Catheter-Based Transplantation of Autologous Bone Marrow Mononuclear Cells Safely Improves Collateral and Capillary Network in Adult Swine With Myocardial Ischemia

Aysegul Yege, Mio Ebato, Fernando Tondato, Burken Ebato, Jianhua Cui, Traci Goodchild, Stephen C. Frohwein, Jesse Rios, James F. Sanzo, Keith Robinson, Mark Ungs, Nicolas A. Chronis, American Cardiovascular Research Institute, Atlanta, GA

Background: To date, it is unclear whether intramyocardial transplantation of autologous bone marrow derived mononuclear cells (BM-MNCs) enhances neovascularization in adult myocardium. We tested the hypothesis that catheter-based delivery of BM-MNCs augments neovascularization in an adult porcine model of chronic ischemia: Methods: Amoroid constrictor was implanted around proximal left circumflex coronary artery (LCX) in adult Yucatan swine. Animals with LCX occlusion of < 90% were excluded from the study. At 4 weeks, pigs were randomized to receive freshly isolated BM-MNCs (n=8) or culture medium (DMEM) as control (n=8). Under general anesthesia, bone marrow (30-50 ml) was aspirated from sternum and if necessary, iliac crest. Mononuclear cells were isolated using density-gradient centrifugation method (Histopaque 1077). A total of 1 x 10^6 cells were injected at 10 sites (5 in the ischemic, and 5 in the non-ischemic region) using Boston Scientific Stiletto™ catheter with intracardiac echocardiography (ICE) guidance. Baseline (4 wk) and follow-up (8 wk) evaluations included coronary angiography (Rentrop score), dobutamine stress echocardiography, and myocardial blood flow by microspheres. Tracking of BM-MNCs was performed in additional pigs (n=3). Tissue samples were stained with PKH-26 to verify cell viability and DAPI (diamino-phenylindole) for intact nuclear DNA, 2 and 4 weeks after delivery. Results: Collateral (Rentrop) Scores: Left-to-left collaterals significantly improved in the BM-MNC treated group (p<0.05), Cell tracking study: Ischemic areas contained higher amount of PKH-26 positive cells co-localizing with DAPI, compared to non-ischemic regions. Transplanted BM-MNCs clustered in areas without abundant cellular structure. A significant increase was found in total capillary area in the LCX (ischemic) region in endocardial (p=0.016) and epicardial (p=0.044) sections in BM-MNC treated pigs compared to the control group. Conclusion: Catheter-based intramyocardial transplantation of autologous BM-MNCs safely enhances collateral and capillary network in adult swine with chronic myocardial ischemia.

Interpretation of the Actual Platelet Inhibition Induced by Clopidogrel: A New Look at How to Represent Drug Response

Paul A. Gurbel, Wael M. Samara, Kevin P. Bilden, Sinai Center for Thrombosis Research, Baltimore, MD

Background: Mean pre- and post-treatment % platelet aggregation is commonly used to describe clopidogrel-induced inhibition and may miss non-responders. Methods: Individual responses to clopidogrel were studied by 5 µM ADP aggregation (A) in pts (n = 68) pre and at 5 days post-stenting. All pts received aspirin 325mg ; 300 mg clopidogrel at the time of stenting ; and 75mg qd. A was recorded as the maximum % change in light transmission from baseline. Individual responses were measured at 5 days as the absolute change in aggregation (ΔA) from pre-to post-treatment. Results: Pre-treatment A was 60 ± 17 and fell to 35 ± 17 after clopidogrel (p<.0001, 42% relative inhibition ) and 16/88 patients (24%) were non-responders ( figure ). Non-responders had higher platelet reactivity (p<.0002). However, total group A was not significantly different from the group of responders ( p = .34 ). By reporting the data as ΔA the presence of non-responders was unmasked (figure). Conclusion: Non-responders are entirely unrecognized by the current practice of reporting mean aggregation data that overestimates the actual drug effect in certain patients. Clinicians should be aware of non-response and its potential effect on outcomes. We recommend a more accurate approach to estimate the drug's effect would be to account for those patients who are non-responsive by reporting the individual change in aggregation from pre-treatment to post-treatment.