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Ferumoxytol-Enhanced Magnetic Resonance Angiography is a Feasible Method for the Clinical Evaluation of Lower Extremity Arterial Disease

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Abstract

Background: Renal toxicity from conventional, iodinated, intravenous contrast agents is a common complication in patients with peripheral artery disease (PAD). Similarly, the potential for serious side effects prevents the use of gadolinium-based agents in many patients with depressed renal function. Ferumoxytol-enhanced magnetic resonance angiography (Fe-MRA) is a novel technique that uses an intravenous, ultrasmall, superparamagnetic, iron oxide preparation, currently approved by the Food and Drug Administration for the treatment of iron deficiency anemia in adults with chronic kidney disease. Our objective was to determine the feasibility of Fe-MRA for clinical decision making in PAD patients.

Methods: This was a prospective pilot study assessing 10 patients with suspected arterial occlusive disease with contrast-enhanced MRA of the aorta and lower extremities. Of those, 5 had renal insufficiency and were imaged with Fe-MRA, whereas the remainder underwent gadolinium-enhanced MRA. Qualitative and quantitative evaluations of deidentified images at each arterial station were independently performed by 4 blinded vascular surgeons.

Results: All patients were men, with an average age of 68 ± 4 years. The 2 groups had similar incidences of diabetes, hypertension, hyperlipidemia, and coronary artery disease. Patients undergoing Fe-MRA had significantly decreased renal function (estimated glomerular filtration rate, 35.4 vs. 77.6; $P = 0.02$). There were no adverse events during contrast administration in either group. No difference was found in the overall quality of the ferumoxytol versus the gadolinium studies (7.1 ± 2.0 vs. 7.4 ± 2.4, $P = 0.67$). Similarly, reviewers felt comfortable basing clinical decisions on the images 89% of the time with both the ferumoxytol and gadolinium groups ($P = 1.00$).

Conclusions: This is the first report of an important alternative to conventional computed tomography angiography and MRA in PAD patients, particularly in the setting of renal insufficiency. Fe-MRA provides a useful tool in patients with suspected lower extremity PAD without the potential risks of gadolinium.

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INTRODUCTION

Peripheral artery disease (PAD) is a common disorder affecting up to 12 million Americans and 20% of patients in primary care.[1] In advanced cases in which revascularization is planned, noninvasive imaging is often performed with intravenous, iodinated, contrast-enhanced computed tomography (CT) or gadolinium-enhanced magnetic resonance imaging (MRI). However, this patient population has a prevalence of chronic kidney disease (CKD) ranging 29–40%, so contrast-induced nephropathy (CIN) from conventional, iodinated, intravenous contrast agents and nephrogenic systemic fibrosis (NSF) from gadolinium represent a significant concern.[2–7]

Contrast-enhanced magnetic resonance angiography (MRA) using an intravenous, ultrasmall, superparamagnetic iron oxide (USPIO) preparation is a novel technique that appears to be well tolerated and, because the agent is cleared by the reticuloendothelial system, has a good safety profile in patients with renal failure.[8,9] Ferumoxytol (Feraheme; AMAG Pharmaceuticals, Cambridge, MA) is the only commercially available USPIO particle in the United States and was approved in 2009 by the Food and Drug Administration with the specific indication of treating iron-deficient anemia in adults with CKD. The particle size is 17–31 nm in diameter, with a molecular weight of 750 kDa. The chemical formula is $Fe_{5874}O_{8752}$-$C_{11719}H_{18682}O_{9933}Na_{414}$. It is a blood pool agent, with a prolonged circulating half-life of 14–15 hr in the intravascular space. A proprietary polyglucose sorbitol carboxymethyl-lether coating is designed to reduce the immunogenicity of ferumoxytol nanoparticles and make them isotonic. These unique characteristics make the agent suitable for a bolus injection; thus, a high dose (510 mg of iron) can be administered rapidly,[10] making ferumoxytol a good first-pass MRA contrast agent. Our objective was to determine the safety and feasibility of lower extremity ferumoxytol-enhanced MRA (Fe-MRA) for clinical decision making in PAD patients.

