Treating In-Stent Restenosis With Combination Laser Therapy

The combination of excimer laser coronary atherectomy followed by brachytherapy has shown positive results against in-stent restenosis.

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In-stent restenosis (ISR) continues to be a challenging entity to treat, even in the era of drug-eluting stents (DESs). There are some "directional" data from single-site and small studies that show promising results in support of DESs for ISR. Currently, there are a variety of approaches and treatment options for ISR, most notably intracoronary brachytherapy, percutaneous transluminal coronary angioplasty (PTCA), cutting-balloon angioplasty, and debulking approaches such as excimer laser coronary atherectomy and rotational atherectomy. Four randomized trials that evaluated the use of brachytherapy for ISR (GAMMA-1, WRIST, START, and INHIBIT) each demonstrated significant relative reductions in angiographic restenosis and target vessel revascularization (TVR) (Figure 1).[1-4]

Histologic studies have identified intimal hyperplasia as a fundamental component of restenosis, including other contributing factors such as early thrombus deposition and local inflammation. With radiation therapy having been proven efficacious in the treatment of neoplastic and benign disorders that arise from abnormal cellular proliferation, catheter-based brachytherapy appears to be ideally suited for treating in-stent restenosis.

PTCA for ISR is common and is associated with similar

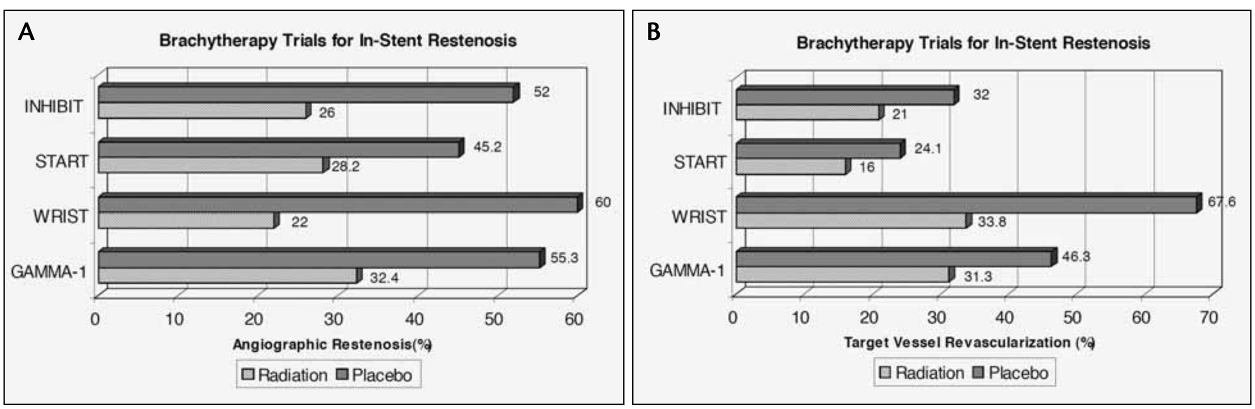

Figure 1. Angiographic (A) and clinical restenosis (B) rates in four randomized brachytherapy trials. GAMMA and WRIST employed the gamma-emitting isotope iridium-192, with START and INHIBIT employing beta-emitting sources strontium-90 and phosphorus-32, respectively.

or better than procedural success rates seen with PTCA for de novo lesions. An alternative balloon-based option for ISR is the cutting balloon. Cutting-balloon angioplasty has experienced some acceptance in the setting of ISR because some physicians believe it minimizes balloon migration during inflation (the so-called watermelon seed effect). However, the major limitations of balloon angioplasty and cutting-balloon angioplasty for ISR appear to be the inability to compress or displace enough tissue within the stent to allow for an optimal luminal result (final diameter).

