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Ferumoxytol-Enhanced Magnetic Resonance Imaging in Late-Stage CKD

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Abstract

Ferumoxytol is a superparamagnetic iron oxide particle encapsulated by a semisynthetic carbohydrate with properties that can be utilized by the nephrologist for diagnosis and therapy. Ferumoxytol is approved by the United States Food and Drug Administration (FDA) for treating iron deficiency anemia in the setting of chronic kidney disease (CKD) but not for clinical diagnostic imaging. It has gained appeal as a magnetic resonance imaging (MRI) contrast agent in patients with an estimated glomerular filtration rate <30 mL/min/1.73 m² in whom gadolinium-based contrast MRI agents are relatively contraindicated in patients because of the association with gadolinium deposition and nephrogenic systemic fibrosis (NSF). Ferumoxytol metabolism is not dependent on kidney function, but rather is removed from the circulation by the reticuloendothelial system of the liver, spleen, and bone marrow. Additionally, the prolonged intravascular half-life (>14 hrs) of ferumoxytol allows for longer image acquisition and repeat imaging, if necessary. In patients with contraindications for gadolinium contrast agents, ferumoxytol is an alternative agent for vascular assessment including patency and course.

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Keywords

ferumoxytol; renal failure; chronic kidney disease (CKD); magnetic resonance imaging (MRI); magnetic resonance angiography (MRA); ultra-small superparamagnetic iron oxide (USPIO); contrast agent

Introduction

Ferumoxytol was initially evaluated as a contrast agent in 2003 for use in clinical radiology.¹ Interest in ferumoxytol as a therapeutic agent for the treatment of iron deficiency anemia, however, eclipsed its use as a MRI contrast agent. Over the last decade, the identification of the association of NSF with gadolinium administration to patients with advanced kidney disease has led to a renewed interest in ferumoxytol as a contrast agent due to its superparamagnetic properties.²⁻⁴ Based on NHANES (National Health and Nutrition Examination Survey) data, an estimated 0.3% of the United States population is living with CKD stage 4⁵, equivalent to 820,000 people according to the 2000 US census⁶. An additional 620,000 patients receive renal replacement therapy. Use of conventional contrast agents, both iodinated or gadolinium-based, in these patient populations are limited by the risks of additional acute kidney injury and nephrogenic systemic fibrosis (NSF), respectively, that must be balanced by the critical nature of the radiologic study for the well-being of the patient.

Case Report

Clinical History and Initial Laboratory Data

A 27-year-old woman with CKD stage 4 was referred for pre-emptive transplant evaluation. Prior contrast study demonstrated occluded inferior vena cava (IVC), without anatomic description of vein patency, due to anomalous pulmonary vein repair at 2 months of age. For feasibility assessment of allograft anastomosis to iliac vessels, a contrast study was necessary. Given CKD, a ferumoxytol-enhanced MRI protocol was proposed. The patient had not received ferumoxytol in the past and had no known history of iron overload. She had no history of anaphylactic reactions to any other intravenous iron formulations. Laboratory data revealed an estimated glomerular filtration rate (eGFR) 17 ml/min/1.73 m² (as calculated by the 6-variable MDRD [Modification of Diet in Renal Disease] Study equation⁷), hemoglobin 14.7 g/dL, iron 106 µg/dL, total iron-binding capacity (TIBC) 230 µg/dL, transferrin saturation ratio 46%, ferritin 50 µg/L, aspartate aminotransferase (AST) 19 units/L, and alanine aminotransferase (ALT) 19 units/L.

Imaging Studies

The referring nephrologist was contacted and agreeable to the proposed imaging protocol. Pre-imaging consent was obtained from the patient for the contrast MRI study. The hospital radiology team crafted an infusion protocol that would provide maximum resolution with the least likelihood for adverse side effect. The patient was pre-medicated (50 mg of diphenhydramine and 25 mg of ranitidine orally) 30 minutes before infusion. Over a 15 minute period, 250 mg of ferumoxytol re-suspended in normal saline (total volume of 100

mL) was infused. During infusion, the patient experienced mild burning sensation at the infusion site. Images were acquired while the patient remained supine in the 3T electromagnetic coil for 45 minutes (Figure 1). The patient remained in the MRI holding suite one hour after the exam. The mild burning sensation resolved, and the patient was discharged.

