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Comparison of angiographic and clinical outcomes between rotational atherectomy versus balloon angioplasty followed by radiation therapy with a rhenium-188-mercaptoacetyltriglycine-filled balloon in the treatment of diffuse in-stent restenosis

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Abstract

Background: The purpose of this study was to compare the efficacy of rotational atherectomy (RA) with simple balloon angioplasty, prior to beta-radiation therapy with a rhenium-188-mercaptoacetyltriglycine (^{188}Re-MAG$_3$)-filled balloon for diffuse in-stent restenosis (ISR).
Methods: After completing 50 cases with RA prior to beta-radiation (Group I), we performed optimal balloon angioplasty followed by beta-radiation in the next 53 consecutive patients (Group II) for the treatment of diffuse ISR. The radiation dose was 15 Gy at a depth of 1.0 mm into the vessel wall.
Results: The baseline clinical and angiographic characteristics were similar between the two groups. The mean length of the lesion was 25.6±12.7 mm in Group I and 22.9±8.6 mm in Group II (p=0.26). Radiation was successfully delivered to all patients, with a mean irradiation time of 179±55 s. The 6-month angiographic restenosis rate was 10% (5/50) in Group I versus 33% (17/51) in Group II (p=0.007). No adverse event including myocardial infarction, death, or stent thrombosis occurred during the 1-year follow-up period. The risk of a target lesion revascularization or a major adverse cardiac event was significantly lower in Group I than in Group II (two patients in Group I vs. nine patients in Group II; OR, 0.20; 95% CI, 0.04–0.96; p=0.04).
Conclusion: Concomitant treatment with rotational atherectomy and beta-irradiation using a ^{188}Re-MAG$_3$-filled balloon for diffuse ISR has a synergistic effect, in terms of 6-month angiographic restenosis and 1-year cardiac event-free survival.

Keywords: Rotational atherectomy; Balloon angioplasty; Radiation therapy; Restenosis

1. Introduction

Intracoronary stenting reduces restenosis, as compared with balloon angioplasty [1,2]. However, in-stent restenosis (ISR) develops in a significant proportion of cases after intracoronary stenting, particularly in those with multiple or long stents. ISR remains an important clinical problem, because the recurrence rate is high with repeat balloon angioplasty, especially in diffuse ISR [3,4]. Atheroablative devices, i.e., excimer laser angioplasty and rotational atherectomy (RA), have been used in an attempt to improve the outcomes [5–7]. However, thus far, no device has significantly improved outcomes for the treatment of diffuse ISR. Recently, intracoronary brachytherapy with gamma- or beta-irradiation in patients with diffuse ISR showed the superior results and is now considered a viable treatment option for these lesions [8–10].

Previously, we have reported the favorable results of beta-radiation using a ^{188}Re-MAG$_3$-filled balloon after RA

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in the R^4 registry [11]. But we could not prove the efficacy of RA prior to beta-radiation therapy in patients with diffuse ISR, because of the lack of a control group. We sought to evaluate whether intracoronary radiation therapy with a ^{188}Re-MAG$_3$-filled balloon after optimal balloon angioplasty alone, without debulking, could result in similar outcomes in patients with diffuse ISR.

2. Materials and methods

2.1. Study group

We previously performed the RA prior to intracoronary beta-radiation therapy with a ^{188}Re-MAG$_3$-filled balloon in 50 consecutive patients (Group I) with diffuse ISR and have reported the results [11]. As the current study was designed to evaluate the efficacy of debulking prior to intracoronary beta-radiation therapy, we prospectively performed intracoronary beta-radiation therapy after optimal balloon angioplasty alone in the following 53 consecutive patients (Group II) with diffuse ISR with same inclusion/exclusion criteria.

Inclusion criteria were diffuse ISR (lesion length >10 mm, diameter stenosis >50%) in a native coronary artery with angina, demonstrable myocardial ischemia, and written informed consent. Exclusion criteria were acute myocardial infarction ≤72 h, poor renal function (serum creatinine >3.0 mg/dl), pregnancy, contraindication to antiplatelet therapy, and concomitant serious disease with expected survival of <2 years. In patients with multivessel ISR, only one lesion was treated with radiation therapy. Additional new stent implantation was strongly discouraged, although not contraindicated. The study was approved by our Institutional Review Board.

