

Scientific Article

Intracoronary brachytherapy for in-stent restenosis of drug-eluting stents

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Abstract

Purpose: Given the limited salvage options for in-stent restenosis (ISR) of drug-eluting stents (DES), our high-volume cardiac catheterization laboratory has been performing intracoronary brachytherapy (ICBT) in patients with recurrent ISR of DES. This study analyzes their baseline characteristics and assesses the safety/toxicity of ICBT in this high-risk population.

Methods and materials: A retrospective analysis of patients treated with ICBT between September 2012 and December 2014 was performed. Patients with ISR twice in a single location were eligible. Procedural complications included vessel dissection, perforation, tamponade, slow/absent blood flow, and vessel closure. Postprocedural events included myocardial infarction, coronary artery bypass graft, congestive heart failure, stroke, bleeding, thrombosis, embolism, dissection, dialysis, or death occurring within 72 hours. A control group of patients with 2 episodes of ISR at 1 location who underwent percutaneous coronary intervention without ICBT was identified. Unpaired *t* tests and χ^2 tests were used to compare the groups.

Results: There were 134 (78%) patients in the ICBT group with 141 treated lesions and 37 (22%) patients in the control group. There was a high prevalence of hyperlipidemia (>95%), hypertension (>95%), and diabetes (>50%) in both groups. The groups were well-balanced with respect to age, sex, and pre-existing medical conditions, with the exception of previous coronary artery bypass graft being more common the ICBT group. Procedural complication rates were low in the control and ICBT groups (0% vs 4.5%, *P* = .190). Postprocedural event rates were low (<5%) in both groups. Readmission rate at 30 days was 3.7% in the ICBT group and 5.4% in the control group (*P* = .649).

Conclusions: This is the largest recent known series looking at ICBT for recurrent ISR of DES. ICBT is a safe treatment option with similarly low rates (<5%) of procedural and postprocedural complications compared with percutaneous coronary intervention alone. This study establishes the safety of ICBT in a high-risk patient cohort.

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Conflicts of Interest: None.

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Introduction

Restenosis after percutaneous coronary revascularization, defined as 50% or greater reduction in luminal diameter at the time of follow-up angiography, remains an important clinical issue. Previous studies have demonstrated restenosis rates ranging from 40% to 50% after balloon angioplasty alone.¹ With the introduction of bare metal stents (BMS), the rate of restenosis decreased to about 20%.^{2,3}

It was hypothesized that intracoronary irradiation may reduce vascular smooth muscle proliferation and neointimal proliferation after a balloon overstretch procedure, which could prevent or reduce in-stent restenosis. Several studies demonstrated significant reduction in the percent area of restenosis with endovascular radiation in animal models.^{4,5} Intracoronary radiation therapy was eventually approved for use as an adjunctive therapy in the setting of in-stent restenosis (ISR) in BMS, with multiple trials demonstrating improved rates of angiographic restenosis, target lesion revascularization, and major cardiac events.^{6,7}

In the early 2000s, the drug-eluting stent (DES) was introduced and further lowered the rate of target lesion revascularization by 50% or more compared with BMS.⁸⁻¹⁰ Two randomized trials were subsequently conducted to compare the efficacy of intracoronary brachytherapy (ICBT) to paclitaxel and sirolimus drug-eluting stents in the setting of ISR of a BMS. Both trials demonstrated significantly lower rates of restenosis at 9 months with DES.^{9,11} As a result, the use of ICBT significantly decreased across the United States.

However, the rate of ISR in DES remains significant, with some studies demonstrating rates of up to 20%.¹² Patients who fail DES have limited salvage options and often multiple medical comorbidities, making them inherently high risk. Additionally, patients who fail DES multiple times in the same location may already have multiple stent layers in place making further interventions more challenging and high risk. After very preliminary data demonstrated some efficacy, our high-volume cardiac catheterization laboratory reinitiated ICBT for patients with recurrent ISR of DES.¹³ In our current series, we report on the baseline characteristics of this high-risk patient population and the safety of the ICBT procedure before initiating any prospective or randomized trials of ICBT for ISR of DES.

Methods and materials

A retrospective analysis of patients treated with ICBT between September 2012 and December 2014 was performed. Patients who developed ISR twice in a single location were eligible for ICBT. Patients with prior ICBT and/or external beam radiation near the heart were not eligible. A control group of all patients who also had 2

episodes of ISR in 1 location and underwent percutaneous coronary intervention (PCI) without ICBT treated over the same period was retrospectively established. Although these patients were eligible for ICBT based on their disease characteristics, ICBT has not yet been consistently incorporated into the treatment paradigm for recurrent ISR of DES. Baseline demographics and pertinent medical histories were recorded for all patients.

