Drug-Coated Balloon and In-Stent Restenosis: A Clinical Strategy to Manage Coronary Artery Diseases

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ABSTRACT

Cardiovascular events are the most common cause of morbidity and mortality worldwide. Coronary artery diseases, including myocardial infarctions, are prevalent among all populations. There are multiple management strategies for coronary artery diseases, but stent implantation is among the most effective interventions. Nevertheless, some patients develop restenosis of the intervened vessel, and the number constitutes about 10%-20% of all patients. In-stent restenosis leads to adverse effects that might end in sudden cardiac death. Restenosis forges a clinical challenge for practicing physicians. A drug-coated balloon has propitious potential and is showing results comparable to stents implantation to overcome in-stent restenosis. This review aims to evaluate the effectiveness and advancement of drug-coated balloons in treating in-stent restenosis as a coronary intervention, along with its benefits and drawbacks.

Keywords—stent implantation, in-stent restenosis, coronary artery disease, drug-coated balloon.

INTRODUCTION

Coronary artery diseases (CADs) are the first cause of death worldwide. The condition results from partially or completed occlusion of one or more coronary arteries. Subsequently, the area supplied by the occluded vessel dies, leading to muscle necrosis, which disrupts the heart's electrical activity and pumping capacity. As a complication, an arrhythmia occurs and imposes a direct cause of death [1-2].

Multiple treatment strategies and management plans for CADs have been developed, including the administration of thrombolytic therapy, especially when the patient presents in the golden first four hours. The facility's capacity involved a role in the management; a center for interventional radiology guaranteed the application of percutaneous coronary intervention (PCI). PCI intervention includes a wide range of management strategies. It includes percutaneous

transluminal coronary angioplasty (PTCA), stent implantation, and drug-coated balloons (DCBs) [3]. There is a rapid improvement in treatment strategies, even at the level of bioengineering technologies. In practice, intervention choice depends on the patient's condition, facility capacity, possible procedure complications, and several other factors that influence practitioners' preference for stent implantation over PTCA. The restenosis rate in PTCA may reach up to 50%. On the other hand, the restenosis rate in drug-coated stent implantation is about 10-20% [4-5]. There are many reported adverse events with in-stent restenosis (ISR), and the presence of these complications is called major adverse cardiovascular events (MACEs). It comprises a group of symptoms that resemble angina pectoris, acute myocardial infarction, and sudden cardiac death.

The use of stents to manage CADs started after 1970. The restenosis complication might also occur with the balloon dilation technique. Balloon dilation works as elastic recoil of the vessel's internal lamina layer. Studies investigating the use of balloon technique in managing CADs reported a rate of restenosis of 30-60% when patients were followed up [6]. The ISR occurred three and six months after the procedure. In the 1980s, bare-metal stents (BMSs) were first used and started their development. BMS procedure was an evolution as it decreased the restenosis rate to less than 30% [6-7]. Although there are several efforts to reduce the restenosis complication, it still occurs. Practitioners sometimes use certain antiproliferative drugs such as paclitaxel and sirolimus to reduce ISR incidence [8]. The insertion of these drugs around the stent is called drug-eluting stents (DESs).

It was reported that ISR is less prevalent in DESs use when compared to BMSs. However, the implantation of stents and the management of CADs remain substantial clinical challenges [9]. The choice of treatment technique never fails to raise controversy among practitioners because the options are dependent on the availability of equipment and the patients' characteristics. Many studies that have discussed the use of drug-coated balloon (DCB) angioplasty and compared it to DES concluded that both are very similar in the complication of ISR [10-12]. Thus, it is imperative to be cautious when selecting management to reduce complications in the patients.

REVIEW

Method

Multiple methods have been used to maintain a high-quality review; databases such as Google Scholar and PubMed were thoroughly searched. Keywords like stent implantation, in-stent restenosis, coronary artery disease, drug-coated balloon were applied. Related studies to the main object and review articles were included. Included persons consisted of men and women between the ages of 18 and 80, excluding adolescents children. All studies incorporated are published in English. This investigation procedure revealed 33 appraised articles.

DISCUSSION

PCI intervention includes a wide range of management strategies. It comprises percutaneous transluminal coronary angioplasty (PTCA), stent implantation, and drug-coated balloons (DCBs) [3]. There is a rapid improvement in treatment strategies, to the point of bioengineering technologies. The intervention choice depends on the patient's condition, facility capacity, and possible procedure complications in clinical practice. Most physicians prefer stent implantation over PTCA because the restenosis rate in PTCA may reach up to 50%. Even though the rate of restenosis in drug-coated stent implantation is about 10-20% [4-5], many reported adverse events occur with in-stent restenosis (ISR), especially three and six months after the procedure. When bare-metal stents (BMSs) were developed to reduce the restenosis complication, ISR still manifests as the main complication. Physicians sometimes prescribe antiproliferative drugs such as paclitaxel and sirolimus to reduce the incidence of ISR [8]. The insertion of these drugs around the stent is called drug-eluting stents (DESs). Many studies that have discussed the use of drug-coated balloon (DCB) angioplasty and compared it to DES concluded that both are very similar in the complication of ISR [10-12].

