Magnetic Resonance Delivery and Monitoring of Empty MR Visible Capsules: Long Term Follow-up

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Introduction: Cell microencapsulation provides immuno-protection in which individual cells are surrounded with a thin shell that is impermeable to antibodies but is permeable to small molecules. We have previously described the synthesis of MR visible microcapsules capable of containing islets (magnetocapsules)[1]. However, basic questions for long-term implantation of a clinical dose of magnetocapsules (140,000) into the portal vein first need to be addressed. Therefore, in this survival study, five swine underwent MR guided transplantation with 140,000 empty magnetocapsules as a first step towards the goal of delivering encapsulated cells as therapy. Long-term effects on the liver and magnetocapsules were assessed in a one-month survival study.

Method:

Synthesis of magnetocapsules

The synthesis of MCs is based on a one-step modification (i.e., Feridex addition) of the original alginate capsule method of Lim and Sun1. The modification also involves the use of an electrostatic (van de Graaff) droplet generator, which produces smaller, stronger, and more uniform capsules compared to the older air-jet technique. This solution was passed through a needle at a flow rate of about 200 ml/min using a nanoinjector pump. Droplets surrounded by the first layer of alginate, were collected in a Petri dish containing 100 mM CaCl2, buffered with 10 mM HEPES, and then washed three times in saline. The gelled droplets were then suspended in 0.05% poly-L-lysine (Sigma, Mw=22-24 kDa) for 5 min to cross-link the alginate and Feridex. The droplets were washed with 0.9% saline and resuspended in 0.15% Keltone HVCR alginate (Monsanto) for 5 min, and then finally washed with 0.9% saline.

MR Guided Delivery of Magnetocapsules

Survival experiments were performed on five healthy swine (40-45 kg) that were sedated with 1 ml/50 lbs of telazol/ketamine/xylazine (100/10/100 mg/ml) followed by general anesthesia. Percutaneous access into the right femoral vein was achieved with an 11-French sheath. All animals were transported to the MR suite for the remaining portion of the procedure. In vivo imaging was performed on a 1.5 T MR scanner (Espree, Siemens) using a 6-channel body phased-array coil and a real-time, steady state free precession sequence (TE/TR=1.2/3.4 ms, FA=45º, receiver BW=125 kHz, slice thickness=7 mm, FOV=30x30 cm, and matrix=128x128). The intravascular puncture of the portal vein was performed using a custom-built, MR-trackable needle. Using a real-time sequence (iRTTT, Siemens) in combination with an interactive scan plane control (IFE, Siemens), three simultaneous orthogonal planes (axial, sagital and oblique axial) were acquired to identify the proper trajectory to puncture the portal vein from the inferior vena cava. Prior to and following the puncture procedure, a contrast-enhanced MR angiogram (MRA) of the mesenteric venous system was obtained after injection of 30 ml gadopentate dimeglumine.

Survival Evaluation

In five swine, 140,000 empty capsules were injected into the portal vein from this transcaval approach. MR imaging of the capsules at baseline and follow-up was performed using a breathhold 3D gradient echo (GRE) sequence. The imaging parameters were TR=12.8 ms, TE=6.3 ms, flip angle=15^{O}, FOV=28 cm, matrix-512x512, slice thickness=1 mm. MR data processing was performed using Amira 3.1 software (Mercury Computer Systems). Portal pressures were obtained at baseline, immediately post procedure at 1 minute, 30 minutes and four weeks after transplantation. In addition, liver function tests (bilirubin, albumin, alkaline phosphatase, Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT) and platelet count) were obtained at baseline and every week up to four weeks. At the end of four weeks, repeat MRI/MRA of the liver was performed as well as direct portal venograms and portal pressures.

Results:

All animals survived the procedure and were followed for 4 weeks after delivery of 140,000 magnetocapsules. Following precise infusion, the magnetocapsules were clearly visualized as magnetic susceptibility-induced hypointensities that represented the distribution of the capsules within the entire liver. When administered in the main portal vein, the magnetocapsule distribution was predominantly in the periphery of the liver with central sparing, which correlated with normal vascular flow patterns in the portal vein (Figure 1). Follow-up MR imaging performed at 4 weeks post-transplantation demonstrated no changes in MR appearance of the capsules. Magnetocapsules were intact at four-week follow-up without disruption or change in distribution. The portal pressures were stable during the four-week period. Although there was a transient rise in portal pressure at 1 min and 30 minutes after the procedure, at four-week follow-up, there was no elevation of portal pressures and no evidence of portal hypertension. Figure 2 shows the changes in portal pressures before, immediately at 1 min, 30 min post procedure and at four week follow up. All blood work was within the normal range of values at baseline and at all time points at follow-up (Figure 3).

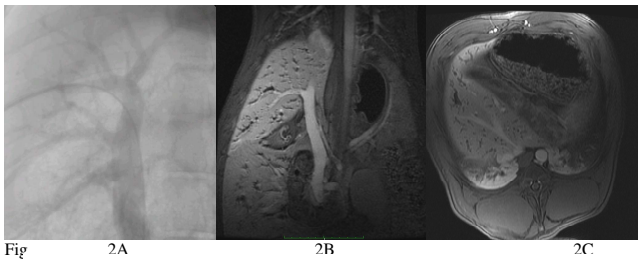

Figure 1: A) Direct portal venogram performed from a transhepatic approach. B) Magnetic Resonance Venogram (MRV) with a coronal view that corresponds to the portal vein in figure 2A. C) Axial view shows capsules in the liver parenchyma.

Conclusion

MR visible magnetocapsules can be tracked using conventional clinical MRI to monitor cellular therapies delivered into the liver. The delivery of the magnetospheres did not affect portal pressures or liver function tests at 4 weeks post delivery.

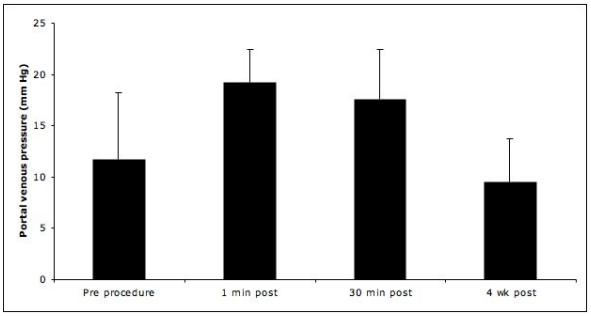

Figure 2: Mean portal venous pressure: pre procedure, 1 min and 30 mins post procedure, and at a four week followup.

	Total Bilirubin	Alkaline Phospate	ALT	AST
Day 0	0.2	145.6	28.8	43.2
Day 7	0.2	104.2	41.2	43.2
Day 14	0.1	88.0	38.2	33.8
Day 21	0.1	134.0	50.2	60.4
Day 28	0.2	114.6	52.0	43.8
Normal	0-1.0	118-395	31-58	32-84

Figure 3: The mean values for liver function tests at baseline and follow-up (n=5). Normal values are listed also for reference.

References: 1) Barnett et al. Nat Med 13, 986-991, 2007. 2) Lim F et al., Science. 210, 908-910, 1980.