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Drug Eluting Balloon

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1. Introduction

Since the first percutaneous transluminal coronary angioplasty (PTCA) performed by Andreas Gruntzig in 1977 the technology has evolved significantly. Progress of PTCA has seen the development of many devices, some of which are still in use and many others that have fallen in disuse. The main limitation of the plain old balloon angioplasty (POBA) was the problem of elastic vascular recoil causing abrupt vessel closure and restenosis. The patho-mechanism of restenosis that occurs following balloon angioplasty involves negative vascular remodeling, elastic recoil and thrombosis at the site of injury {Moreno, 1999}. While the thrombus formation can be reduced by use of antiplatelet drugs, the restenosis threat remains. Early restenosis occurred in as many as 30% of angioplasty cases. This led to the development of the metal stent to exert radial force on the vessel wall and thus prevent elastic recoil. Although stents reduced restenosis, their use led to the realisation of a different and new challenge of in stent restenois (ISR). This occurs mainly due to neointima formation {Mach, 2000,Mudra et al, 1997, Hoffman et al, 1996, Kearney et al, 1997} that is principally composed of proliferating smooth muscle cells (SMC) and extra cellular matrix {Geary et al, 2003, Grewe et al, 1999}. By the late 1990s, it was acknowledged that although the incidence of ISR was lower than that of restenosis following balloon angioplasty {Serruys et al, 1991}, it occurred in 15–30% of patients, and possibly more frequently in certain subgroups {Holmes et al, 2002}.

2. Treatment of restenosis

Over the years there have been intensive research efforts to identify possible pharmacotherapeutic regimens to prevent the neointimal restenotic process. Although most experimental studies and some small initial clinical studies showed promise, subsequent large randomized trials have been disappointing {Faxon, 1995, Bertrand et al, 1997, Boccuzzi et al, 1998, Serruys et al, 2000, Faxon, 2002}. Failure to achieve significant reduction in ISR with systemic drug therapy led to the exploration of the concept of local drug delivery. Local drug delivery (LDD), in theory, should achieve greater local drug concentration with lower overall dose compared to systemic therapy, to help achieve maximal tissue effects while minimizing undesired systemic toxicity. It also has the advantage of being able to utilize drugs with low systemic bioavailability or short half-life. Many devices have been

developed to administer drugs or genetic material locally to the site of injury {Sharma et al, 2011}. Studies have shown that local administration of pharmacologic agents directly at the site of coronary intervention is an effective means of delivering sufficient amount of drug into the injured arterial tissue site to cause an anti-restenotic therapeutic effect { Schwartz et al, 2004}.

Various approaches for local drug delivery have been tried including nanoparticles, contrast media and drug delivery balloons, such as porous {Herdeg et al, 2000} and double balloons {Oberhoff et al, 2001}. Other options for treating ISR included POBA using either conventional or cutting balloons, implanting a stent inside the stent, rotablation or brachytherapy. However, most of these techniques were not adopted into widespread clinical use due to their various shortcomings and limitations. Until recently, stent-based local drug delivery using drug-eluting stents (DES) is still considered the percutaneous treatment of choice for coronary restenosis. As the process of neo intimal hyperplasia occurs locally due to endothelial injury caused by the metallic stent, it seems logical to use the stent itself to deliver a drug locally in order to overcome this problem.

Thus DES have become the mainstay of intervention for coronary atherosclerotic disease {Kirtane et al, 2009}. However, DES use is limited by small but unpredictable risk of late stent thrombosis due to withdrawal of antiplatelet therapy { McFadden et al, 2004}, delayed mal-apposition {Kozuma et al, 1999}, delayed vascular healing as a result of initial anti-proliferative effect {Jakabcin et al, 2008}, or a hypersensitivity reaction to the drug, polymer coating or both { Finn et al, 2007}.

