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Drug-Eluting Balloon: An Overview of Clinical Evidences on Safety and Effectiveness

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ABSTRACT

Background: Recent advances in the intravascular diseases have led to the entrance of drug-eluting balloon (DEB) technology. The DEB is a relatively new and easier way to treat vascular stenosis. In this study as part of rapid health technology assessment, we aimed to assess this technology in comparison with drug-eluting stent (DES), uncoated balloon and bare-metal stent in terms of efficacy and safety in common indications by reviewing available clinical evidences.

Methods: In order to evaluate the safety and effectiveness of DEB, a non-systematic review on electronic databases including Cochrane, PubMed, INAHTA, CRD, Scopus, Medline, Trip database, and Google Scholar was conducted by keywords: “balloon angioplasty," “drug eluting balloon," “drug eluting stent."

Results: DEBs could be suggested as a more effective and safe intervention compared with uncoated balloon angioplasty in patients with in-stent restenosis and peripheral vascular disease however there were not adequate evidences supporting the superiority of DEB compared with DES. There were not also adequate evidences comparing DEB with uncoated balloons or DES for decision making about de novo lesion and small vessel arteries.

Conclusion: Conducting an economic evaluation to assess the cost effectiveness of this technology has to be also taken into account for more adequate decision making.

Keywords: *Drug-eluting balloon, efficacy, safety, review*

1. Introduction

Cardiovascular diseases impose significant burden on societies [1]. In order to manage this and other areas of health care more efficiently, there is an inevitable need for applying an evidence-based policy making approach regarding available and emerging interventions [2].

One of the most progressive and expanding areas in cardiovascular interventional treatments is angioplasty in which balloon angioplasty was one of the first technologies. However, it was faced with some undesirable consequences including: elastic recoil and restenosis by cell proliferation as limiting factors in using this technology. To overcome such constraints, stent technology was developed. Although coronary stenting was able to tackle dissections and elastic recoil and also remove negative remodeling [3,4], risk of stent thrombosis and “neointimal hyperplasia” leading to in-stent restenosis (ISR) remained as major limitations for its use [5].

Addressing the stents' limitations, drug-eluting stent (DES) was developed as one of the most significant clinical advances in the interventional cardiology which has reduced the incidence of ISR [6,7] and target-lesion revascularization (TLR) [8] however the recurrence rate of ISR is still a limitation [8,9]. This technology could also induce vascular wall inflammation and late thrombosis mainly due to the polymer used in its structure [10] and because of that, dual antiplatelet therapy (aspirin and clopidogrel) is necessary for a long time by this technology. This antiplatelet therapy may put patients on the risk of hemorrhage and vascular complications and need monitoring at the same time [11].

Recent advances in the intravascular diseases have led to the entrance of drug-eluting balloon (DEB) technology. The DEB is a relatively new and easier way to treat vascular stenosis, which was introduced in 2003. DEB is a balloon-like device which enters to the blocked arteries and then will be inflated to release anti-proliferative drugs [12,13]. These balloons would be removed from the vessels when the drug was penetrated to their wall. DEB has been proposed recently as a potential alternative to DES for dealing with stenosis. Paclitaxel is considered as the first medication for DEB because of its rapid uptake and long effects [14,15].

Considering growing demand for using DEB technology in Iran by cardiologists, we aimed to assess this technology in comparison with other available ones including DES in terms of efficacy and safety in all probable indications by reviewing available clinical evidences.

2. Methods

In order to evaluate the safety and effectiveness of DEB in comparison with other available interventions, a non-systematic review of published studies was conducted on electronic databases including Cochrane, PubMed, INAHTA, CRD, Scopus, Medline, Trip database, and Google Scholar by keywords: “balloon angioplasty”, “drug-eluting balloon”, “drug-eluting stent”. All types of clinical trials, systematic reviews and meta-analyses and observational studies between 1990 and 2012 with at least one arm of DEB were included in our study.

3. Results

Totally 10 studies were included in our analysis in which all of them were randomized clinical trial except one that was a prospective registry. The general characteristics of these studies are summarized in table 1. Among these studies, Scheller et al. (2008) [18] is re-analysis of Scheller et al. (2006) [17] with more patients and reporting follow-up results to assess long term efficacy and safety of interventions. The included studies were categorized into following four interventions that DEB had been evaluated in one or more of them.

