Evaluation of meglumine gadoterate-enhanced MR angiography (MRA) compared with time-of-flight MRA in the diagnosis of clinically significant non-coronary arterial disease: a pooled analysis of data from two clinical trials

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Objectives: We analysed pooled data from two clinical trials to assess the diagnostic accuracy and safety of meglumine gadoterate (Gd-DOTA)-enhanced MR angiography (MRA) relative to those of non-enhanced time-of-flight (TOF) MRA for non-coronary arterial disease. Both techniques were compared with X-ray angiography as the gold standard.

Methods: Patients were of both sexes, were aged at least 18 years and had suspected non-coronary arterial disease. Each patient was his/her own control and underwent TOF MRA followed by Gd-DOTA-enhanced MRA, and then X-ray angiography. MRA was performed at 1.5 T (USA study) or 3 T (Republic of Korea study). The primary criterion used to evaluate efficacy was the degree to which the MRA examination agreed with X-ray angiography in assessing non-coronary arterial lesions. The performance of Gd-DOTA over TOF was assessed using a one-sided paired *t*-test. We also evaluated the specificity, sensitivity, image quality, examination duration and clinical safety of both MRA procedures.

Results: In total, 192 patients were enrolled and received Gd-DOTA. In the intent-to-treat population (*n*=162), within-patient accuracy was significantly greater for Gd-DOTA than for TOF ($85.8 \pm 19.8\%$ agreement between Gd-DOTA and X-ray angiography compared with $78.3 \pm 24.9\%$ agreement between TOF and X-ray angiography; *p*=0.0001). The sensitivity, specificity, image quality and examination duration were also better for Gd-DOTA than for TOF. There were no serious drug-related adverse events.

Conclusion: We conclude that Gd-DOTA-enhanced MRA is a safe and accurate procedure for detecting arterial stenosis at both 1.5 T and 3 T.

Received 21 July 2009
Revised 9 July 2009
Accepted 31 August 2010

DOI: 10.1259/bjr/16406056

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Magnetic resonance angiography (MRA) is a non-invasive and reliable tool for imaging blood vessels [1]. Furthermore, the use of magnetic resonance contrast agents, such as the paramagnetic agents derived from gadolinium, provides a technique for imaging arteries that is not dependent upon blood flow. Improvements in image quality have also been achieved with the use of contrast-enhanced MRA [1].

The combination of a gadolinium-bolus subtraction technique and a fast gradient-echo sequence has been shown to provide more accurate angiograms of the aortoiliac arteries and arteries of the lower extremities [2–8]. In the context of nephrogenic systemic fibrosis (NSF), however, the need for contrast media injection has to be evaluated carefully; the superiority of contrast-enhanced techniques over unenhanced techniques, including the well-established time-of-flight (TOF) MRA technique [9] and more recent

techniques (gradient echo, phase contrast and inversion recovery techniques, and fast spin echo including fast blood imaging), has to be re-assessed taking into account the latest software and MR equipment.

The TOF MRA technique is still considered, particularly by regulatory authorities, to be a reference in terms of unenhanced MRA techniques. This technique, rather than the contrast-enhanced meglumine gadoterate (Gd-DOTA; DOTAREM®; Guerbet, Roissy CdG Cedex, France) technique, was used in both of the studies assessed in this paper. Gd-DOTA is a paramagnetic gadolinium macrocyclic chelate that is registered for use as a contrast agent in more than 60 countries worldwide. The tolerability and efficacy of Gd-DOTA have been evaluated in 40 clinical trials, involving >3200 patients [10, 11]. These include studies of biological safety and pharmacokinetic parameters in patients with renal failure, in whom no nephrotoxicity was observed [10, 11]. The excellent clinical efficacy and favourable clinical safety profile (with no unconfounded case of NSF reported) of Gd-DOTA has been confirmed in a recent post-marketing surveillance study that involved >24 000 patients [12].

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This clinical trial was supported by Guerbet, France.

In the early 1990s clinical trials were performed at 1.5 T using Gd-DOTA-enhanced MRA to study a variety of vascular structures including pulmonary, renal, carotid and lower limb arteries [13–15]. More recent work has suggested that vascular enhancement is heightened at higher magnetic field strengths, and there is increasing evidence that the use of MRA at 3 T, rather than at 1.5 T, might have advantages in many different body regions [16]. Importantly, vascular signal-to-noise ratio (SNR) is greater at 3 T than in lower field strength systems. It seems relevant, therefore, to confirm the actual superiority of Gd-DOTA-enhanced MRA over TOF MRA at both 3 T and 1.5 T [17]. Thus, two MRA studies with Gd-DOTA were conducted: one in the USA (at 1.5 T; October 2003 to March 2005) and the other in the Republic of Korea (at 3 T; March 2006 to January 2008). These two trials aimed to evaluate the diagnostic accuracy, sensitivity and specificity of Gd-DOTA-enhanced MRA and non-enhanced MRA (TOF technique) in the assessment of arterial stenosis in patients with non-coronary arterial diseases. The two MRA procedures were compared in terms of the degree to which they agreed with X-ray angiography as the gold standard. In addition, data from the two studies were pooled to provide a larger sample in which possible differences between 3 T and 1.5 T and between the USA and Republic of Korea populations were assessed.