Diagnosis

Iliac vein patency was identified on the right with prominent atresia on the left. Compensatory lumbar and gonadal vein dilation was present bilaterally with no identifiable right renal vein or infra-renal IVC. Based on imaging results, the patient's anatomy was deemed adequate for transplantation.

Clinical Follow-up

No further reactions associated with ferumoxytol infusion were identified after 1 month follow-up assessment. The patient was medically and surgically cleared as a transplant candidate.

Discussion

Knowledge of vascular anatomy is essential for optimal management of the kidney transplant candidate. Numerous studies have examined the diagnostic accuracy of ultrasonography as well as computed tomography angiography (CTA), magnetic resonance angiography (MRA), and conventional catheter-based x-ray angiography in the assessment of vasculature.^{8–11} Depending on operator experience, patient habitus, and targeted organ, ultrasound is a potential initial investigative imaging modality. Given multi-planar capabilities (often necessary in the evaluation of stenoses), CTA or MRA is frequently utilized. Both of these techniques provide exceptional anatomic delineation of structures, with less dependence on operators and patient size (Figure 2). Conventional angiography is usually reserved for use in the setting of indeterminate CTA/MRA results, possible endovascular intervention, or for targeted angiography when it is possible to use lower volumes of iodine based contrast in CKD patients. While rapid in image acquisition, CTA involves exposure to ionizing radiation and potential nephrotoxicity due to iodine-based contrast exposure. Conventional catheter-based angiography shares both of these issues, and has limited soft tissue delineation. Also, catheter angiography is an invasive procedure with potential complications arising from sedation and vascular or soft-tissue injury. Current practice limits the use of iodinated contrast in patients with CKD stage 4 or 5, requiring delay of contrast administration until the initiation of dialysis. However, contrast administration is further delayed in patients receiving maintenance hemodialysis in the setting of iodinated contrast agents due to the potential risk of accelerating a decline in residual kidney function.^{12–14} As an alternative, magnetic resonance angiography and imaging allows for morphologic assessment of vascular and non-vascular structures. Non-contrast enhanced MRA (e.g. time-of-flight or phase-contrast techniques) allows visualization of smaller arteries such as the Circle-of-Willis branches. When possible, contrast-enhanced MRA is usually preferred for assessment of larger vascular structures and branch-points, where highflow and turbulence may cause artifacts.¹⁵

Given the availability of superparamagnetic iron oxide, ferumoxytol-enhanced MRA avoids the risk of NSF, which has been associated with the administration of gadolinium-based contrast agents. The classic diagnostic findings for NSF include brawny skin hyperpigmentation, thickening, and contractures with skin biopsy containing phagocytosed gadolinium.¹⁶ Recently, the risk of NSF with the gadolinium-based agent gadobenate dimeglumine in CKD patients has been brought into question.¹⁷ Soulez and colleagues followed 542 CKD patients who underwent contrasted MRI studies. Over 2 years, no patient developed NSF. Despite these results, 26.1% of patients in this study were not available for evaluation after two years with mortality of 9.5% after one year and 3.4% after two years. It is also noteworthy that 20% of cases reported in the literature are associated with gadopentetate dimeglumine, which contains a linear ionic ligand similar to one of the studied agents, gadobenate dimeglumine.

The risk of NSF among patients with CKD undergoing gadolinium-enhanced MRA is typically estimated to be between 2 to 5%, although there are estimates as high as 18%.^{18–20} In 2007, Todd and colleagues evaluated 186 consecutive patients receiving hemodialysis. 25 patients (13%) had NSF based on a standardized physical exam. The incidence in the general population not screened for kidney disease was estimated to be between 0.003% and 0.039% among a group of 217,607 patients undergoing MRI with gadolinium-based contrast enhancement.²¹

In addition to eliminating the risk of NSF, much of the value of ferumoxytol as a vascular contrast agent centers on its prolonged presence in the intravascular space in comparison to most conventional contrast agents.^{22,23} This characteristic facilitates the use of slower, high-resolution MRA techniques that are particularly successful in imaging vascular structures in body segments that have limited motion such as the brain, abdomen, and extremities.²⁴ Pulmonary vasculature is more challenging, but may be interrogated for large pulmonary emboli.

