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Review Article

Internal Medicine Section

Basic Concepts and Clinical Outcomes of Drug-Eluting Balloons for Treatment of Coronary Artery Disease: An Overview

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ABSTRACT

The technology of percutaneous coronary intervention for atherosclerotic coronary artery disease has evolved considerably since its inception. Though Drug-Eluting Stent (DES) reduces the rate of restenosis, long-term safety outcomes and persistent restenosis in complex lesion subset remain area of concern. Recently, Drug-Eluting Balloon (DEB) represents a novel treatment strategy for atherosclerotic coronary artery disease. DEB demonstrated its added value in preclinical studies. Inspired by these results, several clinical trials particularly in complex lesion subsets have been started to explore the value of this novel treatment strategy in a broader range of lesions. This review would summarise material compositions and different characteristics and clinical outcomes of currently available DEB.

Keywords: Balloon angioplasty, Balloon catheter, Drug-coated balloon, Percutaneous coronary intervention

INTRODUCTION

Percutaneous transluminal coronary angioplasty, also known as Plain Old Balloon Angioplasty (POBA), was firstly introduced by Gruentzig AR in 1977 [1,2]. Although, revolutionary initial enthusiasm has been tampered as the technique has been associated with various drawbacks, acute vessel closure and restenosis usually within first six months after the intervention [3,4]. Bare-Metal Stent (BMS) was introduced in an attempt to attenuate acute vessel closure as they provide a scaffold for the vessel wall and thereby stabilize dissection. However, the use of BMS led to realisation of new challenge of in-stent restenosis secondary to neointimal hyperplasia [4,5]. The introduction of DES reduces the restenosis rates to single-digit levels (7.9 - 8.9%) at nine months [6]. Thus, DES has become the mainstay of intervention for Percutaneous Coronary Interventions (PCI). However, unpredictable risk of late Stent Thrombosis (ST) (hazard ratio of up to 0.6 per year) causes delayed vascular healing, hypersensitivity reaction to the drug, polymer coating or both and impaired endothelial function which bring about limited use of DES [7,8]. Moreover, though DES reduces the rate of in-stent restenosis as compared to BMS, it is still reported particularly in complex lesion subsets [8]. These limitations of DES led to a search for alternative treatment strategy.

In recent years, DEB have begun to emerge as a potential treatment alternative in the field of interventional cardiology. This non-stent-based local drug delivery maintains antiproliferation properties of DES but without the limitations of DES viz., subacute ST, stent fractures and stent malapposition [9,10]. The aim of this review is to provide a detailed discussion on rationale, composition, different characteristics and clinical outcomes of currently available DEB devices.

Rationale for DEB

DEBs are developed in an attempt to preserve the benefits of a DES and to eliminate or minimize its potential limitations. DEB provides non-stent based quick and homogeneous delivery of the anti-proliferative drug to the vessel wall which attenuates the process of Neointimal Hyperplasia (NIH). Moreover, the absence of metal or polymer mitigates the risk of vascular inflammatory response which is directly linked to thrombosis events [11]. The absence of stent allows the artery's original anatomy to remain intact and thereby diminish abnormal flow patterns. In addition, owing to lower device profile and greater navigability, DEB may be used in subsets of lesions where DES cannot be delivered or not performed well such as torturous vessels, small vessels, or long diffuse calcified lesions, bifurcated lesions [12]. The DES noticeably reduced in-stent restenosis, by preventing recoil of the vessel wall, late negative remodelling and also significantly inhibiting neointimal hyperplasia formation. However, in-stent thrombosis, prolonged dual antiplatelet therapy and persisting restenosis in complex lesion subsets are other concern in use of DES. The difference of DEB over DES are summarised in [Table/Fig-1] [6,13,14].

On the other hand, DEB cannot overcome potential limitation of old balloon angioplasty. The absence of mechanical scaffolding results into acute recoil [15]. DEB as adjunct therapy to BMS still needs to be more deeply investigated. The variability of pharmacokinetics and control of dosing are other potential limitations of DEB [16].

Material composition of DEB and its technical aspects

DEBs have three components: the balloon, the drug and the carrier. The balloon is usually compliant or semi-compliant. The coated antiproliferative drug on the balloon is released into the vessel wall during balloon inflation with a specific minimal inflation time at nominal pressures [17,18]. Hence, the ideal drugs should be lipophilic enough to have a high absorption rate through the vessel wall and high retention rate by the vessel intima, in order to exert maximal beneficial effects. So far, paclitaxel has been considered as the drug of choice for DEB because of its rapid uptake and prolonged retention [19,20]. The dose of 2-3 $\mu g/mm^2$ of paclitaxel is used in all currently available devices. However, it has restricted transfer on the vessel wall due to its hydrophobicity till the duration of the balloon inflation. Introduction of carrier substance enables transfer of paclitaxel onto the tissues of the vessel wall through a hydrophilic environment. Therefore, carrier substance is considered as a critical component of DEB. It determines pharmacokinetics of the device as well as determines the amount of drug lost in transit. Thus, the carrier highly determines the efficacy of DEB [21].

