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The combined use of **D**rug Eluting Balloon and **E**xcimer Laser for Coronary Artery **R**estenosis **I**n **S**tent **T**reatment: The DERIST STUDY.

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INTRODUCTION

Stents reduce angiographic restenosis in comparison with balloon angioplasty (1-2). The rate of in-stent restenosis (ISR), although less frequent than post-angioplasty restenosis, is becoming increasingly prevalent due to the recent exponential increase in the use of intracoronary stents. Prior studies have shown that tubular slotted stents do not recoil and do not allow geometric arterial constriction, which may account for up to 55% of lumen loss in the restenotic process after angioplasty or atherectomy. (3-4-5). Therefore, ISR is due to intimal hyperplasia (6-7). The introduction of drug-eluting stents (DES) has substantially reduced angiographic restenosis and target lesion revascularization (TLR) in comparison to bare-metal stents (BMS) (8-9-10-11-12-13). However, the higher complexity of the treated lesions and the increased off-label use of DES make the real world restenosis rate higher than the results reported from the clinical randomized trial (14). Numerous mechanisms can underlie the DES ISR pathophysiology such as:

1) Biological factors: resistance to anti-proliferative drugs and hypersensitivity reactions;

2) Technical factors: incomplete stent expansion, geographical miss, and barotraumas to un-stented segments;

3) Mechanical factors: stent fractures, polymer peeling and non-uniform stent strut distribution or drug deposition.

Although ISR is often considered a benign process, recent data have shown that the clinical presentation can vary from stable angina to an acute coronary syndrome (ACS) (15-16-17). Treatment of in-stent restenosis (ISR) with conventional percutaneous transluminal coronary angioplasty (PTCA) causes significant recurrent neointimal tissue growth from 30 to 85% of cases. Therefore, the use of drug eluting balloon (DEB) followed by laser ablation of intrastent neointimal hyperplasia can be an attractive alternative approach. However, the long-term outcomes of such treatments have not been studied thoroughly. This prospective and multi-centric study evaluated angiographic and clinical outcomes of PTCA in combination with the use of excimer laser coronary angioplasty (ELCA) and DEB.

METHODS

This multi-centric case-control study evaluated angiographic and clinical outcomes of PTCA with excimer laser coronary angioplasty (ELCA) and DEB in 80 patients with ISR. 80 patients with focal ISR were enrolled from January 2010 to January 2013. All patients underwent nine months of clinical and a coronary angiography follow up. Excimer laser angioplasty and drug eluting balloon were used to treat in stent restenosis lesions with high success rate. To assess immediate and long-term results of patients treated, we analyzed demographic information and the immediate results of 80 patients who underwent ELCA and DEB. The patients were followed up and assessed for clinical restenosis.

PATIENT CHARACTERISTICS

In this study 80 consecutive patients were prospectively included. Written informed consent was

obtained from all patients under a protocol approved by the Ethics Committee of the Avellino Medical Board. Patients were included if they presented with an in-stent restenosis or a wire able total occlusion within a stent that had been implanted for one month into a native vessel or a coronary artery vein graft. Patients with an evolving myocardial infarction, angiographic evidence of fresh thrombus or lesions in segments with major bifurcations on visual assessment were excluded. The mean age of the 80 patients was 65 ± 10 years (range: 39–76 years); 59 patients were men. Major coronary risk factors were: diabetes mellitus (33 patients/38%) (non-insulin dependent: n 21 (31%), insulin dependent: n 12 [15%]), hyperlipoproteinemia (59 patients/73%), arterial hypertension (65 patients/75%), current or recently stopped smoking (51 patients/63%) and a family history of coronary artery disease (53 patients/62%). The patient group had a high prevalence of known risk factors for recurrent restenosis (21–27) (Table 1). A previous or current total occlusion was present in 23 patients (24%). The stents had been implanted for recurrent restenosis in 21 patients (26%). All stents implanted were drug eluting stents (DES). In 14 patients stents were located in venous bypass grafts (17%). Multiple stents (>2 stents/vessel) had been implanted in 52 patients (65%). Stents were located in small vessels (< 3.00 mm in diameter) in 52 patients (65%). Excimer laser angioplasty was performed within 112 coronary stents. The stents had been implanted for 6 ± 3 months (range: 2–16 months) before the time of intervention (Table 2). There was no intracoronary imaging or FFR used, for the difficulty to cross coronary complex lesion of this study with FFR or intracoronary imaging devices.

PROCEDURAL FEATURES

A) **Excimer laser system and adjunctive balloon angioplasty.** A xenon chloride excimer laser unit operating at a wavelength of 308 nm (Spectranetics CVX-300, Colorado Springs, Colorado) was used in all patients. The laser unit delivered laser pulses of 135ns pulse duration at a frequency (repetition rate) of 25 to 45Hz and an energy density (fluence) of 30 to 60mJ/mm^2. The laser energy was delivered through concentric multifiber laser catheters (Turboelite RX; Spectranetics Corp., Colorado Springs, Colorado) with tips ranging from 0.9, 1.4, and 1.7mm in diameter. Intracoronary saline infusion was initiated 3s before delivery of laser energy and was continued during excimer laser treatment. Multiple passes were performed at the operator's discretion to achieve maximum debulking. Adjunctive balloon angioplasty was performed in all patients using standard techniques.

