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23 November, 2011

Dear Sir or Madam,

Re: Final Study Report on 'Magnetic resonance (MR) angiography with a blood pool contrast medium'

Your reference: 22943/0014-0001

Eudract Number: 2007-002730-11

Protocol Number: A091031

Please find enclosed the Final Study Report for the above study.

Yours sincerely,

Dr Teik Choon See, Consultant Radiologist
FRCS FRCR

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23 November, 2011

Dear Dr Ruben,

Re: Final Study Report on 'Magnetic resonance (MR) angiography with a blood pool contrast medium'

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Yours sincerely,

Dr Teik Choon See, Consultant Radiologist
FRCS FRCR

Trial Title: Magnetic Resonance (MR) Angiography with a Blood Pool Contrast Medium

Authors: **TC See (Chief Investigator)**
Ed Soh (Co-investigator)
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Sponsor trial code number: A091031

EudraCT number: 2007-002730-11

Investigational Product: Vasovist® (gadofosveset trisodium, Schering)

Notes:

- This manuscript is to be submitted to American Journal of Roentgenology, subject to the normal review processes.
- No feedback will be provided to the participants of this trial.

Signature of Chief Investigator:

Date: 24/11/11

Introduction:

Imaging of the central veins to establish patency forms an integral part of assessment in symptomatic and asymptomatic patients undergoing dialysis, parenteral nutrition and complex venous access such as preparation for multi-visceral transplant. Multiple previous catheter insertions and venous interventions frequently lead to varying degrees of thrombo-occlusive disease. The role of imaging is to provide an accurate assessment of the site and extent of any venous disease and to identify possible aetiologies in order to plan subsequent management. Intravenous digital substraction angiography (IV-DSA), colour Doppler ultrasonography (CDUS) and computed tomography (CT) venography are commonly used, usually in combination, in the evaluation of central venous patency.

Contrast enhanced magnetic resonance (MR) angiography of the venous system is also a recognised technique for evaluating the large veins of the chest and abdomen. Diagnostic quality venous imaging can be difficult to achieve when using extracellular agents that rapidly leave the vascular pool. Conventional gadolinium-chelate enhanced first pass and time-resolved techniques have been employed successfully but often require prolonged acquisitions to ensure coverage of the venous system, particularly when abnormal.

Over the past decade "long dwell" gadolinium based contrast media have been developed that persist in the intravascular space and allow vascular imaging during the equilibrium or "steady state" phase following injection and redistribution of contrast medium within the vascular space. These techniques permit longer acquisition times as they are not limited by the first pass temporal limitations of conventional methods and are attractive for venous imaging as the contrast medium does not pass rapidly into the surrounding soft tissues.

The aim of this study was to compare conventional time resolved contrast enhanced time-resolved MR angiography and optimised steady state MR angiography using a blood pool

contrast medium (Vasovist®, gadofosveset trisodium, Schering AG, Berlin, Germany) for evaluating the intra-thoracic and neck central venous system in patients with suspected venous disease).

Materials and methods:

This was a prospective ethically approved and Clinical Trial Authorised (2007-002730-11) open-label feasibility study undertaken from August 2008 to November 2010 with an expected final sample size of 30 patients at Cambridge University Hospitals NHS Foundation Trust. Patients over 18 years old routinely referred for MR angiography of central veins were recruited. Exclusion criteria included patients under 18 years, contraindications to MRI (e.g. pacemaker, aneurysm clips, orbital metal), contraindications to intravenous gadolinium agents (in our institution this includes patients with liver transplants and patients with impaired renal function with estimated Glomerular Filtration Rate of less than 30 ml/min/1.73 m^2), pregnant or lactating women. Following referral from the clinicians for MR angiography of the central veins, a written contact from the radiology department with provision of a letter of invitation to the study and a participant information sheet were made available to the potential subjects. Signed informed written consent was obtained on the day of the study.

MRI Protocol

The examination was performed using a 1.5T MRI system (GE Healthcare, Milwaukee, WI, USA) with an 8 channel cardiac receive array. Patients were placed in a supine position with their arms at their sides. After a three-plane localizer image was acquired, Vasovist® was administered intravenously at a dose of 0.12ml/kg body weight (maximum 10mls) at 0.8ml/s followed by a saline flush of 20ml at 2ml/s. The multiphase first-pass (FP) time-resolved

imaging of contrast kinetics (TRICKS) MR sequences were first obtained in the coronal orientation 5 seconds after Vasovist® administration during shallow breathing, as per our standard acquisition, with the following parameters: FOV 40x40cm; slices:section thickness 42:2.6mm; matrix 418x256; 0.75NEX; flip angle 30°;ASSET factor 2; temporal resolution 10sec, 30 phases acquired. Additional optimised steady-state (SS) imaging was subsequently performed with the following parameters: FOV 40x40cm; slices 64 x1.6mm;matrix 512x512x2.0 NEX interpolated to 1024 x1024; flip angle 30°; acquisition time 4.25min. The SS imaging took approximately 10 minutes. The entire examination took approximately 30 minutes.