PREVIOUS STUDIES

Other treatment options for ISR such as excimer laser atherectomy and directional and rotational atherectomy are designed to ablate or remove the tissue within the stent. Although it would seem that removing excess tissue from within the restenosed stent instead of just compressing the tissue as is done with PTCA would be viewed as a superior approach to ISR, none of these "tissue-removal" devices has enjoyed more widespread acceptance than PTA. However, Mehran et al evaluated 98 patients with 107 restonosed stents that were treated with an excimer laser and adjunctive PTA versus balloon alone, with results favoring the excimer laser arm.[5] Lesions treated with excimer laser and adjunct PTCA resulted in greater lumen gain, more intimal hyperplasia ablation/extrusion, larger cross-sectional area, and a lower occurrence for subsequent need for TVR than did the PTA-alone arm.

In utilizing the excimer laser for ISR, Dahm et al showed that the amount of tissue ablated or removed (as it relates to diameter stenosis) can impact binary stenosis, the TVR rate, and the major adverse cardiac event (MACE) rate.[6] This retrospective study analyzed 82 patients treated with excimer laser coronary atherectomy who were divided into two groups depending upon the post-laser diameter stenosis (diameter stenosis ≤30%; >30% before adjunctive PTCA). In the patient group that had more tissue ablation by excimer laser (diameter stenosis ≤30%; n=69), patients had significantly lower binary stenosis (20% vs 38%), TVR rate (17% vs 31%), and MACE (3% vs 15%) than patients who had less tissue ablation (diameter stenosis >30%, n=13).

Another treatment strategy for ISR is the combination of devices and treatments, such as utilizing an atherectomy device followed by PTCA and brachytherapy. Park et al analyzed a series of 50 patients with diffuse ISR who were treated with rotational atherectomy and beta-radiation.[7] In this series of patients, the binary angiographic restenosis rate was 10.4% at 6 months.

Tuli et al also evaluated a multitreatment strategy that included excimer laser coronary atherectomy/PTCA/brachytherapy of 35 lesions in 32 patients who were treated at Emory University Hospital.[8] Immediate procedural success was achieved in 33 of the 35 cases (94.3%), with the excimer laser not applied in two cases due to an inability to cross the entire lesion. The 30-day MACE rate (as defined by death, nonfatal myocardial infarction, or TVR) was 3.1% (one patient). The 6-month MACE rate was 8.3%, and comprised 24 total patients, with 21 of the patients undergoing either a stress thallium scan or cardiac catheterization. Follow-up at 12 months was available for 22 patients (9.1% MACE).

LAS CRUCES SINGLE-CENTER STUDY

One hundred cases of ISR were identified and treated with the combination of excimer laser coronary atherectomy/PTCA/brachytherapy at Las Cruces Memorial Medical Center in Las Cruces, New Mexico, between January 2001 and November 2004. Patients were treated

TABLE 1. PATIENT AND LESION CHARACTERISTICS

Patient Characteristics	
Patients N=	100
Age mean (range)	67 ± 10 (42-89)
Sex	
Males	71 (71%)
Females	29 (29%)
History of	
Diabetes mellitus	24 (24%)
Hypertension	75 (75%)
Previous MI	20 (20%)
Previous CABG	6 (6%)
HDL	81 (81%)
Smoking	8 (8%)
Coronary Vessel Treated	
LAD	33 (33%)
RCA	39 (39%)
Left circumflex	15 (15%)
Diagonal	10 (10%)
Other	3 (3%)
Lesion length (mm)	16 ± 6
Percent stenosis mean (range)	87% ± 9 (60%-100%)

LAD, left anterior descending
RCA, right anterior descending

with the CVX-300 Excimer Laser System (Spectranetics Corporation, Colorado Springs, CO), routine PTCA, and intracoronary radiation using the Galileo system (Guidant Corporation, Indianapolis, IN). Two of the total 100 patients were treated with the Beta-Cath system (Novoste Corporation, Norcross, GA) due to discontinuation of the Galileo system in April 2004.

The mean lesion length was 16 mm, with 72% of lesions located in either the right coronary artery (39%) or left anterior descending (33%). The culprit lesions ranged from 60% to 100% diameter stenosis, with a mean of 87%. The patient baseline characteristics and treated lesions are shown in Table 1.