3.1. Effectiveness and safety evidences of DEB technology in ISR

A1. Cuculi et al. [16] evaluated the effectiveness of DEBs in ISR and de novo lesion. It was a prospective registry study in which 12-month rates of clinically driven TLR as the outcome of interest was reported 5.4% and 4.8% (P = 1.000) in the ISR group and de novo lesion, respectively. The results also indicated that in the ISR and de novo lesion groups of patients with vessel diameter >2.75 mm, the TLR rate was 4.2% and 2.2%, respectively and in the ISR and de novo lesion groups with vessel diameter >2.75 mm, the TLR rate was 9.5% and 6.2%, respectively.

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Table 1. General characteristics of included studies

Study	Arms of study	Target population	Number of patients	Average of patients age	Setting	Study design
Cuculi, et al. (2012)	(A): DEB (B): No comparator	Patients with ISR and de novo lesions treated with the In.Pact DEB	139 (222 lesions)	69 ± 10	Switzerland (single center)	Prospective registry
Scheller, et al. (2006)	(A): DEB (B): Uncoated balloon	Patients with a single restenotic lesion in a stented coronary artery	(A): 26 (B): 26	(A): 63.6 ± 11.2 (B): 63.5 ± 10.5	Germany (multicenter)	Double-blind randomized pilot trial
Scheller, et al. (2008)	(A): DEB (B): Uncoated balloon	Patients with a single restenotic lesion in a stented coronary artery	(A): 54 (B): 54	(A): 58.3 ± 16.3 (B): 50.3 ± 20.4	Germany (multicenter)	Double-blind randomized pilot trial
Unverdorben, et al.	(A): DEB (B): DES	Patients with a single restenosis in a BMS	(A): 66 (B): 65	(A): 64.6 ± 9.7 (B): 65.1 ± 8.7	Germany (multicenter)	Randomized non-blinded trial
Rittger, et al.	(A): DEB (B): POBA	Patients with DES ISR	(A): 72 (B): 38	(A): 69.8 ± 10.8 (B): 64.0 ± 11.3	Germany (multicenter)	Single-blind, randomized trial
Tepe, et al.	(A): DEB (B): Uncoated balloon	Patients with obstructive lesions, new or restenoses, at least 70% of vessel diameter and at least 2 cm in length, in the superficial femoral artery, the popliteal artery, or both	(A): 48 (B): 54	(A): 69 ± 8 (B): 68 ± 9	Germany (multicenter)	Randomized, multicenter trial
Werk, et al.	(A): DEB (B): Uncoated balloon	Patients with an occlusion or stenosis >70% diameter of the superficial femoral artery and/or popliteal artery with clinical Rutherford stage 1-5	(A): 45 (B): 42	(A): 63.5 ± 76.4 (B): 66.2 ± 77.6	Germany (multicenter)	Randomized controlled trial
Stella, et al.	(A): DEB plus BMS (B): BMS (C): DES	Patients with de novo coronary artery lesions (stenosis >50% and <100%) located at the level of a bifurcation	(A): 40 (B): 37 (C): 40	(A): 63.3 ± 10.4 (B): 61.8 ± 10.1 (C): 65.7 ± 9.3	Belgium, Germany, Netherlands (multicenter)	Single-blind, randomized trial
Cortese, et al.	(A): DEB (B): DES	Patients with small coronary vessels (≤2.75 mm)	(A): 28 (B): 29	(A): 63.3 ± 10.4 (B): 61.8 ± 10.1	Italy (single center)	Randomized controlled trial
Wohrle, et al.	(A): DEB plus EPC stent (B): EPC stent	Patients with a de novo lesion in a native coronary artery			Germany (multicenter)	Single-blind randomized trial

DEB: Drug-eluting balloon; DES: Drug-eluting stent; ISR: In-stent restenosis; POBA: Plain old balloon angioplasty; BMS: Bare-metal stent; EPC stent: Endothelial progenitor cell capturing stent

