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Overview of Intracoronary Brachytherapy for the In-stent Restenosis of a Drug-eluting Stent

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ABSTRACT

Percutaneous coronary intervention with stenting is considered recently as the most common procedure for the treatment of symptomatic coronary. The article reviewed 41 studies published during 1997-2019 on intracoronary brachytherapy for in-stent restenosis of a drug-eluting stent. Intracoronary radiation therapy was finally confirmed in the setting of in-stent restenosis using as adjunctive therapy. Irradiation dose to vessels may result in fibrosis, which can, in turn, cause the late formation of an aneurysm due to the weakness of the vessel wall. Intracoronary brachytherapy is a critical treatment which should not be ignored.

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Introduction

Percutaneous coronary intervention [PCI] with stenting is recently the most usable symptomatic coronary treatment procedure (1). However, these stents may lead to in-stent restenosis (ISR), which requires to repeat revascularization. This issue may increase the rate of mortality and pose a therapeutic challenge (2). The principal mechanism of ISR after the implantation of the stent is the proliferation of neointimal tissue due to the damaged arterial wall (3). Neointimal tissue proliferation might be focal or aligned with the length of the stent distributed uniformly. The ISR, which occurs early during the deployment of the stent, is through elastic recoil and relocation of axially transmitted plaque. The reasons for late (weeks to months) ISR are generally the reorganization of thrombus, neointima remodeling and formation (1).

The negative effect of endothelin-1 on blood vessels may be associated not only with its vasoconstrictor properties but also with its mitogenic effects. There have been a few reports of an increase in the concentration of endothelin-1 after angioplasty, which results from mechanical damage to the vascular wall although it does not appear to be significant in all papers (4).

Neoatherosclerosis is still another factor contributing to ISR. The stimulation of neointima formation occurs due to the injured vessel in the PCI and deployment of the stent. Plenty of these incidents are due to the medial and intimal damage, leading to the proliferation and migration of vascular smooth cells in muscle, the formation of extracellular matrix, which finally activates the coagulation-fibrinolysis system (1, 5, 6). The occurrence of neoatherosclerosis was considerably greater in

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drug-eluting stent (DES) compared to BMS (31% vs 16%, P<0.001) (1).

The independent risk factors for neoatherosclerosis include younger age, longer use of an implant, sirolimus-eluting stent usage, paclitaxel-eluting stent utilization, and underlying unstable plaques (1, 7). Restenosis immediately after percutaneous coronary revascularization is defined as a decrease of 50% or higher in the luminal diameter after angiography. However, on the basis of the literature, the prevalence of restenosis after only balloon angioplasty was 40-50%. Bare metal stents (BMS) eliminates restenosis to almost 20% (8, 9). In the first months of the 2000s, DES plus extenuated were introduced as the target lesion revascularization, which decreased up to 50% or more, compared to BMS (9, 10). The DESs demonstrated the considerable reduction of restenosis and the necessity for recurrent intervention, which was in contrast with bare metal stents in pivotal trials (11, 12). Despite these, the frequency of ISR in DES is up to 20%. Some patients failing DES have confined options of salvage and mostly numerous medical comorbidities, originally increase their risk (8, 9).

It was assumed that intracoronary irradiation can decrease neointimal proliferation and vascular smooth muscle proliferation after the procedure of the balloon overstretch, that can barricade or decrease ISR. Some studies illustrated a considerable decrease in the rating area of restenosis mid endovascular radiation in animal models (9). Treatment with intracoronary radiation was eventually confirmed in the setting of ISR in BMS as adjunctive therapy, using several trials indicating the improved percent of angiographic restenosis, major cardiac incidents, and aimed lesion revascularization (9, 10). Although the best treatment for the recurrent ISR of DES (i.e., restenosis that follows second DES or drug-eluting balloon], this setting in which case brachytherapy can be particularly more beneficial, compared to bare metal stent (13). The foundation for brachytherapy is a conceptualization of the fact that one part of restenosis is neointimal hyperplasia, a natural replication to the tissue injury made by balloon expansion in an arterial segment (8). Cellular proliferation fills in voids in the media and may develop into the arterial lumen. The intracoronary concept brachytherapy is that locally used radiation may eliminate or attenuate neoproliferation (13-15).