MATERIALS AND METHODS

Study Population

The study population consisted of 10 patients from the San Francisco Veteran's Affair Hospital outpatient vascular surgery clinic. MRA studies of the aorta and lower extremities were performed to identify suspected arterial occlusive disease. Patients were recruited to this study using an institutional review board–approved protocol. Of these, 5 consecutive patients with renal insufficiency underwent Fe-MRA between May 7, 2012, and September 8, 2012. Another 5 consecutive patients underwent gadolinium-enhanced MRA (Gd-MRA) using gadodiamide (Omniscan; GE Healthcare, Little Chalfont, United Kingdom) between February 4, 2013, and September 7, 2013. Electronic medical records were used to compile patient's baseline demographics, comorbidities, and indications for imaging.

MRA Contrast Administration

Ferritin levels were checked on all patients receiving ferumoxytol before administration to avoid iron overload. A serum ferritin of 600 ng/mL was used as the maximum acceptable cutoff level for ferumoxytol administration. Ferumoxytol was diluted in the ratio of 1:4 with

sterile saline immediately before use and administered in 2 steps. Contrast agent was injected through an intravenous catheter in the antecubital fossa using a power injector (Spectris Solaris; Medrad, Indianola, PA) at a rate of 2 mL/sec followed by a saline flush. For both Gd- and Fe-MRA, a timing run was performed using a 2-mL contrast agent test bolus followed by a 20-mL saline flush. Both contrast and saline were injected at 2 mL/sec. Low–spatial resolution, three-dimensional, coronal volumes were acquired at 1-sec intervals starting simultaneously with contrast injection. The transit time from injection site to abdominal aorta was defined as the time of acquisition of the image when contrast enhancement was first noted. Each MRA runoff study then used 40 mL of contrast agent injected at 2 mL/sec followed by a 20-mL saline flush, also at 2 mL/sec with image acquisition delayed to start with arrival of the contrast at the aorta. The dose of ferumoxytol represented 0.06 mmol/L of elemental iron per kilogram of body weight for a 70-kg patient. Patients were observed for signs and symptoms of hypersensitivity during and after ferumoxytol administration for at least 30 min to ensure clinical stability.

Magnetic Resonance Imaging

All magnetic resonance (MR) images were obtained on a 3T MR unit (Skyra; Siemens Medical Systems, Erlangen, Germany). The images were obtained using a standard MRI protocol, which is used for all lower extremity vascular imaging studies across different institutions. Images were acquired at 3 stations: the abdomen, the thighs, and the calves with overlapping paracoronal slabs, with 72 slices/slab. Phased-array coils were used over the abdomen and legs, with breath holding in the abdominal station. Mask and subtraction images were acquired for each station, with acquisition parameters of repetition time/echo time, 3.14 msec/1.04 msec; flip angle, 25°; interpolated voxel resolution, $1.7 \times 1.2 \times 1.5$ mm^3 (abdominal and thigh stations) and $1.5 \times 1.1 \times 1.4$ mm^3 (calf station); acquisition times, 11 sec (abdomen), 11 sec (thigh), and 14 sec (calf); generalized autocalibrating partially parallel acquisition acceleration factor of 2; and elliptic centric *k*-space ordering.

Image Analysis

Qualitative and semiquantitative evaluations of deidentified images at each of 4 arterial stations (iliac, femoral, popliteal, and tibials) were independently performed by 4 blinded vascular surgeons. All examinations were presented to the readers in random order on a Web-based picture archiving and communication system (details). All images were evaluated with regard to image quality and stenosis grade. Images at each arterial station were assigned a score for the quality of the images using an ordinal score: 1, very good; 2, good; 3, sufficient; and 4, nondiagnostic. In addition, reviewers recorded an estimation of the highest stenosis at that arterial station: 1, no stenosis; 2, ≤50%; 3, 51–70%; 4, 71–99%; and 5, occluded. Finally, the reviewers were asked if they would base their clinical decision on this study. An answer in the affirmative meant that the surgeons would be willing to base a potential intervention of the MRA in question without the need for further imaging. The evaluation of these images was made on the basis of maximum intensity projection reconstructions and source images in the native paracoronal plane and axial reformats. The severity of stenosis was determined by comparing the stenosis diameter with the luminal diameter at an adjacent normal arterial segment. In case of the presence of multiple stenoses

within 1 arterial segment, we presumed that the lesion with the highest stenosis grade was the one with the greatest hemodynamic effect.

