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Original Article

Use of Paclitaxel Coated Drug Eluting Technology to Improve Central Vein Patency for Haemodialysis Access Circuits: Any Benefit?

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Purpose: Central venous stenosis is a recurring problem affecting dialysis access patency. Increasing evidence suggests that the use of drug-coated balloons (DCBs) improves target lesion primary patency (TLPP) in dialysis access. However, few studies have investigated the use of DCBs specifically in central venous stenosis. Thus, this study presents our initial experience with DCBs in the central vein of a dialysis access circuit.

Materials and Methods: This is a retrospective cohort study of all hemodialysis patients who underwent central vein angioplasty with DCB between February 2017 and March 2018 at Singapore General Hospital. We compared the primary patency post DCB angioplasty to the primary patency of the patient's previous plain old balloon angioplasty (POBA).

Results: We observed a 100% anatomic and procedural success rate with no complications. The median follow-up period was 151 days (interquartile range, 85.5-234 days) and no patients were lost to follow-up. The 30- and 90-day TLPPs after DCB were 93.3% and 75.7%, respectively. The mean primary patency in our study group post-DCB during the follow-up period was 164 days (vs. 140 days in the POBA group). However, no statistically significant difference was detected.

Conclusion: DCB showed a similar TLPP to that for POBA in treating central venous stenosis with a trend toward a longer re-intervention-free period for DCB. However, there were numerous confounding factors and a well-designed randomized controlled trial is warranted to assess the true utility of DCB in treating central venous stenosis.

Key Words: Vascular patency, Balloon angioplasty, Hemodialysis, Paclitaxel, Central venous stenosis

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INTRODUCTION

Central veins form the main outflow in any upper extremity hemodialysis (HD) vascular access. These specifically include the subclavian vein, brachiocephalic vein, and superior vena cava [1]. As such, any central venous stenosis or occlusion could endanger the patency of the arteriovenous fistula (AVF) or graft, as well as the efficacy of HD. While

some patients present with clinical symptoms of upper extremity swelling, pain, or dilated chest wall veins, most present with symptoms of clinical dialysis dysfunction such as elevated venous pressures recorded during HD, abnormal recirculation values, prolonged bleeding after needle withdrawal, or increased pulsatility of the fistula or graft.

Recently, there have been good results of drug-coated balloons (DCBs) for dialysis access stenosis. A meta-analysis by Khawaja et al. [2] seemed to suggest that DCBs conferred some benefit in terms of improving target lesion primary patency (TLPP). An updated meta-analysis recently performed by our institution showed that DCBs appeared to be a better and safe alternative to plain old balloon angioplasty (POBA) in treating patients with HD stenosis based on 6- and 12-month primary patency [3].

However, few studies have investigated the use of DCBs in central venous stenosis because of either availability or cost issues. Although Massmann et al. [4] reported the effective use of a custom-made DCB (Elutax-SV; Aachen Resonance, Aachen, Germany), these are not yet approved by the Food and Drug Administration (FDA) and, thus may not be available in the United States. A single-center randomized controlled trial performed by Kitrou et al. [5] showed promising data of improved intervention-free period following the use of DCBs in symptomatic central venous stenosis using the Lutonix™ 035 12 mm×40 mm (Bard BD Peripheral Vascular, Tempe, AZ, USA), which is one of two commercial 12-mm DCBs currently available in Singapore.

We evaluated the outcome of using the Lutonix™ DCB in symptomatic central venous stenosis in a cohort of HD Asian patients and compared the primary patency to that of POBA in patients with prior POBA as historic controls.

MATERIALS AND METHODS

1) Patients

We retrospectively collected data on all HD patients who underwent central vein angioplasty with DCB at Singapore General Hospital, Singapore, between February 2017 and March 2018. Patient biodata, co-morbidities, prior central vein intervention records, indications for intervention, all procedural and angiographic data, and follow-up data were retrieved from Singapore General Hospital electronic medical records. All interventions were clinically driven; no surveillance imaging was performed. The angiography images were also reviewed to ensure the accuracy of data collection. Singapore General Hospital Institutional Review Board approval was obtained for this retrospective study (IRB no. 2018/2995).