The Beta-Cath System [Novoste, Inc., Norcross, GA] and the CHECKMATE System [Cordis Corp., Miami, FL], confirmed by the Drug and Food Administration in November 2000 for daily usage (16-19), are first two commercial systems for coronary irradiation. The system which is called Novoste is a manually acted hydraulic system that applies a non-centered radioactive particle fount train [2.3-mm diameter] of 90Sr pellets, which give out high-energy b-particles [bmax 2.28 MeV] by the decay of the 90Y daughter (16, 20). In return, the Cordis system is composed of a high-activity [7.4–18.5 GBq] 192Ir wire source that is developed by an automated loader machine (16, 19, 21). Any system which uses a high-dose percent, by a 3-6-min vessel dwell time [i.e., required time to place the radioactive resource in the vessel target area to radiation delivery] for a resource of the Novoste and a 15-20-min dwell time is required for the Cordis machine (16, 17, 47). The whole dose requirements for the Beta-Cath System, as an example, are 23.0 Gy and 18.4 Gy in large and small vessels, respectively, which measures at 2 mm radially from the center of the source, and 8–30 Gy at 2 mm distance from the center of the source for the CHECKMATE system (16, 19, 22). The multiple trials, apply either gamma or beta radiation sources, show the brachytherapy's effectiveness in the decreased occurrence of ISR. The brachytherapy was developed to the era of BMS due to its ease of use and effectiveness resulted in the replacement of DES with the ordinary brachytherapy (15). This study aimed to provide an overview of intracoronary brachytherapy for the ISR of DES.

Materials and Methods

This systematic review of papers addressed the evaluation of the intracoronary brachytherapy for the ISR of DES. In doing so, four databases, including Medline, PubMed, Science Direct, and Google Scholar, were searched for the relevant clinical and experimental studies published during 1997-2019.

The search focused on randomized, clinical, and experimental studies published in English. The literature search was performed using a combination of medical subject headings (MeSH) ("Intracoronary Brachytherapy" or "Drug-Eluting Stent [DES]" or "In-Stent Restenosis [ISR]" or "Percutaneous Coronary Intervention [PCI]").

Results

Various studies have been conducted on this issue in recent years (Table 1). In one of these studies, the researchers examined more than 250 patients who were treated by ICBT after percutaneous transluminal coronary angioplasty. As can be seen in table 1, the obtained results indicated that vascular brachytherapy integration in the catheterization laboratory was both secure and practical (8, 32, 11, 46).

Table 1. Results of clinical studies of adjuvant intravascular brachytherapy

Study group	Year	Article title	Conclusions
Mithun J	2019	Intravascular Brachytherapy for the Management of Repeated Multimetal-Layered Drug-Eluting Coronary Stent Restenosis	Intravascular brachytherapy led to significantly lower major adverse cardiac events in patients with multilayered drug-eluting stents restenosis.
J.M. DeCunha	2018	A new delivery system to resolve dosimetric issues in intravascular brachytherapy	We hope that our proposed delivery system and other developments allow for the introduction of a second generation of intravascular brachytherapy delivery systems that will improve patient outcomes and patient safety and present a viable solution to the problem of DES-ISR.
Ron Waksman,	2017	Diagnosis and management challenges of in-stent restenosis in coronary arteries	Drug-eluting balloons should be used as first line therapy for bifurcation restenosis to prevent excess metal at the carina.
Ron Waksman,	2016	In-Stent Restenosis? The Raiders of the Magic Remedy	The interventional cardiologists will be able to declare success in finding the remedy for DES-ISR by elimination of the stent and its late complications.
Nisha Ohri MD	2016	Intracoronary brachytherapy for in-stent restenosis of drug-eluting stents	Intracoronary brachytherapy is a safe and well-tolerated treatment option that may serve as a form of salvage therapy for high-risk patients with recurrent ISR of DES.

Discussion

Ionizing radiation has efficiently been used as adjunctive therapy if necessary (23-26) for de novo coronary stenosis and ISR in controlled studies. In the early 1990s, endoluminal radiation in atherosclerotic lesions was considered for animal models (27, 28). The implication of restenosis of DES has grown in recent years due to its expanded usage for complex coronary lesions in high-risk patients. The rate of DES-ISR has been reported as 3-20%, which is closely related to DES type, the follow-up date, and the lesions convolution (1, 29). The DES is dependent on lower ISR, compared to BMS (1, 30).