Statistical Analysis

Data are expressed as mean ± standard deviation. Student's *t*-tests, chi-squared tests, and Fischer's exact tests were used when appropriate. A *P* value of less than 0.05 was considered to be significant. All statistical analysis and tests were performed with Stata version 13.0 (StataCorp, College Station, TX).

RESULTS

No adverse events occurred in the study. All study examinations were completed and evaluated. All patients were men with an average age of 68 ± 4 years. The 2 groups had similar incidences of diabetes, hypertension, hyperlipidemia, and coronary artery disease (Table I). Patients undergoing Fe-MRA had significantly decreased renal function (estimated glomerular filtration rate [eGFR], 35.4 vs. 77.6; $P = 0.02$). The Fe-MRA group had critical limb ischemia as their indication for imaging with 3 of 5 having nonhealing wounds as an indication; whereas in the Gd-MRA group, all had claudication as the main indication for their study ($P = 0.167$; Table II).

No difference was found in the overall quality of the ferumoxytol versus the gadolinium studies (7.1 ± 2.0 vs. 7.4 ± 2.4; $P = 0.67$; Table III; Fig. 1). Gd-MRA quality was found to be significantly better in the tibial station (1.8 ± 0.7 vs. 2.4 ± 0.9, $P = 0.02$). However, Fe-MRA was found to be of significantly better quality in the iliac station (1.2 ± .5 vs. 1.8 ± 1.0; $P = 0.03$). Similarly, readers felt confident using the images to make clinical decisions 89% of the time in both the ferumoxytol and the gadolinium groups ($P = 1.00$).

DISCUSSION

We found that the Fe-MRA images were equivalent to those performed with Gd-MRA, as assessed by 4 experienced vascular surgeons. This pilot study demonstrates the safety and feasibility of a novel technique of contrast-enhanced MRA of the lower extremities for the purpose of clinical decision making in patients with PAD. Both gadolinium and ferumoxytol were well tolerated in this small cohort with no adverse reactions. Identical MRA sequences were used for imaging with both agents, and assessment of the study image quality by 4 vascular surgeons found the 2 techniques to be comparable. Importantly, the 5 patients who underwent Fe-MRA were predicted to be at high risk of contrast-related complications because of their severely depressed renal function (eGFR, 35.4 ± 18.6). No significant change in eGFR was observed after ferumoxytol administration (after Fe-MRA, eGFR; 37.3 ± 22.1). One of the 5 patients was on hemodialysis at the time of the study. However, no new initiation of hemodialysis was observed in the remaining 4 patients.

Typical contrast agents are contraindicated in the setting of acute kidney injury (AKI) or CKD. Specifically, iodinated contrast agents used in CT or traditional angiography carry the risk of CIN and worsening renal function. There is consensus that the most important risk factor for CIN is preexisting renal insufficiency. However, there is no universally agreed on

threshold of degree of renal dysfunction beyond which intravascular iodinated contrast medium should not be administered. We do know that the risk of CIN, and even permanent hemodialysis, is inversely and proportionally related to GFR.[11] Several studies have shown that patients with even transient CIN tend to have longer hospital stays, higher mortality, and higher incidences of cardiac and neurologic events.[12] Gadolinium-based agents used in MRI are not without problem in patients with decreased renal function. They are associated with NSF, a debilitating and sometimes fatal disease involving fibrosis of the skin, musculoskeletal system, and visceral organs.[5,13–15] The risk has been estimated between 1% and 7% among at risk patients. Most patients who develop NSF have severe or end-stage CKD (CKD, 4–5); however, 12–20% of confirmed NSF cases have occurred in patients with AKI, often superimposed on CKD.[16,17] And some cases of NSF have developed in patients with AKI without underlying CKD.[18] The alternative of duplex ultrasound, which avoids the nephrotoxic complications, is an inferior imaging modality as these studies are often difficult to interpret because of patient and technologist factors and does not provide the anatomic detail necessary for clinical decision making.

