1176 Percutaneous Intervention: Stem Cells and Adjunctive Antiatherothrombotic Therapy

Tuesday, April 01, 2003, Noon-2:00 p.m.
McCormick Place, Hall A
Presentation Hour: Noon-1:00 p.m.

1176-173 Mesenchymal Stromal Cell Transplantation Contributes to Collateral Response in Tissue Ischemia Through Release of Arteriogenic Cytokines
Tim D. Kinnaird, Eugenio Stabile, Mary Susan Burnett, Matie Shou, Yi Fu Zhou, Richard As anticipated, PCVD provides regional delivery, and PED a novel local distribution.

arct size compared to the controls (3.9 ± 1.6 and 7.9 ± 6.0, vs. 13.9 ± 10.8, ~~0.12 and

fibroblasts identified after 21 days. PED resulted in 98.4% of cells in the anteroseptal

vs 434 pg/mg. p = NS) and MCP-1 (262 pg/mg vs 109 pg/mg, p = NS). Immunoblotting of

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Poster Session

ABSTRACTS - Angiography & Interventional Cardiology 67A

1176-175 Catheter-Based Percutaneous Cellular Cardiomyoplasty Using Allogeneic Bone Marrow Derived Mesenchymal Stem Cells
background: Bone marrow derived mesenchymal stem cells (MSCs) administered by direct injection into a myocardial infarct (MI) improve ventricular remodeling and global function in both large and small animal models. In order to demonstrate the feasibility of this technique for clinical application without renal failure surgery, we treated the hypoxia that MSCs delivered into neovascular tissue via catheter successfully engraft, migrate throughout a region of MI, and demonstrate evidence of myocyte differentiation in pigs. Methods: MI was produced by 90 minute occlusion of the left anterior descending artery in domestic swine (weight 90-45kg). Three days later both 200 million Dil and DAPI-labeled allogeneic porcine MSCs or vehicle alone (randomized; total n=9) were injected into the LV (10-12 sites in the endocardium within the infarct zone) via a high-fidelity needle infusion catheter advanced through a deflatable guide catheter (BioCardia, Inc, CA). Results: Animals were euthanized between 2 to 8 weeks after injection. Pathology revealed transmural anteroserial infarcts. MSC engraftment was observed in all treated animals, with transmural migration of implanted cells from endocardium to epicardium. MSCs were found associated with all vessels wall and co-stained for Factor VIII and CD31. Conclusion: MSCs show promise as a means for tissue regeneration and may participate in neovascularization. Allogeneic MSCs is both safe and effective and will facilitate practical application of stem cell technology in the treatment of MI and potentially other cardiomyopathic processes.

1176-176 Safety of Autologous Bone Marrow Cell Injection in Humans With Severe Ischemic Heart Failure
Hase H. Dohmann, Emerson C, Perin, Andre Luis S. Souza, Radovan Birjevic, Antonio C. Carvalho, Isabel Rossi, Suzana A. Silva, Roberto Esporre, Collette de Lima, Brazil

Background: Severe ischemic heart failure (HF) in patients not amenable to revascularization carries a high mortality. Treatment of this high risk group with injection of myoblasts revealed a high incidence of post-procedural malignant ventricular arrhythmias. We evaluated the safety of transendocardial (TE) injections of bone marrow mononuclear cells (BMNC) to treat pts with severe HF. Methods: Fourteen pts (60 ± 10 yrs, 12 males) with refractory symptoms (CCS/NIH grade IV), LV dysfunction (EF < 19 ± 15%), angina and one cardiac event (n=1), and/or LV hypotension with pulmonary congestion (n=1) and frequent PVCs (n=1) on day 1. CK-MB did not increase (peak 1.0 ± 0.7 ng/ml, normal < 0.4 ng/ml). CRP levels increased from 0.95 ± 0.68 to 2.0 ± 1.25 mg/ml (p = 0.05) at 24h and decreased at 48h (1.2 ± 1.1 mg/ml; p = 0.49). No persistent arrhythmias were detected. No malignant or sustained ventricular arrhythmias were detected post procedure and all pts were discharged after 48h. PVCs at 24h post-procedure were similar to baseline 49.2 ± 103 vs 29 ± 103 (p = 0.12), respectively.

At 6 wks there was a trend to a decrease in PVC's from baseline 10.3 ± 10.8 to 4 ± 4.4 (p = 0.06). Late events included one uncomplicated NSTEMI at 7 days. No deaths occurred. Conclusions: Immediate and short-term follow-up of pts receiving BMNC injections revealed mild elevations in CRP and troponin I at 24h and one cardiac event. No malignant arrhythmias were detected post procedure and in follow-up. BMNC therapy in these high risk pts was feasible in follow up to 8 weeks.

