Original Research Article

Efficacy and safety of paclitaxel drug-eluting balloons in femoropopliteal artery disease: a prospective observational study

Mohammed Hidayathulla*, Nagesh

Department of Cardiology, Sri Jayadeva institute of Cardiovascular Sciences and Research, Bangalore, Karnataka, India

*Correspondence:
Dr. Mohammed Hidayathulla,
E-mail: mdhidayathmd@gmail.com

ABSTRACT

Background: The femoropopliteal artery is most frequently involved artery in peripheral artery disease. To treat femoropopliteal artery disease (FPAD), various revascularization approaches have been available such as simple balloon angioplasty, debulking techniques, stent implantation, and recently the drug-eluting balloon (DEBs). Nowadays, the paclitaxel DEBs have been emerged to treat FPAD with promising outcomes. We therefore evaluate the efficacy and safety of paclitaxel DEBs in patients with lower limb FPAD.

Methods: In total, 25 patients with FPAD were enrolled in the study. All patients underwent peripheral angioplasty using paclitaxel DEBs via antegrade femoral approach or contralateral femoral artery using crossover sheath. Demographics, risk factors, clinical characteristics, and pre- and post-procedure VascuQol-6 score were noted.

Results: Out of 25 patients, the majority of patients (52%) were in the 6th decades of life. The incidence of FPAD was most common in patients with an O +ve blood group. The common risk factors of FPAD, include smoking (88%), diabetes (68%), dyslipidemia (68%), and hypertension (64%). Rest pain (64%) and ulcer (32%) were the most frequent clinical symptoms of FPAD. The percent stenosis was 100% in 17 patients, and 70-99% in 32 patients. A statistically significant difference was found in VascuQol-6 score between pre and post peripheral angioplasty (p<0.001).

Conclusions: We have concluded that the paclitaxel DEBs are safe and efficacious in treating FPAD. Authors recommend that clinician should educate FPAD patients pertaining to modification of controllable risk factors such as cessation of smoking, unhealthy diet, sedentary lifestyle, high blood pressure, and high blood sugar.

Keywords: Balloon, Paclitaxel, Peripheral artery disease, Revascularization, Risk factors

INTRODUCTION

Peripheral artery disease is a leading cardiovascular disease, affecting just over 200 million people globally.[1] This disease is caused by the accumulation of fatty plaque in the peripheral arteries, and usually involves abdominal aorta, iliac arteries, lower limbs, and rarely the upper extremities.[2] The femoropopliteal artery is most frequently associated with peripheral artery disease, and poses some of the greatest obstacles for interventional radiology. The incidence of FPAD has been continuously rising due to risk factors, such as smoking, lifestyle modification, family history, diabetes, hypertension, dyslipidemia and chronic kidney diseases. Patients with FPAD have varied clinical manifestations and course; some patients may remain asymptomatic, while others may develop arterial ulceration, intermittent claudication, resting limb ischemia, and limb loss.[3] Of these, the intermittent claudication is a common symptom likely to

disabled the affected individuals by painful limitation of walking capacity.

Endovascular intervention is an established treatment modality for patients with symptomatic FPAD.[4] The endovascular treatment landscape comprises a wide range of intervention with unique benefits and drawbacks. Bare metal stents generally offer promising clinical outcome than percutaneous transluminal angioplasty alone, but are linked to other complications, such as risk of post procedural restenosis, thrombosis, and stent fracture.[5-7] To address few of these issues and achieve better therapeutic effects, DEBs are an appealing option. A meta-analysis of randomized clinical trials revealed a long term safety and efficacy of DEBs in treatment of FPAD, compared to bare metal stents or percutaneous transluminal angioplasty alone.[8] Notwithstanding the fact that a large and growing body of literature has agreed with better long term outcomes of DEBs, still there have been much inconsistencies in the findings.[8,9] To this end, this study sought to assess the efficiency and safety of paclitaxel DEBs in the treatment of FPAD in patients with intermittent claudication and/or ulcers in lower limb.