2.2. Radiation delivery system, dosimetry, and procedure

The radiation system, dosimetry, and procedure have been described previously [11]. We pretreated all the patients with aspirin (200 mg/day), ticlopidine (500 mg/day) and cilostazol (200 mg/day) ≥2 days. Ticlopidine was given for 1 month, but aspirin and cilostazol were administered for more than 6 months after radiation therapy. Before radiation therapy, we performed RA and adjunctive balloon angioplasty in Group I and optimal balloon angioplasty alone in Group II to obtain an optimal angiographic result (diameter stenosis <20%). We obtained coronary angiograms at each step to determine the actual segment treated with atherectomy and balloon angioplasty. The long conventional balloon (30 and 40 mm in length; Boston Scientific, San Jose, California), which was the same kind of balloon used for the dosimetric study, was selected for irradiation to cover a proximal and distal uninjured margin of at least 5 mm. For long ISR (>30 mm) that could not be covered by a single long balloon, manual stepping was permitted, with minimal overlapping. The ^{188}Re-MAG$_3$-filled syringe and conventional in-deflator device were connected to the balloon by three-way valves. After complete removal of air from the balloon, ^{188}Re-MAG$_3$ solution was manually introduced into the balloon. Inflation of the balloon was maintained with a nominal inflation pressure of 6 atm. Fractionation was allowed in cases with severe angina or significant hemodynamic instability. The prescribed radiation dose was 15 Gy at a depth of 1.0 mm into the vessel wall from the balloon–artery interface. Irradiation procedure was done in the same manner in both groups. We clinically evaluated all the patients during an office visit at 1, 3, and 6 months, and then every 4 months after brachytherapy. A repeat coronary angiography was performed at 6 months after irradiation, or earlier if clinically indicated.

2.3. Quantitative coronary angiography (QCA)

Two experienced angiographers analyzed coronary angiograms using an on-line QCA system (ANCOR version 2.0, Siemens, Muenchen, Germany). Angiographic measurements were made during diastole after intracoronary nitroglycerin administration using the guiding catheter for magnification calibration. Single matched views with the worst diameter stenosis were compared.

2.4. Primary and secondary end points

We evaluated major adverse cardiac events (MACE), including death, nonfatal MI, and repeat revascularization. The primary end point was the occurrence of any MACE during the 12-month follow-up period. Myocardial infarction was diagnosed when cardiac enzymes were elevated threefold or greater, with chest pain lasting >30 min, or with the appearance of new electrocardiographic changes. The secondary end point was the angiographic incidence of restenosis (diameter stenosis >50%) by QCA.

2.5. Statistical analysis

The results are expressed as mean±S.D. for continuous variables and as frequencies (%) for categorical variables. Student's *t*-test was used to compare continuous variables; the chi-square or Fisher's exact test was used to compare categorical variables. We considered a p value<0.05 statistically significant. We performed a stepwise logistic regression analysis to determine independent predictors of binary restenosis at the follow-up angiogram and a MACE at 12 months. We determined cumulative frequency distributions of the minimal luminal diameter in Groups I and II before, immediately after, and 6 months after the procedure. We calculated Kaplan–Meier curves for survival without cardiac events (Q-wave myocardial infarction or revascularization of the target vessel) at 18 months.

3. Results

3.1. Characteristics of the patients

We enrolled 103 patients in the study. Between March 1999 and February 2000, 50 consecutive patients (Group I, 42 men, 56±9 years) underwent successful radiation therapy after RA and adjunctive balloon angioplasty. The following 53 consecutive patients (Group II, 41 men, 59±10 years) underwent radiation therapy after optimal balloon angioplasty alone between March 2000 and May 2001. The procedure was successful in all patients. Baseline clinical, angiographic, and procedural characteristics were similar between the two groups (Table 1). Sixty-one percent of the patients presented with unstable angina. Percutaneous revascularization for ISR other than radiation therapy had been performed in nine patients (seven patients in Group I and two in Group II) before enrollment. The mean burr size of RA in Group I was 2.1±0.2 mm, and the burr/artery ratio was 0.7±0.1. Adjunctive balloon angioplasty was performed in all patients to obtain optimal angiographic results in Group I. Manual stepping with a 30-mm balloon was done in seven patients in Group I and nine in Group II. All patients tolerated the radiation treatment.

