INTRODUCTION

Central veins form the main outflow in any upper extremity hemodialysis (HD) vascular access. These specifical-
ly 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 mmx40 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 mmx4 cm Mustang™ balloon (Boston Scientific, Marlborough, MA, USA). (C) Angiographic run done after POBA showed good results. (D) DCB performed with 12 mmx4 cm Lutonix™ DCB (Bard BD Peripheral Vascular, Tempe, AZ, USA).](image-url)
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

| 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) |
| Total occlusions | 8 (26.7) |
| Site of lesion on angiography |       |
| Brachiocephalic vein | 14 (46.7) |
| Subclavian vein   | 12 (40.0) |
| Both brachiocephalic and subclavian veins | 4 (13.3) |
| Number of patients with concomitant lesions treated | 15 |

Values are presented as median (interquartile range), number (%), or number only. DCB, drug-coated balloon.

Plain old balloon angioplasty, "DCB angioplasty."
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
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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-
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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