METHODS

This was a prospective, observational study comprised 25 patients, who referred to department of cardiology, Sri Jayadeva institute of cardiovascular sciences and research, Bangalore, Karnataka, India during the period of January 2018 to January 2019. The study protocol was reviewed and approved by the local ethics committee. The informed consent form was obtained from all participants before enrollment in the study. Adults (>18 years of age) with more than 70% stenosis of femoral artery or popliteal artery or femoropopliteal artery presented with intermittent claudication and/or critical limb ischemia was the sole criterion for inclusion in the study. Exclusion criteria involved in the study were: untreated ipsilateral iliac artery stenosis, ongoing dialysis, acute thromboembolic disease of the leg, and infra-inguinal aneurysms disease.

Data collection

Based on inclusion and exclusion criteria, patients were selected for the study. The definite diagnosis was made based on clinical examination and peripheral computed tomographic angiography. Baseline demography details, and previous medical, surgical, or drug history was recorded. Ulcers or gangrene if present, were thoroughly examined with respect to its site, position, and the presence of infection. Fontaine and Rutherford classification were used to evaluate severity related to claudication or rest pain.[10] Prior to start angioplasty procedures, routine hematology tests were done. All patients were subjected to peripheral angioplasty using paclitaxel DEBs via antegrade femoral approach or from contralateral femoral artery using crossover sheath. Patients were followed-up at 3 months, 6 months, and 1

year after the intervention. At regular follow-up visits, clinical examination, peripheral arteries examination of both upper limbs and lower limbs, and duplex ultrasound were done. In order to assess the quality of life, pre and post procedure VascuQol-6 scores were reported. The questionnaire was given to patients in order to assess quality of life after the angioplasty procedures (Annexure I). Each question was scored between one and four. The total score was calculated by summing the score of each question. Importantly, a higher value indicates better health status.

Peripheral angioplasty procedure

Following local anesthesia, access to the site was obtained via the ipsilateral femoral artery for mid and distal superficial femoral artery or popliteal artery lesions, whereas for ostial and proximal superficial femoral artery lesions, the contralateral femoral artery approach was accessed using the crossover sheath. The vascular access was obtained using Seldinger's technique. The inguinal crease is highly variable in relation to the common femoral artery bifurcation, identifying the femoral head under fluoroscopy or use of ultrasound imaging allows direct imaging and proper puncture of common femoral artery bifurcation. A 4F-7F arterial sheaths were used in this intervention. Prior to intervention, patients were administered heparin using intravenous bolus of 80-100 units/kg. In case of prolonged procedure, the activated clotting time was checked, and redosing of heparin was given to maintain the activated clotting time >250 seconds. The lesion was crossed using a multipurpose catheter (5F), and angled with a 0.035-inch TERUMO guide wire assembly. Selective angiogram was done to assess the lesion anatomy and planned for intervention. Later, it was exchanged with a 0.014/0.018-inch guide wire. Initial pre-dilatation done using peripheral percutaneous transluminal angioplasty balloon. Later on, the lesions were dilated with paclitaxel DEBs and inflated for 3 minutes. Final angiogram was done to demonstrate the final outcomes and assess complications.

Definitions

Smokers: Smokers defined as those who smoke either beedi, cigarette, or cigar more than four times per week.

Obesity: It is defined as BMI >30 kg/m^2, calculated using Quetlet's index.

Hypertension: It is defined as systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg, or taking medications for hypertension.

Diabetes mellitus: It is described as fasting blood glucose ≥126 mg/dl, or post prandial blood glucose ≥200 mg/dl, or past history of diabetes mellitus, or taking medications for diabetes.

Dyslipidemia: It is characterized as total cholesterol ≥200 mg/dl, triglycerides >150 mg/dl, low density lipoprotein >130 mg/dl, high density lipoprotein <35 mg/dl, or triglycerides >150 mg/dl, or a combination thereof, or known case of dyslipidemia, or taking medications for dyslipidemia.