Methods and materials

Study design

In the USA, a multicentre (seven centres) open-label, fixed sequence paired trial was performed to compare the efficacy and safety of two MRA techniques (Gd-DOTA-enhanced MRA and TOF MRA) in a 1.5 T magnet, using X-ray angiography as the gold standard examination. The study performed in the Republic of Korea involved one centre and used a 3 T magnet. In all other respects, the two studies shared a common design. In each centre, the study was initiated after receipt of approval from local institutional review boards.

TOF MRA examination was performed within 21 days of screening. This was followed within 7 days by Gd-DOTA-enhanced MRA examination [single intravenous (iv) bolus of] Gd-DOTA 0.1 mmol kg^{-1} , injected at a rate of 2 mls^{-1} using a power injector and then X-ray angiography within a further 14 days. Each patient was his/her own control. The chart shown in Figure 1 summarises the stages and timings of the study.

Patients

In each study, approximately 90 patients had to be enrolled to obtain 80 patients with data from all 3 imaging procedures. Eligibility was determined at a screening visit up to 21 days prior to the TOF MRA. Male

or female patients had to be at least 18 years of age or at least the age of legal maturity, strongly suspected of having non-coronary arterial disease that had been detected clinically and/or by previous imaging and scheduled (or to be scheduled) to undergo X-ray angiography (the presence of coronary arterial disease did not exclude patients from the study).

Exclusion criteria included a contraindication to MRI, the presence of any metallic device in the vascular territory that was to be the subject of imaging, congenital morphological vascular abnormalities, known allergy to gadolinium chelates and pregnancy (or planning to become pregnant during the trial) or lactation. Patients were also excluded if they had received a gadolinium complex within the 2 days or iron oxide nanoparticles within the 7 days preceding the Gd-DOTA-enhanced MRA examination.

Informed written consent was obtained from each patient.

Imaging procedures

The imaging procedures used to acquire peripheral, renal and carotid MRA scans (both TOF MRA and Gd-DOTA-enhanced MRA) are summarised in Table 1. All of the MRA images obtained during the trial were read on site by one expert reader.

The X-ray angiography examination was performed, according to the imaging laboratory's standard practice and consistent with the American College of Radiology Standards, not less than 24 h after the injection of Gd-DOTA and not more than 14 days after the Gd-DOTA-enhanced MRA examination. One experienced radiologist reviewed the X-ray angiograms on site and independently of the MRA image results.

In the USA, TOF MRA and contrast-enhanced MRA using Gd-DOTA were performed at 1.5 T using several MRI systems: GE TwinSpeed [General Electric Company (GE), Fairfield, CT], GE Horizon LX (GE), GE LX TwinSpeed (GE), GE Excite (GE), GE TwinSpeed Excite (GE), Philips Intera CV (Philips, Amsterdam, Netherlands) and Siemens Symphony (Siemens Healthcare, Erlangen, Germany). Several different systems were also used for X-ray angiography: Philips V5000 (Philips), Philips Integris (Philips), Siemens Multistar TOP (Siemens), Siemens Angiostar (Siemens), Siemens HICOR (Siemens), GE Advantx DLX (GE), Toshiba DFP (Toshiba, Tokyo, Japan) and Philips Medical System BH 5000C–H5000C Allura (Philips).

In the Republic of Korea, TOF MRA and contrast-enhanced MRA using Gd-DOTA were performed at 3 T using an Achieva (Philips) MRI system. The AXION-ATIS (Siemens), Polyttron-TOP (Siemens) or Integris V (Philips) systems were used for X-ray angiography.

Imaging evaluation criteria

All of the images obtained during the trial were read on site at an image-display workstation. For both MRI

Figure 1. Study design. MRA, MR angiography; TOF, time of flight. DOTAREM MRA manufactured by Guerbet, Roissy CdG Cedex, France.