2) Procedure

All procedures were performed with the patient in the supine position and under local anesthesia and sedation as required. No intravenous antibiotics were administered. The procedures were performed in either the endovascular hybrid operating theater or our interventional nephrology suite, using a flat-panel imaging system (Artis Zeego; Siemens, Munich, Germany). The arteriovenous graft (AVG) or AVF was punctured in an antegrade fashion and an initial venogram was performed with a 5- or 6-Fr sheath, which was later upsized to a 10-Fr sheath to allow DCB insertion. Central venous stenosis was verified based on a lumen diameter reduction of >50% in any of the central veins on contrast angiography, together with the presence of collateral veins. The lesions were crossed intra-luminally using standard 0.035 guidewires and a 4-Fr support catheter. A femoral vein puncture was used if the lesion was unable to be crossed from the initial antegrade position. The lesions

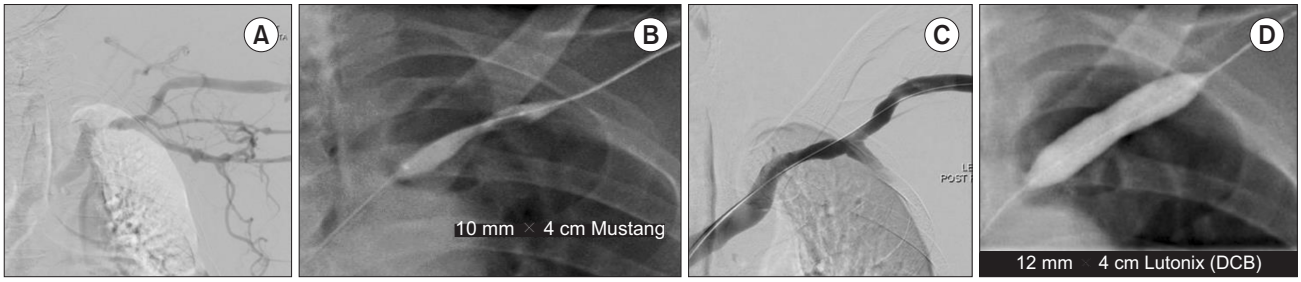

Fig. 1. Example of central vein stenosis treated with plain old balloon angioplasty (POBA) followed by drug-coated balloon (DCB). (A) Tight central vein stenosis noted with significant collateral veins. (B) POBA performed with 10 mm×4 cm Mustang™ balloon (Boston Scientific, Marlborough, MA, USA). (C) Angiographic run done after POBA showed good results. (D) DCB performed with 12 mm×4 cm Lutonix™ DCB (Bard BD Peripheral Vascular, Tempe, AZ, USA).

were first treated with appropriately-sized plain old angioplasty balloons depending on the estimated vein diameter and the stenosis length. The choice of angioplasty balloon, usually a high-pressure non-compliant balloon, pressure, and duration of inflation were determined by the operator. A larger balloon or longer inflation time was used if there was significant recoil. This was defined as greater or equal to 30% of the adjacent normal vein diameter. A full venogram of the entire dialysis circuit including a reflux run of the juxta-anastomosis was also performed and any concomitant lesions along the dialysis circuit were also treated with POBA with or without DCBs. Once the final angiographic result was deemed satisfactory, a Lutonix™ 12 mm×40 mm DCB was applied across the central venous stenosis and inflated to the rated burst pressure (12 atm) for 2 minutes as per instructions for use (Fig. 1). In some cases, post-dilatation with a 14-mm high-pressure non-compliant balloon was performed. Post procedure, the patients were started on dual antiplatelet agents for 3 months.

3) Definitions

For the purposes of our study, standard definitions based on the Society of Interventional Radiology (SIR) guidelines were used [6]. Primary patency was defined as uninterrupted patency after intervention until the next access thrombosis or reintervention. Anatomic success was defined as <30% residual diameter stenosis and procedural success was defined as anatomic success with at least one indicator of hemodynamic or clinical success.