Critical limb ischemia: It is defined as a recurring ischemic rest pain requiring analgesia for >2 weeks or ulceration or gangrene of foot or toes with ankle systolic pressure <50 mmHg or toe systolic pressure <30 mmHg (Fontaine's III and IV).[11]

Data analysis

The statistical analysis was done using the statistical package for social sciences version 16.0 software (SPSS Inc., Chicago, IL, USA). Continuous variables are presented as mean and standard deviation. Categorical variable is expressed as frequency. The paired T test was used to compare pre and post procedure VascuQol-6 score. P value <0.05 was deemed as statistically significant.

RESULTS

Twenty-five patients were enrolled in this study, the prevalence of FPAD was found to be higher (52%) in patients over the age of 61 years. Table 1 provides baseline demographics and lesion characteristics of enrolled patients. Of the 25 patients, 22 patients were male, and 3 patients were female with a male: female ratio of 7.3:1. About 72% of cases belonged to an O +ve blood group, 16% with the B +ve blood group, 8% with A +ve, and 4% to B -ve blood group. The majority of patients (88%) are chronic smokers. Diabetes (68%) and dyslipidemia (68%) followed by hypertension (64%) were the most frequent comorbidities significantly associated with FPAD. The most common symptoms associated with FPAD are rest pain and ulcer, which were present in 64% and 32% of cases, respectively. In our study population, claudication distance less than 200 was present in 80% of cases, and this value was 20% in more than 200 claudication distance. With respect to severity, Rutherford class 2, 3, 4, 5 and 6 were graded in 20%, 16%, 32%, 28%, and 4% of cases, respectively. The percent stenosis was 100% in 17 patients, and 70-99% in 32 patients. Mean length of stenosis was found to be 81.2±31.3mm. Among the 25 patients, PCI was successfully done in 24 patients (96%).

As can be seen from the Table 2, the most commonly used size of paclitaxel DEBs is between 4-6 mm in diameter and 80-150 mm in length.

There was a statistically significant difference in VascuQol-6 score between pre (M=8.6, SD=1.190) and post peripheral angioplasty procedures (M=21.60, SD: 2.693) with p value <0.001 (Figure 1).
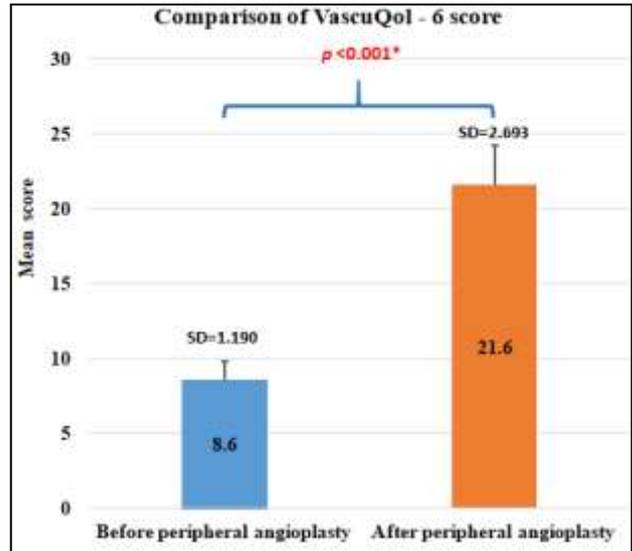
Figure 1: Comparison of VascuQol-6 score between before and after peripheral angioplasty.

Table 1: Baseline demographics and lesions characteristics of subjects, (n=25).

Characteristics	N (%)
Age group (years)	
<50	5 (20)
51-60	7 (28)
>61	13 (52)
Male	22 (88)
Blood group	
A+	02 (8)
B-	01 (4)
B+	04 (16)
O+	18 (72)
Smokers	22 (88)
Co-morbidities	
Hypertension	16 (64)
Dyslipidemia	17 (68)
Diabetes	17 (68)
Ischemic heart disease	3 (12)
Rest pain	16 (64)
Ulcer	8 (32)
Claudication distance by Fontaine grade (meters)	
<200	20 (80)
>200	05 (20)
Rutherford class	
2	5 (20)
3	4 (16)
4	8 (32)
5	7 (28)
6	1 (4)
Percent stenosis	
100	17 (68)
70-90	8 (32)
Mean length of stenosis (mm)	81.2±31.3

† Values are n (%) or mean and standard deviation.

