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Review Article

The Role of the Antiproliferative Therapy in the Treatment of Peripheral Artery Disease

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Introduction

In the last decades the treatment of peripheral artery disease (PAD) recognizes an impressive rise in the number of endovascular procedures. The most sensitive point of this procedures is a limited patency of the revascularization, due to neointimal hyperplasia (NIH). One of the most important achievements during this years was the implementation of ant proliferative therapy in the daily practice, as drug eluted stents or drug coated balloons, which allowed the doctors to get better and better results.

The idea to use ant proliferative drugs to prevent NIH emerged from the chemotherapy, where molecules like paclitaxel were used against different types of cancer. The very first study in an animal model to prove the safety and efficiency of paclitaxel to reduce NIH was conducted by Speck and Scheller in 1999 [1] and was followed in the next years by another studies involving human subjects, like Paccocath ISR I/II and THUNDER, with good results [1]. From that moment a large door was opened for the use of molecules like paclitaxel or sirolimus in the treatment of both coronary and peripheral arterial disease, in a large variety of materials, coating techniques and drug delivery mechanisms [2]. Of course there is a broad spectrum of active substances that can be used as antiproliferative drugs – see (Table 1) [2].

Class of Therapeutic Agent	Examples	Mechanism of Action
Antiplatelet	Aspirin, clopidogrel	Reduces blood clotting
Anti-inflammatory	Glucocorticoids, betamethasone, dexamethasone prednisolone	Inhibits monocyte and macrophage function and influences smooth muscle cell proliferation
Antihyperlipidemic	Statins (simvastatin, pravastatin), probucol	Decreases blood cholesterol level
Antiproliferative	Taxanes (paclitaxel docetaxel) limus (sirolimus, everolimus, tacrolimus)	Inhibits the G1 or G2 phase and the proliferation of cells
Cytotoxic antibiotics	Actinomycin-D	Inhibits the G1 phase and the proliferation of cells
Antithrombogenic agents	Heparin, urokinase	Prevents the formation of thrombin

Table 1: Types of therapeutic agents used in drug-eluting balloons.

In the field of PAD the widest used molecule is paclitaxel, which reduces fibrosis, inhibits proliferation and migration of the smooth muscle cells, has antiinflamatory effects and finally reduces NIH – see (Figure 1) [3].

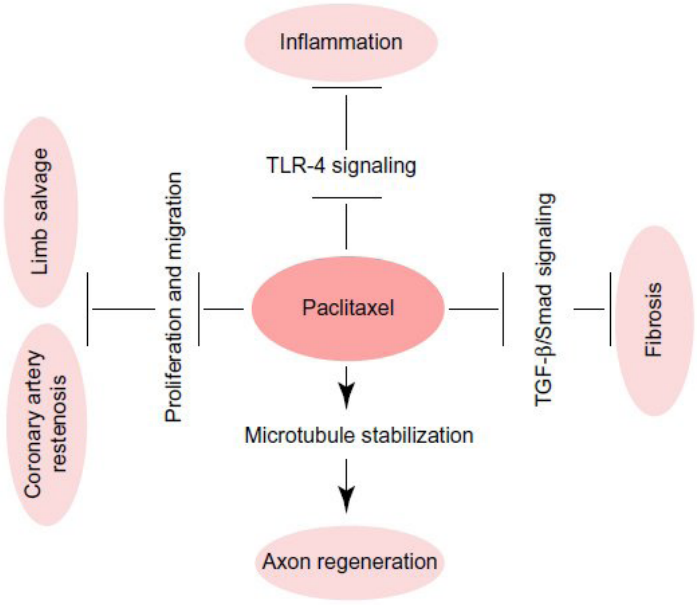

Figure 1: Effects of paclitaxel at the level of arterial wall

A very important matter regarding the use of paclitaxel in humans, since it has a cytotoxic effect, is the safety profile. From this point of view they were proposed different solutions to maximize the absorption at the site of implantation and avoid as much as possible the release in the systemic circulation [2]. Anyway the possible side effects were a matter of concern and also a possible relation between the uses of paclitaxel coated devices and mortality rate. As a result Katsanos et all published in 2018 a study which seemed to establish a correlation between the use of paclitaxel in PAD patients and an increase in the overall mortality rate [4]. This hypothesis was not confirmed by the next studies and it was not found a statistically significant correlation between use of paclitaxel and mortality rate in PAD patients [5-7].