All patients who received ICBT were treated with the Novoste Beta-Cath 3.5F System after PCI. A strontium-90/yttrium-90 isotope was used for the treatment system. The principal radiation emission was beta particles with energies up to 2.27 MeV and a radioactive half-life of 28.8 years. Source lengths of 40 and 60 mm were used, which was determined based on the length of the target lesion. The target vessel received 18.4 or 23 Gy at a depth of 2 mm from the center of the source. The prescribed dose was determined by the vessel diameter. Dwell times typically ranged from 200 to 300 seconds and were determined by both the source length and vessel diameter.

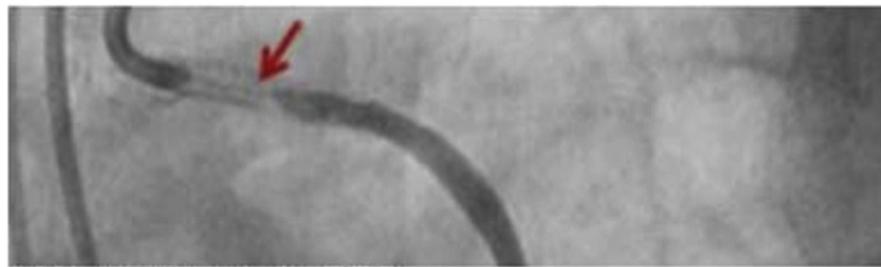
After PCI, a delivery catheter with radiopaque markers was first inserted and localized under fluoroscopy. Once it was properly positioned, the selected delivery device was then attached, and the source was sent by hydraulic pressure. A timer was manually started when the source reached the designated location. After the planned dwelling time elapsed, the source was retracted, and the delivery catheter was removed from the patient. A room survey was performed to ensure no isotope remained inside the patient or outside the delivery system. Overall, the ICBT procedure was generally completed within 10 minutes. [Figure 1](#) illustrates the steps of the ICBT procedure.

Procedural complications occurring during PCI or the ICBT procedure and postprocedural events occurring within 72 hours after PCI were recorded. Readmission rate for any cause at 30 days was also recorded. Unpaired *t* tests and χ^2 tests were used to compare the ICBT and control groups. Institutional review board approval was obtained.

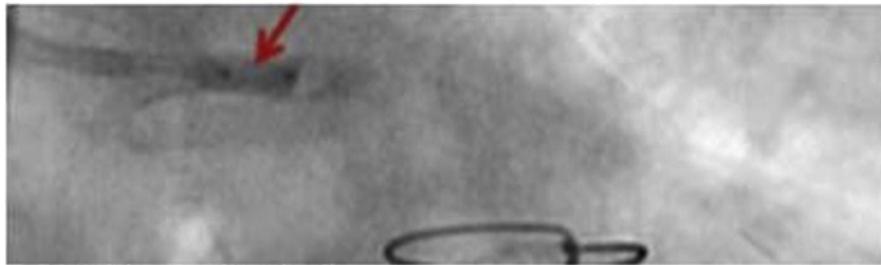
Results

There were 134 (78%) patients in the ICBT group and 37 (22%) in the control group. Six patients in the ICBT group had lesions that were longer than the maximum 60-mm train length and were treated with 2 sources consecutively. In these cases, there was a small area of overlap (<5 mm) with adequate proximal and distal margins. Two patients in the ICBT group were treated to 2 separate lesions on different dates in separate procedures. Additionally, 5 patients were treated to 2 separate lesions in the same procedure, for a total of 141 treated lesions in the ICBT group.

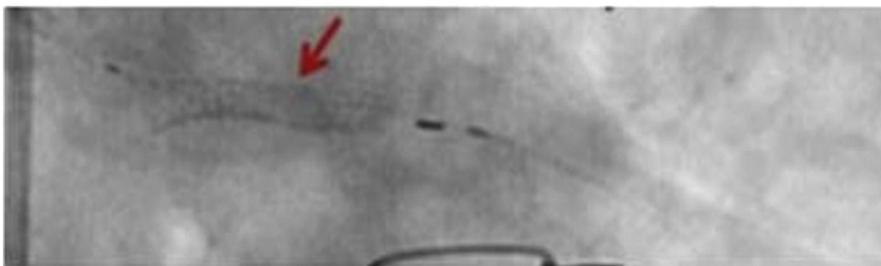
Baseline characteristics and comorbidities for both groups are listed in [Table 1](#). The ICBT and control groups were well-balanced with respect to age, sex, and