Table 2: Procedural characteristics, (n=25).

Parameters	N (%)
Procedural success	24 (96)
Size of DEB (mm)	
4×80	1 (4)
4×120	1 (4)
5×120	4 (16)
5×150	4 (16)
6×120	3 (12)
6×150	5 (20)
6×60	4 (16)
6×80	2 (8)
6×80	1 (4)

DISCUSSION

DEBs are one of the good alternatives with promising outcomes for management of peripheral artery disease. Of all cytotoxic agents, paclitaxel is the drug of choice for DEBs due to lipophilic properties and prolonged duration of anti-proliferative effects. Paclitaxel applied to the inner side of the artery wall during balloon inflation in order to prevent neointimal proliferation, which is the main cause of restenosis.[12] Consistent with the literature, this research found that the incidence of FPAD was more common in older people with more than 60 years of age.[13-15]

In our study, 88% of cases were chronic smokers that has indicated high association between FPAD and smoking. This concurs well with previous findings.[16,17] In addition, Framingham study demonstrated doubled risk of intermittent claudication in smokers than non-smokers, and the odds ratio of developing intermittent claudication was 1.4 per 10 cigarettes smoked daily.[18] In agreement with the Edinburgh artery study, the odds ratios of intermittent claudication, major asymptomatic FPAD, and minor asymptomatic FPAD in current smokers was 3.7, 5.6, and 2.4, respectively.[19] Components of cigarette smoke include carbon monoxide and nicotine, have an impact on endothelial cell function; raise the reactivity, aggregation, and adhesion of platelets; cause vasoconstriction; and allow smooth muscle cells migration, and oxidized low-density lipoprotein containing foam cells into the vessel lining, and ultimately lead to atheroma formation.[20]

In our study, diabetes mellitus (68%) was the most common comorbidity associated with the development of FPAD. The yield in this investigation was somehow lower compared to value reported in INPACT SFA trial (73.3%). The pathophysiological changes, including elevated levels of blood sugar, insulin resistance, elevated production of vasoconstrictor substances, and smooth muscle hyper reactivity are mainly blamed for plaque formation in diabetic patients.

Dyslipidemia is another important determining factor in the formation of atherosclerotic plaques. In our study,

68% of total 25 cases had dyslipidemia as a major risk factor for FPAD development. On the other hand, in LEVANT trial, 89.6% of cases were associated with hyperlipidemia.[21] The atherogenic dyslipidemia includes elevation of low density lipoprotein (LDL) and very low density lipoprotein, and decline of high density lipoprotein. Small dense LDL particles readily get filtered into the arterial wall and get oxidized forming fatty streaks, and lead to the formation of atherosclerosis.

In our study, 64% of the cases were associated with hypertension, whereas, in INPACT SFA trial, 91.6% of cases were found to be hypertensive.[22] Hypertension induces the oxidative stress, leukocyte adhesion, macrophage accumulation, smooth muscle cell migration and proliferation, and intimal thickening of the arterial wall which leads to the formation of atherosclerotic plaque.

Mindy and co-workers were conducted a multi-ethnic study to evaluate co-relation between the blood groups and incidence of FPAD.[23] From the findings, he concluded that blood group A, and the A allele count were significantly associated with FPAD. In contrast, our study demonstrates that the majority of the cases belonged to the O +ve blood group. Of interest, this opens up scope for further studies in Indian population for identification of association between these two entities.

