Treatment of cephalic arch stenosis in dysfunctional arteriovenous fistulas with paclitaxel-coated versus conventional balloon angioplasty

Ren Kwang A. Tng1, Ru Yu. Tan1, Shereen X. Y. Soon2, Suh Chien. Pang1, Chieh Suai. Tan1, Charyl J. Q. Yap2, Apoorva. Gogna3, Tze Tec. Chong2 and Tjun Y. Tang2,4*

Abstract

Background: Treatment of cephalic arch stenosis (CAS) with standard plain old balloon angioplasty (POBA) in dysfunctional arteriovenous fistulas (AVF), is associated with early re-stenosis and higher failure rates compared to other lesions. Paclitaxel-coated balloons (PCB) may improve patency rates. This is a retrospective cohort study. Patients who underwent POBA or PCB for CAS over a 3-year period were included. Outcomes compared were circuit primary patency rates (patency from index procedure to next intervention), circuit primary assisted-patency rates (patency from index procedure to thrombosis), and target lesion (CAS) patency rates (stenosis > 50%) at 3, 6 and 12 months.

Results: Ninety-one patients were included. Sixty-five (71.4%) had POBA, while 26 (28.6%) had PCB angioplasty. There were 62 (68.1%) de-novo lesions. CAS was the only lesion that needed treatment in 24 (26.4%) patients. Circuit primary patency rates for POBA versus PCB groups were 76.2% vs. 60% (p = 0.21), 43.5% vs. 36% (p = 0.69) and 22% vs. 9.1% (p = 0.22) at 3, 6 and 12-months respectively. Circuit assisted-primary patency rates were 93.7% vs. 92% (p = 1.00), 87.1% vs. 80% (p = 0.51) and 76.3% vs. 81.8% (p = 0.77), whilst CAS target lesion intervention-free patency rates were 79.4% vs. 68% (p = 0.40), 51.6% vs. 52% (p = 1.00) and 33.9% vs. 22.7% (p = 0.49) at 3, 6 and 12-months respectively. Estimated mean time to target lesion intervention was 215 ± 183.2 days for POBA and 225 ± 186.6 days for PCB (p = 0.20).

Conclusion: Treatment of CAS with PCB did not improve target lesion or circuit patency rates compared to POBA.

Keywords: Cephalic arch stenosis, Paclitaxel, Angioplasty, Arteriovenous fistula

Background

Vascular access, either via fistula (preferred), graft or catheter is a prerequisite to hemodialysis (Lok et al. 2020; Zavaacka et al. 2020). However, the access is vulnerable to dysfunction with stenosis developing along the circuit. Cephalic arch stenosis (CAS) occurs commonly in brachiocephalic AVFs, with a reported prevalence of up to 77% (Hammes et al. 2008). Treatment of AVF stenosis with standard percutaneous transluminal angioplasty (PTA) is generally associated with high success and efficacy (Yildiz 2020), along with favourable safety profiles despite the risks of trauma to the vessel wall (Zhang et al. 2020). However, PTA for CAS is associated with higher failure and complication rates and a tendency for early re-stenosis compared to other lesions (Sivananthan et al. 2014).
The definition of the cephalic arch varies across literature, with different papers referring to the central perpendicular portion of the cephalic vein as it traverses the deltopectoral groove and joins the axillary vein (Rajan et al. 2003), or the final arch of the cephalic vein before it joins the axillary vein (Kian and Asif 2008). Bennet further divided the cephalic arch into 4 segments, based on the distance from the arch apex to the cephalic-axillary vein junction (Bennett et al. 2014). The causes of stenosis at the cephalic arch have not been clearly elucidated, with various postulated contributing factors including: increased blood flow and pressures resulting in neointimal hyperplasia, extrinsic compression by the deltopectoral and claviculopectoral fascia, morphology of the cephalic arch, and the angle of the cephalic-axillary vein junction with increased turbulent flow, and increased number of valves in the cephalic vein resulting in increased turbulent flows (Sivananthan et al. 2014). These factors have contributed to the occurrence and recurrence of the lesion, and dialysis circuit primary patency and assisted-primary patency rates remain less than ideal with plain old balloon angioplasty (POBA) alone. A systematic review of endovascular management of CAS in failing brachiocephalic fistula also demonstrated effective short-term (6- and 12-months) primary patency rates with the use of stent graphs over endovascular modalities such as bare metal stents (D’cruz et al. 2019). However PTA remained necessary to maintain longer term patency of the stent graphs. Hence, there is a need for a longer term treatment solution for the cephalic arch stenosis.

