MR Guided Islet Cell Transplantation

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Introduction: For patients with type I diabetes mellitus, islet transplantation provides a moment-to-moment fine regulation of insulin that is unachievable by exogenous insulin injection. Good glycemic control is critical in reducing the end-stage complications of diabetes and for this reason islet transplantation has received considerable attention in recent years. Early reports have described insulin-independence success rates ranging from 23-90%[1]. This wide range is largely due to the immunosuppressive regimen employed as most immunosuppressive regimens are highly toxic to isolated islets. For this reason, a means to immunoisolate islets allowing engraftment free of chronic immunosuppressive therapy is needed. One plausible approach is microencapsulation in which individual islets are surrounded with a thin shell that is impermeable to antibodies and other arms of the host's immune system but is permeable to insulin, nutrients, electrolytes, oxygen, and metabolic waste. Small-scale clinical trials have given impressive evidence of the potential of encapsulated cell therapy. Nevertheless, basic questions such as ideal transplantation site, best means of delivery and long-term survival of such grafts are only beginning to be addressed. If microcapsules could be visualized after implantation, their functionality and biodistribution could be evaluated more effectively. Magnetic resonance (MR)-trackable magnetocapsules (MCs) were created to simultaneously immunoprotect pancreatic beta cells and non-invasively monitor, in real-time, portal vein delivery and engraftment using MR imaging (MRI). The purpose of this study was to demonstrate the feasibiltiy of MRI guided delivery and monitoring of islet cell transplantation with MCs containing human islets in a swine model. (xenotransplantation)

Method:

Synthesis of magnetocapsules containing human islets (Figure 1)

The protocol we have developed for synthesizing magnetocapsules is based upon the classic poly-L-lysine (PLL)-alginate protocol utilized for microencapsulation developed by Lim and Sun[2] and has been previously described by our group[3]. The procedure essentially involves using an electrostatic droplet generator to create 350-400 µm alginate/islet microcapsules. Alginate-encapsulated islet cells are produced using an electrostatic generator to create microbeads, which are crosslinked in a calcium choride solution. A second layer of alginate was created after incubation of the microbeads in poly-L-lysine to enhance capsule strength and create uniform porosity. As Feridex is known to complex with PLL through electrostatic interactions[5], we modified the traditional synthesis of capsules by adding a Feridex incubation step following initial incubation of capsules in PLL. Following Feridex incubation, capsules were rinsed in saline and a final layer of alginate was applied. All human islets were procured from the Islet Cell Resource center. After purification and isolation, all human islets were shipped to our institution for immediate encapsulation and transvascular implantation into swine. Using this method, MR visible capsules (MCs) were created with two human islets distributed into each capsule (feridex concentration = 5-10%)

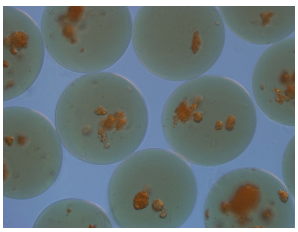


Figure 1: Optical Microscope showing multiple MCs with each capsule containing two islets.

MR Guided Delivery of Magnetocapsules (Figure 2 and 3)

All procedures were performed in a 1.5 T MR scanner (Espree, Siemens Medical Solutions). Imaging was acquired using a combination of external phased array coils and a custom made active intravascular needle. The needle was introduced though a standard clinical 12 F sheath which had been placed in the common femoral vein. Using a real-time TrueFISP sequence in combination with interactive scan plane manipulation (IFE + IRTTT, Siemens) (Figure 2), three simultaneous orthogonal planes (axial, sagittal and oblique axial) were imaged to track the needle and identify the proper trajectory portal vein puncture from the inferior vena cava (TE/TR 1.2/3.4 ms, 45º flip angle, 125 kHz bandwidth, 7 mm slice thickness, 30 cm FOV, 128 x 128 image matrix). After directed puncture into the portal vein, 110-140x10^3 MCs containing human islets were infused and monitored with real time MR imaging in four swine. Portal pressures were obtained at baseline, immediately post procedure at 1 minute, 30 minutes and four weeks after transplantation. In addition, standard liver function tests, platelet count and human c-Peptide levels were obtained at baseline and every week up to four weeks. At the end of four weeks, repeat MRI of the liver (high resolution 3D gradient echo imaging) was performed as well as direct portal venograms and portal pressures. At eight weeks, repeat MRI was performed followed by euthanasia and harvesting of the liver.