ISR continues to occur with DES, although at a lower rate compared to BMS. However, the relative massive increase in number of DES implantations in recent years means the problem of ISR although less in relative terms compared to BMS, still causes a problem in absolute terms requiring a significant number of repeat procedures every year globally and remains a treatment challenge {Maisel, 2007}. Treatment of restenosed DES with a second DES is associated with risk of subsequent restenosis of up to 43% {Lemos et al, 2008}. The ideal treatment of a coronary stenosis would eliminate both the stent and the polymer related late problems, while at the same time deliver an antiproliferative agent to reduce the risk of restenosis.

3. Drug eluting balloons

Old-style balloon angioplasty married to the latest in drug-eluting technology, resulting in a drug eluting balloon (DEB), may be an effective alternative to stenting, in particular to overcome the problems of restenosis and ISR. Such a device would potentially overcome the drawbacks of stenting, polymer-related delayed endothelialization, and stent delivery, while at the same time providing homogenous drug delivery to the vessel wall, allowing earlier endothelialization and flexibility of use in complex lesions. However, its limitations include the failure to provide a mechanical scaffold for the prevention of acute recoil and the problem of not being able to treat dissection flaps.

Drug eluting balloons achieve LDD by means of an angioplasty balloon coated with drugs such as paclitaxel, which are well established in DES technology. One of the commercially approved devices, the SeQuent® Please (Braun, Germany) balloon catheter (Fig. 1) has a

folded balloon, which is homogenously coated with paclitaxel embedded in contrast medium coating. Paclitaxel (3 µg/ 373mm2 balloon surface) is the pharmacologically active substance whereas the contrast medium has a matrix builder function to facilitate immediate release of drug during balloon inflation {Scheller & Speck, 2009}.

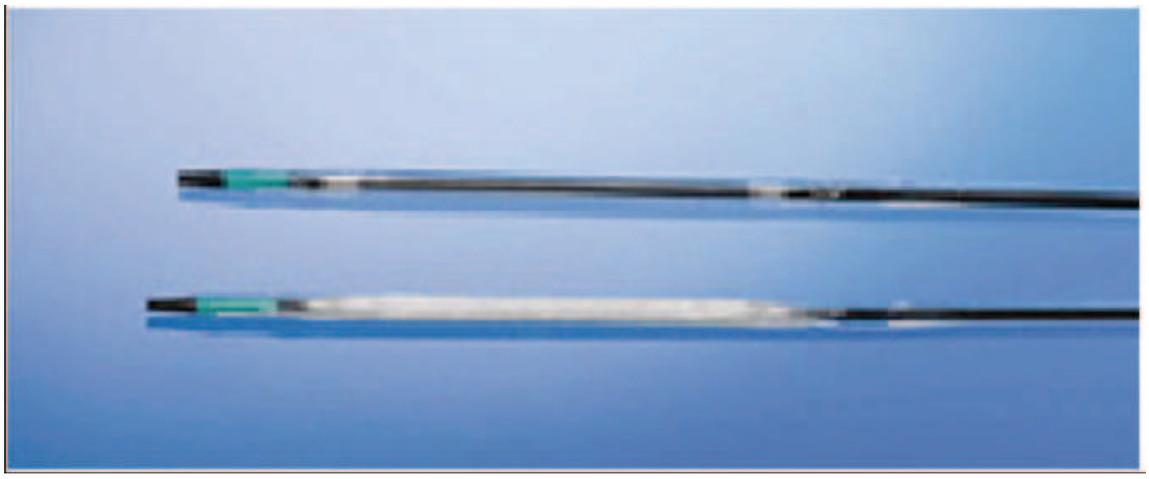


Fig. 1. Photograph of SeQuent (top) and the paclitaxel coated SeQuent® Please balloon catheter (bottom).

