

## **Research Protocol**

### **Paclitaxel-eluting balloon versus plain angioplasty balloon for dysfunctional dialysis access: a prospective double-blinded randomized controlled trial**

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**Objective:**

The aim of this prospective randomized controlled trial (RCT) is to compare the target lesion primary patency rate at 12 months between paclitaxel-eluting balloon (PEB) versus plain balloon angioplasty (BA) for the treatment of venous stenoses of the dysfunctional vascular access patients undergoing haemodialysis (HD).

**Background of research:**

Dysfunctional renal access is problematic amongst renal patients, often requiring insertion of temporary lines and angioplasty intervention in order for HD to be re-established in the pre-existing arteriovenous fistula (AVF) / arteriovenous graft (AVG). Preliminary studies suggest that drug-eluting balloon angioplasty has a superior result, and require fewer re-interventions. Katsanos et al<sup>1,2</sup> has recently conducted a small RCT comparing paclitaxel-coated balloon angioplasty versus plain balloon angioplasty for treating failing dialysis access in 2012, with a significantly higher patency rate in drug-eluting balloon (75%) compared with plain angioplasty (25%) at 6 months. Similar success using drug-eluting balloon was reported by Patane et al<sup>3</sup> in 2014.

**Research setting:**

This is a single centre prospective RCT.

**Inclusion criteria:**

1. Age ranged from 18-80 years old
2. Native AVF or prosthetic AVG in the upper limb
3. Vascular access actively used for HD
4. At least one previous successful session of HD via access
5. Clinical signs of failing access due to presence of significant anatomical stenosis
6. Detection of elevated venous pressure during HD and/or decreased blood flow
7. Angiographically/sonographically proven venous outflow stenosis of >50%

**Exclusion criteria:**

1. Patient unable to provide informed consent
2. Patient unable to abide by study follow-up protocol
3. Patient participating in other relevant or conflicting studies
4. Vascular access circuit placed in lower extremities
5. Previous bare metal stent or stent graft placement in the access circuit
6. Haemodynamically significant stenosis of the central venous system
7. Metastatic malignancy or other terminal medical condition
8. Limited life expectancy (<6 months)
9. Blood coagulation disorders
10. Sepsis or active infection
11. Recent arm thrombophlebitis (<6 months)
12. Allergy or other known contraindication to iodinated contrast media, heparin or paclitaxel
13. Pregnancy

**Randomization method:**

Eligible patients will be randomized in 1 of 2 groups (group A and B) using sealed opaque envelopes containing computer-generated random numbers.

Group A patients will undergo paclitaxel-coated balloon angioplasty

Group B patients will undergo plain balloon angioplasty

The randomization is done only after full pretreatment investigations and has consented to participate in the trial.

**Pre-treatment assessments:**

Patients will be recruited from out-patient clinics and in-patient HD centre. They will undergo pre-treatment duplex ultrasound at the Vascular Laboratory to document the location, degree and length of lesion. They will be assessed in the Vascular Clinic afterwards

**Treatment procedures:**

Surgical techniques are standardized before starting the protocol. Only specialists experienced in angioplasty procedures will perform the procedures.

***Group A – paclitaxel-eluting balloon angioplasty***

All operations are performed under local anaesthesia in the supine position with the affected upper limb abducted at 90 degrees. The vascular access is approached by puncture (AVF) or cut-down (AVG) in either retrograde or antegrade method. A Fr 6 sheath is inserted, a 0.035" Terumo® hydrophilic guidewire and a diagnostic catheter are negotiated through the stenotic segment. A diagnostic angiogram is performed to delineate the location, degree and length of lesion. A plain balloon of appropriate size is introduced and inflated to nominal pressure for predilatation. A paclitaxel-eluting balloon of appropriate size is then introduced and inflated to nominal pressure for one minute. Device success is defined as <30% residual stenosis of the lesion. For device failure, further angioplasty is performed with introduction of a high-pressure balloon of appropriate size and inflation to appropriate pressure for three minutes. In case of a flow-limiting dissection, a bare metal nitinol stent of appropriate size is introduced and placed; and in case of a rupture, a covered stent of appropriate size is introduced and placed. A post-procedure angiogram is performed.