Results (Figure 3 and 4):

Following precise infusion, the magnetocapsules were clearly visualized as magnetic susceptibility-induced hypointensities that represented the distribution of the capsules within the entire liver and were trackable with standard clinical MRI scanners. Follow-up MR imaging at 4 and 8 weeks post-transplantation demonstrated no changes in MR appearance of the capsules. Magnetocapsules were intact at all imagng follow-up endpoints without disruption or change in distribution. The portal pressures were stable during the four-week period. All blood work was within the normal range of values at baseline and at all time points at follow-up. Human C-peptide levels were present in swine after eight weeks (Figure 4A) confirming the functional status of the transplant graft. Histological correlation confirmed the distribution of the MCs as seen with MRI without hepatic ischemia and a normal patent portal vein.

Conclusion:

To the best of our knowledge, this is the first direct vascular transplantation of microencapsulated islets via portal infusion in swine, an animal whose larger vasculature more closely resembles that of humans. Here we have shown the ability to effectively deliver and image magnetoencapsulated human islets in swine with a low rate of complications completely under MR guidance. In addition, we have demonstrated for the first time that magnetocapsules containing islets are intact and functioning at two-month follow-up without any immunosuppresion. These findings are directly applicable to ongoing improvements in islet cell transplantation for human diabetes.

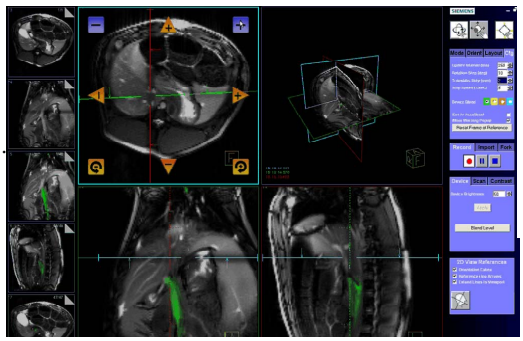
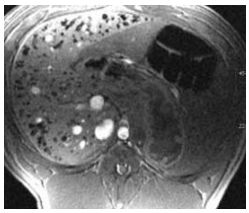


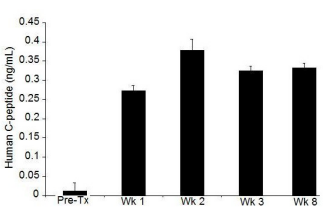
Figure 2: Interventional Front End real time MR flouroscopy (IFE + IRTTT, Siemens) to guide transcaval punctures of the portal vein for islet cell transplantation.

3A

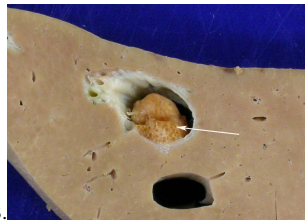


B.

Figure 3: A. MRA after MR guided puncture of the portal vein. Curve arrow= active needle, straight arrow=portal vein displaced. B: Axial T1 post contrast MRI of the liver shows encapsulated Islet cells as small areas of signal void.



4A.



B.

Figure 4: A: Followup up at 8 weeks demonstrate the secretion of human c-peptide levels confirming the viability of islet cells. B. Histological correlation with low-power section of liver show the distribution of magnetocapsules in the portal vein (white arrow) that correspond to MR imaging

References: 1) Ault A. The Lancet. 361, 2054, 2003. 2) Lim F et al., Science. 210, 908-910, 1980. 3) Barnett et al. Nat Med 13, 986-991, 2007 4) Frank JA et al. Radiology 228, 480, 2003. 5) H. Kalish et al., Magn.