B) **Use of drug eluting balloon.** After performed ELCA has been used 93 drugs eluting balloons (Amphirion inpact Medtronic) (DEB). DEB was used as the last step for the lesion treatment with no further ballooning done after DEB to ensure maximum availability of the drug delivered to the vessel wall. The DEB was inflated at the site of ISR for 60 seconds at its nominal pressure. If the lesion length was large and such a size was not available, then two short-length DEBs were used sequentially to completely cover the lesion. Angioplasty was considered adequate at <20% residual stenosis.

C) **Medical treatment before, during and after ELCA.** Pretreatment medication consisted of oral aspirin 100mg/day (or 300mg aspirin, if the patient was not on aspirin therapy before). A standard angioplasty regimen of heparin (10.000 IU intravenous bolus injection) and

intracoronary nitroglycerin (100mg to 200mg) was given before angiography was performed. The permanent medical treatment after the intervention consisted of oral aspirin 100mg/day.

IN-HOSPITAL RESULTS

No acute post procedural complications were observed, including no-reflow and dissection. During the hospital stay, four patients still had angina symptoms and were managed medically.

CLINICAL FOLLOW-UP

Clinical evaluation at six-month follow-up included the record of cardiac adverse events and clinical symptoms defined as: death (death for cardiac or any other cause), myocardial infarction (ST segment elevation 0.10mV in two electrocardiographic leads plus creatine kinase elevation two times above normal value associated with 6% creatine kinase MB fraction or the development of new pathologic Q waves in the electrocardiogram according to the Minnesota Code) (28). At this time the occurrence of angina pectoris, graded according to the classification of the Canadian Cardiovascular Society (CCS) (29), was registered.

RESULTS

A) **Clinical follow-up.** The *acute* results limited to the in hospital safety and feasibility of the technique from a subgroup were reported previously (19). It has been shown that angiographic success (diameter stenosis 50%) was achieved in all patients if the lesion could be crossed with a guidewire (19). 11% of the patients had dissections (1% related to laser treatment, 10% to adjunctive percutaneous transluminal coronary angioplasty [PTCA]); no laser related perforations (19). There was no Q wave infarction and no death (19). During follow-up there was one patient with myocardial infarction leading to hospital admission (1%). One patient with history of current smoking died from sudden death at home approximately one week after the intervention (1%). During follow-up three patients had angina pectoris graded as CCS class I (9%), 20 patients were graded as class II (27%), 14 patients as class III (17%) and four patients as class IV (5%). The overall rate of patients with recurrent angina was 55%. Nine patients had to undergo repeat cardiac catheterization for recurrent angina pectoris earlier as originally scheduled (Table 3). In these patients angiography had to be performed 4,1 ± 0.9 months earlier. Four of these patients were treated interventionally at the site of the previously lasered target lesion.

B) **Quantitative coronary angiography.** Follow-up coronary repeat angiography was obtained in 77 of 80 patients (96%). One patient died before repeat angiography; the other two patients refused to undergo a control angiography because they were completely asymptomatic. The mean reference diameter of the treated vessels was 2.62 ± 0.38 mm before intervention. The percentage diameter stenosis before intervention was 72 ± 10% and

was reduced to 41 ± 12% by laser treatment (p=0.001), (39 ± 11% in vessels > 3.00mm in diameter, 45 ± 9% in vessels <3.00mm in diameter). Adjunctive balloon angioplasty further reduced diameter stenosis to 11 ± 12% (p=0.001). At six-month follow-up the average diameter stenosis had increased to 60 ± 26% (p=0.001) (Table 4). There were 28 patients with a moderate degree of restenosis between 50% and 69% and 45 patients with a high grade of restenosis between 70% and 99%. In addition, there were seven patients presenting with total occlusions. The average lesion length before intervention was 16 ± 9mm (seven total occlusions not included). Before intervention, the majority of patients had long lesions. The incidence of recurrent restenosis in patients with long lesions tended to be higher than in patients with short lesions; however, this difference was not statistically significant. In the group with total occlusions, four patients had a recurrent restenosis, and two patients presented with a recurrent total occlusion.

Discussion

There is an increasing need to evaluate techniques other than balloon angioplasty to treat in-stent restenosis. Excimer laser angioplasty and drug eluting balloon have recently been shown to be safe and efficient alternatives for the treatment of this type of lesion (18 –20). It has been demonstrated that both techniques achieve excellent acute angiographic results (18 –20). The long-term results remain to be analyzed. This report describes a large series of patients treated with ELCA and DEB for in-stent restenosis who were followed-up clinically and angiographically.

Clinical results. This study showed clinical and angiographic long-term success in the 91% of the patients, only 3% had recurrent symptoms of angina pectoris during the follow-up period. The incidence of myocardial infarctions and deaths was lower than the rate after plain balloon angioplasty within the stent (2–7).