Paclitaxel-coated balloons (PCB) have been used successfully to increase the patency of arteriovenous accesses in several large randomized controlled trials (Lookstein et al. 2020; Trerotola et al. 2018; Swinnen et al. 2018; Irani et al. 2018). However, these studies have looked at AV accesses as a whole, and not specifically at the cephalic arch. PCBs were made available in our centre for the treatment of dysfunctional arteriovenous access recently, and the objective of this retrospective audit was to report the dialysis circuit and CAS target lesion patency rates following DCB angioplasty of CAS compared to POBA.

Methods
All patients who presented to the institution with dysfunctional AVFs from January 2017 to December 2019 were retrospectively reviewed. A total of 91 unique patients who had treatment for CAS were included in the analysis. Clinical data and procedural reports were obtained from electronic medical records and all patients had a follow-up of at least 12 months following the index procedure. Demographic characteristics were collected. Outcome measures were circuit primary patency rates, defined as patency following index procedure until the next re-intervention within the access circuit, circuit primary assisted-patency rates, defined as the circuit patency following index procedure until the next access thrombosis, and cephalic arch (target lesion) patency rates defined as a stenosis > 50% at the CAS at 3, 6 and 12 months. The mean time to target lesion intervention was also determined with Kaplan-Meier analysis. This quality audit performed with de-identified data was exempted from Institutional Review Board review (CIRB Ref: 2020/2320).

All procedures were performed in a hybrid operating theatre using standard percutaneous techniques under local anaesthesia and/or sedation. An initial fistulogram was obtained. Cephalic arch stenosis was defined as > 50% stenosis at the cephalic arch. Decision to treat the CAS, as well as the type of balloon used, was operator dependent. The CAS was crossed in the usual way and mandatory pre-dilatation of the target lesion with a standard high-pressure non-compliant balloon (Munro®, Boston Scientific, Marlborough, MA, USA) for 2 min was used, with balloon size matched to the calibre of the adjacent normal vessel. After appropriate lesion effacement (< 30% residual stenosis), the PCB was inserted (sizing 1:1 to pre-dilatation balloon) and inflated for 2 min to a pressure according to the design specifications of the PCB to allow maximal drug transfer to the vessel wall. Balloon length was chosen to be at least 2 cm longer than the area treated during pre-dilatation (1 cm overlap proximal & distal) in order to avoid geographical miss. Post-procedure, all patients received daily aspirin (100 mg) and clopidogrel (75 mg) plus a proton pump inhibitor for 1 month, followed thereafter by single antiplatelet agent therapy.

Continuous variables were summarized as mean ± standard for normally distributed variables, and median (25th percentile, 75th percentile) for variables that were not normally distributed, while categorical variables were reported as frequency counts and percentages. Pearson chi-square test was used to compare categorical variables and student t-test or wilcoxon rank sum test were used for continuous variables. The mean time to target lesion intervention was estimated and compared with Kaplan-Meier analysis. Statistical analyses were conducted using SPSS (IBM, Version 21).

Results
Of the 91 patients included, 65 (71.4%) patients were treated with POBA, while 26 (28.6%) had angioplasty with PCB. Majority of the patients were female gender (53.8%), of Chinese ethnicity (68.1%), with mean age of 65.3 ± 10.6 years (Table 1). The type of access was mainly brachiocephalic AVF (94.5%), with a small proportion of radiocephalic AVF (5.5%). The demographics
of the 2 groups were similar in terms of their co-morbidities of hypertension, hyperlipidemia, diabetes mellitus, cerebrovascular and cardiovascular diseases (Table 1). The indications for intervention are summarized in Fig. 1. Out of 32 PCBs used in 26 patients, 22 (68.8%) were of Paclitaxel dosing of 2 μg/mm², 1 (3.1%) balloon with a dosing of 3μg/mm², 5 (15.6%) with a dosing of 3.5μg/mm², while the Paclitaxel dosing of the 4 (12.5%) remaining PCBs were not stated.