Table 1. MRI procedures

Measurements	TOF MRA	Gd-DOTA-enhanced MRA
<i>Peripheral MRA scan acquisition (aorto-iliac, femoral, popliteal or calf)</i>		
Plane	Axial	Coronal
Mode	2D	3D-SPGR
TE	3.45 ms (3 T)/minimum (1.5 T)	1.89 ms (3 T)/minimum (1.5 T)
TR	22 ms (3 T)/minimum (1.5 T)	5.2 ms (3 T)/minimum (1.5 T)
Flip angle	60	30 (3 T)/45 (1.5 T)
Matrix (frequency × phase)	256 × 256 (3 T) /256 × 128 (1.5 T)	512 × 512 (3 T) /256 × 160 (range 128–192) (1.5 T)
FOV	360 mm (3 T)/36–40 (1.5 T)	360 mm (3 T)/36–40 (1.5 T)
Frequency direction	Right to left	Superior to inferior
Slice thickness	3 mm	2 mm (3 T)/3 mm (1.5 T)
Gap/spacing	0 mm	–1.0 mm (3 T)/0 mm (1.5 T)
<i>Renal MRA scan acquisition</i>		
Plane	Axial	Coronal
Mode	2D	3D-SPGR
TE	3.3 ms (3 T)/minimum (1.5 T)	1.5 ms (3 T)/minimum (1.5 T)
TR	21 ms (3 T) /minimum (1.5 T)	5.1 ms (3 T)/minimum (1.5 T)
Flip angle	60	30 (3 T)/45 (1.5 T)
Matrix (frequency × phase)	256 × 192	256 × 512 (3 T)/256 × 160 (range 128–192) (1.5 T)
FOV	350 mm (3 T)/30 (range 26–32) (1.5 T)	430 mm (3 T)/32 (range 28–40) (1.5 T)
Frequency direction	Right to left	Superior to inferior
Slice thickness	3 mm (3 T)/2.5 mm (1.5 T)	3 mm (3 T)/2.5 mm (1.5 T)
Gap/spacing	–1.5 mm (3 T)/0 mm (1.5 T)	–1.5 mm (3 T)/0 mm (1.5 T)
<i>Carotid MRA scan acquisition</i>		
Plane	Axial	Coronal
Mode	2D	3D-SPGR
TE	4.9 ms (3 T)/minimum (1.5 T)	2.1 ms (3 T)/minimum (1.5 T)
TR	22 ms (3 T)/minimum (1.5 T)	5.3 ms (3 T)/minimum (1.5 T)
Flip angle	60	30 (3 T)/30–45 (1.5 T)
Matrix (frequency × phase)	256 × 256 (3 T)/256 × 192 (range 128–192) (1.5 T)	688 × 688(3 T)/256 × 160 (range 128–192) (1.5 T)
FOV	200 mm (3 T)/20 [16–20] (1.5 T)	320 mm (3 T)/28 [20–36] (1.5 T)
Frequency direction	Anterior to posterior	Superior to inferior
Slice thickness	1.5 mm (3 T)/1.5–2 mm (1.5 T)	0.9 mm (3 T)/1.5–2 mm (1.5 T)
Gap/spacing	0 mm	–0.45 mm (3 T)/0 mm (1.5 T)

FOV, field of view; Gd-DOTA, meglumine gadoterate; MRA, MR angiography; SPGR, spoiled gradient echo; TE, echo time; TR, repetition time; 2D, two-dimensional; 3D, three dimensional.

and X-ray angiography images, the stenosis of arterial segments was analysed by calliper measurements of the lumen diameter made both in the stenotic region and in a normal reference segment distal to the stenosis. If there was no normal-appearing artery distal to the segment, then the normal proximal diameter was used. For MRI, these measurements were made on subvolume maximum intensity projections (MIPs) and multiplanar reformats. Specialist software such as a picture archiving and communications system (in Korea) or a Siemens Leonardo (Siemens) or GE Advantage Windows workstation (in the USA) (GE) was used to interpret the data from both the MIP images and X-ray angiograms. Stenosis percentage was calculated for each lesion: percentage = $100 \times [1 - (\text{narrowest diameter}/\text{normal diameter})]$.

Each lesion was graded as follows: 0=no significant stenosis (0–50%); 1=moderate stenosis (51–69%); 2=severe stenosis (70–99%); and 3=occlusion (100%). Grade 0 lesions were measured only if they appeared close to the 50% threshold. Clinically significant renal and lower extremity arterial stenosis was defined as grade 1 or 2. Clinically

significant carotid stenosis was indicated by a grading of 2. For all regions, a grading of 3 indicated occlusion.

For the purpose of the trial only, just one vascular territory (*i.e.* one field of view) was selected for assessment for each patient. Only the data from that one vascular territory were included in the main efficacy analysis (*i.e.* no vascular territories were explored in this analysis other than the one targeted for inclusion). Where data for multiple vascular territories were available for an individual patient, however, all of the segments were included in the secondary efficacy analysis.