The ideal drugs for local delivery should be lipophilic in nature, rapidly adsorbed and have a high retention rate by the vessel intima, in order to exert maximal beneficial effects {Baumbach et al, 1999}. Paclitaxel is a lipophilic drug and bind tightly to various cell constituents {Rowinsky et al, 1995}, resulting in effective local retention at the site of delivery { Creel et al , 2000} and it exerts a long-lasting effect in the cell due to structural alteration of the cytoskeleton. Thus, paclitaxel, with its lipophilic nature, combined with the fact that adding a small amount of hydrophilic contrast medium {Scheller et al, 2003} enhances its solubility, makes it well suited for delivery on a drug-delivery balloon. Various other drugs like, sirolimus, zotarolimus, rapalog and others are being studied currently as a possible alternative to paclitaxel for coating the PTCA balloon {Schnorr et al, 2010}.

3.1 Pre- clinical data

The first preclinical study was conducted by Scheller et al {Scheller et al, 2004}. In this study stainless steel stents (n = 40; diameter: 3.0–3.5 mm; length: 18 mm) were implanted in the left anterior descending and circumflex coronary arteries of pigs. Both conventional uncoated and three different types of paclitaxel-coated coronary angioplasty balloons were used, and contact with vessel wall was maintained for 1 min. The results were assessed by quantitative angiography and histomorphometric studies of the stented arteries. There was a marked reduction (up to 63%) of parameters characterizing ISR in the paclitaxel-coated balloon group, without evidence of increased inflammation in proximity to the stent struts or any effect on re-endothelialisation of the struts. They also showed that paclitaxel-coated balloons lose only 6% of the drug when introduced into the coronary circulation and retracted without inflation. Approximately 80% of the drug is released during inflation, suggesting

rapid transfer of the drug from the balloon to the vessel wall without much loss. In this study, the percentage of drug recovered from the vessel wall was at a maximum (17.3%) when a premounted stent on a coated balloon was used, compared with postdilatation using a coated balloon (15.6%) or the coated balloon on its own (8.7%).

Speck and colleagues compared non-stent-based drug delivery with DES in reducing neointimal proliferation in a porcine model. The study group was divided into four groups as follows; Group A was the control group with uncoated balloons, BMS and 'plain' contrast medium. Group B was the same treatment as A, but with paclitaxel in the contrast medium. Group C was paclitaxel-coated balloons, with pre-mounted BMS and plain contrast medium. Finally, group D was sirolimus-eluting stents, non-coated balloons, and plain contrast medium. At 4 weeks, assessment of stenosis was carried out using angiography and histomorphometry. The most impressive inhibition of neointimal proliferation was achieved in the coated balloon group – the neointimal area was 2.4 mm2 ± 0.3 ($p < 0.01$ vs. all other groups), compared with 5.2 mm2 ± 0.3 in group A, 4.3 mm2 ± 0.3 in group B, and 3.8 mm2 ± 0.3 in group D {Speck et al, 2006}.

Cremers and colleagues studied the relationship between the inflation time and dose of placlitaxel on the DEB, on effectiveness in reducing neo-intimal proliferation in a porcine model {Cremers et al, 2009 a}. DEB technology was shown to be effective in reducing neointimal proliferation regardless of the balloon inflation time (10 s, 60 s and two 60 s inflations) and dose (up to a total amount of 10 µg paclitaxel/mm² balloon surface). This study showed that drug transfer occurs very early after balloon inflation and also demonstrated the safety profile of applying several balloon inflations within the same vessel either using the same or additional balloons.

In a comparative study of two different types of DEB (Original Paccocath-coating, similar to SeQuent®Please, B. Braun, Germany and DIOR®, Eurocor, Germany) on a porcine coronary overstretch model it was demonstrated that much better results were obtained with the matrix-coated Paccocath DEB compared with the roughened surface DIOR balloon, suggesting that inhibition of neointimal proliferation is dependent on the coating method used {Cremers et al, 2009 b}. In a comparative DEB performance study by Joner et al, in a porcine model of advanced coronary restenosis, significant heterogeneity of neointimal suppression was seen between the devices tested {Joner et al, 2011}