4) Statistical analysis

Descriptive statistics were presented as proportions or medians (range) for categorical and continuous data, respectively. Patency of intervention was defined as the duration between the index intervention to the time another intervention was required to maintain access patency. Each patient received at least one central vein POBA prior to the use of the DCB, thus each patient serves as their own control. We compared the primary patency post-DCB angioplasty to that of the patient's previous central POBA. Patency was presented as Kaplan–Meier curves and compared by paired log-rank tests. P-values <0.05 were considered statistically significant. Statistical analysis was performed using R version 3.4.2.

RESULTS

A total of 30 patients underwent central venous angioplasty with DCB, including 16 male and 14 female patients

Table 1. Patient and access characteristics (n=30)

Characteristic	Value
Median age (y)	62 (56-69)
Male	16 (53.3)
Co-morbidities	
Hypertension	26 (86.7)
Hyperlipidemia	20 (66.7)
Diabetes mellitus	18 (60.0)
Ischemic heart disease	16 (53.3)
Cerebrovascular disease	6 (20.0)
Regular antiplatelet therapy	23 (76.7)
Access types	
Arteriovenous fistula	23 (76.7)
Arteriovenous graft	7 (23.3)
Access laterality	
Left upper limb	15 (50.0)
Right upper limb	15 (50.0)
Access configuration	
Radio-cephalic	3 (10.0)
Brachio-cephalic	11 (36.7)
Brachio-basilic	13 (43.3)
Brachio-axillary	3 (10.0)
Symptoms of central vein stenosis	
Symptomatic with arm swelling/ prolonged bleeding/thrombosis	19 (63.3)
Asymptomatic	11 (36.7)
Previous central vein interventions before DCB angioplasty	
Balloon angioplasty	26 (86.7)
Balloon angioplasty and stenting	3 (10.0)
Median number of previous central venous interventions before DCB angioplasty	4 (2–6)
Types of lesion on angiography	
Stenosis	22 (73.3)[a]/19 (63.3)[b]
Total occlusions	8 (26.7)[a]/11 (36.7)[b]
Site of lesion on angiography	
Brachiocephalic vein	14 (46.7)[a]/11 (36.7)[b]
Subclavian vein	12 (40.0)[a]/12 (40.0)[b]
Both brachiocephalic and subclavian veins	4 (13.3)[a]/7 (23.3)[b]
Number of patients with concomitant lesions treated	15

Values are presented as median (interquartile range), number (%), or number only.
DCB, drug-coated balloon.
[a]Plain old balloon angioplasty, [b]DCB angioplasty.

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with a median age of 62 years (range, 40-80 years). Most of the patients had hypertension (86.7%) and hyperlipidemia (66.7%) and 76.7% were on regular antiplatelet therapy. A total of 76.7% patients had AVFs while the remaining 23.3% had AVGs, and there were equal numbers of left (50.0%) and right upper extremity accesses. Clinically, 63.3% of patients presented with signs of upper extremity swelling, access thrombosis, or prolonged bleeding after dialysis needle removal, while 36.7% presented with only abnormal clinical dialysis parameters (e.g., high venous pressures or recirculation values) necessitating intervention. Prior central vein intervention was noted in 96.7% of patients, with a mean number of 4.79 interventions, and three patients had had previous central venous stenting. A summary of patients' baseline characteristics can be found in Table 1.

Venograms revealed that 63.3% of patients in the DCB intervention had central vein stenosis and 36.7% had chronic total occlusion of the central veins. A total of 36.7% patients had lesions in the brachiocephalic vein, 40.0% had lesions in the subclavian vein and the remainder 23.3% patients had lesions in both. Comparisons with the previous POBA angioplasties (Table 1) showed no significant differences between lesion types between groups. Half of the patients (15/30) had concomitant lesions in other parts of the dialysis circuit, which were also treated in the same setting. Specific to treatment of the central vein lesions, pre-dilatation was performed in 28/30 (93.3%) cases using high-pressure non-compliant angioplasty balloons ranging from 8 mm to 14 mm. Post-dilatation after DCB application was performed in 11/30 (36.7%) cases with a 14-mm-diameter balloon.

There was a 100% technical and procedural success with no immediate major or minor complications after DCB angioplasty. The mean follow-up period was 151 days (interquartile range, 85.5-234 days) and no patients were lost to follow-up.