For each vascular territory, the segments and sub-segments (if applicable) that were evaluated are listed in Table 2 and defined in Table 3. If there were multiple lesions in one segment, the highest score for any one of these lesions was assigned to the segment. If a stenosis or occlusion was at a junction point between two segments, the stenosis or occlusion was assigned to the more distal of the adjoining segments.

The primary efficacy criterion was the degree of agreement between each type of MRA examination and X-ray

Table 2. Segments and subsegments (if applicable) evaluated in each vascular territory included in the study

Vascular territory	Segments evaluated ^a	Subsegments evaluated ^a
Carotid arteries	Common and internal carotids	–
Renal artery	Renal	Ostial (within the first 1 cm), proximal (after ostial but before division) and distal (after division)
Aorto-iliac arteries	Infrarenal aorta, common iliac and external iliac/common femoral arteries	–
Femoral arteries	Superficial and deep femoral arteries	–
Popliteal artery	Popliteal	–
Calf	Posterior tibial, anterior tibial and peroneal arteries	–

^aExcept for aorta, all segments and subsegments are bilateral (*i.e.* left and right). If medically appropriate, however, a unilateral examination was considered to be acceptable for the lower extremities.

angiography in assessing non-coronary arterial lesion(s). To determine agreement at the patient level, each segment score for the TOF and Gd-DOTA-enhanced MRA evaluations was compared with the segment score from the corresponding X-ray angiogram. The percentage agreement by patient (within-patient accuracy) for each MRA examination was defined as the number of segment scores that agreed with the segment scores from the X-ray angiogram, divided by the total number of segments for that patient and then multiplied by 100.

Secondary efficacy criteria included the number of technical failures (at segment level); the specificity and sensitivity of TOF and Gd-DOTA-enhanced MRA examinations at the segment level (which were calculated both including and excluding technical failures); image quality (evaluated as excellent, more than adequate, adequate, less than adequate or non-diagnostic) and artefact quantification; and duration of examination. Technical failure was defined as the absence of diagnostic image from TOF or Gd-DOTA-enhanced MRA.

The duration of examination for TOF MRA was defined as the time between the beginning and the end of the acquisition; for contrast-enhanced MRA, it was defined as the time between the start of the bolus injection and the end of the acquisition (not including the preparation of the injector).

Safety assessments

Safety assessments recorded any adverse events that occurred during the trial as well as injection-site tolerance

and any changes in vital signs (*i.e.* systolic and diastolic blood pressure, pulse and respiratory rate) for up to 24 h (2 h on site) after the Gd-DOTA injection. Adverse events were recorded as mild, moderate or severe.

Statistical analysis

The performance of Gd-DOTA-enhanced MRA over TOF MRA was assessed at the patient level using a one-sided paired *t*-test at $\alpha=0.025$ significance level [18]. Data from all vascular territories were pooled for this analysis.

The sensitivities and specificities of the two MRA procedures were compared at the segment and patient levels [18] using the McNemar's test for paired data with dichotomous outcomes. Sites and vascular territories were pooled for summaries and analyses, and the data were also analysed by vascular territory. Descriptive statistics were performed on all efficacy parameters; 95% confidence limits were calculated when appropriate.

Incidence tables were used to present the number and percentage of patients reporting adverse events.

Four patient populations were identified: all included patients (*i.e.* all patients who met the inclusion/exclusion criteria and had signed the informed consent form); safety (all patients who received contrast agent, regardless of the quantity); intent-to-treat (ITT) efficacy (patients who underwent, and had assessments for, the Gd-DOTA-enhanced and TOF MRA examinations and X-ray angiography); and per-protocol (PP) efficacy patients for whom there were no major deviations from or violations of the study protocol.

Table 3. Definitions of arterial segments

Segment	Definition
Common carotid	From arch to carotid bifurcation
Internal carotid	From bifurcation to base of skull
Renal	From origin at aorta to secondary order divisions
Infrarenal aorta	From level of renal artery (use caudal renal artery if they arise at different levels) to aortic bifurcation
Common iliac	From level of aorta to iliac bifurcation
External iliac/common femoral	From iliac bifurcation to femoral bifurcation
Superficial femoral	From femoral bifurcation to a measured point 30 cm distal to the femoral bifurcation
Popliteal	From a measured point (25 cm proximal to the popliteal bifurcation) to the popliteal bifurcation
Posterior tibial	From popliteal bifurcation to ankle (including posterior-peroneal trunk)
Anterior tibial	From popliteal bifurcation to ankle
Peroneal	From division off the posterior-peroneal trunk to ankle

Results

Patients

A total of 192 patients were enrolled: 100 in the USA and 92 in the Republic of Korea. All 192 patients were eligible for inclusion in the safety analysis. 21 patients were excluded from any efficacy analysis because they left the study prematurely and did not have an X-ray angiogram (no patient discontinued for safety reasons); 162 patients were included in the ITT efficacy analysis and 114 in the PP efficacy analysis.