Laser catheter size was selected based on the vessel diameter, and the percent diameter stenosis (n=100; procedural data are shown in Table 2). The mean diameter stenosis after laser treatment was 25%, a change of 62% versus the baseline mean of 87%. All lesions were aggressively debulked, resulting in a final diameter stenosis (post-laser, then PTCA, and finally brachytherapy), ranging from 0% to 20%, with a mean of 1%. A typical case is shown in Figure 2.

Follow-up data were available for the majority of patients (n=93), with 47 patients (50.5%) having at least 12-month follow-up. Eighteen-month follow-up was available for 30 patients (32.3%), with 10 patients undergoing 24-month follow-up. Thirty-one of the 100 patients underwent repeat catheterization after laser brachytherapy. Repeat cardiac catheterization was only done in patients who had clinical symptoms after the procedure. Of these patients, 24 had stents that remained widely patent, with seven patients (23%) showing angiographic restenosis.

TABLE 2. PROCEDURAL DATA

Procedure	
Laser catheter	
0.9 mm	34 (34%)
1.4 mm	30 (30%)
1.7 mm	21 (21%)
2.0 mm	15 (15%)
Post-laser % DS	25% ± 13% (0%-80%)
PTCA utilized	89 (89%)
Post-PTCA % DS	1% ± 3% (0%-20%)
BT dwell time, min	135 ± 84 (31-501)
Post BT % DS	1% ± 3% (0%-20%)
Complications	3 (3%)