In the daily practice first devices which used antiproliferative therapy were the drug eluted stents (DES). Since the use of stents has some limitations and disadvantages the drug eluted balloons (DEB) became a reasonable alternative which was improved with different molecules used as carriers and different types of coating – see (Figure 2) [2]. Nevertheless, use of a stent or a balloon should be adapted to a specific situation taking into account the characteristics of each one, with their own advantages and disadvantages – see (Table 2) [8].

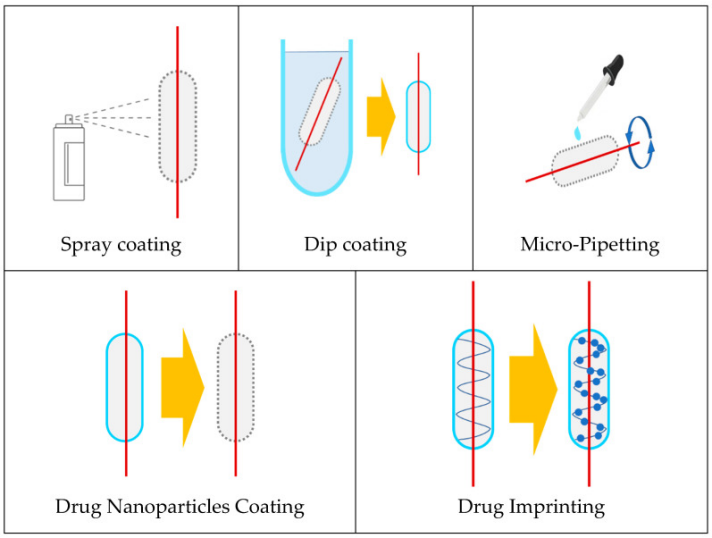

Figure 2: Different types of coating used in practice for drug coated balloons

DES (Drug Eluted Stent)		**DEB (Drug Eluted Balloon)**
Platform of drug delivery	Stent scaffolding	Balloon
Retention	Polymer based	Embedded imprinted
Drug dose	Low: <100 to 200 µg	High: 300 to 600 µg
Release kinetics	Slow and controlled	Fast release
Distribution	Strut-based vascular penetration	Balloon surface homogenous distribution

Advantages	Mechanical support	Leave no implant
	Abluminal trapping	Larger surface area
	Less drug spillage into the circulation	Less drug localization in the vessel wall
	Proven efficacy in many indications	Accessible to complex lesions and long segments
	No acute recoil tackled dissection	May not require prolonged DAPT (dual antiplatelet therapy)

Table 2: DES vs. DEB – pros and cons

As a result of all the improvements in this field now we have available a large variety of DESs and DEBs on the market, which can be found in dedicated catalogues [9]. In this situation the vascular surgeon has a broad spectrum of choices, the most important question being "What is the appropriate device for a specific location of the disease?"

The answer should take into account first of all the level of disease. From this point of view the femoro-popliteal segment is, without any doubt, the most debated and the most targeted. They are many studies regarding the best solution for the lesions of this segment but two landmark papers established the safety and efficacy of using DES for femoro-popliteal lesions, one of them for Zilver PTX (Cook) [10] and another one for Eluvia (Boston Scientific) [11]. Recently the use of DEBs has become more and more frequent, with good results, sometimes even better than use of DESs [12]. Another very challenging situation seems to be the the infrapopliteal level, because the first studies showed no benefit from using antiproliferative therapy, sometimes the use of a specific DEB like IN.PACT Amphibian (Medtronic) being associated with an increase in amputation rate [13]. More recent studies have offered different results [14, 15] so further evaluation is needed. Last but not least when choosing between a DES and a DEB we should also ask about the cost-effective ratio, usually a DEB beeing 4-5 times cheaper than a DES. From this point of view the "leave nothing behind" approach seems to be rational, so the use of a DEB as the first intention and use of a DES as a "bail-out procedure" could be a reasonable option.

The antiproliferative therapy became one of the "cornerstones" in the treatment of PAD but still they are looking for better and safer solutions. The future will come with new devices, new molecules, new carriers which will increase even more the use of DESs and DEBs in PAD patients. That's why the vascular surgeon should keep an eye on this field, in order to be able to offer the best solution to the patients.

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