The 30-, 60-, and 90-day TLPP were 93.3%, 90.0%, and 75.7%, respectively. Although the intervention-free period post-DCB was longer than that for POBA (164 vs. 140 days, P=0.257), the difference was not statistically significant (Fig. 2).

Subgroup analyses showed no differences in primary patency between AVFs and AVGs, between the left and right central veins, or between central vein stenosis and occlusions.

DISCUSSION

Central venous stenosis is often present in patients with end stage renal failure (ESRF), but are often asymptomatic in patients with no upper extremity HD vascular access, likely due to the development of venous collaterals. The prevalence of central venous stenosis in patients referred for vein mapping prior to access creation is estimated to be 10% [7]. After an upper extremity AVF or graft is created, there is increased venous return via the central veins, potentially leading to symptoms such as upper arm swelling, pain, prolonged bleeding post dialysis, high venous pressures during dialysis and dialysis access dysfunction. In certain cases, this could also lead to access infections or thrombosis. Risk factors for central venous stenosis include current or previously tunnelled dialysis catheters, cardiac rhythm devices, previous AVFs or grafts, increased time on

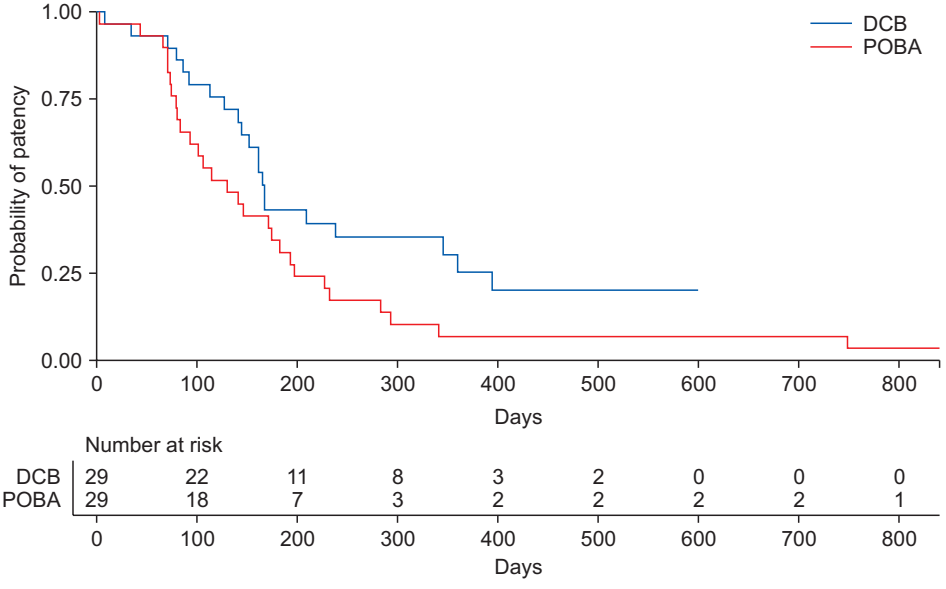

Fig. 2. Kaplan–Meier curve showing primary patency between plain old balloon angioplasty (POBA) and drug-coated balloon (DCB).

hemodialysis and previous renal transplant [7,8]. Central venous stenosis has also been found to occur more commonly on the left side due to anatomical orientation leading to increased contact between the catheter wall and vessel wall on the left side [9].

Based on SIR guidelines, treatment of central venous stenosis is indicated when >50% of the lumen is stenosed and when the AVF or AVG is hemodynamically compromised. In such circumstances, percutaneous angioplasty is the treatment of choice [6].

DCB technology is thought to work due to the antiproliferative effects of drugs on the smooth muscle cells in blood vessels. In vivo, venous smooth muscle cells are thought to be more susceptible to these effects [10]. While the utility of DCBs in peripheral arterial disease has been well investigated, studies on AVF angioplasty have shown mixed results [11-14]. This could be due to intrinsic differences in arterialized vein walls, increased shear stress on the venous walls, or other systemic factors such as uremia in ESRF patients.