Demography and baseline characteristics

Patients included were aged from 22 to 86 years (mean: 63.7 years, median: 64.5 years), 73% were male and 27% were female. A summary of the demographic and baseline characteristics (including the types of arterial disease that were suspected) of the 192 enrolled patients is shown in Table 4. 15 (7.8%) patients presented with renal insufficiency.

Vascular stenosis score

At the segment level, the gold standard X-ray graded 498 (56.9%) segments as normal (no stenosis), 118 (13.5%) as having no significant stenosis and 259 (29.6%) as having significant stenosis.

At the patient level, the gold standard X-ray determined that 41 (22.5%) patients were graded as normal (no stenosis), 21 (11.5%) as having no significant stenosis and 120 (65.9%) as having at least one significant stenosis.

Diagnostic efficacy

Technical failure rates

A total of 182 segments were not assessed by one of the MRA procedures because of technical failures: 161 segments (18.7%) from the TOF procedure and 21 (2.4%) from the Gd-DOTA procedure ($p < 0.0001$). The technical failure rates at 1.5 T were 4.4% for the Gd-DOTA-enhanced procedure and 30.4% for the unenhanced TOF procedure ($p < 0.0001$); the corresponding rates at 3 T were 0.24% and 5.85%, respectively ($p < 0.0001$).

Table 4. Demography and baseline characteristics

Characteristics	Total (n=192)
Age (years) (mean $\pm$ SD, min–max)	63.7 $\pm$ 13.9 (21.9–86.4)
Gender [n (%)]	
Male	140 (72.9)
Female	52 (21.7)
Disease type [n (%)]	
Aorto-iliac	76 (39.6)
Renal	35 (18.2)
Calf	25 (13.0)
Femoral	24 (12.5)
Carotid	23 (12.0)
Popliteal	9 (4.7)
Patients with chronic renal failure	15 (7.8)

SD, standard deviation.

Of the 161 segments that were not evaluated by TOF because of technical failure, renal segments were the most frequently observed (73 segments). Other non-evaluable segments were located in the aorto-iliac (55 segments), femoral (16 segments), carotid (10 segments), calf (4 segments) and popliteal (3 segments) arteries.

Agreement between MRA procedures and X-ray angiography

When assessed at the patient level and averaged over all sites and vascular territories, in the ITT population ($n=162$), $85.8 \pm 19.8\%$ (mean $\pm$ standard deviation) the results of the DOTA-enhanced MRA studies agreed with those of X-ray angiography; this compares with $78.3 \pm 24.9\%$ for unenhanced TOF MRA (Table 5). This difference between Gd-DOTA and TOF MRA ($7.4 \pm 22.1\%$) was statistically significant ($p=0.0001$), indicating that the diagnostic accuracy of Gd-DOTA-enhanced MRA is superior to that of the TOF technique in detecting non-coronary arterial lesions (*i.e.* in our primary efficacy criterion). The PP efficacy analysis of 114 patients confirmed the ITT results, again finding a statistically significant difference ($7.8 \pm 21.5\%$) between Gd-DOTA-enhanced-MRA and TOF MRA ($p=0.0002$; Table 5).

When analysis was performed by vascular territory (a secondary efficacy criterion), statistical significance was observed in the aorto-iliac territory, with mean agreement percentages of 85.8% for Gd-DOTA and 75.6% for TOF observed in the ITT population, a difference of 10.2% ($p < 0.0001$). The non-significance observed in other territories was probably due to the small number of patients with lesions in these areas.

When the data from the USA (1.5 T) and Korean (3 T) studies were analysed separately, the superior diagnostic accuracy of Gd-DOTA-enhanced-MRA compared with TOF MRA was shown at both magnetic field strengths, with a greater difference with 3 T (8.5%) than with 1.5 T (6.2%). The results of the ITT efficacy analysis of both studies are summarised in Table 6. Similar results were observed in the PP population (data not shown).

Sensitivity and specificity of examinations

In the ITT population (technical failures excluded) ($n=162$), analysis of sensitivity at segment level showed

Table 5. Agreement between the MRA and X-ray angiogram results (%) averaged over both sites and all vascular territories (ITT and PP patient populations)

Results	Gd-DOTA	TOF	Gd-DOTA–TOF	<i>p</i> -value ^a
ITT (<i>n</i> = 162)				
Mean	85.8	78.3	7.4	0.0001 ^b
SD	19.8	24.9	22.1	
Median	100	81.7		
PP (<i>n</i> = 114)				
Mean	83.6	75.8	7.8	0.0002 ^b
SD	20.8	24.9	21.5	
Median	100	80		

Gd-DOTA, meglumine gadoterate; ITT, intent to treat; PP, per protocol; SD, standard deviation; TOF, time of flight.

