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Ferumoxytol Negatively Enhances T₂-weighted MRI of Pedal Osteomyelitis *in vivo*

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Keywords

Ferumoxytol; superparamagnetic iron oxide nanoparticles (SPIONs); osteomyelitis

Introduction

The current standard-of-care imaging technique for the diagnosis of osteomyelitis is gadolinium-contrasted MRI (Gd-MRI)^{1,2}. However, Gd-MRI has imperfect specificity for osteomyelitis because signal enhancement also occurs in the presence of Charcot joints and other forms of sterile inflammation^{3,4}. The diagnosis of osteomyelitis has substantial clinical implications; there is a 15–25% lifetime risk of diabetic foot infections in diabetic patients. These infections are the basis for more than half of the non-traumatic lower extremity amputations performed². Furthermore, the intravenous infusion of gadolinium salts in the presence of chronic kidney disease (CKD) can lead to incurable nephrogenic systemic fibrosis⁵.

Recent research has suggested that superparamagnetic iron oxide nanoparticles (SPIONs) present an attractive alternative to gadolinium-based contrast agents for the MRI-aided diagnosis of inflammation and infection. SPIONs are taken up by macrophages and give rise to negative T₂-weighted MRI contrast (darkening) in areas of inflammation. Pre-clinical and clinical studies suggest that iron oxide nanoparticle-contrasted MRI may be superior to gadolinium in distinguishing active osteomyelitis from other sterile forms of inflammation^{6,7}.

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Ferumoxytol is a SPION preparation that has been approved by the Food and Drug Administration (FDA) in the United States for intravenous use as an iron replacement drug for patients with CKD. Unlike gadolinium-containing preparations, ferumoxytol may be safely used in patients who have kidney disease, a common comorbidity in diabetic patients with osteomyelitis. The purpose of this pilot study is to determine if ferumoxytol given to patients with clinically suspected osteomyelitis would cause negative T₂-weighted MRI contrast changes.

Materials & Methods

Patients

This study was approved by the Institutional Review Board and complied with Health Insurance Portability and Accountability Act. Exclusion criteria included patients that were actively septic or clinically unstable, patients with a contraindication to MRI, patients with hemochromatosis, pregnant patients, and prisoners. Female patients with a hematocrit (HCT) > 48% and males with a HCT > 52 % were excluded.

Patient Monitoring

All patients were inpatients in this study. Patient's vital signs were monitored before, during, and for at least 24 hours after the ferumoxytol infusion.

Imaging Protocol

MR images at 1.5 T were obtained at the inpatient MRI facility at the University of New Mexico Hospital with a Siemens Symphony instrument. Initial 192×256 pixel standard-of-care MR images included T₁-weighted spin-echo (TR=347–520 ms, TE=10 ms) and T₂-weighted STIR sequences (TR=3000–5660 ms, TE=34–57 ms). Gadopentetate dimeglumine (Magnevist, Bayer Health Care, Wayne NJ) was used. Within 26–63 hours after the standard-of-care MRI, patients received 7 mg/kg of intravenous (IV) ferumoxytol (Feraheme, AMAG Pharmaceuticals, Cambridge MA), up to a maximum dose of 510 mg, as an infusion over 15 minutes. Ferumoxytol contrasted MRI was performed the day following ferumoxytol infusion (range 14–25 hours), and included a T₂*GRE sequence. Interpretation of the images was performed subjectively by two radiologists (SE and GM) to determine the presence or absence of enhancement.

Histology of Resected Tissues

Bone biopsies and amputations were obtained as indicated by standard-of-care. CD68 is a surface marker for macrophages. CD68 stains used the Dako EnVision FLEX kit (Dako K8000) and the anti-CD68 antibody (Dako M0814) applied at a 1:2000 dilution for a 30 minute incubation. H&E slides were stained with Hematoxylin 2 (Richard-Allan Scientific ref. 7231), followed by Clarifier 2 (Richard-Allan Scientific ref. 7402), and Eosin-Y w/ Phloxine (Richard-Allan Scientific ref. 71304). An experienced surgical pathologist reviewed all the slides. Marrow fibrosis and fragmented necrotic bone spicules were identified in the patients with increased marrow macrophages. These findings histologically confirmed the presence of active osteomyelitis.

Results

The patient's demographics are shown in Table 1.

Patient 1 was a 69-year-old male with a history of type 2 diabetes complicated by peripheral neuropathy who presented with a non-healing ulcer over the 2nd distal phalanx. Our radiologists did not detect obvious pathologic enhancement using either gadolinium-, or ferumoxytol-contrasted MRI (Figure 1). An amputation was performed: histology (Fig. 2A&D) showed no evidence of osteomyelitis nor macrophage infiltration.