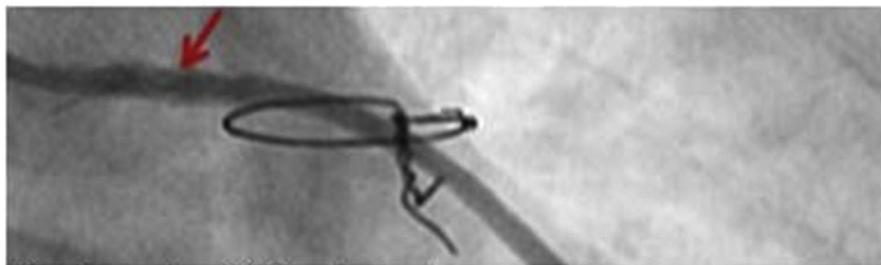
90% restenosis in DES



PCI with cutting balloon



ICBT catheter with source in place



Final result <20% stenosis

Figure 1 Step-by-step ICBT procedure. DES, drug-eluting stents; ICBT, intracoronary brachytherapy; PCI, percutaneous coronary intervention.

pre-existing medical conditions, with the exception of previous coronary artery bypass graft being more common the ICBT group. Before PCI, the majority of patients in both the ICBT and control groups presented with stable angina (55.2% vs 54.1%, $P = .899$) or unstable angina (31.3% vs 43.2%, $P = .176$). A source length of 60 mm was used for 81 of the 141 lesions treated with ICBT (57.4%). The prescribed dose was 23 Gy for 52.1% of lesions.

Procedural complications included grade 3 vessel dissection, perforation, tamponade, slow or absent blood

flow, side branch closure, and vessel closure, which are listed in [Table 2](#). The overall procedural complication rates were low for both groups (0% control group vs 4.5% ICBT group, $P = .190$).

Postprocedural events included myocardial infarction, coronary artery bypass graft, congestive heart failure, stroke, bleeding, thrombosis, embolism, dissection, dialysis, or death occurring within 72 hours after PCI and are listed in [Table 3](#). Five patients (3.7%) in the ICBT group experienced a myocardial infarction compared with none

Table 1 Baseline characteristics and comorbidities

	Control n = 37 (%)	ICBT n = 134 (%)	P value
Age, median (years)	61	65.5	.080
Male gender	25 (67.6)	100 (74.6)	.391
Pre-existing medical conditions			
Hyperlipidemia	36 (97.3)	134 (100.0)	.056
Hypertension	37 (100.0)	133 (99.3)	.598
Diabetes mellitus	24 (64.9)	79 (59.0)	.516
Previous MI	10 (27.0)	59 (44.0)	.062
Previous CABG	9 (24.3)	62 (46.3)	.017
Stroke	6 (16.2)	20 (14.9)	.847

CABG, coronary artery bypass graft; ICBT, intracoronary brachytherapy; MI, myocardial infarction.

in the control group ($P = .233$). One patient (2.7%) in the control group required dialysis compared with none in the ICBT group ($P = .056$). No additional events were recorded. Readmission rate for any cause at 30 days was low in both the ICBT (3.7%) and control (5.4%) groups ($P = .649$).

Discussion

Although the introduction of DES has markedly reduced the rate of ISR compared with BMS, a significant number of patients still develop ISR of DES.¹² These patients are often very high-risk cardiac patients who have failed standard therapies and have limited salvage options. Furthermore, because patients have multiple levels of stents within 1 lesion, additional procedures carry increased risk. To address this clinical issue, our high-volume cardiac catheterization laboratory is investigating the role of ICBT in patients with recurrent ISR of DES. Our study examines the baseline characteristics of this patient population and assesses the safety and toxicity of the ICBT procedure. To our knowledge, this study represents the largest recent series looking at ICBT in the setting of ISR of DES.

Table 2 Procedural events

	Control n = 37 (%)	ICBT n = 134 (%)	P value
Grade 3 vessel dissection	0 (0)	1 (2.2)	.598
Perforation	0 (0)	2 (1.5)	.455
Tamponade	0 (0)	0 (0)	
Slow or absent blood flow	0 (0)	3 (2.2)	.359
Side branch closure	0 (0)	1 (0.7)	.598
Vessel closure	0 (0)	0 (0)	

ICBT, intracoronary brachytherapy.

Table 3 Postprocedural events occurring within 72 hours after PCI

	Control n = 37 (%)	ICBT n = 134 (%)	P value
MI	0 (0)	5 (3.7)	.233
CABG	0 (0)	0 (0)	
CHF	0 (0)	0 (0)	
Stroke	0 (0)	0 (0)	
Bleeding	0 (0)	0 (0)	
Thrombosis	0 (0)	0 (0)	
Embolism	0 (0)	0 (0)	
Dissection	0 (0)	0 (0)	
Dialysis	1 (2.7)	0 (0)	.056
Death	0 (0)	0 (0)	

CABG, coronary artery bypass graft; CHF, congestive heart failure; ICBT, intracoronary brachytherapy; MI, myocardial infarction; PCI, percutaneous coronary intervention.