^aOne-sided p-value from a paired t-test testing that the mean difference (Gd-DOTA–TOF) is >0 .

^bIndicates a statistically significant difference at the 0.025 level.

Table 6. Agreement between the magnetic resonance angiogram and X-ray angiogram results for each study (%): averaged over all sites in each country and all vascular territories (intention-to-treat efficacy patient population)

Study results	Gd-DOTA	TOF	Gd-DOTA-TOF	p-value ^a
USA study, 1.5 T (n=76)				
Mean	86.2	80.0	6.2	0.0245 ^b
SD	22.2	29.2	23.7	
Median	100	100		
Republic of Korea study, 3 T (n=84)				
Mean	85.4	76.8	8.5	0.0003 ^b
SD	17.5	20.4	20.7	
Median	100	80		

Gd-DOTA, meglumine gadoterate; SD, standard deviation; TOF, time of flight; USA, United States of America.

^aOne-sided *p*-value from a paired *t*-test testing that the mean difference (Gd-DOTA-TOF) is greater than 0.

^bIndicates a statistically significant difference at the 0.025 level.

that 93.3% of segments with significant stenosis were correctly diagnosed with Gd-DOTA-enhanced MRA, compared with 85.7% with TOF MRA. This 7.6% difference in sensitivity was statistically significant in favour of the Gd-DOTA-enhanced procedure ($p=0.0004$). Similarly, in the PP population ($n=114$), 93.4% of the segments with significant stenosis were correctly diagnosed using Gd-DOTA-enhanced MRA, compared with 87.8% using TOF MRA ($p=0.0076$).

In the ITT population (technical failures excluded) ($n=162$), analysis of the specificity at segment level showed that 89.7% of the segments with no significant stenosis or no stenosis were correctly diagnosed with Gd-DOTA-enhanced MRA, compared with 84.4% with TOF MRA. The 5.3% difference observed in specificity was statistically significant in favour of the Gd-DOTA-enhanced procedure ($p=0.0019$). Similarly, in the PP population ($n=114$), 87.4% of the segments with no significant stenosis or no stenosis were diagnosed with Gd-DOTA-enhanced MRA, compared with 81.8% with TOF MRA ($p=0.0152$).

When sensitivity and specificity were evaluated by vascular territory, statistical significance at the 0.05 level was observed only in the aorto-iliac territory (in both the ITT and PP populations). The non-significance observed in other territories was probably due to the small number of patients with stenosis in these areas.

Procedure duration

When averaged over all vascular territories, the Gd-DOTA-enhanced MRA procedure, with a mean duration of 2.2 min (range 1 to 31 min), was on average more than 6 min shorter than TOF MRA (mean 8.9 min, range 2–71 min) and almost 45 min shorter than X-ray angiography (mean 47.1 min, range 7–149 min). These data show that although both MRA procedures were considerably shorter than X-ray examination, TOF MRA took four times longer than Gd-DOTA MRA. The same trend was seen in each individual vascular territory (Figure 2). Similar results were found in the PP population (data not shown).

Image quality

In the ITT population ($n=162$), the overall image quality obtained by Gd-DOTA-enhanced MRA was

superior to that obtained by TOF MRA and comparable with that from X-ray angiography. The proportion of patients with an image quality rated as “excellent”, “more than adequate” or “adequate” was statistically higher with Gd-DOTA-enhanced MRA (95.7%) than with TOF MRA (71.0%) and similar to that achieved with X-ray angiography (96.9%) (Figure 3). Similar results were seen in the PP population (Figure 3).

Assessment of image quality at segment level showed that there were no image issues (such as venous contamination or motion) in 83.3% (573/688) of segments imaged by Gd-DOTA-enhanced MRA, compared with 53.0% (365/689) of segments in TOF MRA images and 92.0% (634/689) of segments in the gold standard X-ray angiograms. Similar results were found in the PP population.

Examples of images obtained with contrast-enhanced MRA using Gd-DOTA, with TOF MRA and with X-ray angiography are shown in Figure 4.

Safety evaluation

The safety population included 192 patients who received Gd-DOTA contrast agent, regardless of the quantity received. The mean injected dose received was 14.4 ml (0.24 m kg^{-1}) at 3 T and 18.3 ml (0.21 m kg^{-1}) at 1.5 T. Of a total of 20 adverse events in 16 patients (8.3%), 7 were reported as possibly or probably related to treatment and were rated as mild or moderate (increased blood pressure, abdominal pain, pruritus, rash and elevated white blood cell count were each reported in 1 patient; 2 patients experienced pain at the injection site). Four cases of injection site pain and one case of syncope (classified as a serious adverse event) were reported as unrelated to treatment. No clinically significant effects on patients' vital signs were reported.

