MR-guided Portal Vein Delivery and Monitoring of Magnetocapsules: Assessment of Physiologic Effects on the Liver

Thomas W. Link, MS, David Woodrum, MD, Wesley D. Gilson, PhD, Li Pan, PhD, Di Qian, MS, Dara L. Kraitchman, VMD, PhD, Jeff W.M. Bulte, PhD, Aravind Arepally, MD, and Clifford R. Weiss, MD

ABSTRACT

Purpose: The authors previously developed magnetic resonance (MR)–trackable magnetocapsules (MCs) that can simultaneously immunoprotect human islet cells and noninvasively monitor portal delivery and engraftment in real time with MR imaging. This study was designed to assess the physiologic effects of the delivery of a clinical dose of MCs (140,000 capsules) into the portal vein (PV) in swine over a 1-month period.

Materials and Methods: MCs were formed by using clinical-grade alginate mixed with a clinically applicable dosage of ferumoxide. Percutaneous access into the PV was obtained by using a custom-built, MR-trackable needle, and 140,000 MCs were delivered under MR guidance in five swine. Portal pressures and liver function data were obtained over a 4-week period.

Results: A transient increase in portal pressure occurred immediately after MC delivery that returned to normal levels by 4 weeks after MC delivery. Liver function test results were normal during the entire period, and the appearance of the MCs on MR imaging did not change.

Conclusions: A clinically applicable dose of 140,000 MCs has no adverse effects on portal pressures or liver function in this normal swine model during the first month after delivery.

ABBREVIATIONS

MC = magnetocapsule, PV = portal vein

Islet cell transplantation is an attractive treatment for patients with type 1 diabetes mellitus, but success has been limited, partially as a result of cytotoxic immunosuppressive regimens (1–4). To avoid immunosuppressive therapy, microencapsulation has been proposed as a method of protecting transplanted cells from the immune system. By surrounding individual islets with thin semiporous alginate membranes that are permeable to insulin and metabolites but impermeable to antibodies, microencapsulation provides a way to immunoisolate cells while preserving cell function and integrity.

Delivery and placement of these microcapsules remains an important unresolved issue in their use for cell therapy. Currently, injection under fluoroscopic guidance into the liver via the portal vein (PV) is thought to be the optimal means for transplantation because of a high nutrient

From the Departments of Biomedical Engineering (T.W.L., J.W.M.B.) and Interventional Radiology (A.A., C.R.W.), Division of Magnetic Resonance Research, Russell H. Morgan Department of Radiology and Radiological Science (T.W.L., W.D.G., L.P., D.Q., D.L.K., J.W.M.B., A.A., C.R.W.), Cellular Imaging Section and Vascular Biology Program, Institute for Cell Engineering (T.W.L., J.W.M.B.), and Department of Chemical and Biomolecular Engineering (J.W.M.B.), Johns Hopkins University School of Medicine; Center for Applied Medical Imaging (W.D.G., L.P.), Siemens Corporate Research, Baltimore, Maryland; and Department of Radiology (D.W.), Mayo Clinic, Rochester, Minnesota. Received November 25, 2010; final revision received March 11, 2011; accepted March 15, 2011. **Address correspondence to** A.A., Department of Interventional Radiology, Mayo Clinic, 1984 Peachtree Rd. NW, Suite 505, Atlanta, GA 30309; E-mail: aarepal@gmail.com

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A.A. and C.R.W. contributed equally to this manuscript.

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and oxygen supply (5,6). Although delivery into the liver through PV access has shown some success in sustaining cell function (5,6), further improvement is needed. Specifically, assessment of the accuracy of delivery and extent of engraftment of microencapsulated cells is needed to correlate long-term islet function with anatomic location and route of delivery (7). This assessment would be possible if the microencapsulated cells could be visualized during and after delivery.

Magnetic resonance (MR) imaging can provide this visualization sensitivity as a result of its excellent soft-tissue contrast, high resolution, and whole-body imaging capability; moreover, MR imaging has been used to reliably track magnetically labeled cells in animal models as well as in patients (8). We have previously developed magnetocapsules (MCs) that are trackable by MR imaging and capable of sustaining viable islets for at least 1 month (9). These trackable MCs provide a powerful method to monitor the delivery of encapsulated islets and examine their stability over time. However, before MCs can be adopted for clinical use, the effect of MCs on portal pressure and liver function must be ascertained. To determine whether intraportal delivery of MCs is a viable option for treatment of patients with type 1 diabetes mellitus, we evaluated portal pressures and performed several liver function tests over the course of 1 month after delivery in an animal model.

