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Short-Term Outcomes Using a Drug-Coated Balloon for Transplant Renal Artery Stenosis

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Background: This study aimed to evaluate the early and mid-term outcomes of drug-coated balloon (DCB) use in patients who underwent intervention for transplant renal artery stenosis (TRAS).

Material/Methods: We retrospectively reviewed the records of TRAS patients who received endovascular therapy with DCB in our institution from March 2016 to January 2017. Statistical analysis of pre-/postoperative levels of serum creatinine (Scr), systolic blood pressure (SBP), and renal artery peak systolic velocities (PSV) were performed.

Results: Fourteen patients presenting with TRAS, which were mostly located at the anastomosis (n=9) and transplanted artery proximal portion (n=2), were treated with DCB. Three TRAS patients with in-stent restenosis (ISR) were also included in the series. The procedure technique success rate was 100%. The mean follow-up time was 8.6 months. The Scr level decreased from 481.8 µmol/L (208.5–746.2µmol/L) pre-operation to 154µmol/L (89.1–301.2 µmol/L, p<0.01) at 1 month post-intervention. The SBP varied from 161.4 mmHg (152–173 mmHg) to 144.8 mmHg (136–154 mmHg, p<0.01). Renal artery PSV decreased from 364.1 cm/s (217.6–511.9 cm/s) to 134.9 cm/s (79.8–184.2 cm/s, p<0.01). Eleven patients finished mid-term (>6 months) follow-up. The statistical results were not significant compared to those at 1 month, although they all slightly decreased. No re-intervention was performed.

Conclusions: The endovascular approach to TRAS with DCB was a safe and effective treatment for restore and maintain the artery flow and renal function in short-term follow-up.

MeSH Keywords: Angioplasty • Endovascular Procedures • Kidney Transplantation • Renal Artery Obstruction

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Background

Transplant renal artery stenosis (TRAS), which is evidenced by refractory hypertension and graft dysfunction, has become an increasingly recognized cause of poor long-term patient and allograft survival [1]. It is reported that the incidence of TRAS ranges from 6% to 23%, depending on the diagnostic criteria, which shows wide variability among reports [2]. The commonly accepted definition of hemodynamically significant TRAS is arterial lumen stenosis greater than 50% and/or a peak systolic velocity (PSV) exceeding 200 cm/s as measured by ultrasound, computed tomography angiography (CTA), and digital subtraction angiography (DSA) [1–3].

The etiological mechanism of TRAS has not been determined. Apart from bend-kink, suture, and donor procurement, intimal hyperplasia, fibrosis or scarring, and immunological disorder are the main risk factors of TRAS [4]. Percutaneous transluminal angioplasty (PTA), alone or using a stent, was accepted as initial therapy for TRAS [4,5]. However, the incidence of restenosis for PTA alone ranges from 15% to 28% [3]. The rate after stenting is reported to be superior to PTA alone, but remains as high as 15% for bare-metal stents (BMS) and 15.7% for drug-eluting stents (DES) [3].

Use of a paclitaxel-coated balloon, inhibiting arterial smooth muscle cell proliferation and migration as well as extracellular matrix formation, has been shown to decrease the intimal hyperplasia and confer increased vessel patency in the treatment of femoral and popliteal arteries [6,7]. Few studies have evaluated the safety and efficiency of drug-coated balloon (DCB) use in patients who undergo endovascular intervention for TRAS. Thus, we present our short/mid-term clinical outcomes in patients with TRAS, using DCBs in transplanted renal arteries.

Material and Methods

We performed a retrospective, single-institution review of all patients who had the diagnosis of TRAS and received DCB therapy from March 2016 to January 2017. The local Research Ethics Committee approved the study and all patients gave informed consent.