In-Stent restenosis

There are several definitions of ISR, but the agreed one is the occlusion of at least 50% of the vessel lumen caused by a new proliferative lesion on top of a stent or involving 5 mm adjacent to the stent seen the coronary angiography [9-10]. It is reported that ISR occurs after a successful PCI procedure. The complication materializes on average one year after the procedure following failures to maintain the vessel's patency, which resulted from either restenosis or new thrombosis. The difference is that the restenosis process is gradual, and the thrombus is acute. Therefore, choosing the procedure is critical, and the patient should be the center of care in the choice. Some

studies mentioned that the restenosis might occur three months following the procedure [11]. The patient presents with symptoms of myocardial infarction, chest pain, and angina pectoris. The condition is actual for about 10% of patients [12-13]. The goal of the management is to restore the vascularization.

Physicians classified the ISR into two categories according to the pattern of occlusion. Type one is the restenosis within less than 10 mm length to the side of the stent, which is called focal or localized lesions. Type one is further classified into sub-types called focal multiple or diffuse, which is a lesion of more than 10 mm of length or not confined to the stent edges. Type two of the lesion is confined to the stent edges. Lastly, there is a diffuse type that extends over the stent edges, which is type three. Type four completely occludes the stent.

ISR Pathology

It is known that ISR pathology results from the proliferation of smooth muscle cells and the infiltration of macrophages at the site of the stent. A high amount of elastic fibers are found in the wall of arteries, especially the coronary arteries; hence it is essential to provide recoil characteristics to the vessels as they distend [14]. When an artery is occluded as the PCI procedure is performed, the recoil occurs within seconds. When the vessel wall undergoes hyperplasia, restenosis occurs. The vessel wall hyperplasia arises from various causes, such as an injury that leads to inflammatory response and subsequent lumen narrowing at the stent site. The pathophysiology of the new restenosis is the same as vessel thrombus and platelets play the most significant role in this pathology [15].

The management of ISR is conducted by inserting a balloon at the stent site and inflating it to contrast stenosis. The procedure will dilate the vessel lumen again [15-16]. However, in some cases where tears existed in the vessel's intimal and media layers, there should be an increase in the balloon's inflation to decrease the minimal luminal diameter (MLD) of the stenosis [16]. The process of restenosis takes months to develop, and in most cases, it is completed in 6 months. The redistribution of proliferative cells throughout the vascular wall causes some patients to present at an earlier or later period from the first procedure. The process is dependent on the rapidity of the cells' redistribution [16].

Table 1. Time-related assessment of in-stent restenosis (ISR)

Early (within days)	Late (weeks to months)
Elastic recoil	Reorganization of thrombus
Relocation of axially transmitted plaque	Neointima proliferation
	Cell proliferation
	Cell migration
	Cell matrix synthesis
	Remodeling
	Resolution of inflammation

New Atherosclerosis

When restenosis occurs, it is attributed to new atherosclerotic changes in the vessel wall. Restenosis is defined as the new accumulation of lipid-laden macrophages foam cells within the stent in the occluded vessel. The complication occurs with or without the formation of necrotic tissue or new calcification in the vessel wall [17]. Restenosis is mostly initiated by a mechanical injury to the arterial wall, which stretches it and makes the vessel more susceptible to atherosclerosis. The presence of previous risk factors of increasing LDL-cholesterol increases the rate of new atherosclerosis. While it is known that atherosclerosis takes years to develop for the first time, atherosclerosis can rapidly advance at the stent site. The phenomenon is due to the fact that endothelium is already damaged by the original injury that required the first stent implantation. Additionally, the damage may be induced by the original PCI procedure. In other cases where DESs is used, the antiproliferative drugs might play a role in making the condition worse [18]. Hence, there is a growing need to use intravascular imaging and optical coherence tomography. The implementation of intravascular imaging and optical coherence tomography is potential to deliver a higher rate of accurate diagnosis of the underlying problem in stent failure [18].

Clinical Management

The clinical management of ISR developed and changed over the years since the introduction of stents in 1970. There are two recent meta-analyses focused on which strategy is the best management modality to treat ISR. The first one was conducted by Siontis et al. [19], which included 27 trials and 5923 patients followed up at six months and one year. The authors reported that DES was found to be the most superior technique statistically. The primary outcome of the study was to measure the percent of restenosis and the secondary outcome is to look at the

complications. DCB was in second place in managing the ISR. The second meta-analysis conducted by Giacoppo et al. [20] included 24 trials and 4880 patients. The primary outcome is the lumen loss determined by angiography. The results were similar to the first meta-analysis in which DCB and DES were the superior techniques to other modalities. However, late lumen loss was found to be lower when using DCB compared to DES.