Discussion

The results of this pooled analysis of two studies show that Gd-DOTA-enhanced MRA offers statistically superior within-patient accuracy when compared with TOF MRA, taking X-ray angiogram as the gold standard. Sensitivity and specificity were also superior with Gd-DOTA-enhanced MRA compared with TOF MRA when evaluated at the segment level. In addition, the duration of the MRA procedure was shortened substantially with Gd-DOTA, and this technique also provided better image quality. Moreover, the technical failure rate for Gd-DOTA-enhanced MRA was considerably lower than that for TOF MRA. All of these results were confirmed at both 1.5 T and 3 T.

Since its inception, MRI has been able to identify blood flow and to allow visualisation of the structure of larger blood vessels. A series of technical improvements has increased the spatial resolution of MRI enough to make MRA a valuable diagnostic procedure in many regions of the body [3–5, 19–21]. Studies have demonstrated that MRA is as accurate as conventional (X-ray) intra-arterial digital subtraction angiography in pathologies such as carotid artery stenosis and lower-extremity atherosclerotic occlusive disease [7, 8, 22]. In these and other clinical

Figure 2. Mean durations of image acquisition (minutes) in six vascular territories using time-of-flight (TOF) MR angiography (MRA), X-ray angiography (X-ray) and contrast-enhanced MRA using meglumine gadoterate (Gd-DOTA).

studies, MRA has shown sensitivity and specificity comparable to those of conventional invasive X-ray angiography, with a predicted lower cost and lower risk

to the patient because it does not require the use of ionising radiation, iodinated contrast agents or blood vessel catheterisation [21, 23]. Meta-analyses of studies of various

Figure 3. Percentages of patients in the intention-to-treat (ITT) or per-protocol (PP) populations with image quality rated "excellent", "more than adequate" or "adequate" when images were obtained using time-of-flight (TOF) MR angiography (MRA), X-ray angiography (X-ray) or contrast-enhanced MRA using meglumine gadoterate (Gd-DOTA).

Figure 4. Images obtained with contrast-enhanced MR angiography (MRA) using meglumine gadoterate (DOT), time-of-flight (TOF) MRA and X-ray angiography (X-ray) at 3 T. This 75-year-old patient has stenosis of the right common iliac artery. The TOF image is of non-diagnostic quality and the stenosis was missed upon assessment of this image. By contrast, the stenosis is well visualised on the DOT image.

disease states and anatomical regions of clinical importance have confirmed the clinical value of MRA [24–26].

The clinical utility of MRA is associated with the size of the blood vessels being studied, the disease under investigation and the technical limitations of the MRA scanning process.

MRA imaging of peripheral blood vessels has proved to be particularly challenging because of the large anatomical area that must be covered in an arterial phase at high spatial resolution. However, there have been many technical advances in recent years. MRA techniques that may be used to image the arteries include “black-blood” imaging, phase-contrast imaging, TOF imaging and contrast-enhanced imaging [27]. Although contrast-enhanced MRA is the principal MRA technique for the evaluation of vascular disease, black-blood imaging is a useful technique for evaluation of the vessel wall. Phase-contrast flow imaging is especially important for quantifying blood flow, two-dimensional (2D) and TOF MRA still has some well-validated applications, such as the evaluation of distal peripheral vascular disease [27].

TOF MRA procedures are still considered as reference methods in terms of unenhanced MRA procedures, but they are known to have major drawbacks, including their relatively long duration and high rates of technical failure [7]. The substantial rate of technical failures observed with TOF MRA in the current studies is consistent with rates published previously, especially those for imaging of the renal arteries using an axial TOF acquisition scheme.

Unenhanced TOF MRA was used as a comparison with Gd-DOTA-enhanced MRA in the current analysis to meet the requirements of guidelines issued by the United States Food and Drug Administration (FDA) [28]. Moreover, because innovative technologies such as steady-state

non-contrast sequences for MRA and time-resolved MRA were not widely available at the time these studies were planned and conducted, most of the eight investigational centres did not have access to those technologies and the studies were performed using well-established MRA technology in accordance with the respective imaging capabilities of the individual centres.