Of the 25 cases, one patient had developed ischemic rest pain after 24 hours of angioplasty procedure. Distal pulses were also absent, and duplex ultrasound revealed absence of wave forms distal to left mid superficial femoral artery, therefore this patient was treated with femoropopliteal bypass procedure. Another patient developed rest pain, ischemic ulcer, gangrene of the toes after 8 months of procedure and had to undergo a redo procedure with a DEB. This patient had uncontrolled diabetes and renal dysfunction secondary to diabetic nephropathy. One more patient presented with lower limb rest pain without ulceration after 12 months of the procedure. This patient was diabetic, smoker, and not cured with the medications, hence had to undergo a redo procedure.

In our study, procedure success rate was good compared to earlier reported data, and that was 96%. 2-year data from INPACT SFA trial revealed 78.9% success rate with paclitaxel DEBs, whereas 83.9% success rate was reported in LEVANT 2 trial.[21,22] In our study, there was a statically significant difference in VascuQol-6 score between pre- and post-peripheral angioplasty procedures (p<0.001). This result suggested that overall quality of life was improved after peripheral angioplasty.

Several limitations of this study should be acknowledged. First, the sample size was small in this study, hence, further study with the lager sample size is of mandate to draw a definite conclusion. Finally, the study was a single

center design, so extrapolation of these findings on entire Indian population may create bias.

CONCLUSION

This study sheds a light on the use of safety and efficacy of paclitaxel DEBs in treatment of FPAD. Diabetes, dyslipidemia, and hypertension were the major risk factors associated with the development of FPAD. Rest pain and ulcer were the most common symptoms of FPAD among our populations, and the patients with O +ve blood group were more prone to develop FPAD. The peripheral angioplasty procedure success rate in our study population was 96%. After peripheral angioplasty procedure, the post VascuQoL-6 score was improved that suggestive of improved quality of life.