3.2 Use of DEB in the human coronary

The first reports of DEB use in humans were the Paccocath ISR I and ISR II studies in 2006. These were randomized, double-blind German multicenter clinical trials to assess the efficacy and tolerability of a paclitaxel-coated balloon catheter in the treatment of coronary ISR {Scheller et al, 2006, 2008}. Scheller and colleagues enrolled 108 patients (52 and 56 patients in each study) with a single ISR lesion to undergo balloon angioplasty either using a 3mcg/mm2 iopromide-paclitaxel coated balloon (PACCOCATH, Bayer Schering Pharma) or a standard uncoated balloon of the same type. The primary end point of angiographic in-segment late lumen loss was markedly different in the two groups. They reported that at 6-month follow-up, in-segment late lumen loss was 0.81 ± 0.79 mm in the uncoated balloon group, versus 0.11 ± 0.45 mm ($p < 0.001$) in the drug-coated balloon group. By 12 months, only two patients in the coated balloon group required target vessel re-vascularization ($p =$

0.001), compared with 20 in the control group. A sustained clinical effect of the DEB was noted at 24 months with no subacute thrombosis or other safety concerns.

The Paclitaxel-Eluting PTCA-balloon catheter in Coronary Artery Disease (PEPCAD I-SVD) was a Phase II nonrandomized, open label, uncontrolled, efficacy study evaluating the use of a DEB catheter (SeQuent Please, B. Braun, Germany) for the treatment of small vessel coronary artery disease in 118 patients (reference diameter of 2.25–2.8 mm and lesion length ≤ 22 mm). If the angiographic result was not satisfactory at the end of the procedure, the subjects could be treated with any device, but a bare metal stent was recommended. After 6 months, de novo lesions treated solely with DEB or in combination with BMS (28% of patients) showed a 17.3% binary restenosis rate, and at 1 year 11.7% target lesion revascularization (TLR) and 15% major adverse cardiovascular event rate {Scheller, 2008}. However, in the patients who received DEB alone (n = 82) without additional stent insertion, the binary restenosis rate was only 5.5%. The somewhat higher restenosis rate in the total population may have been attributable to 'geographic mismatch' between the DEB-treated area and the subsequently stented surface area.

The PEPCAD II-ISR trial was a prospective, randomized study directly comparing the paclitaxel-eluting balloon catheter (SeQuent Please, B. Braun, Germany) to the paclitaxel-eluting stent (Taxus®, Boston Scientific, MA, USA) in 131 patients with ISR, followed up for 6 months. The main inclusion criteria encompassed diameter stenosis of ≥70% and ≤22 mm in length, with a vessel diameter of 2.5 to 3.5 mm. In 6.2% of the Taxus stent group, the stent was undeliverable and a balloon catheter had to be used instead. Clopidogrel was given for 3 months post treatment to the balloon group and 6 months to the stent group. Patients treated with the drug-eluting balloon experienced a 7.0% ISR compared with 20.3% in the group. Adverse cardiac events occurred in 22% of the stent group and in 9% of the coated balloon group (p = 0.08), driven predominantly by reduced need for target lesion revascularisation (TLR), which was 6.3 and 15.4% in the balloon and stent groups, respectively {Unverdorben et al, 2009}. These findings suggested that DEB is at least as efficacious and as well tolerated as DES in treating ISR.