The angiographic data are shown in Table 2. The mean balloon/artery ratio was higher in Group I than in Group II (1.23±0.20 vs. 1.11±0.14, respectively, p=0.02). Six patients in Group II received additional new stent implantation; five for edge dissection and one for intramural hematoma. The mean length of the lesion was 25.6±12.7 mm in Group I and 22.9±8.6 mm in Group II (p=0.26). The mean length of the irradiated segment was 37.6±11.2 mm in Group I and 41.6±10.3 mm in Group II (p=0.09). The lengths, presented as median [25%, 75%] of lesion (21.1mm [15.8, 34.1] in Group I vs. 23.4 mm [16.9, 27.6] in Group II) and of irradiated segment (40 mm [36, 40] in Group I vs. 40 mm [36, 40] in Group II) did not differ statistically between the two groups.

Table 1
Baseline characteristics of the patients

Characteristics	Group I (n=50)	Group II (n=53)	P value
Age, years	56±9	59±10	0.09
Male sex, %	42 (84%)	41 (77%)	0.46
Risk factors, %			
Hypertension	19 (38%)	23 (43%)	0.69
Diabetes mellitus	13 (26%)	15 (28%)	0.66
Total cholesterol ≥240 mg/dl	12 (24%)	13 (25%)	0.97
Current smoker	31 (62%)	38 (72%)	0.43
Prior myocardial infarction	8 (16%)	5 (9%)	0.22
Unstable angina	33 (66%)	30 (57%)	0.54
Left ventricular ejection fraction, %	60±7	60±9	0.86
Rotablation procedure			
Mean burr size, mm	2.1±0.2		
Burr/artery ratio	0.7±0.1		
Radiation therapy			
Length of irradiated segment, mm	37.6±11.2	41.6±10.3	0.09
Overlap of two balloons	7 (14%)	9 (17%)	0.79
Fractionation	6 (12%)	18 (34%)	0.08
Exposure time, s	202±62	157±37	0.001

Table 2
Angiographic characteristics at baseline and 6 months

Characteristics	Group I (n=50)	Group II (n=53)	P value
Artery treated, %			
Left main coronary artery	1 (2%)	0	0.49
Left anterior descending artery	34 (68%)	36 (68%)	1.0
Left circumflex artery	5 (10%)	5 (9%)	1.0
Right coronary artery	10 (20%)	12 (23%)	0.81
Balloon/artery ratio	1.23±0.20	1.11±0.14	0.02
Lesion length, mm	25.6±12.7	22.9±8.6	0.26
Reference vessel diameter, mm	2.89±0.40	2.97±0.47	0.36
Diameter stenosis, %			
Before intervention	80±14	76±12	0.17
Immediately after intervention	7±12	12±12	0.03
At 6 months	19±23	34±35	0.02
Minimal lumen diameter, mm			
Before intervention	0.60±0.44	0.71±0.37	0.17
Immediately after intervention	2.68±0.39	2.61±0.45	0.37
At 6 months	2.31±0.60	1.94±0.87	0.02
Acute gain, mm	2.08±0.46	1.90±0.52	0.06
Late loss, mm	0.36±0.64	0.67±0.95	0.06
Late-loss index	0.17±0.31	0.36±0.56	0.04
Binary restenosis, %	5/50 (10%)	17/51 (33%)	0.007

3.2. In-hospital outcomes and procedural results

There was no procedure-related complication in the study patients. There was no in-hospital death and no Q-wave infarction. The creatine kinase MB level was more than three times the baseline value in two patients (4.0%) in Group I and in four patients (7.7%) in Group II (P=0.68) without a new development of a Q-wave on an electrocardiogram.