Iron-based agents are not associated with NSF and appear to have few significant deleterious adverse effects. Because ferumoxytol is an iron-based agent designed specifically for use in patients with advanced CKD, its safety profile in this population is excellent, although the reported rate of serious hypersensitivity reactions such as anaphylaxis is somewhat higher (0.2%) than that associated with gadolinium-based agents such as gadoteridol (0.03%) or gadodiamide (0.01%).[19–21] The agent should be avoided in patients with a known allergy or hypersensitivity to injectable forms of iron or any condition that may result in iron overload (hemochromatosis). Ferritin levels should be checked routinely before ferumoxytol administration to avoid iron overload. Because of its long intravascular half-life, if the initial timing of the contrast bolus misses the arterial phase, venous contamination will preclude repeat imaging. In addition, ferumoxytol is not recommended if tumor surveillance is ongoing, given that images can be confounded for up to 6 months after administration. However, ferumoxytol has the added benefit of clearance by the reticuloendothelial system. It is taken up by macrophages, which can subsequently be imaged by MRI, making it feasible as an inflammation-imaging agent as shown by Hasan et al.[22] Finally, it must be noted that there is a cost differential between gadolinium and ferumoxytol, with ferumoxytol costing several hundred dollars more. Depending on care setting, this may be a major drawback for widespread adoption. As a contrast agent, ferumoxytol causes shortening of the T1 relaxation time and, at certain concentrations, appears similar to gadolinium-based agents on many MRI pulse sequences.[23–25] In addition, Sigovan et al.[26] found that Fe-MRA provided better image quality and reduced flow artifacts compared with noncontrast time-of-flight MRA in dialysis fistula evaluation, with a much shorter acquisition time. In our initial experience, Fe-MRA has demonstrated excellent depiction of the lower extremity vasculature, consistent with Gd-MRA. This is evidenced by the willingness of the vascular surgeons to base clinical decisions on these images at an identical rate. This was true despite the fact that several of the patients in the ferumoxytol group had more severe clinical disease than the patients in the gadolinium group. Comparing image quality in an MR runoff study across nonmatched individuals is impacted by a combination of technological factors such as the contrast agent and patient physiology. The 3 patients with nonhealing wounds had lower

qualitative scores for the tibial arterial station, which lowered the apparent quality for ferumoxytol studies at that station. Gadolinium's seemingly better performance at this station may have just been an indication of less-severe disease here relative to the other group. Our study is limited by the small single-center nature. The small numbers reflect the purpose of this study, which was only intended as a pilot study to prove that ferumoxytol is a feasible option in lower extremity imaging of patients who do not have the option of a gadolinium study. Furthermore, our results suggest that the results between Fe-MRI and Gd-MRI are comparable. In addition, our images were not compared with the "gold-standard" of catheter-based angiography to determine the sensitivity and specificity. However, this was not possible given the clinical scenario of our patients. Nevertheless, this study demonstrates that Fe-MRA is a viable approach for evaluating PAD in this population.

CONCLUSIONS

Our results highlight a safe and novel alternative to conventional computed tomography angiography and MRA in PAD patients with CKD. Fe-MRA provides a useful tool in patients with suspected lower extremity PAD without the risk of serious side effects associated with gadolinium or the risk of nephrotoxicity associated with iodinated contrast.