PEPCAD III {Hamm, 2009} was a prospective, randomised, multi-centre, Phase II pilot study which compared the combination of paclitaxel-coated DEB plus BMS (Coroflex® DEBlue, B. Braun) with the sirolimus eluting CYPHER® stent in the treatment of de novo native coronary stenoses with stent diameters between 2.5 and 3.5 mm and less than 24 mm in length. The primary end point was late lumen loss in treated segment at 9 months assessed angiographically. The 637 patients with stable or unstable angina or documented ischemia (ST-elevation myocardial infarction and non-ST-elevation myocardial infarction excluded) were randomized to undergo PCI with either the paclitaxel DEB plus BMS (n = 312) or the sirolimus DES (n = 325). The in-stent late lumen loss was 0.41 ± 0.51 mm in the DEB + BMS group compared with 0.16 ± 0.39 mm in the DES group (p < 0.001). In segment late lumen loss in the two groups were 0.20 ± 0.52 mm and 0.11 ± 0.40 mm (p = 0.06), respectively. Target-vessel revascularization (13.8 vs. 6.9%, p < 0.01) and TLR (10.5 vs. 4.7%, p < 0.01) rates were also significantly higher in the DEB + BMS subgroup at 9 months. Of the safety end points, the rate of myocardial infarction at 9 months was 4.6 and 0.3% (p < 0.001) in the DEB plus BMS and DES groups, respectively. In addition, stent thrombosis by Academic Research Consortium criteria was 2.0 and 0.3%, respectively (p < 0.05). These

results show that the drug-eluting balloon-stent system did not meet the non-inferiority criteria versus the CYPHER stent and the safety aspects need further investigation

In a study of 20 patients, in the Drug-Eluting Balloon In Bifurcation Utrecht [DEBIUT] registry {Fanggiday et al, 2008}, Fanggiday assessed the efficacy and safety of different type of DEB in treating bifurcation lesions. The bifurcation lesions (main and side branch) were treated with the paclitaxel-coated DIOR balloon followed by BMS implantation only in the main branch. At 4-months follow-up, no major acute coronary events and no subacute vessel closure were reported. There was no angiographic follow-up performed in this study, making it difficult to assess the results, although the fact that major adverse cardiovascular event rates were not elevated after 4 months indicates that the coating of this balloon is well tolerated, but the small number of cases makes this woefully underpowered.

Recently, The PICCOLETO Trial {Cortese et al, 2010} failed to show the 'non-inferiority' of a paclitaxel-eluting balloon (DIOR, Eurocor, Germany) compared with a paclitaxel eluting stent (Taxus Liberte, Boston Scientific, MA, USA) in terms of restenosis for the treatment of small coronary arteries (≤2.75 mm). This was a small, single-centre, randomized controlled study that intended to randomize eighty patients with stable or unstable angina undergoing PCI in small vessels (≤2.75 mm) to receive either a DES (Taxus Liberte) or a DEB (DIOR). The enrolment into this study was halted after two thirds of the originally intended number of patients because of a marked outcome difference in the two groups. The 6-month angiographic follow-up of the 57 patients revealed that the primary end point was not met, because the DEB group showed higher per cent diameter stenosis (43.6% vs. 24.3%, p=0.029); angiographic restenosis was higher as well (32.1 vs. 10.3%, p=0.043), whereas MACE was 35.7% in the PCB group and 13.8% in the DES group (p=0.054).

The results of the PEPCAD V were presented at the Transcatheter Therapeutics 2009 {Mathey, 2009}. This was a small feasibility and safety trial using DEBs (SeQuent Please, B. Braun) for the treatment of coronary bifurcation disease, specifically by using DEB in main and side branches, a BMS in the main branch, and a provisional BMS strategy in the side branch. Twenty-eight patients were treated in 2 German centres. Achievement of the primary end point (<30% stenosis in the main branch, <50% stenosis in the side branch) at 9 months follow up occurred in 97% and 89% of vessels, respectively. Although there were no deaths during the follow-up, 2 late stent thromboses occurred in the main branch where DEB was used with BMS. Thus this small study indicated evidence of efficacy but the observed late stent thrombosis raised the issue of safety of DEBs used in combination with BMS.

There are several other studies ongoing, evaluating the role of DEB in treatment of coronary artery disease in various clinical settings. Some of them are listed in the table 1.

4. Limitations of DEB

Apart from the uncertainty about the choice of drug and the method used to coat the balloon there are still many more unanswered questions regarding the use of DEB. There have not been many studies to compare the efficacy and safety of different coating methods used. There is a potential risk of systemic toxicity with the loss of drug. As the device is

meant for single use it may not be very cost-effective in long lesions or other situations requiring multiple inflations and with each application the systemic toxicity is potentially higher. It definitely lacks the scaffold effect of a stent that is highly desirable in many clinical situations such as the treatment of acute vessel dissection and acute vessel recoil. With ongoing studies hopefully the device should improve and perhaps overcome some of these limitations.