3.3. Angiographic results

We obtained 6-month angiographic follow-up data in 98.1% of the study patients (100% in Group I and 96.2% in Group II). Follow-up angiographic data are shown in Table 2 and Fig. 1. The minimal luminal diameter at 6 months was significantly greater in Group I than in Group II (2.31±0.60 vs. 1.94±0.87 mm, respectively, p=0.02). The benefit of RA was seen with a 53% reduction in the late loss index (0.17±0.31 vs. 0.36±0.56, respectively, p=0.04). The rate of binary restenosis was significantly lower in Group I (10%, 5/50) than in Group II (33.3%, 17/51) (p=0.007). In six patients who received additional stenting, the rate of binary restenosis was significantly higher than in other patients (5/6, 83% vs. 17/95, 18%, respectively, p=0.002). Even if six patients with additional stenting were excluded in this angiographic analysis, the restenosis rate was also significantly lower in Group I

(10%, 5/50) than in Group II (26.7%, 12/45) (p=0.032). There was no evidence of aneurysm formation in the study patients. Detailed angiographic analysis revealed that the incidence of geographic miss, defined as the edges that were touched by angioplasty balloon but were not sufficiently coved by radiation, was similar in both groups (56% in Group I vs. 45% in Group II, p=0.273). The incidence of restenosis within the irradiated segment was higher in Group II than in Group I (17.6% vs. 4%, p=0.052), although the difference was not statistically significant. The incidence of edge restenosis did not differ statistically between the two groups with three (6%) patients in Group I and eight (15.7%) in Group II (p=0.20). In multivariate analysis, the RA prior to radiation therapy (OR=0.31, 95% confidence interval 0.10–0.98, p=0.04) and additional stenting procedure (OR=13.8, 95% confidence interval 1.45–129.99, p=0.02) were independent predictors of binary restenosis.

3.4. Clinical events

We obtained clinical follow-up data at 12 months for all patients. Death, myocardial infarction, or stent thrombosis did not occur in any patients during the 12-month follow-up period. The risk of a target lesion revascularization or a MACE was significantly lower in Group I than Group II (two patients in Group I vs. nine patients in Group II; odds ratio, 0.20; 95% CI, 0.04–0.96; p=0.04; relative risk reduction=76%). In the current study, there was no additional target vessel revascularization other than the target lesion revascularization. In multivariate analysis, the RA prior to radiation therapy (OR=0.21, 95% confidence interval 0.04–0.96, p=0.04) and additional stenting procedure (OR=11.12, 95% confidence interval 1.92–64.42, p=0.007) were independent predictors of MACE at 12 months. Fig. 2 shows event-free survival over a period of 18 months.

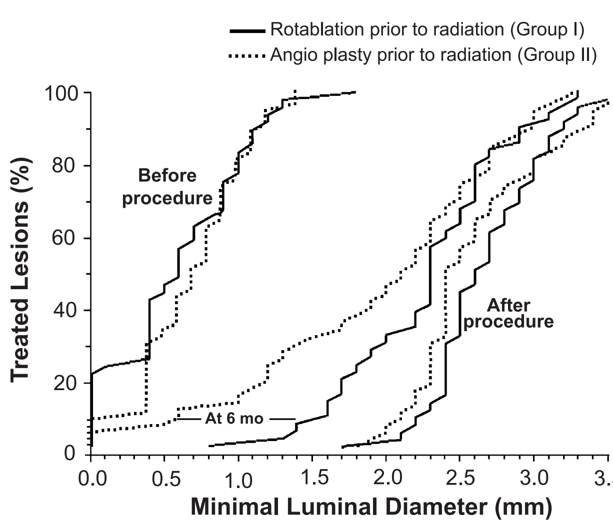

Fig. 1. Minimal luminal diameter in the rotational atherectomy followed by radiation therapy (Group I) and balloon angioplasty alone followed by radiation therapy (Group II) before and after angioplasty and at 6 months.

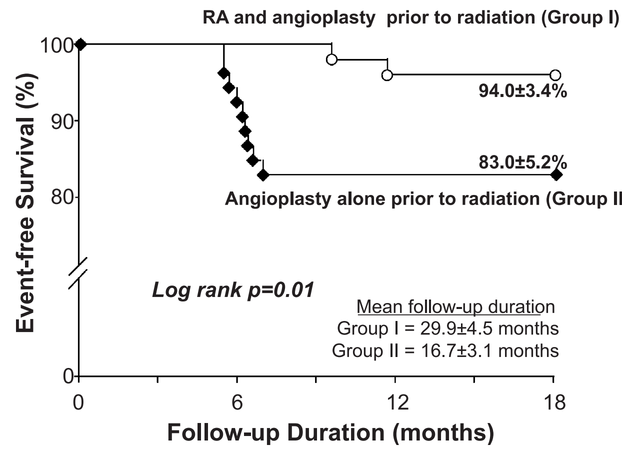

Fig. 2. Event-free survival at 18 months. Event-free survival was defined as survival without Q-wave myocardial infarction or target lesion revascularization.

