Comparison of Primary Patency Rate between Drug-Coated Balloon and Plain Balloon Angioplasty in Hemodialysis Access

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ABSTRACT

Objective: Hemodialysis adequacy in end-stage renal disease patients plays a crucial role in their quality of life. Repeated stenosis at the anastomotic site of arteriovenous fistula and synthetic arteriovenous graft are a major cause of access failure resulting in hospitalization, catheter usage, and contributing substantially to increased health care costs. Although standard plain balloon angioplasty (PBA) is successful, the patency rate over time is often poor. Drug-coated balloons (DCB) delivering an anti-restenosis agent, Paclitaxel, may improve patency. In this study, we aimed to investigate whether there is an increase in primary patency rate in drug-coated balloon angioplasty compared to conventional plain balloon angioplasty.

Materials and Methods: We performed a retrospective analysis of 55 patients with stenotic arteriovenous fistulas (AVF), and arteriovenous grafts (AVG) treated with DCB or PBA. Thirty-five patients were treated with drug-coated balloons, while twenty patients were treated with the standard plain balloon angioplasty. Follow up assessment was scheduled at three months, six months, and nine months. Our primary outcome was the primary patency rate, defined as the interval from the time of intervention until hemodialysis inadequacy.

Results: There were 55 patients including twenty-one males and thirty-four females participated in the study. The average age of the 55 patients was 65.43 ± 12.89 years. Thirty (54.5%) patients were diabetes mellitus and 40 (72.7%) patients had hypertension. Seven patients (12.7%) had dyslipidemia. Eight patients (14.5%) had ischemic heart disease. And four patients (7.3%) had hyperparathyroidism. No significant differences in patency rate were found between gender, age group and patients' underlying diseases. The proportion of primary patency rate comparing between the DCB and PBA treatment was 96.3% versus 73.9% at 6 months (P=0.017) and 92.6% versus 40% at 9 months (P<0.001). After multivariable analysis was performed (adjusted for sex, age, and underlying diseases), we found that stenosis was more likely to occur in patients who had undergone plain balloon angioplasty rather than drug-coated balloon angioplasty (HR 15.75; 95% CI 2.5%-99.1%, P=0.003).

Conclusion: Drug-coated balloon angioplasty, when compared with plain balloon angioplasty, achieves a more desirable primary patency rate at 6 months and 9 months after the procedure.

Keywords: Arteriovenous fistula (AVF); Arteriovenous graft (AVG); Paclitaxel, Drug-Coated Balloon (DCB); Plain Balloon Angioplasty (PBA); primary patency; hemodialysis access (Siriraj Med J 2022; 74: 388-394)

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INTRODUCTION

The prevalence of chronic kidney disease (CKD) is significantly rising globally. Its association with major morbidity and mortality demands distinct attention as one of the growing public health concerns. Currently, amongst Thais, there are nearly 12 million people affected with CKD and roughly 6 million people with advanced stage CKD. Over one hundred thousand patients require dialysis.[1] The Thailand renal replacement therapy (TRT) noted that an addition of 15,462 new patients on hemodialysis, 3,598 new patient on peritoneal dialysis and 719 new patients performed kidney transplant in 2020, has brought the total number to 19,722 patients.[2] For these patients, hemodialysis is the preferred treatment to substitute for kidney function and ensure their survival.

Presently, two techniques have been used to facilitate hemodialysis: these are arteriovenous fistula (AVF) and arteriovenous graft (AVG). The **K**idney **D**isease **O**utcomes **Q**uality **I**nitiative (KDOQI) vascular access guideline prefers AVF due to ease of care and has suggested AVG only when AVF is unattainable. Nevertheless, both artificial vasculatures often come with complications such as repeated stenosis which led to hemodialysis failure, hospitalization and even death. The primary failure rate of AVF is approximately 20% higher than that of AVGs.[3]

The first line of approach to hemodialysis failure, caused from stenosis of hemodialysis access, is balloon angioplasty. Plain balloon angioplasty (PBA) is currently the procedure most commonly performed. However, repeated stenosis occurs regularly. Alternate techniques, such as bare metal stents, have been investigated to combat the obstruction but none have had promising results.[4] Recently, one multicenter randomized trial found that a drug-coated balloon (DCB) appeared to reduce the occurrence of stenosis. The drug, paclitaxel, when applied to the balloon, caused the reduction of vessel wall remodeling and fibromuscular hyperplasia, and prevented neointimal hyperplasia from causing stenosis.[5,6]

In this study, we aimed to investigate whether there is an increase in the primary patency rate of AVF or AVG stenosis treated with drug-coated balloon angioplasty (DCB) with AVF or AVG stenosis treated with plain balloon angioplasty (PBA).