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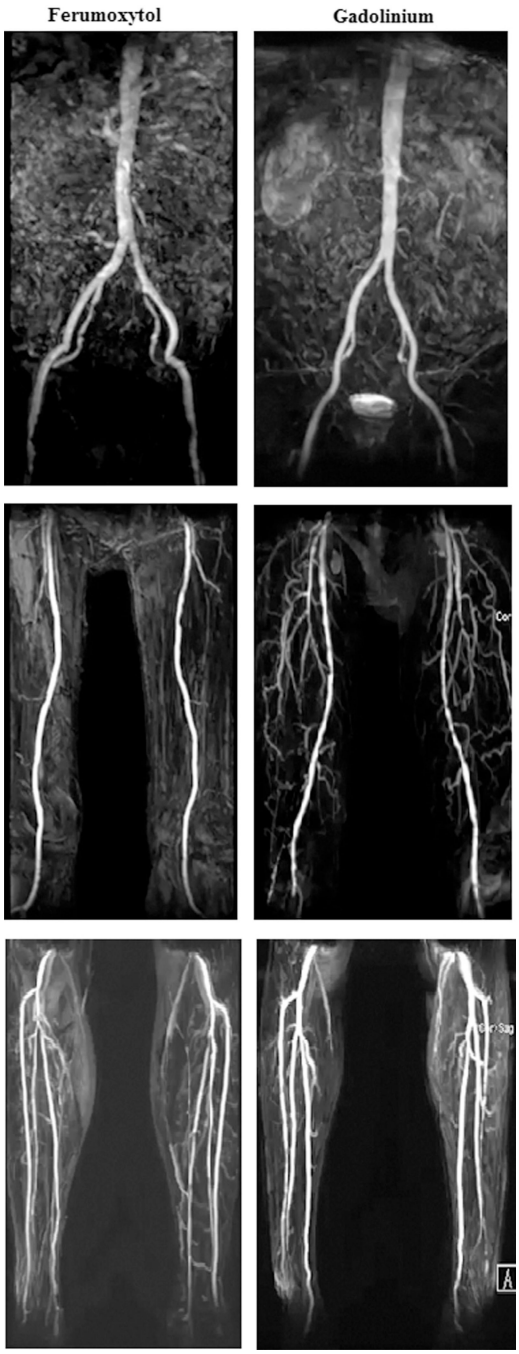

Fig. 1.
Representative patient images.

Table I.

Demographics and baseline laboratory measurements mean ± standard deviation or *n* (%)

Demographics	**Ferumoxytol, *N* = 5**	**Gadolinium, *N* = 5**	***P* value**
Age, years	68.0 ± 6.3	67.8 ± 1.5	NS
Hypertension	4 (80)	4 (80)	NS
Dyslipidemia	4 (80)	4 (80)	NS
Coronary artery disease	3 (60)	3 (60)	NS
Diabetes	4 (80)	2 (40)	NS
Laboratory measures eGFR, mL/min	35.4 ± 18.6	77.6 ± 16.3	**0.02**

eGFR, estimated glomerular filtration rate; NS, not significant. Bold values represent *P* statistically significant at <0.05.

Table II.

Indications for imaging

Patient	Contrast agent	Indication
1	Ferumoxytol	Nonhealing wounds
2	Ferumoxytol	Claudication
3	Ferumoxytol	Nonhealing wounds
4	Ferumoxytol	Nonhealing wounds
5	Ferumoxytol	Claudication
6	Gadolinium	Claudication
7	Gadolinium	Claudication
8	Gadolinium	Claudication
9	Gadolinium	Claudication
10	Gadolinium	Claudication

Table III.

Mean qualitative score by each arterial station represented as mean (standard deviation)

Segment	Ferumoxytol, *n* = 5	Gadolinium, *n* = 5	*P* value
Iliacs	1.2 (0.52)	1.8 (0.97)	**0.03**
Femorals	1.6 (0.60)	1.9 (0.85)	0.21
Popliteal	1.9 (0.97)	2.0 (1.17)	0.77
Tibials	2.4 (0.94)	1.8 (0.72)	**0.02**
Total	7.1 (2.00)	7.4 (2.39)	0.67

Bold values represent *P* statistically significant at <0.05.