Table 2 summarizes the details of the characteristics of the cephalic arch stenosis while Table 3 summarizes the other lesions treated concurrently during the index
procedure. Majority of the CAS was de novo (68.1%). In patients with recurrent CAS, median time from prior intervention was 236 (Interquartile range (IQR) 163, 564) days and was similar between the 2 groups. CAS was the only lesion that needed treatment in 24 (26.4%) patients. There were a total of 106 other treated lesions in the remaining 70 AVFs, with juxta-anastomotic stenosis being the most common lesion (23.7%) followed by mid-cephalic vein (8.1%), cannulation zone (7.6%), central venous system (5.1%), proximal cephalic vein (4%), distal outflow (2%) and proximal basilic vein (0.5%). The severity of CAS was greater in the PCB group with percentage of stenosis being 83 ± 10.4% compared to 75 ± 12.4% for the POBA group (p = 0.001).

There were 6 deaths and 5 abandoned AVFs during the 12 month audit period. The circuit primary patency rates for POBA versus PCB groups were 76.2% vs. 60% (p = 0.21), 43.5% vs. 36% (p = 0.69) and 22% vs. 9.1% (p = 0.22) at 3, 6 and 12-months, respectively. The circuit assisted primary patency rates were 93.7% vs. 92% (p = 1.00), 87.1% vs. 80% (p = 0.51) and 76.3% vs. 81.8% (p = 0.77) while target lesion intervention free patency rates were 79.4% vs. 68% (p = 0.40), 51.6% vs. 52% (p = 1.00) and 33.9% vs. 22.7% (p = 0.49) at 3, 6, and 12-months, respectively (Table 4). The mean time to target lesion intervention was estimated to be 225 ± 186.6 days for POBA and 215 ± 183.2 days for PCB (p = 0.300) (Fig. 2).

**Discussion**

In this retrospective analysis, the overall target lesion patency rates of CAS following PTA at 3, 6 and 12-months were 76.1%, 51.7% and 30.9%, respectively, which were comparable with the reported rates in literature (D’cruz et al., 2018). The target lesion patency rates following PTA with PCB at 3, 6 and 12-months were 68%, 52% and 22.7% respectively, with no significant differences compared to treatment with POBA. Mean estimated cephalic arch primary patency rates were also similar for the 2 groups.

While the superiority of PCB over POBA in preventing arteriovenous access re-stenosis has been demonstrated in several large scale randomized controlled trials in

**Table 2** Characteristics of cephalic arch stenosis

|                           | Total (n = 91) | POBA (n = 65) | PCB (n = 26) | P-value |
|---------------------------|---------------|---------------|--------------|---------|
| **Cephalic arch**         |               |               |              |         |
| Single lesion             | 24 (26.4)     | 16 (24.6)     | 8 (30.8)     | 0.409   |
| Percentage stenosis, %    | 78 ± 12.3     | 75 ± 12.4     | 83 ± 10.4    | 0.006   |
| Prior stenting, n (%)     | 6 (6.5)       | 2 (3.1)       | 4 (15.4)     | 0.053   |
| De novo                   | 62 (68.1)     | 46 (70.8)     | 16 (61.8)    | 0.545   |
| Recurrent                 | 29 (31.9)     | 19 (29.2)     | 10 (38.5)    |         |
| Median time from prior intervention, days (25th, 75th percentile) | 236 (163, 564) | 236 (174, 608) | 268 (98, 452) | 0.463   |