A2. Scheller et al. [17] examined the effectiveness of paclitaxel coated balloon compared with uncoated balloon in a multicenter, randomized, double-blind trial on 52 patients. In this study, late luminal loss was considered as a primary outcome and restenosis rates and major cardiovascular events were as secondary outcomes of interest. The results showed that in 6 months, absolute difference of late lumen loss for uncoated balloon group versus paclitaxel-eluting balloon group was 0.70 (95% confidence interval [CI] 0.28-1.12, P = 0.002). Also, the absolute difference of both ISR and in-segment restenosis was 0.39 (95% CI 0.15-0.63, P = 0.002) in patients of uncoated balloon group versus DEB group. Also in 12 months, the absolute difference for the rate of major adverse cardiac events in uncoated-balloon versus the coated-balloon groups was 0.27 (95% CI, 0.07-0.47, P = 0.010). The results of this study showed significant superiority of the DEBs in patients with ISR.

A3. In another study [18] which was the extension of the former study conducted for long-term evaluation of paclitaxel-eluted balloon versus uncoated balloon in a larger population, 108 patients from two separate randomized, double-blind clinical trials were examined in terms of effectiveness and safety. Inclusion criteria consist of diameter stenosis of >70%, length of less than 30 mm, and vessel diameter of 2.5-3.5 mm. Primary and secondary outcomes were similar to the previous study. After 6 months, late lumen loss has been reported 0.81 ± 0.79 and 0.11 ± 0.45 mm, in non-DEB group and DEB group, respectively. The binary restenosis for uncoated balloon group and DEB was 51% and 6%, respectively. After 12 months of following the procedure, TLR rate for non-DEB group and DEB was 40% and 4%, respectively. This study showed that the use of paclitaxel-coated balloons could reduce restenosis recurrence up to 2 years.

A4. In another clinical study (The PEPCAD II study), safety and effectiveness of ISR patients have been studied in two groups of receiving DEB and drug-eluting stents (DESs) [19]. A total of 131 patients were enrolled in the study. The primary outcome, late lumen loss, the absolute difference between DES and DEB was 0.21 (95% CI 0.40-0.02, P = 0.030) after 6 months (0.38 ± 0.61 mm for DES and 0.17 ± 0.42 mm for DEB). Also, the difference of DES and DEB in term of binary in-segment restenosis rate was 0.13 (95% CI 0.27-0.01, P = 0.060). As side effect, major cardiac event rate was 7.1% for DEB and 18.3% for DES with the absolute difference of 0.09 (95% CI 0.22-0.03, P = 0.170).

The drug-coated balloon was superior to the DES with respect to the primary end point. This intervention was also associated with fewer adverse clinical events despite shorter period of dual anti-platelet therapy; however, it was not statistically significant.

A5. In a prospective, single-blind, multicenter, randomized trial (PEPCAD-DES study), paclitaxel coated balloon angioplasty and uncoated balloon angioplasty was compared with each other in DES restenosis located in a native coronary artery [20]. The late lumen loss as the primary outcome indicated superiority of DEB versus uncoated balloons (0.43 ± 0.61 mm vs. 1.03 ± 0.77 mm [P < 0.001]). Restenosis rate was also significantly reduced from 58.1% to 17.2% (P < 0.001) by DEB.

3.2. Effectiveness and safety evidences of using DEB in peripheral vascular disease (PVD)

B1. In THUNDER study conducted by Tepe et al. [21], effectiveness of uncoated balloon catheter, paclitaxel-coated balloon and uncoated balloon with paclitaxel dissolved in contrast medium were compared in 154 patients with stenosis or occlusion of femoropopliteal artery. In this multicenter study which had been conducted on 154 patients, late lumen loss after 6 months was considered as a primary outcome, and the secondary outcome was TLR. In term of late lumen loss, the difference between patients treated with paclitaxel DEBs and uncoated balloon group was 1.30 (95% CI 0.65-1.95, P < 0.001). In term of TLR at 24 months, the percent difference between paclitaxel DEB group and simple balloon group was 37 (95% CI 21-54, P < 0.001).

In term of safety, during the intervention, Tepe study has reported three serious complications (6%) in the DEB group, and two serious complications in the simple balloon group (4%) which was not a statistically significant difference. From 2 weeks to 6 months after the intervention, 52% of simple balloon and 46% of DEB group experienced at least one serious complication which was not a statistically significant difference.