The patients enrolled in this study had their transplantations from January 2014 to June 2016. During that period, 1175 patients had their kidney transplantation at our hospital. All the patients who received either a cadaveric or living donor renal allograft were followed up after transplantation in our hospital. The donor artery was anastomosed either end-to-side to the external iliac artery or end-to-end to the internal iliac artery. Serum creatinine (Scr) levels and blood pressure values were evaluated on routine follow-up. In case of suspicious symptoms such as refractory hypertension or unexplained graft dysfunction, patients were further ultrasonically evaluated by LOGIQ C9 and E9 XD CLEAR (GE Medical Systems, Milwaukee, WI) with a 2–5 MHz transducer. Our ultrasound criteria for TRAS was a peak systolic velocity (PSV) exceeding 200 cm/s. Patients with positive ultrasound criteria for TRAS had their diagnosis confirmed by CTA. Angiography was performed just before the endovascular procedure for treatment.

Operative procedure

All of the procedures were accomplished in our hybrid operation room by our endovascular team. Under local or general anesthesia, percutaneous access was obtained by femoral puncture. A nonselective angiography was performed preliminarily to confirm TRAS location and rule out iliac obstructive disease. Then, TRAS was crossed using a 0.035 or 0.018 guidewire and appropriate catheters. According to the transplanted renal artery, a DCB (orchid/dahlia, Acotec Scientific Co., Ltd., China) properly sized to cover the TRAS segment, was dilated and maintained for 60 s after pre-dilation with a standard balloon less than 1 mm smaller than the reference diameter of the target artery. Diluted contrast, digital subtraction, and roadmap allowed the minimum usage of iodinate contrast material. A completion angiography was performed to confirm technique success and femoral hemostasis was obtained by using the ProGlide closure system (Abbott, USA). Figure 1 illustrates the endovascular approach.

Statistical analysis

Data are expressed as means and ranges. Preoperative and postoperative levels of systolic blood pressure (SBP), Scr, and renal artery peak systolic velocities (PSV) were compared using the paired two-sample t test. Statistical analysis was performed using Prism 6.0 software (GraphPad Software Inc., San Diego, CA). A value of $P<0.05$ was considered significant.

Results

From March 2016 to January 2017, 14 patients were confirmed as TRAS and their pre-procedure base-line parameters are shown in Table 1. There were 6 men and 8 women, with a median age of 46.7 years (range, 23–69 years). The 14 TRAS patients all received DCB treatment and were under surveillance by ultrasound and serum testing in our hospital.

In all patients, end-to-side anastomosis with use of the external iliac artery was performed. The initial clinical symptom was refractory hypertension in 11 cases and graft dysfunction in 4 cases. All of the stenoses were confirmed by CTA. The mean serum creatinine before treatment was 481.8 µmol/L (range,

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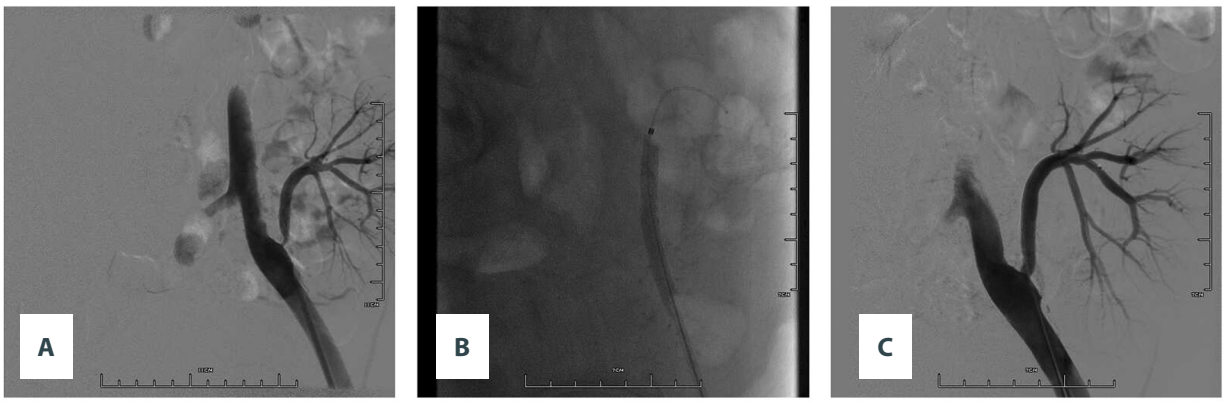

Figure 1. Intraoperative angiography. (**A**) Stenosis of the transplanted renal artery at the anastomosis (left external iliac artery-transplanted renal artery). (**B**) A DCB was used in the procedure. (**C**) Satisfactory diameter retrieval after ballooning.