MATERIALS AND METHODS

Study design

This retrospective cohort study was conducted in chronic kidney disease patients suffering from primary patency failure of either AVF or AVG at the department of surgery, Burapha University, Thailand duration between August 2016 to October 2019. A total of 55 patients were enrolled. The inclusion criteria were the patient with chronic kidney failure stage 5 and at least 15 years of age diagnosed with the first episode of hemodialysis access failure. The diagnosis criteria of hemodialysis access failure were; 1) inadequate blood flow rate on the dialysis chart 2) presence with clinical of venous hypertension (high venous pressure more than 200 mmHg, arm swelling, upper extremity superficial vein dilatation) and 3) thrombosed of hemodialysis access. The diagnosis was confirmed with CT venography or venous duplex ultrasound, or intra-operative venography. The reduction of intraluminal more than 50% of actual diameter was defined as a significant stenosis lesion. This study aimed to investigate and compare the efficacy of both PBA and DCB in repairing stenosis and maintaining stenosis-free arteriovenous shunts in short- and mid-term scenarios.

Patient allocation and data collection

After informed consent, patients were given information about plain balloon angioplasty and drug-coated balloon angioplasty. Patients were allowed to choose which treatment they preferred. All patients were followed up every three months to evaluate hemodialysis adequacy and restenosis (failure of primary patency rate). The venipuncture site was assessed for prolonged bleeding and the general condition of the arm. The hemodialysis chart was reviewed. The protocol of patient's participation was approved by the Burapha University ethics committee (IRB Issue#280/2562) and was accomplished according to the Declaration of Helsinki and WHO guidelines. There was no external financial support provided.

Procedures

For the patient with clinical of inadequate blood flow rate or present with clinical of venous hypertension, CT venogram or duplex ultrasound was used to confirm the stenotic lesion which more than 50% luminal diameter reduction concerned significant stenosis. The procedure was performed under local anesthesia with monitor anesthetic care (MAC). PBA or DCB did the balloon angioplasty with actual venous diameter. The procedural success was dilatation of stenotic lesion to 80-100% of the actual venous diameter.

Graft thrombectomy was performed with forgarty catheter under local anesthesia with monitor anesthetic care (MAC) for those with graft thrombosis. After successful thrombectomy, intra-operative venography was performed to figure the stenosis portion. PBA or DCB did the balloon angioplasty with the actual size of the stenosis vein. The

final venogram was evaluated the operative result. The operative success was an enlargement of stenosis portion increased up to 80-100% of the actual venous diameter.

Post-operative surveillance

During the follow-up at 3, 6, and 9 months, the circuit pressure while hemodialysis in hemodialysis chart was reviewed to determine proper blood flow during dialysis (adequate arterial flow ≥ 300 ml/min and venous pressure < 200 mmHg). Primary patency rate is defined as the interval from the time of intervention (DCB or PBA) until the time of hemodialysis inadequacy. These following situations ended the primary patency; inadequate blood flow, thrombosed hemodialysis access, high venous pressure (more than 200 mmHg), recurrent arm swelling, or upper extremity superficial vein dilatation and confirmed with CT venography, venography, or duplex ultrasound.

Statistical analysis

The calculation of the sample size was based on two independent proportions formula references from Katsanos study.[8] Results are presented using descriptive statistics. The mean and standard deviations are represented for the continuous data. The comparison between groups was using the chi - square test for the categorical variables. While the continuous variables were compared with the student t-test. The Kaplan-Meier analysis was used to compare the event-free survival. All the statistics were calculated by SPSS, version 19.0 (SPSS Inc., Chicago, Illinois).

RESULTS

A total of fifty-five patients were enrolled in this study. Twenty patients were assigned to the control group (plain balloon angioplasty) (PBA), while 35 patients were assigned to the drug-coated balloon angioplasty (DCB) group. The overall average age was 65.43 ± 12.89 years. Baseline patient demographic data are shown in Table 1. Although there are more patients with diabetes mellitus and ischemic heart disease in the control group, there are no significant differences in baseline demographics between the two groups.

