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Drug-eluting balloons for treatment of SFA and popliteal disease – A review of current status

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ABSTRACT

The endovascular treatment of atherosclerotic disease of the infra-inguinal arteries has changed significantly over the last decades. In an attempt to overcome the high restenosis rates that characterize plain balloon angioplasty and stenting using bare mate stents drug-eluting balloon technology has been applied in the treatment of lesions of the superficial femoral and popliteal artery. This paper will give an overview of the rationale and the technology of drug-eluting balloons and will review currently available data from registries and randomized controlled trials.

1. Introduction

In the last decades new techniques and technologies have been developed for the endovascular treatment of arterial occlusive disease affecting the superficial femoral artery and infrapopliteal arteries. This development allowed to treat complex and very extensive lesions with a high technical success and a low complication rate. Restenosis, and in particular in-stent restenosis, remains a problem that significantly affects mid- and long-term outcome of SFA stenting [1]. Two studies that demonstrated a statistically significant benefit of primary stenting over angioplasty with bail-out stenting still yielded high Duplex derived re-stenosis rates of 18.7% at 1 year [2] and 37% at 2 years [3]. Restenosis is caused by smooth muscle cell proliferation as a result of a sustained inflammatory response caused by the stent. This reaction follows a response-to-injury sequence of events that is comparable to that of wound healing [4]. In order to overcome the problem of restenosis drug-eluting stents have been used. At this moment outcomes of one randomized trial regarding the use of drug-eluting stents in the SFA have been published. This study demonstrated a primary patency rate at 1 year of 83.1% in patients that were primarily treated with drug-eluting stents, indicating that also with the use of drug-eluting stents restenosis remains an issue [5]. The biomechanical properties of the superficial femoral artery expose stents to the risk of stent fractures, and whether these are relevant remains unclear. Although Scheinert et al. demonstrated that stent fractures were associated in approximately two-thirds of cases with adverse outcome [6], more recent reports do not demonstrate a correlation between restenosis rate and incidence of stent fractures [2]. The lower incidence of stent fractures is related to changes in stent design/geometry. Finally, there are indications in the animal model that the extensive and long-term exposure to paclitaxel at a low-dose (as commonly used in drug-eluting stents) might be associated with negative long-term effects with regard to inflammation and late in-stent restenosis [7], although the 5 year results from the Zilver PTX study showed durable results with a primary patency rate of 66.4% [8]. Even when these results are satisfactory, the disadvantages of a permanent implant (like impairment of remodeling and changes in vascular compliance) remain however also when using drug-eluting stents.

This paper will describe the characteristics of the currently available drug-eluting balloons and will give an overview of the results from large single center registries and multi-center randomized trials of the use of drug-eluting balloons in the treatment of primary lesions of the superficial femoral and popliteal artery. In-stent restenosis will not be dealt with.

2. Technical and practical considerations

The concept of drug-eluting balloons is based on the local delivery of drugs on site, with an exact control of the drug dosage, thus achieving an effective and sufficient local concentration, and avoiding systemic exposure to the drug. Advantages of the technology are the possibility of a homogeneous drug transfer as compared to stent-mediated drug release where the drug is only delivered at the level of contact of the stent struts with the vessel wall (approximately 85% of the stented vessel wall area is not covered by the stent struts). This results in low tissue concentrations of the anti-proliferative agent in the

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Table 1
Comparison of characteristics of drug-eluting stents vs. drug-eluting balloons [14].

Drug-eluting stent	Drug-eluting balloon
• Slow release	• Immediate release
• Persistent drug exposure	• Short-lasting exposure
• ~100–200 μg dose	• ~300–600 μg dose
• Polymer	• No polymers
• Stent mandatory	• Premounted stent optional
	• Carrier optional

areas that are not in direct contact with the stent [9,10]. Furthermore drug-eluting balloons allow for a drug concentration that is highest at the time of the vessel wall injury that occurs during balloon angioplasty and therefore can prevent the initiation of the chain of events that will eventually lead to neointimal proliferation [11]. Drug eluting balloons combine the advantages of local drug delivery without a permanent implant. The absence of metal struts makes the technique suitable for treatment of long lesions (especially in small diameter vessels), and areas where flexion and compression of stents may occur. Finally the absence of a stent allows the original anatomy of the artery to remain intact, which is especially of importance in lesion locations where stenting is considered undesirable or impractical (arterial bifurcations), or in anatomy that is challenging (re-PTA, treating a potential anastomosis site for surgical bypass without compromising the distal anastomosis site). By not using stents any future treatment options are preserved.

The absence of polymer that is needed in most drug-eluting stents could decrease chronic inflammation and the trigger for late thrombosis and thus obviate the need for long-term dual antiplatelet therapy [12,13]. Table 1 lists a comparison of the different characteristics of drug-eluting stents and balloons (adapted from Scheller [14]).

The following three components are essential during the development of a drug-eluting balloon: the balloon platform, the active drug and the so-called excipient or carrier.