REFERENCES

1. Benjamin EJ, Muntner P, Alonso A, Bittencourt MS, Callaway CW, Carson AP et al. Heart Disease and Stroke Statistics-2019 Update: A Report From the American Heart Association. Circulation. 2019;139(10):e56-28.
2. Aboyans V, Ricco J-B, Bartelink M-LEL, Björck M, Brodmann M, Cohnert T et al. 2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, in collaboration with the European Society for Vascular Surgery (ESVS): Document covering atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal, upper and lower extremity arteriesEndorsed by: the European Stroke Organization (ESO)The Task Force for the Diagnosis and Treatment of Peripheral Arterial Diseases of the European Society of Cardiology (ESC) and of the European Society for Vascular Surgery (ESVS). Eur Heart J. 2018;39(9):763-816.
3. Krishna SM, Moxon JV, Golledge J. A review of the pathophysiology and potential biomarkers for peripheral artery disease. Int J Mol Sci. 2015;16(5):11294-322.
4. Rooke TW, Hirsch AT, Misra S, Sidawy AN, Beckman JA, Findeiss LK et al. 2011 ACCF/AHA Focused Update of the Guideline for the Management of Patients With Peripheral Artery Disease (updating the 2005 guideline): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2011;58(19):2020-45.
5. Laird JR, Katzen BT, Scheinert D, Lammer J, Carpenter J, Buchbinder M et al. Nitinol stent implantation vs. balloon angioplasty for lesions in the superficial femoral and proximal popliteal arteries of patients with claudication: three-year follow-up from the RESILIENT randomized trial. J Endovasc Ther. 2012;19(1):1-9.
6. Iida O, Uematsu M, Soga Y, Hirano K, Suzuki K, Yokoi H et al. Timing of the restenosis following nitinol stenting in the superficial femoral artery and the factors associated with early and late restenoses. Catheter Cardiovasc Interv. 2011;78(4):611-7.
7. Krankenberg H, Tübler T, Sixt S, Fischer M, Schmiedel R, Schulte KL et al. German multicenter real-world registry of stenting for superficial femoral artery disease: clinical results and predictive factors for revascularization. J Endovasc Ther. 2014;21(4):463-71.
8. Katsanos K, Spiliopoulos S, Karunanithy N, Krokidis M, Sabharwal T, Taylor P. Bayesian network meta-analysis of nitinol stents, covered stents, drug-eluting stents, and drug-coated balloons in the femoropopliteal artery. J Vasc Surg. 2014;59(4):1123-33.
9. Giacoppo D, Cassese S, Harada Y, Colleran R, Michel J, Fusaro M et al. Drug-coated balloon versus plain balloon angioplasty for the treatment of femoropopliteal artery disease: an updated systematic review and meta-analysis of randomized clinical trials. JACC: Cardiovasc Interv. 2016;9(16):1731-42.
10. Hardman RL, Jazaeri O, Yi J, Smith M, Gupta R, editors. Overview of classification systems in peripheral artery disease. Seminars in interventional radiology, Thieme Medical Publishers. 2014.
11. Kavey RE, Daniels SR, Lauer RM, Atkins DL, Hayman LL, Taubert K. American Heart Association guidelines for primary prevention of atherosclerotic cardiovascular disease beginning in childhood. Circulation. 2003;107(11):1562-6.
12. Scheller B, Speck U, Abramjuk C, Bernhardt U, Böhm M, Nickenig G. Paclitaxel balloon coating, a novel method for prevention and therapy of restenosis. Circulation. 2004;110(7):810-4.
13. Abdulhannan P, Russell D, Homer-Vanniasinkam S. Peripheral arterial disease: a literature review. British medical bulletin. 2012;104:1.
14. Paquissi FC, Cuvinje ABP, Cuvinje AB. Prevalence of Peripheral Arterial Disease among Adult Patients Attending Outpatient Clinic at a General Hospital in South Angola. Scientifica. 2016;2016:2520973.
15. Guerchet M, Aboyans V, Mbelesso P, Mouanga AM, Salazar J, Bandzouzi B et al. Epidemiology of peripheral artery disease in elder general population of two cities of Central Africa: Bangui and Brazzaville. Eur J Vasc Endovasc Surg. 2012;44(2):164-9.
16. Ness J, Aronow WS, Ahn C. Risk factors for symptomatic peripheral arterial disease in older persons in an academic hospital-based geriatrics practice. J Am Geriatr Soc. 2000;48(3):312-4.
17. Leng G, Lee A, Fowkes F, Lowe G, Housley E. The relationship between cigarette smoking and cardiovascular risk factors in peripheral arterial

disease compared with ischaemic heart disease: The Edinburgh Artery Study. Eur Heart J. 1995;16(11):1542-48.

18. Kannel W, McGee D. Update on some epidemiologic features of intermittent claudication: the Framingham Study. J Am Geriatr Soc. 1985;33(1):13-8.

19. Gerald R. Fowkes F, Housley E, Riemersma RA, Macintyre CC, Cawood EH, Prescott RJ et al. Smoking, lipids, glucose intolerance, and blood pressure as risk factors for peripheral atherosclerosis compared with ischemic heart disease in the Edinburgh Artery Study. Am J Epidemiol. 1992;135(4):331-40.

20. Lu JT, Creager MA. The relationship of cigarette smoking to peripheral arterial disease. Rev Cardiovasc Med. 2004;5(4):189-93.

21. Rosenfield K, Jaff MR, White CJ, Rocha-Singh K, Mena-Hurtado C, Metzger DC et al. Trial of a paclitaxel-coated balloon for femoropopliteal artery disease. N Engl J Med. 2015;373(2):145-53.

22. Laird JR, Schneider PA, Tepe G, Brodmann M, Zeller T, Metzger C et al. Durability of treatment effect using a drug-coated balloon for femoropopliteal lesions: 24-month results of IN. PACT SFA. J Am Coll Cardiol. 2015;66(21):2329-38.

23. Pike MM, Larson NB, Wassel CL, Cohoon KP, Tsai MY, Pankow JS et al. ABO blood group is associated with peripheral arterial disease in African Americans: The Multi-Ethnic Study of Atherosclerosis (MESA). Thromb Res. 2017;153:1-6.