208.5–746.2 µmol/L) and the mean systolic blood pressure was 161.4 mmHg (range, 152–173 mmHg).

TRAS were located at the anastomosis in 9 patients and in the transplant artery proximal portion in 2 patients. Three patients with restenosis in the BMS which were implanted in our department were also enrolled in the series. Their stent sizes were 5×20 mm, 5×20 mm, and 5×40 mm, respectively, and the times from when the BMS was deployed to the time of DCB treatment were 18 months, 26 months, and 16 months, respectively. The mean PSV of transplanted renal arteries was 364.1 cm/s (range, 217.6–511.9 cm/s).

The 14 TRAS patients all received DCB treatment and were under surveillance by ultrasound and serum testing in our hospital. The procedure technique success rate was 100% and a properly sized DCB was used for each case according to the diameter of the normal renal artery (Figure 1). The 2 transplanted artery proximal portion stenosis cases were performed with 3.5×80 mm DCBs. For the rest of the patients, 5-mm DCBs were used in most in the procedures and 40 mm length was enough for the stenosis. The 3 ISR patients were ballooned with relatively longer DCBs (60 mm) to cover the whole stent. No complication was observed during hospitalization in this series.

The mean follow-up time was 8.6 months (range, 3–13 months). All of the patients had finished ultrasound and serum testing by 1 month after discharge, and 11 patients finished follow-up by 6 months after the procedure. Thus, we could collect the early (1 month) and mid-term (>6 months) results. Figure 2 illustrates the early and mid-term statistical outcomes.

Early outcomes

The mean serum creatinine level at 1 month after endovascular treatment was 154 µmol/L (range, 89.1–301.2 µmol/L). There was a significant decrease in serum creatinine levels ($t=8.9$, $p<0.0001$), and similar results were found in SBP and PSV. The mean SBP at 1 month after the procedure was 144.8 mmHg (range, 136–154 mmHg), which was markedly decreased from the pre-intervention result ($t=8.8$, $p<0.0001$). PSV was measured by 2 ultrasound physicians. During the early follow-up, we observed a sharp decrease in PSV ($t=7.6$, $p<0.0001$), from 364.1 cm/s (range, 217.6–511.9 cm/s) to 134.9 cm/s (range, 79.8–184.2 cm/s). No acute restenoses or occlusions were detected.

Mid-term outcomes

Eleven patients finished mid-term follow-up (>6 months) and the mean follow-up time was 10.1 months. No postoperative deaths occurred. The Scr level in the 11 patients was 135.4 µmol/L (range, 87.7–189.3 µmol/L) at latest follow-up. This result was not significant compared with the early outcome ($t=2.2$, $p=0.06$). Three patients had a slightly increased SBP, but the mean level remained at 143.5 mmHg (range, 136–152 mmHg), which was unchanged from the early result ($t=1.0$, $p=032$). Neither arterial occlusion nor restenosis needing re-intervention was found at latest follow-up. All of the patients who underwent DCB treatment maintained the patency of transplanted renal arteries. None of the treated patients developed a pseudoaneurysm at the site of treatment at latest follow-up. The mean renal artery PSV was 134.3 cm/s (range, 80.4–183.4 cm/s). Although the results were a bit lower than those of early outcomes, they were not significantly different ($t=0$, $p>0.99$ and $t=1.6$, $p=0.13$).

Discussion

The findings of this retrospective study indicate that angioplasty of TRAS with DCB is safe and effective. The Scr level, SBP, and renal artery PSV were decreased significantly after the therapy, and the restenosis was maintained at a low rate

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Table 1. Summary of reviewed cases.