DS, diameter stenosis; BT, brachytherapy

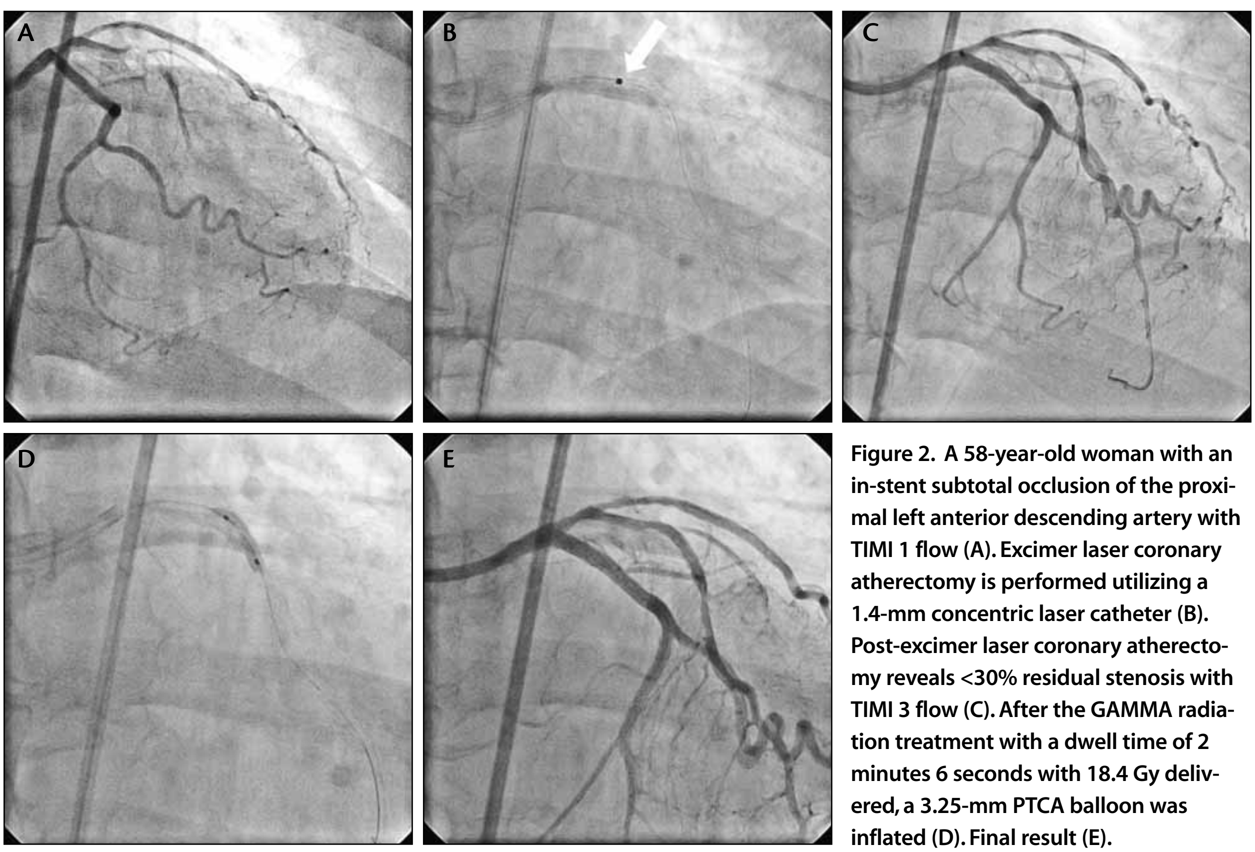

Figure 2. A 58-year-old woman with an in-stent subtotal occlusion of the proximal left anterior descending artery with TIMI 1 flow (A). Excimer laser coronary atherectomy is performed utilizing a 1.4-mm concentric laser catheter (B). Post-excimer laser coronary atherectomy reveals <30% residual stenosis with TIMI 3 flow (C). After the GAMMA radiation treatment with a dwell time of 2 minutes 6 seconds with 18.4 Gy delivered, a 3.25-mm PTCA balloon was inflated (D). Final result (E).

TABLE 3. PATIENT FOLLOW-UP AND MACE

Follow-Up				MACE
Years	N=93	Cumulative	%	N=5
>2.5	1	1	1.1%	1
2.0 - 2.5	9	10	10.8%	0
1.5 - 2.0	20	30	32.3%	0
1.0 - 1.5	17	47	50.5%	1
0.5 - 1.0	23	70	75.3%	1
<0.5	23	93	100%	2

Surprisingly, nine of the 31 patients showed a stenosis below the previously treated area (laser/brachytherapy).

Exercise myoviews or stress echocardiograms were obtained from 23 patients. Only one patient underwent myoview and cardiac catherization. Two of the 23 patients (9%) had positive myoviews in the territory of laser/brachytherapy treatment. A total of 53 patients underwent further diagnostic treatment, with nine of 53 (17%) having evidence of ISR.

There were no deaths, urgent coronary artery bypass, or myocardial infarctions during the laser or brachytherapy procedures. There was follow-up available for 93 of the 100 patients, with five patients having a MACE sometime during follow-up. Table 3 outlines patient follow-up durations and MACE.

The 30-day MACE rate as defined by death, nonfatal myocardial infarction or TVR was 0%. At 6 months, the MACE rate was 2.2% (two patients), and at 1 year, it had increased to 4.3% (four patients). These four adverse events comprised three deaths and one TVR.

DISCUSSION

The efficacy of laser debulking for ISR with angioplasty and brachytherapy has most recently been studied and shown by Tuli et al.[8] In their study of 35 patients, the 30-day MACE rate was 3.1%, increasing to 9.1% at 1 year. This study also showed a low rate of TVR, which supports a role for excimer laser coronary atherectomy in treating ISR.

The current study of 100 ISR cases shows a MACE rate of 2.2% at 1 year. The combination of excimer laser coronary atherectomy followed by PTCA and then brachytherapy was both safe and effective. Elective cases were scheduled for 1 day each month, which allowed for efficient use of the radiation physicist, radiation oncologist, and the surgical standby team. Support staff for the Galileo system could also be utilized. On average, four to six cases per month could be performed in a 5- to 6-hour period. Timing also allowed us to use a "hot" radiation source, reducing dwell time.

Many centers now use a DES "sandwich" for ISR, with encouraging preliminary reports. The true role of a DES in this application awaits the results of randomized trials. In the mean time, excimer laser coronary atherectomy may have a real role in debulking ISR before brachytherapy.[9]

CONCLUSION

With millions of stents currently implanted, restenosis will be a growing clinical problem over the next few years. We have shown that laser combined with brachytherapy is a safe and effective alternative for the treatment of in-stent restenosis. ■

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