***Group B – plain balloon angioplasty***

All operations are performed under local anaesthesia in the supine position with the affected upper limb abducted at 90 degrees. The vascular access is approached by puncture (AVF) or cut-down (AVG) in either retrograde or antegrade method. A Fr 6 sheath is inserted, a 0.035" Terumo® hydrophilic guidewire and a diagnostic catheter are negotiated through the stenotic segment. A diagnostic angiogram is performed to delineate the location, degree and length of lesion. A plain balloon of appropriate size is introduced and inflated to nominal pressure. Device success is defined as <30% residual stenosis of the lesion. For device failure, further angioplasty is performed with introduction of a high-pressure balloon of appropriate size and inflation to appropriate pressure for three minutes. In case of a flow-limiting dissection, a bare metal nitinol stent of appropriate size is introduced and placed; and in case of a rupture, a covered stent of appropriate size is introduced and placed. A post-procedure angiogram is performed.

**Evaluation:****Post-treatment Assessment**

1. Sonographic assessment of location, degree and length of lesion at:
  - 1 week
  - 3 months
  - 6 months
  - 9 months
  - 12 months
2. Clinical assessment at subsequent HD sessions of clinical success and venous pressure
3. Complications of procedure
4. Need of re-intervention

**Outcome measurement:**

The primary endpoint is primary patency of the target lesion at 12 months.

The secondary endpoints are device success (defined as residual stenosis <30% without high pressure balloon post-dilatation), technical success (defined as final residual stenosis <30%), clinical success (defined as smooth HD for 3 consecutive sessions), venous pressure during HD sessions, median days of patency, complications of angioplasty and re-intervention rate

Patient clinical history, baseline characteristics, indications and results of procedure, intraoperative findings, as well as hospital course and postoperative follow-up were prospectively recorded.

**Sample Size:**

A sample size of 17 patients per group is required to detect a difference of 25% in patency rate with a power of 80% and a Type I error of 5%. With the assumption of 10% loss of follow-up in each group, a sample size of 20 patients per group is required.

**Statistical Analysis:**

All data will be prospectively collected and computerized in a database. Categorical variables are compared by  $\chi^2$  test. Continuous variables are compared by the Student *t* test or the Mann-Whitney *U* test, depending on distribution. All *P* values are two-sided. A *P* value of <0.05 indicates a statistically significant difference. All data are analyzed on an intention-to-treat principle. Primary and secondary outcomes are reported as relative risk and 95% confidence intervals.

**Potential hazard to patients:**

Angioplasty is a well established and widely used treatment for dysfunctional renal vascular access. The potential risk

PEB has been widely used in angioplasty for peripheral vascular disease with its safety established, and no significant systemic side effects have been reported in literature. All participating surgeons performing the treatments will have substantial experience with the procedure. All patients will receive the standard treatment and care. If technical difficulty or complications are encountered during the procedure, the procedure will be abandoned. The potential complications of angioplasty include puncture-related problems (bleeding, haematoma formation, pseudoaneurysm), vascular injury, contrast allergy and failure of procedure. The procedure related mortality rate is less than 1% as usual.

**Expected study duration:**

According to previous case load experience, we estimate that 1 years' time will be needed to recruit the target number of patients. Interim analysis will be performed at 6 months' time. The project is expected to be completed in 2017.

**Consent:**

Written voluntary consent will be obtained after full explanation of the trial to the patient before randomization.

**Conflict of Interest:**

All investigators have no financial interest in the materials used in the trial. This trial will not receive any financial support from any organizations that have any relationship with the material used in this trial.

**Ethical Concern:**

Drug eluting balloon is more commonly used in lower limb endovascular intervention but very few studies report the potential benefit on drug eluting balloon on dialysis access in terms of higher patency rate.

The issue of confidentiality is the major ethical issue, and will be solved by recording the data in a manner that does not allow the participants to be identified (ie. using a non-recognizable code for each patient). A review of medical records that have been already recorded as part of clinical care, therefore this poses no physical risks.

This study complies with the ICH-GCP Guidelines.

**References:**

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2. Kitrou PM, Spiliopoulos S, Katsanos K, Papachristou E, Siablis D, Karnabatidis D. Paclitaxel-Coated versus Plain Balloon Angioplasty for Dysfunctional Arteriovenous Fistulae: One-Year Results of a Prospective Randomized Controlled Trial. *J Vasc Interv Radiol* 2015; 26:348-354
3. Patane D, Giuffrida S, Morale W, L'Anfusa G, Puliatti D, Bisceglie P, Seminara G, Calcara G, Di Landro D, Malfa P. Drug-Eluting Balloon for the Treatment of Failing Hemodialytic Radiocephalic Arteriovenous Fistulas: Our Experience in the Treatment of Juxta-Anastomotic Stenoses. *J Vasc Access* 2014; 15(5):388-43