Number	Gender	Age	Stenosis location	DCB (mm×mm)	Follow-up	Scr (μmol/L)		
						Pre procedure	1 month post procedure	Latest follow-up
1	Male	43	Anastomosis	5×40	13	387.4	216.4	189.3
2	Female	33	Transplanted artery proximal portion	3.5×80	12	294.3	102.4	94.2
3	Male	51	Anastomosis	5×40	12	655.1	179.5	133.5
4	Female	47	Anastomosis	4×40	12	537.6	233.6	157.5
5	Female	23	In-stent	5×60	11	521.2	167.3	171.8
6	Male	69	Anastomosis	5×40	11	208.5	90.4	91.2
7	Female	61	In-stent	5×60	9	413.8	112.7	104.1
8	Male	44	Anastomosis	4×40	9	746.2	301.2	187.9
9	Female	32	Transplanted artery proximal portion	3.5×80	8	572.4	156.7	174.3
10	Male	52	Anastomosis	4×40	7	613.9	89.1	98.4
11	Female	46	Anastomosis	5×40	7	661.7	127.4	87.7
12	Female	25	In-stent	5×60	4	376.2	112.8	94.8
13	Male	67	Anastomosis	5×40	3	481.5	152.1	107.3
14	Female	64	Anastomosis	5×40	3	275.8	114.2	99.4

Number	Gender	Age	SBP (mmHg)			Renal artery PSV (cm/s)		
			Pre procedure	1 month post procedure	Latest follow-up	Pre procedure	1 month post procedure	Latest follow-up
1	Male	43	163	147	141	389.2	103.2	110.5
2	Female	33	157	151	150	412.6	79.8	80.4
3	Male	51	153	146	152	319.5	145.6	140.6
4	Female	47	162	154	146	247.8	184.2	183.4
5	Female	23	167	143	140	474.1	104.7	106.8
6	Male	69	155	136	145	511.9	84.5	88.5
7	Female	61	164	151	139	357.8	125.3	131.4
8	Male	44	167	147	140	217.6	152.8	155.7
9	Female	32	173	143	136	274.9	183.5	180.1
10	Male	52	169	145	140	352.4	143.6	146.1
11	Female	46	152	140	149	428.5	149.5	153.7
12	Female	25	157	142	143	281.5	137.2	138.9
13	Male	67	160	143	142	453.7	138.5	140.8
14	Female	64	161	139	134	376.5	155.9	146.7

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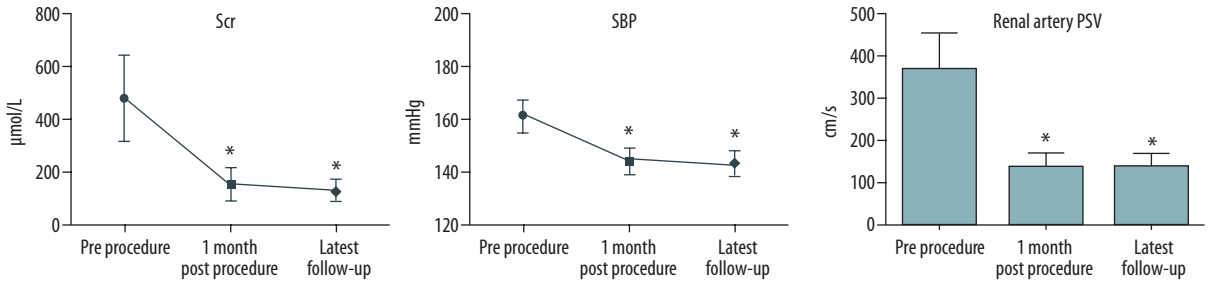

Figure 2. Evolution of Scr, SBP, and renal artery PSV. Scr – serum creatinine; SBP – systolic blood pressure; PSV – peak systolic velocities; * denotes a significant statistical result compared to pre-intervention, p<0.05.

during follow-up. Our results also demonstrate the DCB can offer a reasonable approach to treating TRAS of ISR, decreasing the need for repeat revascularization.