Data analysis

The FP and SS data sets were anonymised and then assessed independently in randomised fashion on a PACS workstation (Centricity, GE Healthcare). The FP images were used as the reference standard for correct diagnosis. Nine venous segments were assessed: superior vena cava (SVC), left and right branches of brachiocephalic, subclavian, internal jugular, and axillary veins. The boundary between the subclavian vein and the axillary vein was defined 5 cm from the junction with the internal jugular vein.

On each examination and for each venous segment, assessments were made of the following four areas:

1) Image quality in terms of vessel conspicuity using a five-point scale: excellent (optimal visualisation of the vessel with no signal loss), good (slight signal loss but good overall visualisation of the vessel), moderate (decreased signal intensity but images remain diagnostic), poor (insufficient signal intensity such that the vessel is not completely identifiable and the image is not diagnostic, or very poor (no or hardly any signal intensity and the vessel cannot be identified).

2) Presence of stenosis using a six-point scale: no (0%) stenosis, mild (1-30%) stenosis, mild-to-moderate (31-50%) stenosis, moderate (51-75%) stenosis, severe (76-99%) stenosis, or total vessel occlusion. Each venous segment was evaluated for the highest degree of stenosis within that segment. Diameters were measured by using electronic caliper on the workstation by readers. Assessment of the degree of stenosis was not performed if a vessel could not be fully evaluated due to poor or very poor image quality.

3) Presence of thrombosis using a three-point scale: no thrombosis, partial thrombosis (1-50% occlusion), complete thrombosis. Each venous segment was evaluated for the highest degree of thrombosis within that segment. Diameters were measured by using electronic caliper on the workstation by readers. Assessment on the presence of thrombosis was not performed if a vessel could not be fully evaluated due to poor or very poor image quality.

4) Presence of artefacts using a three-point scale: none, mild (artifacts present but not impairing diagnostic information), or major (extensive artifacts impair diagnosis).

All images (including time-resolved MIP images and high-spatial-resolution source images) were assessed in consensus by three consultant radiologists with 20, 7, and 2 years of experience in MRA reporting, respectively. The readers were allowed to individually adjust window centers and level settings of the MR data sets. The FP and SS images were assessed independently and the order in which they were viewed was alternated with each successive study participant to reduce recall bias. The readers were blinded to all clinical and demographic information. Any adverse events or adverse reactions were evaluated by the investigators and, where indicated reported to the sponsor for evaluation.

Statistical methods:

The FP and SS images were compared separately in terms of (i) their image quality; (ii) presence of stenosis; (iii) level of thrombolysis detected; and (iv) presence of artefact. The number of patients with discrepancies between the FP and SS images was tabulated for all venous segments, and the discrepancies were classified according to the level of discrepancy that was observed. Percentages were presented with corresponding 95% confidence intervals calculated using Newcombe's method.

In order to assess agreement between the FP and SS imaging techniques, kappa statistics were produced. In addition, for the image quality and stenosis comparisons, results were compared by means of a Wilcoxon's signed rank test. This non-parametric test is appropriate for paired data, and was performed to test against the null hypothesis of no difference in scores between the FP and SS imaging techniques. For the thrombolysis and artefact comparisons, since there were only 3 categories for each of these variables, the number of categories was deemed to be too low to perform a Wilcoxon's signed rank test, so a McNemar's test was performed instead on a reduced 2 by 2 table of counts.

Results:

Thirty two subjects were recruited for this study; one subject did not complete the study due to claustrophobia, one subject did not have all appropriate images taken, and steady state imaging was not obtained in one subject due to an operator error and was excluded from analysis; imaging from twenty nine subjects was therefore analyzed. These figures have been verified by local monitors during trial closure procedures. No adverse events or reactions were reported. A total of 261 venous segments were assessed in both FP and SS imaging, respectively.