2.1. Balloon

The balloon platform can be either compliant or non-compliant, but more important is the choice of balloon material. The importance of balloon material has been emphasized by the (negative) results of the IN.PACT DEEP trial. The different balloon material used on the study-device as compared to the material used on the SFA balloon from the same manufacturer may have been (one of the) cause(s) for failure [15]. Other factors of influence are the method of balloon wrapping and its inflation pattern [16].

2.2. Drug

When selecting the optimal drug to inhibit re-stenosis with a single balloon inflation several features are important.

The chemical structure of the drug: lipophilic drugs show better transfer into the arterial wall as compared to hydrophilic drugs. The drug should be able to be transferred rapidly (i.e. in less than 60 s). Efficiency of drug delivery should be optimal, with a low rate of drug loss during crossing through the introduction sheath and vessel (animal studies have demonstrated that as much as 70–80% of the drug dose might be lost in the bloodstream [17]). Differences in drug concentration and elution kinetics may have an influence on the outcome [18]. Toxicity should be low, and the therapeutic window should be wide. Furthermore the entire system should be stable, which includes a good chemical stability and characteristics that allow standard packaging and storage, and a good shelf-life.

The two drugs that have been examined for topic application using angioplasty balloons are rapamycin and paclitaxel. Pharmacological studies have demonstrated an inferior tissue uptake of rapamycin as compared to paclitaxel [16]. All currently available drug-eluting balloons use dry state paclitaxel.

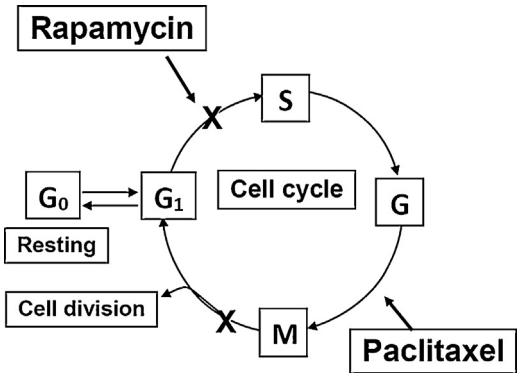

Fig. 1. Schematic representation of cell cycle and the mechanism of action of rapamycin and paclitaxel.

Paclitaxel is a substance that originates from the bark of the pacific yew tree (*Taxus brevifolia*) and is synthetically manufactured as an antineoplastic drug (Taxol®). It is highly lipophilic (this allows a rapid cellular uptake and retention at site of delivery). Paclitaxel is cytotoxic and restrains the cell division, which prevents a progression of intimal hyperplasia; paclitaxel acts on the cell when going from pro-metaphase into metaphase, which subsequently leads to apoptosis (Fig. 1). Paclitaxel is a potent inhibitor of smooth muscle cell proliferation, smooth muscle cell migration, and extracellular matrix formation in vitro by enhancing the formation of stable but dysfunctional polymerized microtubules, with all three phases of the restenosis process inhibited effectively [19–22]. The lipophilic properties of paclitaxel prevent adventitial washout and prolong anti-proliferative effects, enhancing the interactions with lipids in the vessel wall [10].

Paclitaxel is the active ingredient of Taxol® that has been approved and is widely used in oncological therapy. In oncology applications, paclitaxel is typically infused intravenously up to a dose of 175 mg/m^2 body surface equivalent, a dosage that is equivalent to about 300 mg/patient. Typically an oncological treatment is repeated several times with a treatment-free interval of 1 month. No relevant side effects were reported in a study where ≤70 mg of paclitaxel was administered intravenously [23]. A study reporting hematologic analyses after the use of multiple paclitaxel-coated balloon catheters in femoro-popliteal vessels up to a dose of circa 25 mg/patient showed plasma concentrations that were always below a level and duration known to cause systemic side effects [24]. In the animal model, drug-coated balloons appeared to be effective at a dose of 1 μg/mm^2. An incremental anti-restenotic effect was noted up to 3 μg/mm^2. Beyond this value no further reduction of the neointimal restenotic area was seen [25]. The dose of paclitaxel that is used by almost all manufacturers is either 2 μg/mm^2 or 3 μg/mm^2 of the balloon surface. With this dosage regimen the total dose of paclitaxel administered to the patient remains well below the dosage schemes used in cancer treatment (for example 3 μg paclitaxel/mm^2 balloon surface results for a 6 mm × 120 mm balloon in about 8 mg). This means that also in the treatment of long lesions (using 3–4 drug-eluting balloons) the total dosage remains within the safety limits.

Paclitaxel is available in two formulations: crystalline and amorphous, and side-effects like vessel wall toxicity (characterized histologically by excess fibrin, and collagen deposition) and microparticulate embolization may be related to the type of paclitaxel formulation used. Long-term tissue retention is affected by drug morphology and resulting solubility. First generation drug-eluting balloons with a high level of crystallinity were associated with a high loss of particulate matter during balloon inflation [26]. Newer coating technologies allow for a lower level of crystallinity. When comparing these newer crystalline formulation with an amorphous formulation in an animal model it was seen that at 1 h after balloon inflation paclitaxel tissue concentrations