Angiographic results. The angiographic results were satisfactory. There was a small lumen late loss at the nine-month follow-up angiographic control, which led to a binary restenosis rate of 9%. The recurrent restenosis rate appeared to be higher in small compared with long lesions, particularly in diabetic patients, and was extremely low in the small group of patients who were treated for total occlusions within a stent. The high incidence of recurrent restenosis in patients presenting with an in-stent occlusion is in good agreement with data from a recently published report that showed a need for target vessel revascularization in 83% of patients with total in-stent occlusions, regardless of the device used (25). An important finding was a target lesion revascularization (TLR) defined as any repeat revascularization procedure (percutaneous or surgical) of the original target lesion site, which includes the stented plus edge (typically 5mm proximal and distal to the stent) segments. Thus, TLR is perceived to be the best clinical surrogate for angiographic restenosis. TLR is typically driven by clinical evidence of ischemic symptoms or positive stress-induced ischemia test, because asymptomatic patients with non-functional angiographic stenosis experience a benign course without re-intervention. In our study, the TLR was 2%, which has important clinical relevance because in patients in whom the restenosis was found after ELCA and DEB there were no signs of evidence of ischemic symptoms. In our study, the routine angiographic follow-up found out in stent restenosis, also in the patients in which there are not clinical evidence of ischemia. We

conclude that TLR is not a satisfactory tool to evaluate the rate of in-stent restenosis because in our study we performed an angiographic follow-up in 100% of patients, where several other studies that followed-up in their patients was only performed on clinical features. This remains a relatively small study. Further studies with a large number of patients and longer follow-up will be required to confirm the clinical superiority of ELCA and DEB for treatment of in stent restenosis. An interesting trial like RIBS IV, evaluated the comparative efficacy of drug-eluting balloons (DEB) and everolimus-eluting stents (EES) in patients presenting with DES-ISR. This study demonstrated the superior efficacy of EES compared with DEB in patients with DES-ISR. The Derist study, instead showed that Excimer laser angioplasty and drug eluting balloon may be an alternative treatment for in-stent restenosis (ISR).

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Patient Characteristics

- The Mean age of the 80 patients was 65 ± 10 years (range: 39–76 years); 59 patients were men.

- Major coronary risk factors were:
  - diabetes mellitus (33 patients/38%):
    - non-insulin dependent: n 21 (31%)
    - insulin dependent: n 12 [15%]),
  - hyperlipoproteinemia (59 patients/73%),
  - hypertension (65 patients/75%),
  - current or recently stopped smoking (51 patients/63%),
  - family history of coronary artery disease (53 patients/62%).

Table 1

Patient characteristics

- The patient group had a high prevalence of known risk factors for recurrent restenosis,
- A previous or current total occlusion was present in 23 patients (24%),
- The stents had been implanted for recurrent restenosis in 21 patients (26%). *All stents implanted were drug eluting stents (DES),*
- In 14 patients stents were located in venous bypass grafts (17%),
- Multiple stents (>2 stents/vessel) had been implanted in 52 patients (65%),
- Stents were located in small vessels (< 3.00 mm in diameter) in 52 patients (65%),
- Excimer laser angioplasty was performed within 112 coronary stents,
- The stents had been implanted for 6 ± 3 months (range: 2–16 months) before the time of intervention.

Table 2

Results: efficacy endpoints

- Angiographic success (diameter stenosis 50%) was achieved in all patients if the lesion could be crossed with a guidewire;
- 11% of the patients had dissections (1% related to laser treatment, 10% to adjunctive PTCA;
- There was no Q wave infarction and no death;
- During follow-up there was one patient with myocardial infarction leading to hospital admission (1%);
- One patient died from sudden death at home approximately one week after the intervention (1%);
- Three patients had angina pectoris graded as CCS class I (9%), 20 patients were graded as class II (27%), 14 patients as class III (17%) and four patients as class IV (5%);
- The overall rate of patients with recurrent angina was 55%;
- Nine patients (11%) had to undergo repeat cardiac catheterization for recurrent angina pectoris earlier as originally scheduled.

Table 3

Results: safety endpoints

- Mean reference diameter of the treated vessels: 2.62 ± 0.38 mm (before intervention)

- Percentage diameter stenosis before intervention was: 72 ± 10%

- Diameter stenosis was reduced to 41 ± 12% by laser treatment (p=0.001):

    - 39 ± 11% in vessels > 3.00 mm in diameter

    - 45 ± 9% in vessels <3.00 mm in diameter

- Adjunctive balloon angioplasty further reduced diameter stenosis to 11 ± 12% (p=0.001)

- At six-month follow-up the average diameter stenosis had increased to 60 ± 26% (p=0.001)

Tabe 4

HIGHLIGHTS

1. The Derist study is a Multicenter study conducted in 6 centers in Italy;

2. The study evaluate the results of treatment of in-stent restenosis (ISR) performed by the combined use of excimer laser (ELA) and Drug eluting Balloon (DEB);

3. The study evaluate the presence of new angiographic restenosis and the incidence of MACE in the study population.