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Optimization of dose prescription protocol and its impact on delivered dose and vascular response after β-radiation for in-stent restenosis. A randomized trial with serial volumetric intravascular ultrasound and dose volume histograms☆

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Abstract

Aim: The incidence of restenosis within stented segment after intravascular brachytherapy with recommended dose prescription protocols is up to 25%. Therefore, we designed a randomized trial comparing recommended dose prescription protocol with dosing adjusted for the source-to-target distance.

Methods: Fifty-one in-stent restenosis (ISR) lesions in 48 patients underwent centered source β-irradiation with serial intravascular ultrasound. Patients randomly received 20 Gy at 1 mm either beyond lumen surface [n=25, standard group (S)] or external elastic membrane [n=26, dosing-adjusted (DA) group]. Minimum dose absorbed by 90% of adventitia ($DV_{90\%Adv}$) was calculated.

Results: $DV_{90\%Adv}$ was higher for the DA group than for the S group (21.63±5.67 vs. 12.05±4.88 Gy, P<.001). After 8.9±4.5 months there was complete lumen preservation in DA vs. lumen decrease subsequent to neointimal hyperplasia (NIH) in S group (0.10±1.20 vs. −0.61±1.29 mm^3/mm, P<.05). Vessel volume increased significantly in the DA group and was unchanged in S group (+1.73, P=.002 vs. 0.14 mm^3/mm, P=NS). $DV_{90\%Adv}$ correlated inversely with NIH volume and positively with vessel volume change (r=−.405, P=.007 and r=.363, P=.017, respectively).

Conclusion: For β-irradiation of ISR, dosing adjusted for the source-to-target distance leads to significant increase in target delivered doses, which is associated with complete NIH inhibition and induction of positive vessel remodeling.

Keywords: In-stent restenosis; Dosimetry; Intravascular brachytherapy

1. Introduction

Long-term results of drug-eluting stents use for treatment of either de novo or in-stent restenosis lesions (ISR) imply complementary to the newest therapeutic advance and novel applications of vascular brachytherapy [1–3]. Intravascular brachytherapy (IVB) remains a treatment of choice for ISR.

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Continuous progress in technical and procedural variables determining the IVB long-term results proved to result in the trend toward improved clinical outcome [4,5]. Therapeutic dose levels of irradiation and tissue target (adventitia) were established based on the animal studies [6]. Consequently, two types of dose prescription protocols are used nowadays: (1) fixed and (2) tailored to the reference lumen size — assessed angiographically or with intravascular ultrasound (IVUS) [7,8]. Fixed and angiography-guided dosing models are substantially affected by coronary artery remodeling and vessel tapering [9,10]. Consequently, actually target-delivered doses are significantly lower than assigned [11–13]. Respecting actual lesion geometry and thus overcoming angiography-based dosing shortcomings, online IVUS measurements of source to target distance were applied for the most accurate treatment planning [8,14]. But, regardless of dosimetry protocol, radiation failure affects 15–30% of treated patients with up to 25% of restenosis rate confined to the stented segment [15,16]. Ineffectiveness of initial IVUS-guided attempts of dosing optimization may be contributed to use of noncentered sources and thus dose heterogeneity. Moreover, avoidance of doses >30 Gy for the nearest targets and simultaneous acceptance of doses <8 Gy led to actually target-delivered doses similar to those achieved with fixed dosimetry.

Therefore, we designed a randomized trial comparing the long-term antirestenotic effectiveness of the conventional ("INHIBIT-like") dosimetry with "true" IVUS-guided dose prescription protocol.

2. Methods

2.1. Study design

This study is a prospective, randomized, single-center trial to evaluate the safety and efficacy of the IVUS-guided, adjusted for the source-to-target distance, dose prescription protocol [20 Gy at 1 mm beyond external elastic membrane (EEM)] compared with the conventional dosimetry (20 Gy at 1 mm beyond reference lumen surface), in the setting of β-centered-source IVB for ISR treatment [7]. Included were ISR, non-ostial, nonbifurcation lesions in native coronary arteries. All patients underwent postprocedural and either clinically driven or follow-up imaging scheduled after 6 months (angiography and IVUS). All subjects were treated with aspirin and thienopiridine for 1 year following IVB. The local council on human research approved the study protocol, and patients signed informed consent.

2.2. Irradiation procedure

Brachytherapy was performed with the Guidant Galileo System that uses a ^{32}P β-radioactive source within a centering balloon catheter [7]. After successful balloon angioplasty (residual stenosis <30%), an IVUS transducer was inserted into the target artery. Online IVUS measurements of the vessel (EEM) and lumen diameters at the proximal and distal reference sites were performed. References were the least diseased (largest lumen with least amount of plaque) vessel segments within 10 mm proximal and distal to the treated segment, but before any major side branches. Special care was taken to full (delivered dose >90% of planned) and complete exposure (with ≥5 mm both radiation margins) of the injured vessel segment to irradiation. All target lesions were then randomly assigned 1:1 to one of the treatment groups.

The standard (S) group consisted of 25 lesions in 24 patients with dose of 20 Gy aimed at 1 mm beyond reference lumen surface. In this group, dwell time was determined on the basis of mean values of the proximal and distal reference lumen (lumen–lumen) diameters and source activity.

The dosing-adjusted (DA) group consisted of 26 lesions in 24 patients with dose of 20 Gy prescribed at 1 mm beyond the reference EEM border. Dwell time was determined on the basis of mean reference EEM diameter (EEM–EEM) and source activity.

2.3. Angiographic analysis

All cineangiograms (postprocedural and follow-up) were analyzed off-line with a computer-assisted automated edge-detection algorithm. The contrast-filled catheter was used for calibration. Within the stented segment the minimal lumen diameter (MLD) from the worst view was selected and measured. Distal and proximal references were measured in angiographically normal segments adjacent to stent. Lesion length was measured from shoulder to shoulder. Angiographic definition of restenosis was a MLD smaller than 50% of mean reference diameter.

2.4. IVUS imaging and off-line analysis

All lesions underwent serial (postprocedural and follow-up) IVUS examination after intracoronary bolus of 100–200 μg of nitroglycerine using a commercially available system (20 MHz Avanar, Volcano Therapeutics). An ultrasound catheter was inserted at least 10 mm beyond the distal edge of the stent and pulled back automatically up to the ostium of the vessel at the constant speed of 0.5 mm/s.

Off-line quantitative IVUS analysis (Endosonics System) was performed every 1 mm of the stented segment length and reference sites [17]. Measurements included vessel (V), stent (S) and lumen (L) cross-sectional areas. Simpson's rule was used to calculate respective volumes of traced structures. Calculations included plaque and media (P&M), residual and follow-up neointima volumes. All volumetric parameters were then adjusted by respective stented segment length (vol. mm^3/mm). Neointimal hyperplasia (NIH) as well as absolute changes (Δ) of all IVUS parameters during follow-up were calculated and divided by postprocedural value to get relative change (%), except for: