European Journal of Radiology 84 (2015) 418–423

Contents lists available at ScienceDirect

European Journal of Radiology

journal homepage: www.elsevier.com/locate/ejrad

Drug-eluting versus plain balloon angioplasty for the treatment of failing dialysis access: Final results and cost-effectiveness analysis from a prospective randomized controlled trial (NCT01174472)

Panagiotis M. Kitrou[a,*], Konstantinos Katsanos[b], Stavros Spiliopoulos[a], Dimitris Karnabatidis[a], Dimitris Siablis[a]

[a] Department of Interventional Radiology, Patras University Hospital, School of Medicine, Rion 26504, Greece
[b] Department of Interventional Radiology, Guy's and St. Thomas' Hospitals, NHS Foundation Trust, King's Health Partners, London SE1 7EH, United Kingdom

ARTICLE INFO

Article history:
Received 15 May 2014
Received in revised form
25 November 2014
Accepted 28 November 2014

Keywords:
Drug-eluting balloons
Dialysis
Restenosis
Neointimal hyperplasia

ABSTRACT

Objective: To report the final results and cost-effectiveness analysis of a prospective randomized controlled trial investigating drug-eluting balloon (DEB) versus plain balloon angioplasty (BA) for the treatment of failing dialysis access (NCT01174472).
Methods: 40 patients were randomized to angioplasty with either DEB ($n=20$) or BA ($n=20$) for treatment of significant venous stenosis causing a failing dialysis access. Both arteriovenous fistulas (AVF) and synthetic arteriovenous grafts (AVG) were included. Angiographic follow up was scheduled every two months. Primary endpoints were technical success and target lesion primary patency at 1 year. Cumulative and survival analysis was performed. Incremental net benefit (INB) and incremental cost effectiveness ratio (ICER) were calculated and the cost-effectiveness acceptability curve (CEAC) was drawn.
Results: Baseline variables were equally distributed between the two groups. At 1 year, cumulative target lesion primary patency was significantly higher after DEB application (35% vs. 5% after BA, $p<0.001$). Overall, median primary patency was 0.64 years in case of DEB vs. 0.36 years in case of BA ($p=0.0007$; unadjusted HR = 0.27 [95%CI: 0.13–0.58]; Cox adjusted HR = 0.23 [95%CI: 0.10–0.50]). ICER was 2198 Euros (€) per primary patency year of dialysis access gained. INB was 1068€ (95%CI: 31–2105€) for a willingness-to-pay (WTP) threshold of 5000€ (corresponding acceptability probability >97%).
Conclusion: DEB angioplasty may be a cost-effective option that significantly improves patency after angioplasty of venous stenoses of failing vascular dialysis access. Further large-scale randomized trials are warranted.

1. Introduction

Plain balloon angioplasty (BA) has been considered for years the method of choice for endovascular treatment of venous stenosis in failing arteriovenous fistula (AVF) or synthetic arteriovenous graft (AVG) dialysis access [1,2]. However, short-term restenosis leading to increased re-intervention and access thrombosis events has limited its clinical efficacy [1]. In 2010, results from a multi-center randomized trial reported that self-expandable stent graft deployment is a valid alternative that may outweigh traditional BA for the treatment of venous juxta-anastomotic stenosis of AVGs [3].

Recently, percutaneous transluminal angioplasty using drug-eluting balloons (DEB) has been reported to inhibit neointimal hyperplasia and consequently reduce restenosis in the superficial femoral artery [4] and in coronary artery in-stent restenosis [5]. DEB technology is based on the combination of angioplasty and local drug delivery made possible through specially designed carriers applied on the balloon surface, that enable the adhesion and effective delivery of the cytotoxic drug on the vessel wall. The main advantage of DEB drug-delivery technology over drug-eluting stents is the inhibition of neointimal hyperplasia without the permanent placement of a metallic mesh known to incite a continuous inflammatory and a chronic mechanical irritation to the vessel wall [6]. This motivated the authors to investigate DEB for angioplasty of failing dialysis access.

Previously published interim 6-month outcomes of the present study have shown that DEB angioplasty resulted in significantly

* Corresponding author at: Patras University Hospital, Interventional Radiology Department, Patras P.C. 26500, Greece Tel.: +30 2613603218; fax: +30 2613603218.
E-mail address: panoskitrou@gmail.com (P.M. Kitrou).

http://dx.doi.org/10.1016/j.ejrad.2014.11.037
0720-048X/

increased primary patency rates when compared with BA in the treatment of failing dialysis circuits [7]. We herein report the final outcomes of this single-center, randomized controlled trial that compared paclitaxel-eluting versus plain balloon angioplasty for the treatment of venous stenosis in failing dialysis access. The authors have also performed a relevant cost-effectiveness analysis to explore the cost-utility ratio of paclitaxel-coated balloons in this setting.