The Coronary Sinus: A Safe and Effective Route for Percutaneous MyoParastomy Transplantation

Camille Brassat, Claire Carron, Patrick Brunewald, Didier Heudes, Kathy Schwartz, Albert Haepke, Jean-Thomas Vircin, Emmanuel Messias, Michel Desnos, Antoine Ferrat, Philippe Menasché, Hospital Européen Georges Pompidou, Paris, France, Institut de Myologie, Paris, France

The potential of autologous skeletal myoblast (SM) transplantation to improve function of injured myocardium has been previously documented using epicardial injections. In search for an alternate, less invasive approach, we assessed the safety and feasibility of percutaneous SM injection through the coronary sinus system. Two pigs and 4 sheep underwent transendocardial catheterization of the anterior interventricular vein using a dedicated catheter (TransAccess®, Transvascular, Menlo Park, CA) which incorporates a tip-activated array ultrasound probe for guidance and an endless needle for myocardial access. Upon correct positioning, the needle was pulled forward to puncture the venous wall and a micromanipulation catheter was advanced through it to inject the cell suspension. Cultured SM (2x10^6) were thus intramyocardially delivered in 4 staged sites along the catheter tract. Two hours later, the hearts were explanted and processed for

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Poster Session
Combination of a Direct Thrombin Inhibitor, Argatroban, and Glycoprotein IIb/IIIa Inhibitor is Effective and Safe in Patients Undergoing Percutaneous Coronary Intervention

In Yong Jang, Bruce E. Lewis, William H. Matthai, Neal S. Kleinman, Massachusetts General Hospital, Boston, MA, Baylor College of Medicine, Houston, TX

Background: Argatroban, a small molecule direct thrombin inhibitor, has been shown to block clot bound thrombin more effectively than does unfractionated heparin. Argatroban has not been systemically tested in patients undergoing percutaneous coronary intervention (PCI) with concurrent glycoprotein (GP) IIb/IIIa inhibitors. Methods: In this multicenter, prospective, pilot study argatroban was administered in patients undergoing PCI at 200 mcg/kg bolus followed by 15 mcg/kg/min during the procedure. Additional boluses of 150 mcg/kg were given if ACT did not reach the target range of 275-325 sec. GP IIb/IIIa inhibitor was administered simultaneously. The primary efficacy endpoint was vascular death, myocardial infarction (MI), or urgent revascularization at 30 days. The safety endpoint was in-hospital major bleeding. MI was defined as CKMB elevation more than 3 times the upper limit of normal or cardiac symptoms with supportive cardiac marker or EKG evidence. Results: A total of 101 patients were enrolled and completed the PCI procedure. There were 72 males and the mean age was 65 years. Abbocorr was given to 59 patients and double bolus eptifibatide to 2 patients. 76 patients had one target lesion treated and the rest, two or more lesions. 96 patients were treated with stenting. Second and third bolus of argatroban were required in 22 and 7 patients, respectively. The target ACT was achieved in 94 patients. The primary efficacy endpoint occurred in 3 (3.0%) patients (no vascular death, 3 MI and 2 urgent revascularizations). Conclusion: Argatroban in combination with GP IIb/IIIa inhibitors provides adequate anticoagulation with acceptable bleeding risk. These data suggest that further investigation of argatroban in patients undergoing PCI is warranted.

Unfractionated Heparin Increases Platelet-Monocyte Binding in Vitro and in Patients Undergoing Percutaneous Coronary Intervention

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Background: Unfractionated heparin is currently considered to be the anticoagulant of choice in patients undergoing percutaneous coronary intervention (PCI). Unfractionated heparin may be associated with adverse platelet activation. Platelet-monocyte aggregation (PMA) is a sensitive marker of platelet activation and may mediate pro-inflammatory cytokine release, tissue factor expression and augmented adhesion molecule expression. We compared the effects of unfractionated heparin, a low-molecular-weight-heparin (enoxaparin), and a direct thrombin inhibitor (lepirudin) on PMA in vitro. We also investigated the effects of unfractionated heparin on PMA in patients prior to PCI.

Methods: Peripheral venous blood was collected from 18 healthy volunteers into sodium citrate alone or sodium citrate with unfractionated heparin (1 U/mL), enoxaparin (0.8 U/mL) or lepirudin (0.6 U/mL). Blood was also drawn into sodium citrate tubes from 14 patients immediately before and five minutes after administration of 100 U/kg of unfractionated heparin, prior to elective PCI. PMA was determined by 2-color flow-cytometric analysis.