Study Name	Brief Description of study	Estimated completion
DEB-AMI	Use of DEB in STEMI	2013
PEPCAD DES	DEB use in DES ISR	May 2011
KISSING DEBBIE	Use of kissing DEB in Bifurcation lesion	2011
PEPCAD-BIF	DEB in bifurcation lesions	November 2012
ISAR DESIRE 3	Treatment of ISR with DEB vs. DES vs. POBA	July 2014
SEDUCE	OCT analysis of DEB vs. DES treatment of restenosis	December 2015
PEPCAD IV	DEB in native coronary stenosis of Diabetic patients	September 2011
PEPCAD CTO	DEB in treatment of chronic total occlusion	September 2014
INDICOR	BMS +DEB post dilatation vs DEB predilation + BMS implantation	April 2012
PEPCAD DEB	DEB vs. DES in De-novo coronary stenosis	March 2015
WinDEB Study	Pressure wire guided DEB vs. DES use in SVD	Not Recruiting yet
VIBER	IVUS assisted DEB use	Recruiting

Table 1. Ongoing trials for DEB use in coronary intervention (Source Clinical Trials.gov)

5. Summary

With increasing numbers of coronary revascularisations taking place globally, the challenges and late complications of percutaneous intervention are also growing. The search

for an ideal device for PTCA is ongoing. The problem of restenosis is very well described as the 'Achilles heel' of coronary intervention. It not only necessitates repeat procedures but also significant symptoms in patients and the treatment is challenging. After the failure of systemic pharmacotherapy, local drug delivery at the coronary lesion site is the current treatment strategy for restenosis and the stent-based platform is the most extensively used. The limitations of DES {Sharma et al, 2010} and problems of late stent thrombosis have shifted the treatment goal from procedural success to keeping the long-term problems minimal.

The concept of DEB originated more than a decade ago but only has come into clinical use recently. Although it showed some initially promising results in animal study and first in man trials, the subsequent studies have failed to demonstrate their superiority over more traditional approaches. DEB certainly seems to offer promise in the treatment of ISR, and possibly in de novo lesions in small coronary vessels. In such scenarios it has several advantages over DES: it helps to avoid the double/triple metal layer which results in making the coronary vasculature into a metal jacket, thereby distorting the anatomy; it potentially provides homogenous drug distribution in the vessel wall, thus reducing the effects of delayed endothelialization of stent struts; it is free of the polymer matrix used in DES, thus removing the stimulus for late thrombosis; advantages are observed despite a shorter period of dual antiplatelet therapy usage, thus probably reducing costs and problems associated with prolonged dual antiplatelet treatment; and may have a role in small, tortuous, heavily calcified coronaries or bifurcation lesions, where DES continues to underperform.

The 2010 European Society of Cardiology Myocardial revascularisation guidelines suggest considering DEB use in treatment of BMS restenosis and for DEB with proven efficacy/safety profile, according to the respective lesion characteristics of the studies {ESC & EACTS, 2010}. Overall the data available so far does not convince us that DEB will replace all DES. Further studies are required in selective lesion subtypes. It is definitely a promising new treatment strategy on the coronary interventionist's shelf.

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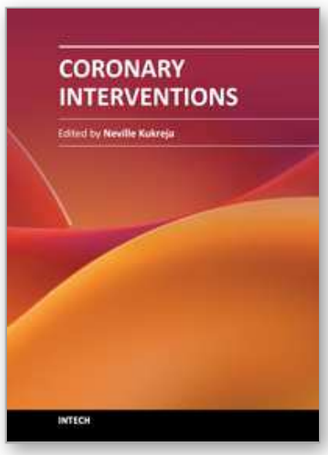
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