Ferumoxytol-enhanced cardiac MRI is a theoretical option for patients with CKD stages 4 and 5 given the blood pool characteristics of the agent. The burden of cardiac disease among patients with CKD is well-recognized.^{25,26} There is heightened concern in those with CKD stage 4 and 5 often listed on the deceased-donor kidney transplant waitlist.^{27,28} In our institution and others, ferumoxytol-enhanced MRI can identify patency of the proximal right coronary artery more consistently than the left coronary artery (Figure 3).²⁴ The primary limitation is cardiac motion artifact, which is more pronounced in regions progressively distal from the origins of the right and left coronary arteries. Motion artifact can be reduced through the use of respiratory and EKG dual gating, which increases the acquisition time for the study. This has less impact when using a blood pool agent like ferumoxytol than when using more conventional gadolinium-based contrast agents.

Ferumoxytol recently received an FDA boxed warning in March 2015 to alert physicians of the potential for hypersensitivity reaction including anaphylaxis.²⁹ As a result, providers have proactively slowed the infusion of Ferumoxytol in the treatment of iron deficiency anemia. Previously, manufacturer recommendations allowed a rapid infusion rate (510 mg dose administered over 17 seconds). In MRI, a slower infusion rate limits hemodynamic

information as both arteries and veins contain contrast at time of imaging. Assessment is then based on knowledge of origin and distribution of vascular beds. However, dynamic information is obtainable depending on timing of image acquisition and injection rates.¹¹ Although ferumoxytol has not been approved by the FDA as a contrast agent for clinical diagnostic imaging other investigators have shown safety and utility in its use in pediatric patients with CKD.³⁰ Research continues on the use of lower ferumoxytol-enhanced MRI doses, patient safety, and image quality.

In this case, a contrast vascular study was necessary, and ferumoxytol-enhanced MRI provided critical information to proceed with kidney transplantation. The study delineated extensive collateralization with the gonadal veins as a potential alternative venous anastomotic site. Ferumoxytol-based vascular imaging has the potential to offer a practical solution to both gadolinium-based and iodinated contrast agents when assessing vessel patency.

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Figure 1.

Ferumoxytol-enhanced magnetic resonance imaging for kidney transplant evaluation. (A) 3D reconstruction of venous circulation in the patient described in the text, a 27-year-old woman with thrombosis of the inferior vena cava (IVC) during infancy. Cavernization of collateral veins including the gonadal veins and paralumbar veins is present to compensate for a thrombosed IVC (†). Left iliac vein (*) is atretic with reduced venous blood flow in the left paralumbar vein. Right kidney shows no venous outflow, with all kidney function provided by the left kidney. (B) Axial cross section at the level of L5 (gray planar slice in panel A) with confirmation of patency of the right external iliac vein and right internal iliac vein.

Figure 2. Gadopentetate dimeglumine-enhanced magnetic resonance imaging in individuals without (A) and with (B) a kidney transplant. (A, left image) 3D reconstruction of MRA during arterial phase of scanning protocol. (A, right image) Short-axis axial cross section showing patency of the bilateral internal and external iliac arteries. (B, left image) 3D reconstruction of the arterial and venous circulation with a viable kidney transplant. (B, right image) Short-axis cross section showing patency of the external iliac artery, external iliac vein, internal iliac artery, and internal iliac vein bilaterally.

Figure 3.

Ferumoxytol-enhanced magnetic resonance imaging of the coronary circulation in a patient on hemodialysis being evaluated for kidney transplantation. (A) From left to right, images show right coronary artery origin, proximal portion, and mid-segment. Arrows denote path of right coronary artery. (B) Clockwise from left, images show left coronary artery circumflex (solid arrow) and left anterior descending (dashed arrow); left main (solid arrow); and left anterior descending (dashed arrow) and left circumflex (solid arrow). Abbreviations: RA, right atria; RV, right ventricle; LA, left atria; LV, left ventricle; A, aorta; Ar, aortic root.