DEB characteristics

Currently, there are several commercially available DEBs (CE approved). All these DEBs use paclitaxel as an active drug but

DEB	DES
Characteristics of DEB and DES	
Conventional semi-compliant angioplasty balloons	Peripheral or coronary stent (a scaffold)
One of the long-awaited new transcatheter technologies to help reduce high restenosis rates in peripheral artery disease	Specifically address the problems of restenosis, for treating narrowed heart arteries
A novel method of drug delivery to the vessel wall without need for a polymer or stent which can reduce or eliminate the vascular inflammatory response, which is directly linked to very late thrombosis events	Polymer-based drug coatings
Rapid delivery of drug kinetics to the vessel intima within 30-60s balloon inflation	Slow and controlled release of drug kinetics to block cell proliferation
Dose of drug is 100 to 200 µg and persistent drug exposure	Dose of drug is 300 to 600 µg and short-lasting exposure
Balloon surface homogenous distribution through the vessel wall	Strut based vascular penetration through the vessel wall
Advantages of DEB and DES	
Less drug localization in the vessel wall Large surface area and Leave no implants, Accessible to complex lesions and long segments, Less requirement of prolonged DAPT	Mechanical support Less drug spillage into the circulation, and Albuminal trapping and No acute recoil tackled dissection

[Table/Fig-1]: Characteristics and advantages of DEB and DES.
DAPT: dual antiplatelet therapy; DEB: drug-eluting balloon; DES: drug-eluting stent

DEB	Coating method	Dose	Techniques used
Sequent please [25]	Paclitaxel+ Paccocath (Iopromide)	3µg/ mm^2	Developed with modified coating and a different balloon platform
In.Pact Admiral [26, 27]	Paclitaxel+ Urea	3.5µg/ mm^2	Proprietary matrix coating with hydrophilic spacer (urea)
DIOR – II [21, 28]	Paclitaxel+ Shellac	3µg/ mm^2	Micropipetting
Elutax [30]	Paclitaxel	2µg/ mm^2	Matrix of pure paclitaxel without additives
Moxy [31]	Paclitaxel+ Hydrophilic carrier	2µg/ mm^2	Proprietary hydrophilic nonpolymeric carrier
Pantera Lux [32]	Paclitaxel+ Butyryl-trihexyl Citrate	3µg/ mm^2	Proprietary hydrophilic nonpolymeric carrier
DIOR – I [21, 35]	Paclitaxel + Crystalline	3µg/ mm^2	Shielding technique

[Table/Fig-2]: Overview of CE (Conformité Européenne) approved and/or current clinical trials of DEBs.

different coatings and thereby different release kinetics and several characteristics of those DEBs are enlisted in [Table/Fig-2] [13,16].

The Paccocath® technology based Cotavance® balloon catheter (Bayer AG, Leverkusen, Germany) was the first DEB developed for clinical trials [22]. In this technology, the balloon is coated with a proprietary drug matrix which is developed by Ulrich Speck and Bruno Scheller; Bayer Schering Pharma AG (Berlin, Germany). On this platform, hydrophilic iopromide is embedded with paclitaxel, which increases the hydrophilicity of paclitaxel and enable transfer to the vessel wall [23,24]. The SeQuent® Please (B. Braun, Berlin, Germany) balloon catheter was developed with Paccocath formulation with a modified coating and a different balloon platform [25].

A coating namely FreePac™ used in series of DEBs of IN.PACT (Medtronic-Invatec, Frauenfeld, Switzerland) for coronary and peripheral applications. It is a proprietary matrix coating with a hydrophilic spacer (urea) and antiproliferative drug (paclitaxel). The hydrophilic spacer separates paclitaxel molecules and facilitates their absorption into the vessel wall. The dose of paclitaxel with urea excipient is 3.5 µg/mm^2 on balloon surface of IN.PACT [26,27].

Name	Number of Patients	Angiography FU	Clinical FU	Angiography results FU	Clinical results FU
Elutax [30]	59 (PEB+BMS)	9 months	9 months	-	MACE: PEB+BMS 29%; TLR: PEB+BMS 25%
Pantera Lux [32]	45	6 months	6 months	LLL ;0.03 ± 0.35	MACE: PEB 7.7% TLR: 2.6%
Paccocath [33]	54	6 months	1 year	LLL;PEB 0.14±0.46	MACE: PEB 9%; TLR 4%
SeQuent Please [34]	25	9 months	1 year	LLL; PEB 0.28	MACE: PEB 4.2%; TLR 4.2%
DIOR-I [35]	40 (PEB+BMS)	6 months	1 year	LLL;PEB+BMS Proximal:0.58±0.65 Distal: 0.41±0.60	MACE: PEB+BMS 20%; TLR: PEB+BMS 15%
DIOR-II [36]	49 (PEB+BMS)	1 year	1 year	LLL 0.32 ± 0.73	MACE: PEB+BMS 14.3%

[Table/Fig-3]: Summary clinical outcome of major drug-eluting balloon (DEB) studies.
BMS: Bare metal stent; FU: Follow-up; LLL: Late lumen loss; MACE: Major adverse cardiac events; PEB: Paclitaxel eluting balloon; TLR: Targeted lesion revascularization.

