CLINICAL STUDY

Paclitaxel-Coated Balloons for the Treatment of Symptomatic Central Venous Stenosis in Dialysis Access: Results from a Randomized Controlled Trial

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ABSTRACT

Purpose: To compare the clinically-assessed intervention-free period (IFP) of paclitaxel-coated balloon (PCB) vs conventional balloon angioplasty (CBA) for the treatment of symptomatic central venous stenosis (CVS) in dialysis access.

Materials and Methods: Within 20 months, 40 dialysis patients (19/40 arteriovenous fistulae [AVFs] and 21/40 arteriovenous grafts [AVGs]) were randomized to undergo angioplasty either with a PCB (PCB group, n = 20; 14/20 male; age: 56.7) or CBA (CBA group, n = 20; 15/20 male; age: 57). There were 15/20 restenotic lesions in PCB group and 12/20 in CBA group. In 25/40 cases, patients had an ipsilateral catheter insertion in the past. Primary endpoint was clinically-assessed intervention-free period (IFP) of the treated segment at 6 months, while secondary endpoints included complication rates during follow-up period and identification of factors influencing IFP.

Results: Median IFP was significantly better in PCB group (PCB group: 179 days, vs CBA group: 124.5 days, $P = .026$). Mean follow-up period was 180 days (range, 5–479). There was no significant difference between AVGs and AVFs ($P = .17$), treatment of de novo vs restenotic lesions ($P = .33$), or prior presence of catheter insertion ($P = .21$). No complications were observed. In restenotic lesions in PCB group, longitudinal comparison between treatments also showed a significant difference in favor of PCB treatment (median IFP in PCB* group 177 vs 91 days in CBA* group; $P = .01$).

Conclusions: In this prospective study, PCB had significantly better results compared with CBA for the treatment of symptomatic central venous stenosis in dialysis access. Retrospective longitudinal comparison of treatments in the same patients also showed a significant difference in favor of PCBs.

ABBREVIATIONS

CBA = conventional balloon angioplasty, CI = confidence interval, CVS = central venous stenosis, DSA = digital subtraction angiography, HR = hazard ratio, PCB = paclitaxel-coated balloon, QVA = quantitative vessel analysis, SVC = superior vena cava

Although it is an incidental finding in many cases, central venous stenosis (CVS) could become symptomatic, resulting not only in inadequate dialysis performance but also in clinical manifestations such as ipsilateral neck, arm, or breast swelling (1). Previous insertion of foreign materials, mainly central venous catheters, accompanied by actual use of the access circuit for dialysis, are the main causes of CVS in dialysis recipients (2).

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Standard interventional practice for CVS is conventional angioplasty, but this is associated with patency rates as low as 28.9% at 6 months and 25% at 1 year (3,4). These patency rates may be twice as high when high-pressure balloons are used (eg, 60% at 6 mo) (5,6). Immediate elastic recoil is another possible problem in the treatment of CVS (subclavian vein, brachiocephalic vein, superior vena cava [SVC]) (7–9). Placement of a bare metal stent (BMS) is proposed in these "bailout" cases and in cases in which restenosis occurs in less than 3 months after conventional balloon angioplasty (CBA), and has been reported to be associated with assisted patency rates between 33% and 56% at 1 year (10,11). Data from recently published studies suggest stent grafts as a valid alternative for persistent CVS even in the setting of in-stent restenosis (12,13).

Paclitaxel-coated balloons (PCBs) have been tested for their safety and efficacy in the treatment of dysfunctional dialysis access in a few randomized studies and retrospective analysis of cases, with encouraging results so far (14–18). In two randomized controlled trials that used PCBs in arteriovenous fistulae (AVFs) and the venous outflow of arteriovenous grafts (AVGs) (14,15), the use of PCBs demonstrated significantly better results than conventional angioplasty. However, central venous stenoses were not treated in any of these studies.

The present randomized controlled trial was designed to investigate the safety and effectiveness of PCB use in the treatment of symptomatic CVS in dialysis access compared with CBA.

MATERIALS AND METHODS

Study Design

This was a prospective, single-center, single-blinded, randomized controlled trial approved by the hospital's ethics and scientific committee. A dedicated informed consent form was signed by all patients recruited in the study. Patients and referring physicians were blinded to the treatment received, but, because of the special characteristics of the catheters, operators were not.

Randomization

Patients referred from their dialysis center with clinical signs of CVS (arm swelling; pain, tenderness, and/or erythema of the ipsilateral extremity; breast or neck swelling; visible collateral venous network; or access dysfunction) ipsilateral to their dialysis circuit were subjected to digital subtraction angiography (DSA). Patients with CVS observed and estimated as nonsignificant (< 50% stenosis) or a vessel > 12 mm in diameter by visual estimation were excluded from the trial (**Fig 1**). Other exclusion criteria were presence of a BMS or stent graft or vascular access thrombosis. In cases of contrast medium allergy, the procedure was performed with the use of CO_2. If the aforementioned factors did not occur and the rest of the inclusion and exclusion criteria were fulfilled (**Table 1**), patients were randomized to receive CBA or CBA plus PCB angioplasty in separate procedures on the same day. Randomization was performed on a 1:1 basis by using sealed opaque envelopes.

Study Characteristics

From January 2014 to August 2015, 59 patients visited our department with clinical signs of CVS. Of those, 19 patients were excluded from the study because they did not meet the inclusion and exclusion criteria, and 40 patients were finally recruited: 20 in each group (**Fig 1**). The lesions treated were situated in the subclavian vein in the majority of cases (n = 12 in the PCB group; n = 13 in the CBA group). Lesions were also located in the brachiocephalic vein (n = 5 in each group) and SVC (n = 3 in the PCB group; n = 2 in the CBA group). No concomitant lesions were present. Additionally, most lesions were restenotic; that is, they had been treated with CBA before patient recruitment in the study (15 of 20 [75%] in the PCB group and 12 of 20 [60%] in the CBA group). There was a balance between AVFs and AVGs in both groups, and previous ipsilateral catheter insertion was common (13 of 20 [65%] in the PCB group and 12 of 20 [60%] in the CBA group; **Table 2**).

Device

The device under investigation was the Lutonix balloon (Bard Peripheral Vascular, Tempe, Arizona), which is coated with paclitaxel at a dose of 2 μg/mm^2. Paclitaxel exerts its potent cytotoxic action by inhibiting the disassembly of microtubules in the mitotic phase of the cell cycle, thereby causing cell apoptosis. The role of PCBs in the peripheral arterial bed has been well investigated, mainly in the superficial femoral artery (19). This specific device is available in diameters as large as 12 mm. It is a semi-compliant balloon with a maximum burst pressure of 12 atm and is mainly used as a drug delivery device rather than a percutaneous transluminal angioplasty balloon catheter. Therefore, vessel wall preparation is necessary for better contact of the drug to the vascular wall during inflation and therefore better drug distribution.

Procedure

Access was gained, and a hydrophilic catheter (Terumo Europe, Leuven, Belgium) was advanced to the inferior vena cava. A new DSA study was performed before angioplasty. When the wire had been placed in the inferior vena cava, 5,000 IU of heparin was administered.

In the CBA group, angioplasty was performed with a 2-minute inflation of one of several high-pressure balloons (Atlas, Conquest, Dorado [Bard Peripheral Vascular], or Mustang [Boston Scientific, Marlborough, Massachusetts]). In case of residual stenosis (> 30% by visual estimation), a second prolonged inflation was performed (4 min). If judged necessary by the physician, a balloon 1 mm larger in diameter was used. The aim was to achieve residual stenosis of < 30% by visual estimation on orthogonal projections