However, DES has noticeably decreased the rate of ISR compared to BMS. There is a considerable number of patients with high risks of cardiac problems, who have developed ISR of DES and they have gained the desirable results from standard treatments (8, 9). Furthermore, since patients have different stents levels in the lesion, extra procedures carry incremented risk. To explain this clinical event, the high volume cardiac catheterization laboratory plays the key role in the intracoronary brachytherapy (ICBT) of patients who have recurrent ISR of DES (8).

The utilization of ionizing radiation for the decrease of restenosis due to myointimal hyperplasia after the endovascular intervention is a promising innovative tool (31, 32). The safety of intracoronary brachytherapy procedure has already been documented by a German group in 2000 (8, 33).

Besides the Novoste Beta-Cath system, ICBT implied non-stent restenosis and ISR for treatment of de novo lesions. A total number of 92 patients with 104 lesions were treated through this method using the dose range of 14-20 Gy. There were no reports of acute complications, including deaths, related to the procedure, stent thrombosis, or infarcts. The other Dutch group published the outcomes of ICBT in 2000 (8, 34).

However, brachytherapy is technically a simple method, which poses numerous difficulties, such as dosimetry exposures of cardiac catheterization laboratory staff and patient as well as time limitations (35). Exposure to radioactive substances, particularly gamma radiation, needs numerous safety precautions. Furthermore, routine shielding is essential for the laboratories of cardiac catheterization. Radiation sources [Ir or Sr] have confined half-life, so renewal is important. Treatment procedure takes 20 min for gamma and 3-10 min for beta radiation, and it needs time to advance and remove the catheters (36, 37). If ICBT implies into routine practice, then its practicality and effectiveness have the same importance. At present ICBT generally needs to the transfer of the patient to a radiotherapy suite, which can add 30±45 min to the procedure; however, the real irradiation element needs only 200±656 s.

Vascular brachytherapy is accessed in some centers in the United States and is used initially for the DES-ISR recurrence; however logistic issues and absence of radiation oncology support hinder its utilization (1). Considering the obtained outcome of experimental dosimetric studies, the tissue reaction's morphology was documented on endoluminal radiation therapy (38, 39), such as the primary phase I and II brachytherapy trials. Moreover, these randomized trials revealed that the rate of subacute thrombosis and even thrombosis with delay could be higher, compared to the expected rate (37, 40). The term subacute thrombosis is applied for incidents happening during 1-6 months, but thrombosis with a delay is used for events of 6 months (37).

The other possible problem is related to the formation of an aneurysm at the treatment location. Irradiation dose to vessels may result in fibrosis, which can, in turn, cause the late formation of an aneurysm due to the weakness of the vessel wall (32, 40, 42). The obtained results revealed that although the regeneration of endothelial after brachytherapy decreased for 6-12 months, each reaction of an inflammatory was followed with neoendothelial hyperplasia in several cases. This means that restenosis was not prevented but delayed in time (37).

Another factor which can be related to the polymer is long-term inflammation or hypersensitivity reaction (41). According to the papers on brachytherapy using angiographic follow-up, it revealed that restenosis was more frequent at the stent edges. Numerous names have been utilized to explain this event, such as the effect of the candy wrapper, which is due to the mitotic stimulation of low-dose radiation in the segment's edges of the radiating catheter (37, 43). This event considerably reduces the benefits of brachytherapy and needs alternative treatment. In this regard, it has been proposed endothelial trauma is essential apart from the decreased dose of radiation at the edges of the stent. For inhibition, we must radiate the longer segments of the arterial wall, although this solution could not solve the problem completely (37).

There is no evidence for local problems, including local malignancy or damages of nerve after a relatively short follow-up period. However, numerous studies have only enrolled elderly patients due to the potential possibility of malignancy progress (44-46). However, our recent outcomes illustrated that ICBT is a secure and well-tolerated procedure in high-cardiac-risk patients. The more studies about the ICBT efficacy as a form of salvage therapy is warranted for recurrent the ISR of DES are accepted (8, 9).

Conclusion

The DES's in-stent restenosis is a significant clinical issue. Intracoronary brachytherapy is a secure and well-tolerated treatment option, which can serve as a type of salvage therapy for high-risk patients with the recurrent ISR of DES. Intracoronary brachytherapy is a critical treatment, which should not be ignored.

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Conflict of Interest

Authors declared no conflicts of interests.

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