All participants completed the nine-month follow-up examination. At three months, the data displayed no significant differences in post-intervention primary patency rate between both groups (95% for the PBA group and 100% for the DCB group; p=0.192). However, a distinction between the two groups appeared at the six months and 9-months follow-up. At six months, the DCB group exhibited a significantly higher patency rate than the PBA group, 96.3% and 73%, respectively (Fig 1A). And even more evident at nine months, achieving up to 92% for the DCB group versus 40% for the PBA group (Fig 1B).

The chi-squared test showed in Table 2 indicated that sex, age, underlying (HT, DM, DLD, IHD, and hyperparathyroidism) were no effective defenses of patency rate. The restenosis was occurred in a patient with PBA than DCB within nine months (p-Value < 0.001)

Cox regression analysis was accomplished on all variables shown in Table 3. As expected, no significant

TABLE 1. Baseline patient demographics.

	Plain balloon (n=20)	Drug coated balloon (n=35)	P-value
Sex			
Male	5 (25%)	16 (45.7%)	
Female	15 (75%)	19 (54.3%)	0.128
Age (year)	66.63 ± 13.11	64.75 ± 12.91	0.607
Underlying conditions			
Hypertension	15 (75%)	25 (71.4%)	0.775
Diabetes mellitus	14 (70%)	16 (45.7%)	0.082
Dyslipidemia	1 (5%)	6 (17.1%)	0.194
Ischemic heart disease	5 (25%)	3 (8.6%)	0.096
Hyperparathyroidism	1 (5%)	3 (8.6%)	0.624
Follow up time (days)	7.64 (3.74, 13.15)	13.31 (5.74, 17.48)	0.172

Value presented as mean ± SD. or median (IQR) and n (%). P-value corresponds to independent t-test or Mann-Whitney test and Chi-square test.

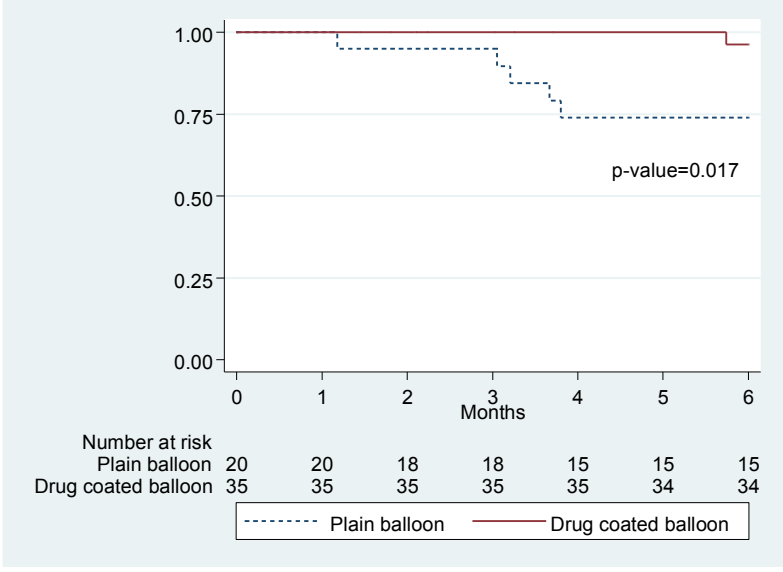

Fig 1A. Kaplan-Meier Curve of PBA group vs DCB group at 6 month follow up (p-value by log rank test)

