Inhibition of In-Stent Restenosis in Porcine Coronary Arteries by Copper Chelation

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Background: In-stent restenosis is a complex process mediated by inflammatory cytokines and growth factors, which regulate inflammatory cells recruitment to the vessel wall as well as vascular smooth muscle cell migration and proliferation. Since intracellular copper metabolism plays a crucial role in the stress-induced release of FGF-1 and IL-1α, both of which are important for neointima development after vessel injury, we examined the effect of tetrathiomolybdate (TTM), a clinically proven copper chelator, on in-stent restenosis in a porcine stent model.

Methods: Seventeen stents were implanted in the left anterior descending coronary artery of 17 male pigs using a stent to artery overstretch ratio of 1.2:1. Nine pigs (Gr.1) were treated daily with 10 mg/kg TTM p.o. starting 14 days prior to stent implantation and continuing until sacrifice at 28 days follow-up, whereas 8 pigs (Gr.2) served as controls. The effect of TTM on in-stent restenosis was assessed by biplane quantitative coronary angiography before and immediately after stenting as well as at 28 days follow-up. Serum ceruloplasmin activity, an indirect indicator of total copper level, was measured weekly.

Results: The two groups were comparable regarding baseline data including animal age and body weight, stent size, vessel reference diameter, and ceruloplasmin activity. Post-interventional minimal lumen diameter and overstretch ratio were similar for both groups. However, at 28 days follow-up, there was a marked difference of all parameters relevant to the in-stent restenosis in favor of the TTM-treated group: minimal lumen diameter was 2.2±0.6 mm in Gr.1 vs. 1.5±0.4 mm in Gr.2, p<0.05 and diameter stenosis was 32±18% in Gr.1 vs. 42±17% in Gr.2, p<0.05. During the entire follow-up period, ceruloplasmin activity in the TTM group was significantly decreased from 50% to 80% (p<0.0001) of its baseline level.

Conclusions: This study is the first to provide evidence that copper chelation by tetrathiomolybdate can markedly prevent in-stent restenosis. Our data also suggest that this simple and inexpensive approach is a potential tool in the management of vascular restenosis after percutaneous interventions in clinical settings.

Long-Term Clinical Follow-Up After Diffuse In-Stent Restenosis

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Background: Although diffuse in-stent restenosis (ISR) is known to be refractory to repeated percutaneous coronary intervention (PCI), long-term outcome of those patients has not yet been established. Methods: To evaluate long-term (7-11 yrs) clinical outcome after ISR, follow-up (FU) information was analyzed in 78 patients (pts) or 78 lesions (78±93%) with ISR. Baseline patient and lesion characteristics were similar among the groups. Results: The occurrence of balloon slippage (“watermelon seeding”) (WMS) during treatment of patients with in-stent restenosis (ISR) has been described, but predisposing factors and the potential implications of this phenomenon remain unknown. Methods: To the Restenosis Intra-stent: Balloon angioplasty versus elective Stenting (RIBS) randomized study, 450 patients with ISR were included. Of these, 42 patients (9%) presented WMS during the procedure. Results: WMS was detected in 26 patients (12%) in the balloon arm and 16 (7%) in the stent arm (p=0.11). In the stent arm, WMS was only noticed during balloon predilation, never during stent implantation. As compared with 408 patients without WMS, patients with WMS tended to have more [% diameter stenosis (72±13% vs 76±12%, p=0.08), TIMI flow 0-1 (21% vs 8%, p=0.01)] and diffuse (length ≥15 mm; 48% vs 34%, p=0.08) ISR lesions. Patients with WMS required more balloon inflations (5.7±2.2 vs 3.5±1.9, p=0.001), longer total inflation time (184±116 vs 150±106 seconds, p=0.04), and had more frequently cross-over to stenting or ended the procedure with residual dissections (26% vs 15%, p=0.04) and eventually obtained poorer acute results (minimal lumen diameter 2.35±0.5 vs 2.53±0.5 mm, p=0.03). In addition, at 6-month follow-up patients with WMS had a smaller minimal lumen diameter (1.26±0.7 vs 1.61±0.7, mm, p= 0.007) and a higher restenosis rate (56% vs 37%, p=0.017). On logistic regression analysis the WMS phenomenon emerged as an independent predictor of recurrent restenosis (Adjusted RR 2.1, 95%CI 1.1-4.1, p=0.04). Conclusions: The WMS phenomenon is frequently seen during treatment of patients with ISR. Long and severe lesions appear to predispose to this technical problem that never occurs during stent deployment. In patients with ISR, WMS is associated with poorer acute and long-term angiographic results.

The Presence of Side Branches Impacts Periprocedural Enzyme Elevation and Clinical Outcome in Patients Undergoing Brachytherapy for In-Stent Restenosis

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Background: Major side branch (diameter >1.5mm, SB) involvement within the lesion subjected for Percutaneous Coronary Intervention (PCI) is known to be a contributing background for periprocedural cardiac enzyme elevation (CE). We aimed to assess the impact of SB on CE and 6 month outcome in-patients undergoing brachytherapy for in-stent restenosis (ISR).

Methods: Retrospective analysis of the data of 248 consecutive patients with a single vessel ISR with SB (Gp1, n=146) and without SB (Gp2, n=102) who underwent brachytherapy using both beta and gamma emitters was conducted. The procedural complications, CE, in-hospital course and 6 month clinical outcome were compared. Results: The baseline patient and lesion characteristics were similar among the groups. Procedural variables were similar except that stent usage was more in Gp1. Baseline Creatine Phosphokinasoe (CPK)-MB levels were similar, but post procedure CPK-MB levels were higher in Gp1. In hospital complications were similar between the two groups. Six months follow up revealed higher restenosis and Major Adverse Cardiac Events (MACE) in Gp1. Conclusions: Presence of SB within the restenotic segment when treated with PCI and brachytherapy is associated with higher procedural CE and MACE at six months. Special care should taken when treating ISR lesions with SB.