Specific to central vein pathology, few studies have assessed the use of DCBs. A randomized controlled trial by Kitrou et al. [5] showed a longer intervention-free period following the use of DCBs for symptomatic central venous stenosis. However, they excluded patients with vessel diameters >12 mm, and the mean balloon size was 9.75 mm, which, in retrospect, showed undersizing. A previous computed tomography imaging study found the mean diameter of the left brachiocephalic vein in adults to be 13 to 14 mm [9]. Our study included patients with central veins of all sizes and 11 patients required post-dilatation with a 14-mm-diameter balloon after application of the 12-mm-diameter DCB. The size discrepancy between vein and DCB diameters could explain the negative results in our study cohort.

To overcome the size discrepancy in commercially available DCBs, other authors have used either custom-made paclitaxel-coated balloons [4] or two smaller DCBs placed side by side [15], both with promising results.

In our study, a significant number of patients (7/30, 23.3%) had lesions in both the brachiocephalic and subclavian veins. Due to cost constraints, only one DCB was used per patient and the 40-mm-length DCB, which is the maximum length available commercially might not have been enough to cover a long lesion or more than one focal lesion, possibly also leading to the lower primary patency seen as compared to those reported in other studies applying DCBs in the central veins [4].

A total of 36.7% patients did not have upper extremity symptoms and decision for intervention was based purely on abnormal dialysis parameters. Monitoring of dialysis parameters such as venous pressure is routinely performed in our local dialysis centers and patients are often referred for treatment based on these findings, even without clinical symptoms such as arm swelling or prolonged bleeding. In addition, 96.7% of our patient cohort had prior central venous intervention, with a mean of 4.79 interventions per year. These demographics reflect our institution's unique practice of preserving any upper arm dialysis access for as long as possible despite the need for frequent repeated procedures. DCBs are relatively expensive compared to plain old angioplasty balloons, and there have been some recent safety concerns regarding paclitaxel DCBs [16]. While we recognize that this may not be the most cost effective or conventional practice in other centres, there are little alternatives for these patients in our setting. A very large proportion of our patients have lower limb peripheral arterial disease, and thus lower limb AVGs are relatively contraindicated. The cost of a Hemodialysis Reliable Outflow graft (HeRO® graft; Merit Medical, South Jordan, UT, USA) is also extremely prohibitive in our setting and we have not been able to achieve acceptable primary patency with the HeRO® graft in our local patients.

Despite treating these highly recalcitrant central vein lesions, we achieved an improvement in the intervention-free period with the use of DCBs and without any scaffolding technology. While the difference was not statistically significant, this is probably due to our small sample size and the natural history of these lesions, which may otherwise have shown a reduced intervention-free period with each subsequent intervention.

The limitations of our study included its small sample size, as well as the heterogeneity of our patient population. Many of our patients had central vein multi-level disease or chronic total occlusions, which might have affected patency outcomes. At the time of the study, we did not have a specific protocol pertaining to pre-dilatation and vessel preparation, and inadequate vessel preparation could have an effect on the efficacy of the DCB. In addition, the short 40 mm length of the DCB available might not have been adequate to cover the entire length of the lesions in the central vein. While there is some data that antiplatelet therapy can be useful for preventing vascular access thrombosis [17], there is no direct data regarding the efficacy of antiplatelets or anticoagulants on central vein stenosis, or in the setting of DCB treatment in the dialysis circuit.

CONCLUSION

The results of this study failed to show a superior TLPP rate for DCB compared to POBA for central vein stenosis although a trend toward a longer intervention-free period in favor of DCB was observed. The results could be con-

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founded by numerous factors including vessel preparation, stenosis length, ratio of balloon diameter to vessel diameter, number of DCBs used, and inadequate post-dilatation. A well-designed randomized controlled trial is warranted to evaluate the true utility of DCB in treating central venous stenosis.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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AUTHOR CONTRIBUTIONS

Concept and design: TTC, HYY, TYT. Analysis and interpretation: HYY, CST, QSL, SLC, IJYW. Data collection: HYY, CST, QSL, SLC, IJY. Writing the article: TTC, HYY, TYT. Critical revision of the article: TTC, TYT. Final approval of the article: TTC, HYY, TYT. Statistical analysis: HYY, CST, QSL, SLC, IJYW. Obtained funding: none. Overall responsibility: TTC, HYY, TYT.

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