack of data on the long-term outcome and complications of stenting in TxRAS. In our study, only 3 patients required stenting, 1 for dissection, and 2 for restenosis. Based on our experience, we do not feel that primary stenting is justified, and further studies will need to be performed comparing stenting to repeated angioplasties.

Conclusion

Our experience shows that PTA is safe and effective in the management of symptomatic TxRAS and should be the primary treatment of choice. Close surveillance for restenosis is required and when diagnosed re-angioplasty can be performed effectively.

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