It is well established that Gd-DOTA-enhanced MRA has a greater sensitivity than TOF for the lower limbs. Therefore, in the detection of significant stenoses in non-coronary arteries, the degree of agreement (at the patient level) and sensitivity (at the lesion and segment levels) of Gd-DOTA-enhanced MRA when compared with X-ray angiography are expected to be significantly greater than those of 2D TOF MRA. The results of the current studies confirmed this. When each vascular territory was analysed separately, the results showed that the greatest difference between the Gd-DOTA-enhanced and TOF MRA procedures came from the aorto-iliac vascular territory, showing agreement between Gd-DOTA-enhanced MRA and X-ray angiogram results that was 10.2% greater than that between TOF MRA and the same X-ray angiograms. This difference was statistically significant ($p < 0.0001$). A recently published Health Technology Assessment reviewed the diagnostic accuracy and cost-effectiveness of various imaging techniques for the assessment of lower limb arterial disease [29]. The results of this review showed that contrast-enhanced MRA was more accurate than TOF MRA and concluded that, where available, it may be a viable alternative to contrast X-ray angiography.

High-resolution time-resolved MRA is a novel contrast-enhanced MRA method that has been shown to provide definition of arterial segments in the lower extremities that is superior to that offered by TOF MRA [30]. In a

study that compared time-resolved contrast-enhanced projection reconstruction MRA with 2D TOF MRA for the identification of potential bypass graft target vessels in patients with peripheral arterial disease, the TOF images were found to be of inferior quality [30]. The reasons for the poorer image quality with TOF MRA were moderate spatial resolution, lower contrast-to-noise ratio, greater flow-related artefacts and the absence of temporal resolution [30].

In addition, a number of recent publications have reported the development and clinical implementation of steady-state non-contrast sequences for MRA. In balanced steady-state free precession (SSFP) imaging without arterial spin labelling (ASL), image contrast is determined by T_2/T_1 ratios, producing bright-blood imaging without reliance on in-flow [31, 32]. However, SSFP without ASL can be difficult to implement successfully because these sequences are susceptible to heterogeneities. To improve homogeneity, there may be a requirement for local shimming, which is not usually required for fast spin-echo sequences [31].

The majority of MRI systems currently in use are 1.5 T but stronger magnets are becoming increasingly available. In particular, 3 T scanners are gaining widespread acceptance for both clinical practice and research studies [33]. There is increasing evidence that performing MRA at 3 T may have substantial clinical advantages over imaging at 1.5 T [16]. In the current analysis, however, Gd-DOTA-enhanced MRA proved to be a robust and accurate diagnostic technique at both 1.5 T and 3 T. Technical failures were dramatically reduced at 3 T, but even at 1.5 T Gd-DOTA proved superior to TOF MRA. This pooled analysis is not free of limitations. There was one Republic of Korean centre and seven USA centres, and the only site that used 3 T was in the Republic of Korea. In addition, we used one reader per site for image interpretation, and so interobserver and/or intra-observer variability could not be calculated.

The potential role and possible limitations of CT angiography (CTA) for the evaluation of peripheral arterial disease also warrant discussion. A 72.6% agreement has been reported between multi-detector row CTA and the gold standard of histological examination in carotid plaque characterisation [34, 35]. Scanning with 1.25-mm collimation seems adequate for a routine CTA examination of most arteries and veins on a 16-detector CT. One study has compared the costs and efficacy of three non-invasive imaging tests (CTA, MRA and duplex sonography) as the initial imaging test in the diagnostic assessment of patients with peripheral arterial disease [37]. The results of this study suggest that CTA and MRA are clinically more useful than duplex sonography, and that the total costs were lower for CTA than for MRA or duplex sonography when used as the initial imaging evaluation of peripheral arterial disease [36]. The two main concerns with multidetector row CTA are the delivery of potentially high radiation doses and false-positive interpretation due to calcification. The average patient radiation dose reported in the literature in the assessment of peripheral arterial disease with CTA is 7.47 mSv [37]. Therefore, contrast-enhanced MRA or digital subtraction angiography might be advised for patients with critical limb ischaemia who are likely to have extensive calcification of smaller arteries [36].

In summary, the results of this analysis show that Gd-DOTA-enhanced MRA provided statistically greater diagnostic accuracy, sensitivity and specificity when compared with non-enhanced MRA in the diagnosis of clinically significant non-coronary arterial disease, even at high field strength. The difference in technical failure rates observed between the two studies may have been due to differences in the territories evaluated, the method of image evaluation or the field strength, or a combination of these factors. In addition, Gd-DOTA demonstrated a very good safety profile. Nevertheless, among the three procedures used, Gd-DOTA-enhanced MRA demonstrated many advantages, including non-invasiveness, ease and speed of use, and good image quality. Our findings indicate that, alongside a diagnostic efficacy similar to that of X-ray angiography, Gd-DOTA-enhanced MRA offers additional benefits, including savings in time and costs and reductions in the risks associated with iodinated contrast media and radiation exposure.

In conclusion, Gd-DOTA-enhanced MRA provided greater accuracy than the well-established TOF MRA technique at both 1.5 T and 3 T, but further clinical evaluation will be needed to compare Gd-DOTA-enhanced MRA with other new unenhanced techniques.

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