MATERIALS AND METHODS

Synthesis of MCs

The synthesis of MCs was based on a one-step modification of the original alginate encapsulation method of Lim and Sun (10), and has been described in detail elsewhere (9,11). Briefly, Feridex, a commercial-brand superparamagnetic iron oxide nanoparticle, was mixed with ultrapure alginate to produce an alginate solution that is 20% Feridex by volume. By using a high-voltage power supply and a nano-injector pump, gel droplets were formed and crosslinked with 0.05% poly-L-lysine, following which a second layer of alginate was added.

Animal Model

The study was approved by the appropriate institutional animal care and use committee. Five healthy swine (40–45 kg) were sedated with an intramuscular injection of a mixture of ketamine (22 mg/kg), acepromazine (1.1 mg/kg), and atropine (0.05 mg/kg). An intravenous catheter was placed in the marginal ear vein and the animal was induced with sodium thiopental (20 mg/kg body weight), intubated, and mechanically ventilated with 1%–2% isoflurane. A single dose of intramuscular penicillin G (Dual-Cillin, 300,000 U/mL) was administered before vascular access was obtained.

MR-guided Delivery of MCs

Percutaneous access into the right femoral vein was achieved with an 11-F sheath (St. Jude Medical, St. Paul, Minnesota). All animals were then transferred to the MR suite for the remaining portion of the procedure. All procedures were performed in a 1.5-T MR scanner (MAGNETOM Espree, Siemens, Erlangen, Germany). Imaging was acquired by using a combination of external phased-array coils and a custom-made active intravascular needle, as described previously (9,12–14). The needle was introduced into the venous system via the right femoral vein through the previously placed 11-F sheath. By using an interactive real-time TrueFISP sequence (BEAT_IRTTT; Siemens) in combination with the Interactive Front End graphical interface (Siemens), which enables interactive scan plane manipulation, three simultaneous imaging planes (axial, sagittal, and oblique axial) were imaged to track the needle and identify the proper trajectory for PV puncture from the inferior vena cava (**Fig 1**). The imaging parameters were a 1.7-ms echo time, 3.4-ms repetition time, 45° flip angle, bandwidth of 977 Hz/pixel, 7-mm slice thickness, 300-mm field of view, and 128 × 128 image matrix. Before and after the puncture procedure, a contrast-enhanced MR angiogram of the mesenteric venous system was obtained after injection of 30 mL gadopentetate dimeglumine (Magnevist; Bayer, Leverkusen, Germany) in the marginal ear vein. After directed puncture into the PV, the needle system was advanced over a 0.035-inch Rosen wire (Cook, Bloomington, Indiana) further into the portal system for stability during MC delivery. A total of 140,000 MCs in a volume of approximately 100 mL was infused into the PV over a period of approximately 10 minutes with this transcaval approach. With one islet per MC, 140,000 MCs represents a "clinically relevant dose" for an animal of this weight according to the Edmonton protocol (2).

Follow-up Evaluation

MR imaging of swine at baseline and at follow-up was performed by using a six-element body matrix phased-array coil in combination with 12 elements of the integrated spine array and a breath-hold, three-dimensional gradient echo sequence. The imaging parameters were a 4.99-ms repetition time, 2.32-ms echo time, 72 slices, 320-mm field of view, flip angle of 10°, matrix of 256 × 256, receiver bandwidth of 360 Hz/pixel, time of acquisition of 29 seconds, and three-dimensional voxel size of 1.3 × 1.3 × 2.5 mm. MR data were analyzed by using Amira 3.1 software (Mercury Computer Systems, Berlin, Germany). Portal venograms were obtained before and after delivery of MCs as well as at the 4-week follow-up. Direct portal pressures were measured with a pressure transducer attached to a 5-F pigtail catheter (Cook) at baseline and at 1 minute, 30 minutes, and 4 weeks after MC delivery. In addition, hematologic liver function markers such as bilirubin, albumin, alkaline phosphatase, aspartate aminotransferase, alanine