The DIOR™ catheter (Eurocor GmbH, Bonn, Germany) was the first DEB adopting the shielding technique for coating antiproliferatives, which has three folded antiproliferative drug, paclitaxel (3 µg/mm^2) on non-inflated DEB. This distinctive shielding technique protects the antiproliferative drug during insertion and tracking of the coronary lesions from an early wash-off effect [28]. The first generation DIOR-I™ is no longer in use because of low delivery dose of the drug into the vessel wall, which was coated with a crystalline drug on roughened balloon surface [21]. The presently available DIOR-II™ is coated with a 1:1 mixture of paclitaxel and shellac which is prepared by a micro-pipetting procedure [21,28]. When this hydrophilic shellac-network comes in contact with body tissues, it swells and opens the structure for the pressure-induced fast release of paclitaxel on the inflated balloon. To deliver the adequate amount of drug to the vessel tissue, the recommended inflation time is 30-45 seconds [29].

The Elutax® balloon (Aachen Resonance, Aachen, Germany) uses a two-layer drug matrix (without excipient) that serves as a depot for homogeneous paclitaxel release, and uses a lower paclitaxel dose of 2 µg/mm^2 compared with the other DEBs [30]. The Moxy drug-eluting balloon (Lutonix, Inc. Maple Grove, MN, USA) is a paclitaxel-coated balloon with a hydrophilic carrier. The device consists of semi-compliant balloon which is made from a polyamide material capable of achieving high inflation pressures. It is evenly distributed at a surface concentration of 2 µg/mm^2 [31]. Pantera Lux™ (Biotronik AG, Germany) uses Butyryltrihexyl Citrate (BTHC) as a carrier for paclitaxel [32].

Clinical outcomes

Based on the current clinical trials data represented in [Table/Fig-3], total of 54 patients were presented with iopromide-paclitaxel-coated balloon (PACCOCATH). At six months angiographic follow-up, Late Lumen Loss (LLL) was 0.14±0.46 mm and Major Adverse Cardiac Events (MACE) and Target Lesion Revascularization (TLR) were 9% and 4% in patients at one year clinical follow up, respectively [33]. However, SeQuent™ Please DEB incorporated 86 patients showed significant angiographic in-segment LLL (0.28 mm), MACE (4.2%) and TLR (4.2%) [34]. Nine months follow-up, Elutax (Paclitaxel eluting ballon, PEB with BMS) were implanted into 59 patients demonstrated with 29% of MACE and 25% of TLR [30]. In addition, DIOR-I were implanted into 40 patients with PEB and BMS angiographic in-segment LLL (0.58±0.65 mm) at six months FU and MACE (20%) and TLR (5%). However, total of 49 patients were involved in DIOR-II (PEB + BMS) study, showed LLL and MACE was 0.32 ± 0.73 mm and 14.3% respectively [35,36]. PEPCAD II was a multicenter, randomized trial of the SeQuent DEB versus the TAXUS

DES in 131 patients with coronary BMS in-stent restenosis. The primary end point of six months in-segment LLL was significantly less with the DEB compared with the DES [23]. [Table/Fig-3] data suggest that, DEB-only strategy has been favoured by some investigators as the ideal coronary application for DEB technologies. This concept involves careful lesion identification and depending on the findings following pre-dilatation, the operator decides whether to proceed with DEB only or the use of a stent/scaffold in case of major dissection (type C or higher) and significant residual stenosis [20]. This approach aims to avoid the use of unnecessary stents and shorten the duration of dual antiplatelet therapy.

LIMITATION

The major limitations of polymer-based DES are long-lasting use of DAPT and late stent thrombosis, which lead to the spotlight on DEB than DES. However, it is uncertain to achieve favourable safety-efficacy ratio of DEB due to different kinds of drug coating (iopromide), method of retention of drug and its elution. In addition, randomized trials and consecutive real-world patients data with long-term follow-up periods is necessary to for evaluation of safety and efficacy parameters of the DEBs. Moreover, paclitaxel is the only available anti-proliferative drug that is coated onto the DEB, and a zotarolimus-eluting balloon has been tested in a swine model. Yet no publications are available for other proliferative drugs except paclitaxel.

CONCLUSION

The drug-eluting balloon is a revival of an old technology. The outstanding feature of this evolving technology is its ability to dilate stenosis along with effective transfer of anti-proliferative drug nothing behind left neither metal nor polymer, which could trigger delayed biological reaction. However, DEB technology possesses challenges in release kinetics as well as issue of elastic recoil concerns whether it can be coupled successfully to BMS. Aside from technical improvements, it will be interesting to see whether DEBs based on drugs like zotarolimus, sirolimus or everolimus except paclitaxel, will provide further improvements. The development of new techniques of DEBs is difficult to understand whether they assures the safety of patients or will remain a promise for new development. Various safety and efficacy aspects are yet to be clarified in real-world population studies. However, a new-generation zotarolimus/sirolimus-eluting DEB may overcome the high restenosis rates in small vessels and provides a key to existing problems.

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