Results: In healthy volunteers, PMA was higher in blood anticoagulated with sodium citrate and unfractionated heparin (20.1 ± 1.9%) compared to sodium citrate alone (16.2 ± 1.6%) or sodium citrate with enoxaparin (16.9 ± 2.0%), p<0.01 or lepirudin (17.0 ± 2.2%), p<0.01. There were no differences in PMA in blood anticoagulated with sodium citrate alone, sodium citrate and enoxaparin, or sodium citrate and lepirudin (p>NS). Administration of unfractionated heparin to patients prior to PCI was also associated with increased PMA (24.2 ± 2.6% vs. 16.9 ± 2.4%, p<0.01).

Conclusions: In contrast to enoxaparin and lepirudin, unfractionated heparin increases PMA in vitro; an effect that was also demonstrable in patients receiving unfractionated heparin prior to PCI. Given that PMA is a sensitive measure of platelet activation and may have proatherosclerotic consequences, the use of alternative anticoagulant regimens may reduce PMA associated complications.

Safety and Efficacy of Subcutaneous Enoxaparin in Early Invasive Strategy of Unstable Angina

Jean-Philippe Collet, Gilles Montalescot, Jean-Louis Golmard, M. Tanguy, Remi Chousat, Gerard Dubinski, Armin Axon, Nicolas Vignoles, Daniel Thomas, Pitie Salpetriere, Paris, France

Introduction: We have demonstrated previously that subcutaneous (s/c) enoxaparin (1mg/Kg/12h) given during at least 48 hours provided good anticoagulation and clinical results in post- GT DVT IVH patients undergoing percutaneous coronary intervention (PCI) within 8 hours of the last injection. We evaluated whether an early invasive (E) strategy with only 2 injections of s/c enoxaparin was as good as a delayed invasive (DI) strategy with 2 injections or more.

Methods and results: We compared NSTE-ACS patients who underwent PCI after 2 injections of s/c enoxaparin (E, n=117) with those referred later on to DI (S, 9,54,2 s/c injections, n=295). Anti-Xa at the time of catheterization, safety and major coronary events (death/MI) were assessed at 30 days. Baseline characteristics were similar in the 2 groups of patients. The period of medical stabilization was 20.5±1.0 hrs in the "E" and 38.2±3.1 hrs in the "DI" group, respectively (p=0.001). Anti-Xa values were not different between both groups (1.7±4.8% for "E" and 1.6±1.8% for "DI", p=0.17). MI was achieved in 94 patients. The primary efficacy endpoint occurred in 3 (3.0%) patients (no vascular death, 3 MIS and 2 urgent revascularizations). Two additional patients had bleeding or required urgent revascularization.

Conclusions: Intravenous enoxaparin at clinically relevant doses, increases ACT levels with this standard test.

Assessment of Anticoagulation Using Activated Clotting Times in Patients Receiving Intravenous Enoxaparin During Percutaneous Coronary Intervention

Mark Lawrence, Timothy Mixon, Donald Cross, Gregory Denmer, Scott and White Clinic, Temple, TX

Background: Intravenous (IV) unfractionated molecular weight heparins have many advantages over unfractionated heparin. They have been used safely during percutaneous coronary intervention (PCI) when given intravenously (IV) with and without glycoprotein 2b/3a receptor inhibitors. Interventionists have been reluctant to use this therapy because of the inability to monitor the anticoagulant effect of IV enoxaparin. We measured activated clotting time (ACT) before and after IV enoxaparin, to determine if anticoagulation could be assessed with this standard test.

Methods: 45 consecutive patients undergoing PCI received either 0.75 mg/kg IV exovaarin if they also received eptifibatide, or 1 mg/kg IV enoxaparin if no eptifibatide was administered. We measured ACT before the injection of s/c enoxaparin (E, n=117) with those referred later on (DI, 5.9±4.2 s/c injections, n=389), respectively.

Results: After 0.75 mg/kg enoxaparin, mean ACT increased from 112.2±23.2 sec to 207.2±25 sec, p<0.001. After 1 mg/kg enoxaparin, ACT increased from 121.2±28 sec to 212.2±32 sec, p<0.001. The mean increase in ACT value was 74.2±25 sec (range 47 to 132) in the 0.75 mg/kg group (n=36) and 92±28 sec (range 32 to 120) in the 1 mg/kg group (n=8). None of the patients had transient abrupt closure, thrombus formation, major bleeding or required urgent revascularization.

Conclusion: Intravenous enoxaparin at clinically relevant doses, increases ACT levels in patients undergoing PCI with and without eptifibatide. Those data suggest that ACT may be useful in the measurement of enoxaparin anticoagulation.