POBA Plain Old Balloon Angioplasty, PCB Paclitaxel Coated Balloon

![Fig. 1 Reasons for re-intervention (index procedure)](image-url)
recent years, these studies have generally looked at ar-
teriovenous accesses, and not specifically at the cephalic
arch (Lookstein et al. 2020; Trerotola et al. 2018; Swin-
nen et al. 2018; Irani et al. 2018). The pathophysiology
of development of stenosis differs across different ana-
tomical sites in AVFs and may influence the treatment
outcomes of PTA. This audit specifically compared PCB
vs. POBA in the treatment of cephalic arch lesions and
our findings failed to demonstrate a significant differ-
ence in terms of circuit primary and assisted patency
rates and target lesion patency rates. This is likely due to
the etiology of CAS being multifactorial in nature, with
the anti-proliferative properties of PCB only addressing
one of the many factors involved, and hence may not be
superior to POBA alone. In addition, the structural
properties of the cephalic arch will not be altered by the
PCB, with the cephalic arch being compressed by sur-
rounding rigid structures of the deltopectoral and clavicu-
lopectoral fascia causing haemodynamically significant
stenosis which is susceptible to recoil post-PTA. Another
reason contributing to the lack of difference between PCB
vs. POBA for our audit could be due to a difference in
Paclitaxel dosing of the PCB, with the majority of PCB used
in our audit being of a dose of 2μg/mm² compared to other
studies with higher dosing of 3.5μg/mm² (Lookstein et al.
2020; Swinnen et al. 2018; Irani et al. 2018).

Several studies have explored different technologies
for prolonging the cephalic arch patency rates. In a small
retrospective study including 17 patients with CAS, the
use of cutting balloon angioplasty showed 3, 6, and 12-
month patency rates of 94%, 81% and 38% respectively
(Heerwagen et al. 2010). Although the patency rates ap-
peared better than the reported rates in our audit and
existing literature, the study did not directly compare
cutting balloon angioplasty with POBA.

Bare metal stents serve as a metallic scaffold that pre-
serve luminal gain following PTA and was thought to be
able to prevent recoil and re-stenosis caused by extrinsic

**Table 3** Distribution of other lesions treated during the index procedure

| Other treated lesions                      | Total (n = 106) | POBA (n = 88) | PCB (n = 18) |
|-------------------------------------------|----------------|--------------|-------------|
| Juxta-anastomotic Segment                 | 47 (44.3)      | 43 (48.9)    | 4 (22.2)    |
| Mid-Cephalic                              | 16 (15.1)      | 12 (13.6)    | 4 (22.2)    |
| Cannulation zone                          | 15 (14.2)      | 13 (14.7)    | 2 (11.1)    |
| Central Venous System                     | 15 (14.2)      | 14 (15.9)    | 1 (5.6)     |
| Proximal Cephalic                         | 8 (7.5)        | 5 (5.7)      | 3 (16.7)    |
| Distal outflow                            | 4 (3.8)        | 1 (1.1)      | 3 (16.7)    |
| Proximal Basilic                          | 1 (0.9)        | 0            | 1 (5.6)     |

POBA Plain Old Balloon Angioplasty, PCB Paclitaxel Coated Balloon

**Table 4** Circuit and target lesion (CAS) patency rates at 3, 6, and 12 months

|                     | All   | POBA | PCB   | P-value |
|---------------------|-------|------|-------|---------|
| **3-month outcomes**|       |      |       |         |
| N                   | 88    | 63   | 25    |         |
| Circuit primary patency, n (%) | 63 (71.6) | 46 (76.2) | 15 (60) | 0.209   |
| Circuit primary assisted patency, n (%) | 82 (93.2) | 59 (93.7) | 23 (92) | 1.000   |
| Target lesion patency, n (%)         | 67 (76.1) | 50 (79.4) | 17 (68) | 0.395   |
| **6-month outcomes**             |       |      |       |         |
| N                   | 87    | 62   | 25    |         |
| Circuit primary patency, n (%)      | 36 (41.4) | 27 (43.5) | 9 (36)  | 0.685   |
| Circuit primary assisted patency, n (%) | 74 (85.1) | 54 (87.1) | 20 (80) | 0.508   |
| Target lesion patency, n (%)        | 45 (51.7) | 32 (51.6) | 13 (52) | 1.000   |
| **12-month outcomes**            |       |      |       |         |
| N                   | 81    | 59   | 22    |         |
| Circuit primary patency, n (%)      | 15 (18.5) | 13 (22)  | 2 (9.1) | 0.219   |
| Circuit primary assisted patency, n (%) | 63 (77.8) | 45 (76.3) | 18 (81.8) | 0.767   |
| Target lesion patency, n (%)        | 25 (30.9) | 20 (33.9) | 5 (22.7) | 0.485   |

POBA Plain Old Balloon Angioplasty, PCB Paclitaxel Coated Balloon
compression. However, results on the use of bare metal stents to treat CAS have been variable (D’cruz et al., 2018). Theoretically, in-stent re-stenosis can still occur due to cellular proliferation through the bare stent fenestration. Hence, deploying a stent without combating neointimal hyperplasia may not prolong the patency rates of the cephalic arch.