Patient 2 was a 62-year-old male with a history of type 2 diabetes who presented with a purulent ulcer overlying the 1st distal phalanx. Positive enhancement was observed on T₁-weighted sequences using gadolinium (Fig. 3B) consistent with osteomyelitis. MR images taken after ferumoxytol administration demonstrated a negative enhancement (image darkening with contrast) on T₂-weighted sequences (Fig. 3D). The patient underwent toe ray amputation, and osteomyelitis was confirmed by histology (Fig. 2E). The bone sample also showed macrophage invasion that was confirmed by CD68 immunohistochemistry (Fig. 2 B & inset). Culture of the osseous tissue was positive for enterococcus and candida (Table 2).

Patient 3 was a 42-year-old male diagnosed with osteomyelitis of the 5th distal phalanx by the initial radiologist interpreting his standard-of-care MRI. Our study radiologists did not see obvious pathologic enhancement changes with gadolinium nor ferumoxytol. The patient improved with intravenous antibiotics, and no histology was obtained.

Patient 4 was a 25-year-old male with history of a shotgun injury to the foot, who presented with worsened erythema and pain in the foot. The standard-of-care MRI was read as osteomyelitis of the second metatarsal extending into the proximal phalanx, including positive gadolinium enhancement on T₁-weighted MR sequences (Fig. 4B). Administration of ferumoxytol resulted in negative signal enhancement in the second metatarsal on T₂-weighted sequences (Fig. 4D). A toe ray amputation was performed and histology confirmed osteomyelitis with macrophage infiltration into the bone (Fig. 2F). Excised bone culture was positive for methicillin-resistant staphylococcus aureus (MRSA: Table 2).

None of the four patients developed sepsis within 24 hours of ferumoxytol infusion, nor did they develop concerning vital sign changes or evidence of a hypersensitivity reaction.

Discussion/Conclusion

In this pilot study, negative enhancement on ferumoxytol-contrasted MRI correlated with macrophage infiltration and culture evidence of osteomyelitis. A possible weakness of our study is that there was some degree of variation between timing of ferumoxytol infusion and MRI. This was due to time limitations on the inpatient scanner. Future studies may include a time course to determine optimal imaging times. We believe that further studies are warranted to investigate the possibility of ferumoxytol-contrasted MRI for the diagnosis of osteomyelitis.

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Figure 1. Patient 1: No clear evidence of 2nd distal phalanx osteomyelitis by imaging
T₁-weighted images were taken prior to (A) and subsequent to (B) the injection of gadolinium. T₂-weighted scans were also obtained prior to (C) and 25 hours subsequent to (D) the injection of ferumoxytol. The 2nd distal phalanx is indicated by red arrows in the images.

Figure 2.

Histology of the amputated tissues from patients #1 (A & D), #2 (B & E), and #4 (C & F).

The top row of images (A-C) are stained by immunohistochemistry for CD68 for macrophages, while the bottom row are stained with hematoxylin and eosin. Panels A & D show normal bone marrow without macrophage invasion, while the remaining panels (B, C, E, F) show infiltration by large numbers of macrophages reflecting osteomyelitis. The insets are magnified by 1.8X (A&D), 2.6X (B&E) and 2.2X (C&F).

Figure 3. Patient 2: First distal phalanx osteomyelitis

MRI images. Shown is a T₁-weighted image pre-gadolinium contrast (A), as well as post-gadolinium contrast (B). Note that the post gadolinium T₁ image demonstrates enhancement in the area of osteomyelitis in the first distal phalanx (denoted by the red arrows). T₂-weighted STIR images pre-ferumoxytol (C), and post-ferumoxytol demonstrated negative enhancement in the area of osteomyelitis (D). A T₂*-weighted GRE sequence post-ferumoxytol (E) also showed negative enhancement in the area of infection.

Figure 4. Patient 4. Second metatarsal osteomyelitis

T₁-weighted images were taken prior to (A) and subsequent to (B) the injection of gadolinium. Subsequently, T₂-weighted scans were obtained prior to (C) and 14 hours subsequent to (D) the injection of ferumoxytol. Note the brightening of the 2nd metatarsal (denoted by the red arrows) in (B) and the darkening of this site in (D) consistent with the diagnosis of osteomyelitis in this patient.

Table 1

Male Patient demographics (the normal ranges are in parentheses).

Patient #	Age	Hemoglobin A1c (4.4-5.6%)	Creatinine (55-147µM)	Diabetes [Y/N]	Erythrocyte Sedimentation Rate (0-25mm/hr)	CRP (0-30nM)
1	69	6.4	95	Y (Type II)	16	57
2	62	8.9	38	Y (Type II)	36	419
3	42	5.6	87	N	23	67
4	25	5.3	67	N	105	1505

Table 2

Comparison of MRI results with histology.

Patient #	Osteomyelitis standard of care MRI?	Osteomyelitis ferumoxytol- contrasted MRI?	Bone culture results	Evidence of osteomyelitis on histology?	Presence of macrophages in marrow by CD68 stain?
1	Yes	No	No organisms seen	No	No
2	Yes	Yes	Enterococcus & Candida	yes	Yes
3	Yes	No	NA	NA	NA
4	Yes	Yes	MRSA	Yes	Yes