As expected, our results show a high prevalence of comorbid conditions in the ICBT cohort, demonstrating that this is an inherently high-cardiac-risk patient population. Still, the ICBT procedure was a well-tolerated treatment with very low rates of procedural and postprocedural events. Additionally, comparing the ICBT group with a control group with similarly high rates of comorbid conditions, there was no significant difference in procedural or postprocedural event rates. These results demonstrate that ICBT is a safe treatment option, even in a high-risk patient population in which acute events represent a significant cause of morbidity, and may have a role as salvage therapy for patients with recurrent ISR of DES. We believe this study supplies the safety data needed to initiate a prospective trial within our institution to assess the efficacy of ICBT for treatment of ISR of DES.

The safety of the intracoronary brachytherapy procedure was previously documented by a German group in 2000. With the Novoste Beta-Cath system, ICBT was used to treat de novo lesions, restenosis without stents, and in-stent restenosis. Ninety-two patients with 104 lesions were treated, with doses ranging from 14 to 20 Gy. There were no acute complications including procedure-related deaths, infarcts, or stent thrombosis.¹⁴ Another group from the Netherlands published its experience with ICBT in 2000. From that series of more than 250 patients treated with ICBT after percutaneous transluminal coronary angioplasty, the group found that the integration of vascular brachytherapy in the catheterization laboratory was both feasible and safe.¹⁵

In 2001, Leon et al published a multicenter randomized study examining the safety and efficacy of intracoronary gamma radiation with iridium-192 in the setting of ISR of BMS. Patients were randomized to conventional interventional techniques, such as balloon dilation, followed by catheter based delivery of iridium-192 or a nonradioactive placebo. Early events including death,

myocardial infarction, thrombosis, or revascularization of the target lesion occurring within 30 days from the procedure were recorded. About 5% of patient in the ICBT group experienced an early complication. Compared with the control group, patients in the ICBT group had a lower composite rate of death, myocardial infarction, emergency bypass surgery, and target vessel revascularization (28% vs 43.8%, $P = .02$) at a follow-up of 9 months.⁶ Although our data demonstrates similar rates of procedural and postprocedural events, our patients failed DES and likely represent a more high-risk population. Additionally, our treatment technique with a strontium isotope delivers a different type of radiation with less penetration, which should lower the risk of treatment-related complications.

There are few studies that have examined the efficacy of ICBT in the setting of ISR of DES. An observational series by Torguson et al in 2006 compared outcomes of patients with ISR of DES who underwent vascular brachytherapy ($n = 61$) or repeat DES placement ($n = 50$). In this series, there were no procedural or in-hospital events, again demonstrating the safety of the ICBT procedure. At 8 months' follow-up, target vessel revascularization rates were 10% and 18%, respectively ($P =$ not significant). However, there were significantly fewer major adverse cardiac events in the vascular brachytherapy group (10% vs 24%, $P = .044$).¹⁶ Another observational series by Bonello et al in 2008 demonstrated a target lesion revascularization rate of 11% and major adverse cardiac event rate of 26% at a follow-up of 12 months after ICBT.¹⁷ These studies were limited, however, by their retrospective nature and small sample sizes.

More recently, a meta-analysis comparing percutaneous treatment strategies for ISR of BMS and DES was published by Siontis et al. Twenty-seven trials with 5923 patients were included, and the primary outcome was percent diameter stenosis at angiographic follow-up. PCI with everolimus-eluting stents was found to be the most effective treatment for ISR, followed by drug-coated balloons, other drug-eluting stents, vascular brachytherapy, and bare metal stents. Balloon angioplasty and rotablation were the least effective treatment modalities. Of note, fewer than 40% of patients included in this analysis had ISR of DES. Our cohort of patients with recurrent ISR of DES likely represents a more high-risk population based on both pre-existing comorbidities as well as the presence of multiple stent layers at the time of PCI.¹⁸

This study represents the largest recent known series examining the use of ICBT for patients with recurrent ISR of DES and the safety of the ICBT procedure in this high-risk population. There are inherent limitations to the retrospectively established control group, with possible bias introduced when selecting patients to receive ICBT. Additionally, although acute

toxicity represents a major cause of morbidity, there is a lack of data on potential long-term complications associated with ICBT. Still, however, our current results demonstrate that ICBT is a safe and well-tolerated procedure in a high-cardiac-risk patient population. We believe that further investigation into the efficacy of ICBT as a form of salvage therapy for recurrent ISR of DES is warranted.

Conclusions

In-stent restenosis of DES is an important clinical issue. 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. Additional investigation into the efficacy of ICBT in this setting is warranted.

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