The stent graft, a type of covered vascular stent to impede neointimal hyperplasia and tissue in-growth, may therefore have the best potential to maintain the patency of the cephalic arch. Although only studied in small populations, the use of stent grafts have been encouraging with positive results reported. Rajan et al. reported target lesion patency at 3, 6 and 12-month of 100%, 100%, 29% respectively for stent graft vs. 60%, 0, 0 for PTA (Rajan and Falk 2015). Shemesh et al. compared bare metal stents to stent grafts for the treatment of CAS, and showed superior primary access patency rates of 39% vs. 82% at 3-months, and 0 vs. 32% at 12-months. It was however surprising to note that the 12-month CAS following stent graft deployment was similar to the reported rates of POBA in the current audit and several other studies (D’cruz et al., 2018; Shemesh et al. 2008). There have been increasing evidence showing that neointimal hyperplasia can occur at stent edges at a later stage, limiting flow and resulting in patency loss. As such, a combination of stent or stent graft with PCB may be the future direction for the treatment of CAS. In a prospective proof of concept study of 8 patients, a combination of helical stent and PCB have been shown to result in primary patency rates of 83.3% at 1-year (Tang et al. 2020). Although the stents used were bare metal stents, the positive results from this small study suggest that stent or stent graft placement in the cephalic arch with PCB treatment in-stent or along the stent edges may prevent neointimal hyperplasia and help to maintain long-term patency for CAS.

Besides endovascular techniques, acute restoration of AVF function and CAS treatment with surgical management has also been described. Davies et al. demonstrated superiority in patency rates of cephalic arch transposition or bypass compared to PTA or bare metal stent placement (Davies et al. 2017). However, the results were confounded by the fact that surgical interventions...
were offered only to younger and healthier patients. The risks of open surgery may outweigh its benefit in older patients with higher cardiac risk compared to endovascular treatment.

Our audit is limited by several factors: being a single centre audit, the findings may not be generalizable to other patient populations. Due to the inherent limitations of a retrospective audit, the results may have potential confounders. Furthermore, selection bias could not be excluded. Specifically, the group of patients who received PCB had a greater severity of CAS in terms of percentage of stenosis compared to POBA, which may have contributed to the failure to achieve patency improvement with PCB. However, recurrent and de novo stenosis, median time from prior intervention and previous stenting were similar (Table 2). In addition, due to the small sample size of the audit, a type 2 error cannot be excluded. Nonetheless, it is a unique study reporting PCB use solely in one location i.e. the cephalic arch and comparing to a POBA group performed over a similar period of time and by the same operators.

Conclusions
In conclusion, treatment of CAS with PCB did not improve target lesion or access patency rates compared to POBA. Mechanical scaffolding is required in this unique location of the AVF circuit.

Abbreviations
CAS: Cephalic arch stenosis; PTA: Percutaneous transluminal angioplasty; POBA: Plain old balloon angioplasty; PCB: Paclitaxel-coated balloons

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Authors’ contributions
TYT researched the literature and conceived the study, TYT, CJQY, SXYS, SCP, CST, AG, and TTC was involved in gaining ethical approval, patient recruitment, and data collection. SXYS was involved in data analysis and interpretation. RKAT, and TYT drafted the manuscript. All authors reviewed and edited the manuscript and approved the final version of the manuscript.

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Availability of data and materials
The datasets generated and/or analysed during the current study are not publicly available due to the Singhealth Centralised Institutional Review Board requirements but are available from the corresponding author on reasonable request.

Declarations
Ethics approval and consent to participate
This quality audit performed with de-identified data was exempted from the Singhealth Centralised Institutional Review Board review (CIRB Ref. 2020/2320).

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interest.

Author details
1Department of Renal Medicine, Singapore General Hospital, Singapore, Singapore. 2Department of Vascular Surgery, Singapore General Hospital, Singapore, Singapore. 3Department of Vascular Interventional Radiology, Singapore General Hospital, Singapore, Singapore. 4Duke NUS Graduate Medical School, Singapore, Singapore.

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