Evidence-Based Practice Of Using DCBs

The introduction of DCB to the management of CADs and ISR makes it easier to administer antiproliferative agents without leaving any additional stent strut layers. It has been reported that this modality is useful in patients with BMS-ISR and DES-ISR. Table 2 shows the clinical trials conducted to investigate the drug-coated balloon technique. The studies revealed that DCB is superior to plain old balloon angioplasty (POBA). When patients were followed at six months, it was found that angiographic results were better in patients who underwent DCB. Another study examined and compared the effectiveness of paclitaxel-DES and paclitaxel-coated DCB. The authors found that DCB reduced the late angiographic loss more significantly than the other technique. The RIBS V trial concluded that late angiographic findings in patients undergoing DES were lower than patients who underwent DCB. Accordingly, we can conclude that most studies and trials recommended the use of DCB to be superior to all other techniques in managing CADs and ISR [21-24].

On the other hand, several studies assessed the use of DCB in patients with DES-ISR. The studies demonstrated that DCB is superior in both clinical and angiographic results when compared to POBA alone. The result was approved by another trial in which patients had DES-ISR and underwent DCB. Furthermore, another study concluded that DCB is almost equivalent to paclitaxel-DES in patients with DES-ISR. The patients in the study had a lumen loss of 0.46 mm at one year follow up [25-27].

Eventually, we can say that DCB proves reliable effectiveness when compared to most other modalities. Table 2 shows more trials and their results. A recent study that assessed ISR of DES patients compared the second-generation DES versus DCB treatment. The second-generation DES is Paclitaxel- and Everolimus-Eluting Stent. The study found that results are favoring the use of second-generation DES over DCB. However, the controversy follows on the use of which modality. It is also still unknown whether the DCB efficacy can be improved by lesion preparation

using a scoring system. The questions mentioned above will be discussed in the ongoing ISAR-DESIRE 4 randomized trial.

Table 2. A comparison table of studies involving the clinical trials conducted to investigate the drug-coated balloon technique with their subsequent findings.

Reference	Trial name	Findings
21	PACCOATH ISR I	At 6-month follow-up, LLL: 0.03 ± 0.48 mm versus 0.74 ± 0.86 mm ($P= 0.002$); TLR 23% versus 0%
22-23	PACCOATH ISR II	At 6 or 12 months, LLL: 0.81 ± 0.79 mm versus 0.11 ± 0.46 mm ($P< 0.001$); 37% versus 4%
24	PEPCAD II	At 6 months, LLL: 0.17 ± 0.42 mm versus 0.38 ± 0.61 mm ($P= 0.03$); 6.3% versus 15.4%
25	ISAR-DESIRE3	At 9 months, diameter of in-stent restenosis: 38%: 37.4% versus 54.1% (noninferiority $P= 0.007$)
26	PEPCAD-DES	At 6 months, LLL: 0.43 ± 0.61 mm versus 1.03 ± 0.77 mm ($P<0.001$)
27	PEPCAD China ISR	At 9 months, LLL: 0.46 ± 0.51 mm versus 0.55 ± 0.61 mm (noninferiority $P<0.0005$)
28	DELUX registry	At 6 and 12 months, MACE: 8.5% and 15.1%
29	Habara et al.	At 6 months, LLL: 0.18 ± 0.45 mm versus 0.72 ± 0.55 mm ($P= 0.001$)
30	SeQuent Please World Wide Registry	At 9 months, TLR: 9.6% versus 3.8% ($P<0.001$)
31	Valentines I	At 8 months, MACE: 0 : 23.8% ($P= 0.002$)
32	PEPPER	At 6 months, LLL: 0.05 ± 0.28 mm versus 0.19 ± 0.29 mm ($P= 0.001$)
33	RIBS IV	At 3-years follow-up, MLD: 2.03 ± 0.7 mm versus 1.8 ± 0.6 mm

Note: LLL, late lumen loss; TLR, target lesion revascularization; DES, drug-eluting stent; MACE, major adverse cardiovascular events; MLD, minimal lumen diameter.

CONCLUSION

The introduction of new methods to manage CADs has significantly reduced the incidence rate of ISR. However, the management of ISR is still challenging for physicians. The current systematic review suggests that DES and DCB are the most superior techniques in managing CADs with the least ISR rates. When a patient needs more than two metal stents in the same ISR lesion, the need increases the long-term detrimental outcomes, even with newer DCB that proves superior to manage ISR. There is a need for further research and trials to spotlight the role of these current management techniques and modalities to improve patients' clinical outcomes and provide a guide for practicing physicians.

DISCLOSURE

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Conflict of Interest

The author declares there is no conflict of interest regarding all aspect of the study.

Author Contribution

PHW is responsible for the study from the literature search, data gathering, data analysis, until reporting the results of the study by a narrative form of literature review.

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