4. Discussion

The major finding of this study is that RA and adjunctive balloon angioplasty prior to beta-irradiation using a ^{188}Re-MAG$_3$-filled balloon for diffuse ISR provide a more beneficial effect in terms of 6-month angiographic restenosis and 1-year event-free survival than beta-irradiation after optimal balloon angioplasty alone. This result indicates that concomitant treatment with beta-irradiation and RA for diffuse ISR has a synergistic effect.

4.1. Treatment strategies for diffuse ISR—past efforts

Various types of treatment strategies, including repeated balloon angioplasty, additional stenting, directional atherectomy, laser angioplasty, RA, cutting balloon angioplasty(CBA), or intracoronary brachytherapy, have been suggested for treatment of diffuse ISR. Although repeat balloon angioplasty was reported to be effective and safe for treatment of ISR, the restenosis rate is high (>50%) despite successful repeat balloon angioplasty [3,4]. Additional new stent implantation (stenting the stent or sandwich stenting) provides a larger acute lumen gain and prevents the early loss phenomenon by inhibiting reintrusion of neointimal tissue, but with more exuberant tissue accumulation and with a higher recurrence rate [12,13]. Atheroablation techniques, such as laser angioplasty, RA, and directional atherectomy, have been used in an attempt to improve the acute results by increasing lumen areas through ablation of neointimal tissue, but they did not significantly improve the recurrence rate or clinical outcomes [5–7,14]. A comparison of balloon angioplasty, laser angioplasty, RA, and additional stenting in a large series of 821 restenotic lesions concluded with the statement that "all interventional strategies are disappointing", demonstrating a similar late clinical outcome independent of device choice [15]. Adamian et al. [16], reported favorable angiographic and clinical outcomes of cutting balloon angioplasty for the treatment of focal ISR, but these could not be generalized to diffuse ISR. Currently, intracoronary brachytherapy is a promising technology with the potential to reduce the restenosis rate. Intracoronary brachytherapy with gamma- or beta-irradiation in patients with diffuse ISR showed a 35–70% reduction in the recurrence rate of restenosis and is considered a viable treatment option for these lesions [8–10].

4.2. Debulking before radiation therapy

It has been hypothesized that debulking prior to radiation therapy improves acute and long-term results. Recently, two studies, the Stents and Radiation Therapy (START) using beta-radiation with Sr-90 (18.4 Gy, 23 Gy at 2 mm from source axis) and the gamma radiation trials using ^{192}Ir (15 Gy, 18 Gy at 2 mm from the source), have assessed the effect of debulking prior to radiation therapy on clinical and angiographic outcomes, but did not show any advantages of debulking in combination with radiation therapy in patients with ISR [17,18]. These results were not consistent with those of our study showing that debulking before beta-radiation had a lower incidence of angiographic restenosis and MACE than balloon angioplasty before beta-radiation in our radiation system. Previous two studies were not designed to evaluate the effect of device selection prior to radiation therapy, performed in a retrospective manner and had uneven distribution of number of study population, which were major limitations of previous studies. However, our study was aimed to evaluate the debulking effect before beta-radiation using a ^{188}Re-MAG$_3$-filled balloon (15 Gy at 1.0 mm from the balloon surface) in a prospective manner with similar number of study population. Therefore, although the results of the present study cannot be directly compared to those of the previous studies, these different results may be partly attributed to different types of radiation sources, delivery methods, and interventional devices.