2. Materials and methods

2.1. Study design

The protocol was approved by the local hospital's Ethical and Scientific Review Board and was registered on an open access public dedicated database according to international guidelines regarding prospective randomized clinical protocols (www.clinicaltrials.gov; NCT01174472). This was a prospective, single-center, single-blinded, randomized trial designed to compare the 1-year angiographic and clinical outcomes of paclitaxel-eluting over plain balloon angioplasty for the management of venous stenosis in AVGs and AVFs. For the non-inferiority design, a 15% margin of difference between the two treatment methods was used ($\alpha = 0.05$ and statistical power set at 0.80). The expected 1-year primary patency rate was estimated to be 50% in the active treatment group and 25% in the reference treatment control group. All patients were explained the potential risks and benefits of both procedures (DEB and plain balloon angioplasty) and provided written informed consent prior to the procedure. Patients eligible for the study suffered from at least one angiographically confirmed significant venous stenosis that caused a failing dialysis access according to standard international clinical and surveillance protocols. Both AVFs and AVGs were included in the study. Exclusion criteria comprised vessels with diameter <3 mm and >7 mm and patients with any general contraindications to endovascular therapy [7]. Randomization was performed on an intention to treat basis using predetermined envelopes on a 1:1 rate and patients were enrolled either in the active comparator group (DEB group) or the control group (BA group). All patients were scheduled to undergo angiographic follow up every two months. The study's inclusion and exclusion criteria and a detailed outline of the study design, statistical power and treatment protocol have been published previously [7].

2.2. Devices

The IN.PACT over-the-wire balloon paclitaxel-eluting, dilatation catheters (Invatec-Medtronic, Brescia, Italy) were used in patients randomized in the experimental comparator group (DEB group). The balloon's surface is coated with a paclitaxel-eluting formulation using urea as a spacer. This highly hydrophilic combination enables a better contact of the lipophilic paclitaxel with the vascular wall. The specific balloon catheters are available at a maximum diameter of 7 mm and a maximum length of 80 mm, while the dose of paclitaxel on the balloon's surface is 3 $\mu g/mm^2$. Paclitaxel is a cytotoxic agent and its mechanism of action is based on the disassembly of microtubules implemented in cellular mitosis. Patients randomized to the control group (PB group) underwent angioplasty with a variety of high-pressure balloon catheters [Dorado PTA balloon dilatator catheter (Bard Peripheral Vascular, Tempe, AZ, USA), Blue Max PTA (Boston Scientific, Natick, MA, USA), Conquest PTA Dilatation Catheter (Bard Peripheral Vascular, Tempe, AZ, USA)].

2.3. Procedure

All patients were referred for a failing dialysis access and recruited in the study on the basis of well-accepted indications according to the KDOQI (Kidney Disease Outcomes Quality Initiative) recommendations; i.e. persistent swelling of the arm, presence of collateral veins, prolonged bleeding after needle withdrawal, or altered characteristics of pulse or thrill in a graft or outflow vein [2]. The patients' demographics and medical history were recorded. Bolus Cephalosporin 750 mg i.v. was administered for prophylaxis prior to the procedure. In brief, vascular access was obtained on a non-aneurysmal part of the AVG or AVF, using a micro-puncture set (Venastick Set; Angiotech, PBN Medicals, Stenlose, Denmark), under local anesthesia. Digital subtraction angiography (DSA) was performed through the 4Fr catheter of the micro-puncture set, to accurately detect the location and morphology of the stenosis. Successively, the sheath was upsized to 6Fr and a single bolus dose of 5000 IU of heparin was administered. Balloon size was chosen to match or exceed by 1 mm the target vessel diameter according to visual estimation. Balloon pre-dilatation or post-dilatation was performed only if deemed necessary by the first operator. Final angiogram of the entire vascular access was always performed in order to evaluate the procedural result, to exclude any immediate complications and to serve as a reference DSA for all subsequent regular bimonthly follow up angiograms.

2.4. Outcome measures

The study's primary endpoints were technical success, defined as <30% residual stenosis after DEB or BA, in comparison to the reference diameter of the most proximal non-aneurysmal vein segment, and target lesion primary patency at 1 year, defined as <50% angiographic restenosis with no need for any additional percutaneous or surgical procedure within the previously treated area. Loss of primary patency was recorded in the event of clinically significant binary (>50%) restenosis compared with the most proximal non-aneurysmal venous site, or clinically driven re-intervention (surgical or percutaneous), or dialysis access thrombosis. Residual stenosis and restenosis were calculated using a semi-automated quantitative vessel analysis (QVA) dedicated software (Allura Xper FD20; Xcelera Release 7.2; Philips Medical Systems, Amsterdam, The Netherlands). Clinically driven surgical or percutaneous reintervention was performed in target lesion restenosis of $\geq$50% associated with clinical and/or hemodynamic abnormality. Secondary endpoints included overall circuit survival, defined as a functional vascular access regardless of any interim procedures, minor and major complication rates according to internationally accepted reporting standards [2].

2.5. Cost-effectiveness

A cost-effectiveness analysis was performed in the context of the present randomized controlled trial by considering only direct healthcare expenditures of the two angioplasty approaches under investigation. In the absence of relevant cost-utility and quality of life information, the incremental cost-effectiveness ratio (ICER) was calculated as direct extra costs per year of primary patency gained. Costs were expressed in Euros (€) and derived from information on local reimbursement of devices used. Diagnosis-related group (DRG) tariff for the procedure was 1494 Euros for both groups and the only incremental price difference between the 2 groups was the cost of the paclitaxel-coated device in case of the DEB group. The net price of the IN.PACT paclitaxel-eluting dilatation catheter (Invatec-Medtronic, Brescia, Italy) was 950€ during the period that the study was conducted. The Central Limit Theorem (CLT) was employed for calculation of incremental net benefits (INB), cost-effectiveness acceptability curve (CEAC) and confidence ellipses with the relevant 95% confidence. The CLT states that whatever the observed shape of the distributions of the recorded costs and treatment effects, they will tend to