POSTER SESSION

1176 Percutaneous Intervention: Stem Cells and Adjunctive Antithrombotic 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

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Background: Mesenchymal stromal cell (MSC's) transplantation is reported to contribute to angiogenesis through cell donation to new vessel formation. However, the humoral contribution of MSC's to collateral response is less well characterized. Methods and Results: Murine MSC's were purified using double magnetic bead separation of cultured bone marrow. Flow cytometry confirmed absence of CD34, CD45, CD31 and CD117 surface markers, and the presence of SH2 and Sca-1 surface markers. Conditioned media (CM) was collected after 72 hours of MSC culture. Using ELISA, we demonstrated release of: VEGF (375 pg/mg protein in normoxia vs 698 pg/mg protein in 1% hypoxia, p<0.01), bFGF (2320pg/mg vs 3970 pg/mg, p<0.05), placental growth factor (410pg/mg vs 434pg/mg, p=NS) and MCP-1 (262 pg/mg vs 109 pg/mg, p=NS). Immunoblotting of MSC protein extracts established the presence of metalloproteinase-9, angiopoetin-1 and angiopoetin-2. CM enhanced proliferation of endothelial cells by 92% and of smooth muscle cells by 74%, and increased tube-formation in a dose dependant manner. 10mg/ml of anti-VEGF antibody only partially attenuated these effects (40% reduction in proliferation, no effect on tube formation). Balb/C mice (n=8) underwent distal femoral artery ligation; 24 hours later $5x10^5$ MSCs were injected into the adductor muscle. Compared to controls injected with media alone (n=8), foot perfusion in MSC-treated mice increased by 63% at day 7 and by 67% at day 10 (p=0.02). MSC transplantation improved limb function (ambulatory score 1.25 vs 0.5, p<0.05), lessened limb ischemia (ischemic score 1.0 vs 2.75, p<0.05) and reduced the incidence of auto-amputation (13% vs 50%) compared to controls. Conclusions: Injection of mesenchymal stromal cells into the ischemic hindlimb contributes to collateral responses through release of arteriogenic cytokines.

1176-174 Percutaneous Endocardial Versus Selective Coronary Venous Cellular Delivery: Comparisons of Transplant Efficiency, Distribution, and Efficacy in Reducing Infarct Size and Improving Myocardial Function

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Background: Cellular transplantation is an emerging option for the treatment of ischemic cardiomyopathy. Percutaneous endocardial delivery (PED) and percutaneous coronary venous delivery (PCVD) offer potential advantages in safety, transplant efficiency, and targeted distribution for preservation of myocardium.
Methods: A total of 22 swine were studied: 6 PED and 4 PCVD for acute feasibility arm; and 4 PED, 4 PCVD, and 4 combined controls for chronic efficacy arm (LAD infarct by balloon occlusion). Porcine fibroblasts labeled with iron nano-particles were used for transplantation. Between $2\text{-}2.5x10^6$cells were injected into the infarct area either by PED using a BioCardia™ helical infusion catheter, or by PCVD using a single high-pressure (100-200 mmHg) injection through a balloon-tipped catheter in the anterior interventricular vein (AIV). Ejection fraction (EF) was measured at infarct induction (day 0), cell delivery (day 7), and sacrifice (day 28). Horizontal cross-sections of the left ventricle were stained with tetrazolium for infarct size, then with H&E and Prussian Blue for cell identification. A linear computational model was used to estimate transplant efficiency.
Results: Acute studies demonstrated safe, targeted transplantation using both modalities. In infarcted animals, PED and PCVD resulted in 17.3 ± 24.3% and 15.7 ± 11.6% of fibroblasts identified after 21 days. PED resulted in 98.4% of cells in the anteroseptal walls, with 95.8% localized to the endocardial half, at an average depth of 3.4 ± 3.9 mm. PCVD resulted in 97.6% of cells in the anteroseptal walls, a radial 21.8 ± 7.9 mm from the AIV, with 60.1% localized to the endocardial half. With both modalities >96.0% of cells were within 5 mm of the infarct zone. Both PED and PCVD trended in reduced infarct size compared to the controls (3.9 ± 1.6 and 7.9 ± 6.0, vs. 13.9 ± 10.8, p=0.12 and p=0.37 respectively), and improved EF (26.0 ± 3.2 and 26.8 ± 12.6 vs. 17.0 ± 9.8, p=0.13 and p=0.27 respectively).
Conclusions: PED and PCVD provide comparable efficiency and targeted distribution. As anticipated, PCVD provides regional delivery, and PED a more local distribution. Studies are underway to further establish the efficacy of both modalities.