4.3. Rotational atherectomy and intracoronary brachytherapy—potential mechanism of synergism

The predominant vascular response to radiation delivered at the therapeutic doses for vascular brachytherapy is chromosomal damage in the vascular smooth muscle cells, fibroblasts, and, when present, endothelial cells, which results in the loss of the cells' ability to reproduce with consequent mitotic cell death [19]. Heterogeneous doses are delivered to the atheromatous plaque from any point source used for endovascular irradiation with a gradient from the luminal surface outwards. This heterogeneity may be increased if the source is not centered within the vessel lumen. As a result, attempts to improve dose homogeneity with centering devices have been developed. Liquid rhenium-filled balloon catheters have a potential advantage over noncentered radioactive wires and seeds, in that they may provide a more uniform dose to the vessel wall. However, even with a centered source, dose heterogeneity to the atheromatous plaque will result from irregularity of plaque thickness (due to an eccentric atheromatous plaque) or from a very thick atheromatous plaque that results in a lower irradiation dose delivered to the deeper portion of the plaque. According to the dosimetric findings of liquid rhenium-filled balloon catheters, the delivered radiation dose dropped exponentially from the balloon surface [20]. In the 2-mm depth from the balloon surface, the radiation dose was less than 50% compared with the dose at 1 mm in depth from it. Balloon angioplasty alone, followed by intracoronary brachytherapy with beta-radiation for treatment of diffuse ISR, may be less effective because of the abundant extracellular matrix of the intimal hyperplasia inside and outside the stent. Furthermore, if large amounts of neointima are present, the radiation dose heterogeneity to the neointima will lessen the effect of ionizing radiation. In contrast, RA is effective for the debulking of neointima within stented segments and can produce a more concentric and thinner neointimal structure. Therefore, after effective debulking, theoretically effective dose of beta-radiation would be delivered to the target tissue. On the basis of theoretical advantages of debulking in our radiation system, in the current study, we confirmed the beneficial effect of debulking prior to beta-radiation on angiographic and clinical outcomes. However, these results cannot be extrapolated to ISR lesions treated with different kinds of radiation system.

4.4. Additional stenting during the brachytherapy

In the early intracoronary brachytherapy trials, late stent thrombosis and exaggerated intimal hyperplasia were associated with new stent deployment and early discontinuation of antiplatelet therapy [21–23]. As a result, guidelines for intracoronary brachytherapy include the recommendation to avoid re-stenting. Additional stenting, however, is often unavoidable even with a meticulous technique to obtain good angiographic results. In this study, we observed that additional stenting procedure during intracoronary brachytherapy was related to higher restenosis and adverse cardiac events. Thus, during intravascular brachytherapy, avoidance of repeat stenting is strongly recommended. In this study, when six patients with additional stenting were excluded in the angiographic analysis, the restenosis rate was also significantly lower in Group I than in Group II, which suggested the RA prior to beta-radiation therapy using a ^{188}Re-MAG$_3$-filled balloon could be a valuable therapeutic option in treatment of diffuse ISR.

4.5. Selection of device before beta-radiation therapy

Cutting balloon has been frequently used to treat ISR. Cutting balloon has been shown to effectively dilate the ISR without slippage (watermelon seed effect) [24,25]. Recent studies demonstrated that the combination of CBA and beta-radiation was effective in treating diffuse ISR [26,27]. However, the synergistic effect of CBA prior to beta-radiation therapy has not been sufficiently evaluated thus far. We suppose that a prospective randomized study comparing RA and CBA before beta-radiation therapy should be performed to identify the most effective treatment modality.

4.6. Study limitations

First, the results are based on the registry data of the consecutive patients with ISR. Thus, the patients were not randomly assigned to each treatment modality. However, the clinical and angiographic characteristics were not significantly different between the two groups. To limit the selection bias, all the patients with diffuse ISR were recommended to be prospectively included. Second, the number of study patients was small. Finally, the results of the current study were obtained using ^{188}Re-MAG$_3$-filled balloon system. Therefore, the synergistic effect of RA prior to beta-radiation using ^{188}Re-MAG$_3$-filled balloon may not be generalized to other debulking methods such as laser angioplasty and directional atherectomy.

5. Conclusion

Concomitant treatment with rotational atherectomy and beta-irradiation using a ^{188}Re-MAG$_3$-filled balloon for diffuse ISR has a synergistic effect in terms of 6-month angiographic restenosis and 1-year cardiac event-free survival.

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