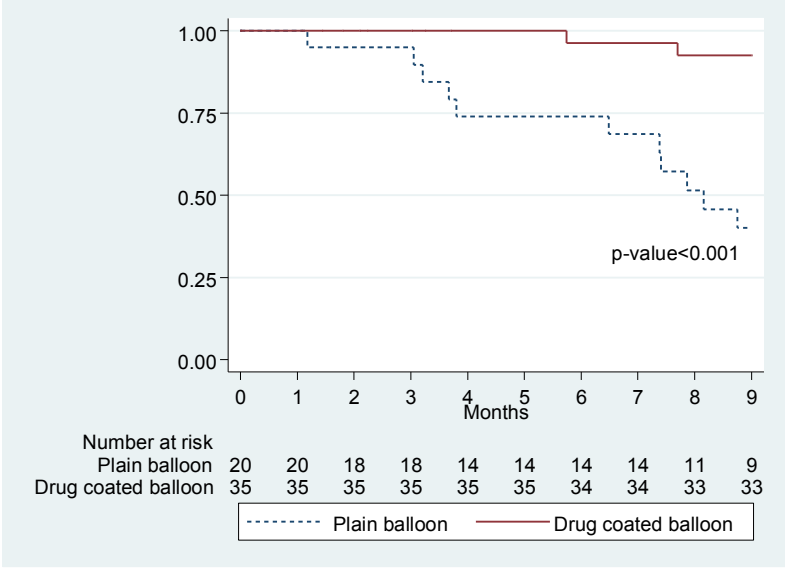

Fig 1B. Kaplan-Meier Curve of PBA group vs DCB group at 9 month follow up (p-value by log rank test)

TABLE 2. Categorical variables associated with patency at 9 months compared by chi-squared test.

	Patency (n=42)	Stenosis or occlusion (n=13)	P-value
Sex			
Female	26 (61.9%)	8 (61.5%)	0.981
Male	16 (38.1%)	5 (38.5%)	
Age (year)	65.26 ± 13.7	65.99 ± 10.31	
Underlying			
Hypertension	30 (71.4%)	10 (76.9%)	0.697
Diabetes mellitus	21 (50%)	9 (69.2%)	0.224
Dyslipidemia	6 (14.3%)	1 (7.7%)	0.533
Ischemic heart disease	4 (9.5%)	4 (30.8%)	0.058
Hyperparathyroidism	3 (7.1%)	1 (7.7%)	0.947
Treatment			
Plain balloon	9 (21.4%)	11 (84.6%)	<0.001*
Drug coated balloon	33 (78.6%)	2 (15.4%)	

TABLE 3. Univariates and multivariate cox regression analysis between two groups.

	Univariate		Multivariate	
	HR (95%CI)	P-value	Adj HR (95%CI)	P-value
Sex				
Female	1.04 (0.34, 3.19)	0.941	1.25 (0.32, 4.93)	0.75
Male	Reference	1	Reference	1
Age (year)	1 (0.96, 1.05)	0.948	0.98 (0.92, 1.03)	0.407
Underlying				
Hypertension	1.69 (0.46, 6.16)	0.425	2.17 (0.43, 10.97)	0.35
Diabetes mellitus	1.95 (0.6, 6.34)	0.267	1.5 (0.37, 5.99)	0.57
Dyslipidemia	0.85 (0.11, 6.54)	0.874	5.73 (0.44, 74.48)	0.183
Ischemic heart disease	2.79 (0.86, 9.08)	0.088	4.21 (0.76, 23.41)	0.101
Hyperparathyroidism	0.91 (0.12, 7.02)	0.929	3.52 (0.27, 45.8)	0.336
Treatment				
Plain balloon	11.71 (2.58, 53.08)	0.001*	15.75 (2.5, 99.1)	0.003*
Drug coated balloon	Reference	1	Reference	1

differences in patency rate were connected to age, sex, and underlying diseases. Nonetheless, after multivariable analysis was performed (adjusted for sex, age, and underlying diseases), we found that restenosis was more likely to occur in patients treated with PBA than DCB within nine months (HR 15.75; 95% CI 2.5%-99.1%, P=0.003) (Table 2).

DISCUSSION

There are currently two types of long-term hemodialysis access, arteriovenous fistulas (AVFs), and arteriovenous grafts (AVGs).[7] According to the Kidney Disease Outcomes Quality Initiative (KDOQI) vascular access guidelines, they recommended placement of AVF over AVG due to the low rate of infection and ease of care.[3] Praditsuktavorn demonstrated that the 12-months primary patency of a snuffbox arteriovenous fistula is roughly about 60%.[8] Although the primary patency rate of the AVFs is lower than AVGs, the long-term patency is superior to AVGs.[3] Two major publications compared the failure rate between AVFs and AVGs. The failure rate of AVFs and AVGs were approximately 40% and 20%, respectively. Conversely, with the long-term patency, AVFs were superior to AVGs (5 versus 2 years).[9,10] In the thrombosed AVG group, Puangpunngam et al. showed no difference in patency between endovascular or open thrombectomy.[11]