1176-175 Catheter-Based Percutaneous Cellular Cardiomyoplasty Using Allogeneic Bone Marrow Derived Mesenchymal Stem Cells

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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 therapeutic applicability without need for surgery, we tested the hypothesis that MSCs delivered percutaneously via catheter successfully engraft, migrate throughout a region of MI, and demonstrate evidence of myocyte differentiation in pigs. **Methods**: MI was produced by 1-hour occlusion of the left anterior descending artery in domestic swine (weight 30-45kg). Three days later either 200 million DiI and DAPI-labeled allogeneic porcine MSCs or vehicle alone (randomly assigned; total n=9) were injected into the LV (10-12 sites in the endocardium within the infarct zone) via a helical needle infusion catheter advanced through a deflectable guide catheter (BioCardia, Inc, CA). **Results**: Animals were euthanized between 2 to 8 weeks after injection. Pathology revealed transmural anteroseptal infarcts. MSC engraftment was observed in all treated animals, with transmural migration of implanted cells from endocardium to epicardium. MSCs were found associated with blood vessel walls and co-stained for factor VIII, consistent with neoangiogenesis. Transplanted MSCs expressed muscle specific proteins including phospholamban, myosin heavy chain and alpha-actinin, which were not present before implantation, suggesting myogenic differentiation. Implanted MSCs were not found in regions of myocardium remote from the injection site, or systemically. There was no evidence of immunorejection. No deaths, perforations or arrhythmias resulted from the catheterization or injections. **Conclusions**: MSCs can be successfully delivered via percutaneous catheter. Transplanted cells engraft, migrate transmurally, express myocyte phenotypic markers and may participate in neoangenesis. We conclude that catheter-based delivery of 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

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Background: Severe ischemic heart failure (HF) in patients not amenable to revascularization carries a high mortality. Treatment of this high risk gorup witn 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/NYHA III-IV), LV dysfunction (EF 19 ± 10 %) were included in the study. Bone marrow (50ml) was aspirated and BMNCs were isolated. TE injections (15±2 sites, 0.2cc) were performed using the Myo-Star catheter (NOGA, Biosense). Pts were evaluated for post-procedural in-hospital events and 24h-Holter was performed as well as serial echocardiograms, cardiac enzymes and C- reactive protein (CRP) at baseline, 6h, 12h, 24h and 48 hours. Eight wks follow-up included 24h-Holter and CRP levels. Student's T-test was used for comparison.
Results: No in-hospital major events were observed. Minor events included transient hypotension with pulmonary congestion (n=1) and frequent PVCs (n=1) on day 1. CK-MB did not increase (peak 3.0±1.5 mcg/l, normal <5 mcg/l) and Troponin I was mildly elevated (peak 1.0±0.7 ng/ml, normal < 0.4 ng/ml).CRP levels increased from 0.95± 0.68 to 2.0 ± 0.70 mg/dl (p=0.003) at 24h and decreased at 8 weeks (1.27±1.1 mg/dl; p=0.4). No pericardial effusions were detected by echo. No malignant or sustained ventricular arrhythmias were detected post procedure and all pts were discharged after 48h. PVC's at 24h post-procedure were similar to baseline 49.2 $x10^3$ vs $29x10^3$ (p=0.12), respectively.At 8 wks there was a trend to a decrease in PVC's from baseline $10.3x10^3$ (p=0.08). Late events included one uncomplicated NSTMI at 7 days. No deaths occured.
Conclusion: Immediate and short-term follow-up of pts recieveing BMNC injections revealed mild elevations in CRP and troponin I at 24 hours and one cardiac event. No malignant arrhythmias were detected post procedure and in follow-up. BMNC therapy in these high risk pts was safe in follow-up to 8 weeks.

1176-177 The Coronary Sinus: A Safe and Effective Route for Percutaneous Myoblast Transplantation

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The potential of autologous skeletal myoblast (SM) transplantation to improve function of infracted myocardium has been previously documented using epicardial injections. In search for alternate, less invasive approach, we assessed the safety and feasibility of percutaneous SM transfer through the coronary sinus system. Two pigs and 4 sheep underwent transfemoral catheterisation of the anterior interventricular vein using a dedicated catheter (TransAccess®, Transvascular, Menlo Park, CA) which incorporates a tipped-phase-array ultrasound probe for guidance and an extendable needle for myocardial access. Upon correct positioning, the needle was pulled forward to the puncture the venous wall and a microinfusion catheter was advanced through it to inject the cell suspension. Cultured SM (2x108) were thus intramyocardially delivered in 4 staged sites along the catheter tract. Two hours later, the hearts were explanted and processed for