B2. In the FemPac study [22], 87 patients with femoropopliteal peripheral artery disease were randomly assigned to two groups of DEB

and conventional uncoated balloons. After 6 months, late lumen loss in the DEB group was significantly lower than simple balloon group (0.5 ± 1.1 vs. 1.0 ± 1.1 mm; P = 0.031). The percentage of binary restenosis was also significantly lower in paclitaxel coated balloon groups compared with uncoated balloon (19% vs. 47%, P = 0.035). TLR rate in the DEB group was 7% and in the conventional balloon group was 33% (P = 0.0024).

B3. In an international, multicenter, randomized, single-blind study [23] to evaluate the angiographic and clinical outcomes of T-stenting technique in three groups of DEB plus bare-metal stent (BMS), BMS, and DES, 117 patients with coronary bifurcation lesions were classified into three groups. Late luminal loss after 6 months as the primary outcome was not statistically significant different between combination of DEB and bare-metal stent (BMS) with BMS. Also in secondary outcomes including binary restenosis after 6 months and major cardiac events after 12 months, including death, myocardial infarction, and target vessel revascularization no statistically significant difference was observed between these two groups.

The results indicate that pre-treatment with DEBs by provisional T-stenting technique has no superiority to BMS, but angiographic results of DESs comparison with BMS are significantly different.

3.3. Effectiveness and safety evidences of DEB in small vessel arteries

One study has been published in this field [24]. In this study (PICCOLETO study), 57 patients with small coronary artery disease were enrolled. Both DEB and DES technology with paclitaxel were evaluated. This study has been finished early, due to a high priority of one arm over the other. The incidence of stenosis was 43.6% in the DEB group and 24.3% in the DES group (P = 0.029). The angiographic restenosis rate in DES and DEB was 10.3% and 32.1%, respectively (P = 0.043). Major cardiovascular events were reported 35.7% in DEBs and 13.8% in DES group (P = 0.054).

3.4. Effectiveness and safety evidences of DEB in de novo lesions

In a prospective, single-blind multicenter randomized clinical trial [25], 120 patients with a de novo lesion in a native coronary artery were randomly assigned to treatment with paclitaxel-coated balloon plus endothelial progenitor cell capturing (EPC) stent or EPC stent alone. In-stent late lumen loss as the primary outcome in DEB plus EPC group was 0.34 ± 0.45 mm versus 0.88 ± 0.48 mm (P < 0.001) in EPC alone group. The re-stenosis rate was also lower in DEB plus EPC group (23.2% to 5.1% (P = 0.006)). This study concluded paclitaxel-coated balloon plus EPC stent implantation as superior to EPC stent implantation alone for treatment of de novo coronary artery disease.

4. Discussion

In this study, the clinical evidences on safety and efficacy of DEB were reviewed as part of a rapid health technology assessment. Considering this review result, DEBs could be suggested as more or similar effective and safe intervention (regarding different studies and outcomes) compared with uncoated balloon angioplasty in patients with ISR and PVD however there were not enough evidences supporting the superiority of DEB compared with DES. Although the only available evidences failed to conclude the non-inferiority of DEB in comparison with DES in small vessel restenosis and showed superiority of DEB in de novo lesion, but these two studies do not seem to be adequate for decision making.

The results of this study could be used by policy makers to make a better decision on this technology especially in reimbursement issues. In this study, we did not consider economic aspects of DEB in comparison with alternatives. A cost analysis in Korea has shown that using DEB instead of DES could save 34% and 48% of the total cost in ISR and small vessel disease patients, respectively [26]. An economic evaluation study in Germany with a Markov model indicated that DEB is a cost effective strategy compared with DES and plain balloon angioplasty [27]. Although DEB could be evaluated as a clinically rational intervention in interventional cardiology but developing an economic evaluation to assess, its cost effectiveness has to be also taken into account for more adequate decision making.

4.1. Limitation

Some eligible studies could have been missed because of non-systematic structure of our search through databases.

5. Conclusion

Considering this review result, DEBs could be suggested as more or similar effective and safe intervention (regarding different studies and outcomes) compared with uncoated balloon angioplasty in patients with ISR and PVD however there were not enough evidences supporting the superiority of DEB compared with DES. There is not also enough evidences for making decision about using DEB in small vessel restenosis and de novo lesions. Conducting an economic evaluation to assess the cost effectiveness of this technology has to be also taken into account for more adequate decision making.

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