Numerous factors induce early AVF failure: small vessel diameter; wall damage during a surgical procedure; newly-developed accessory veins after placement; fluid shear stress at anastomosis; genetic predisposition to vasoconstriction neointimal hyperplasia; pre-existing venous neointimal hyperplasia; and preceding venipunctures.[12] Late AVF failure is usually caused by fibromuscular hyperplasia (fibrotic lesion formation) due to increased shear stress in the thin-walled outflow vein. Venous neointimal hyperplasia (VNH) is characterized by stenosis and subsequent thrombosis, which is a majority of the pathology of graft failure.[13] Roy et al. demonstrated that VHL was characterized by 1) Presence of smooth muscle cell/myofibroblast, 2) Accumulation of extracellular matrix component, 3) Angiogenesis within the neointimal and adventitia, and 4) Presence of an active macrophage cell layer lining graft material. This leads to blood flow reduction or stasis and subsequent thrombosis formation.[12]

Although PBA has been the conventional method to revise failing vascular access, the procedure itself initiates local inflammatory and proliferative repair responses. This consequently increases the rate of short-term restenosis, lowering the clinical efficacy of PBA.[14,15] Even with drug-eluting stents (DES), this obstacle is still present. A potential solution has been presented with the use of drug-coated balloon (DCB) technology in other settings such as in-stent restenosis in coronary artery disease or enhancing the patency of the treatment in peripheral arterial disease. This has led to the use of DCB for the revision of dialysis access failures.[5,16,17]

To further specify, the drug widely used to coat these balloons is called paclitaxel. A substance that is both lipophilic and cytotoxic, initiating local anti-proliferation of human arterial smooth muscle cells (haSMCs) and causes inhibition of access restenosis.[18] It is also selected to treat hemodialysis patients due to its pharmacokinetic properties. Paclitaxel renal clearance is very minimal (approximately 1-8%), making it relatively easy and safe to use and requiring no dosage modification for renal impairments. Paclitaxel is metabolized via other routes, such as hepatic, biliary, and fecal elimination.

Several randomized controlled trials have compared DCB and PBA efficacy in the treatment of failing vascular access.[17,19-22] A study by Katsanos et al. found that the primary patency of the DCB group was almost 3 times that of the PBA group. Hence, repeated procedures' requirement rate was lower in the DCB-treated lesions than the PBA (25% vs. 70%, p=0.002). The study also showed DCB had better mid-term primary patency than PBA.[20]

Similar results were also demonstrated by Yanqi Yin et al. where DCB demonstrated a higher primary patency rate at 6 months without evidence of unfavorable side effects.[14] However, the result suggested otherwise in another trial by Trerotola O et al. Where DCB showed no increase in effectiveness at six months compared to the conventional PBA.[17] This study has raised uncertainty among physicians trying to determine the role of DCBs in treating hemodialysis access stenosis.

The significant improvement of short- and mid-term secondary patency of hemodialysis access in DCB-treated angioplasty was proved in a recent meta-analysis by Chen et al.[19] However, further studies on long-term side effects are needed to investigate the safety of paclitaxel-coated angioplasty in patients with end-stage renal disease. A meta-analysis by Chenyu Liu et al., published by the journal of the American Heart Association in 2021, was derived from multiple randomized controlled trials comparing the safety and efficacy of these two methods. The results showed that DCB angioplasty was superior in maintaining target lesion primary patency and further showed no increase in the risk of mortality when compared with PBA.[21]

To the best of our knowledge, this is the first study in Thailand that compares traditional PBA and new DCB angioplasty for the treatment of failing dialysis vascular access circuits. Furthermore, although our study was a retrospective study, it is the first step in our effort to prove our hypothesis.

Study limitations

There are two core limitations in this study that could be noted for future research. First, the study is based on existing data from only one hospital, creating a possible bias from being non-blinded and single centered. Secondly, the patient sample size was less than initially calculated due to time constraints. Fortunately, some results are statistically significant. Drug-coated balloon angioplasty may show compelling results at three months with larger sample size.

CONCLUSION

This article is the first retrospective study in Thailand that shows that drug-coated-balloon angioplasty using paclitaxel-coated balloons has better long-term patency results when compared to standard plain balloon angioplasty. Blood vessel patency was improved at 6 and 9 months after the initial procedure. However, further studies are needed to assess the cost-effectiveness and mortality of end-stage renal disease patients.

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