The etiology of TRAS is not fully understood; however, intimal hyperplasia, fibrosis or scarring, and immunological disorder are thought to be the main risk factors of TRAS [8,9]. In our study, most stenoses were located at the anastomosis or in the proximal portion of the transplant artery, suggesting that intimal hyperplasia caused by intimal injury during suturing or an immune-mediated reaction with donor tissue are the main features of TRAS. An important milestone in percutaneous revascularization was the discovery that local delivery of an antiproliferative agent at the site of the lesion is the most important factor in reducing intimal hyperplasia. For this purpose, attention has turned to the use of DES due to the incidence of restenosis associated with BMS placement. Recent studies have reported that primary stenting with either DES or BMS was a safe and effective therapy for TRAS, but DES conferred no significant advantage in terms of rate of restenosis compared to BMS [4].

Several disadvantages in using a stent as a vehicle were inferred theoretically according to the mechanism of DES. Firstly, drug distribution from stent to arterial wall is inhomogeneous. DES do not cover a large area (75% to 85%) of the vessel wall between stent struts, resulting in low tissue levels of the antiproliferative agent in these areas and incomplete suppression of neointimal hyperplasia [10]. Polymeric matrices on the DES, which control drug release kinetics, can lead to chronic inflammation and thrombosis and these materials can cause delayed and incomplete reendothelialization. Patients are usually required to take long-term dual antiplatelet agents, which is potentially harmful to their transplanted kidneys. In addition, DES is a permanent implant, which can induce neointimal hyperplasia by itself.

In this study, single DCB was used in each patient instead of DES, and satisfactory early and mid-term outcomes were observed. Importantly, the renal artery PSV remained at a reasonable level as shown by the ultrasound examination, which proved the sustained antiproliferative effect of DCB at the stenosis site.

When compared to a DES, a DCB offers several advantages able to overcome all of the drawbacks related to a DES. DCBs can cover the entire lesion site during inflation and homogeneously provide rapid release of a high concentration of drug to the transplanted renal artery wall. At the same time, no polymer-related chronic inflammation is induced by DCB, which potentially decreases the incidence of late thrombosis. Without the presence of a permanent implant stent, the overdependence on antiplatelet therapy, especially dual antiplatelet therapy, can be avoided. In addition, the original arterial anatomy and flow pattern are better maintained using DCB.

Another obviously better beneficial effect offered by DCB is the unique advantage in treating ISR. The lumen re-narrowing continues to occur and represents a challenging clinical problem despite the widespread use of either DES or BMS. Multiple treatment options such as balloon angioplasty, repeat stenting, and debulking have been investigated in patients with femoropopliteal ISR [6,7]. However, there is no established optimal treatment strategy because no single therapy is particularly more effective or superior to others. Fortunately, the DCB has been proved to have superior efficacy in comparison to plain balloon angioplasty with femoropopliteal ISR, providing a new therapy for these patients [6,7]. Instead of atherosclerotic diseases, the mechanism of ISR in the transplanted renal arteries is intimal hyperplasia, which is the direct target of antiproliferative agents. Thus, the DCB theoretically has better clinical results in treating ISR of transplanted renal arteries. In the present study, the 3 ISR cases were all successfully treated and had follow-up periods of 11, 9, and 4 months. Compared to the early results, renal artery PSV were not statistical changed, suggesting that the antiproliferative effect of DCB is a main feature of ISR therapy.

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Our study is limited by the small number of included patients, the retrospective process, and the absence of a control group of TRAS patients treated with plain balloons. The small number of subjects is a common problem in most TRAS investigations and is a large obstacle to any potential retrospective or prospective study.

Conclusions

We found the endovascular approach to TRAS with DCB was safe and had a high rate of success. It was an effective treatment to restore and maintain the artery flow and renal function in short-term follow-up. A study with longer follow-up is required to demonstrate the long-term performance of DCB.

Conflicts of interest

None.

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