Table 1 shows the results between the two techniques in terms of image quality. The proportion of images with no discrepancy in image quality was 57% with a 95% confidence interval of 51% to 63%. This interval contains the true population proportion of images with no discrepancy with 95% probability. In the remaining 43% of venous segments where discrepancies occurred, SS imaging showed better image quality in 5% by 2 or 3 points scale (10 of these 12 venous segments were the right sided central veins) and 26% by 1 point scale (38 of these 69 venous segments were the left sided central veins). The result suggests that image quality was usually better for SS imaging compared to FP, but this was not always the case. For example, in 5 (2%) out of the 261 venous segments, the image quality was substantially worse using the SS technique compared to FP.

Table 1 Assessment of Image quality

Image Quality	N	No discrepancy	Image quality better using SS by 2 or 3 points	Image quality better using SS by 1 point	Image quality worse using SS by 1 point	Image quality worse using SS by 2 or 3 points
SVC	29	19 (66%)	0	6	4	0
RB	29	16 (55%)	2	8	3	0
RS	29	14 (48%)	1	12	1	1
RA	29	16 (55%)	4	3	5	1
RIJV	29	21 (72%)	3	2	3	0
LB	29	18 (62%)	1	8	1	1
LS	29	16 (55%)	0	10	2	1
LA	29	11 (38%)	0	13	4	1
LIJV	29	17 (59%)	1	7	4	0

Total	261	148 (57%)	12 (5%)	69 (26%)	27 (10%)	5(2%)

SVC= superior vena cava; RB= right brachiocephalic vein; RS=right subclavian vein; RA=right axillary vein; RIJV=right internal jugular vein; LB= left brachiocephalic vein; LS= left subclavian vein; LA= left axillary vein; LIJV= left internal jugular vein; N= number; SS= steady-state

Table 2 shows the SS image quality scores against the FP image quality scores. A Wilcoxon signed-ranks test to test if the SS imaging produced images of a significantly higher quality compared to the FP imaging produced a Z score of -4.30 with a significant corresponding p-value of <0.0001. Therefore, there was evidence to suggest that SS imaging produced images of a significantly higher quality *on average*. Nevertheless, the table shows that 4 venous segments graded as excellent or good quality using FP imaging were found to be poor using the SS imaging. The kappa statistic for agreement was calculated to be 0.30, indicating only fair agreement between the two imaging techniques in terms of image quality.

Table 2 Image quality scores between first pass (FP) and steady-state (SS) imaging techniques

Image quality		SS				Total
		Excellent	Good	Moderate	Poor	
FP	Excellent	28	4	1	1	34
	Good	43	98	19	3	163
	Moderate	10	23	22	4	59
	Poor	1	1	3	0	5
Total		82	126	45	8	261

Table 3 shows the results between the two imaging techniques in assessing the degree of stenosis. There were 13 venous segments where assessments were not possible due to non-diagnostic image quality. The proportion of images with no discrepancy in stenosis was 88% with a 95% confidence interval of 84% to 92%. This indicates that for the vast majority of images there was no discrepancy in terms of stenosis. The table also shows that where discrepancies occurred, they usually involved SS showing lower (or much lower) degree of stenosis compared to FP imaging. For 5 subjects the discrepancy was very severe.

Table 3 Assessment of stenosis

N	No discrepancy	Lower levels of stenosis according to SS by 4 or 5 points	Lower levels of stenosis according to SS by 3 points	Lower levels of stenosis according to SS by 2 points	Lower levels of stenosis according to SS by 1 point	Higher levels of stenosis according to SS by 1 point
29	26 (90%)	0	0	1	2	0
29	25 (86%)	0	0	0	2	2
28	23 (82%)	2	0	2	1	0
24	23 (96%)	1	0	0	0	0
29	26 (90%)	0	0	0	2	1
29	22 (76%)	0	0	4	3	0
27	24 (89%)	1	0	1	1	0
24	23 (96%)	1	0	0	0	0
29	27 (93%)	0	0	0	2	0
248	219 (88%)	5 (2%)	0	8 (3%)	13 (5%)	3 (1%)

See table 1 for abbreviation

Table 4 shows the SS stenosis scores against the FP stenosis scores. A Wilcoxon signed-ranks test was performed on the data to test if the SS imaging results in grading of the level of stenosis significantly differently to the FP imaging. The test statistic using a normal approximation was $Z = -4.25$ with a corresponding p-value of <0.0001. Therefore, there waas evidence to suggest that the SS imaging resulted in significantly lower level of stenosis grading than the FP imaging on average. However, the kappa statistic for agreement was calculated to be 0.75, indicating good agreement between SS and FP in grading the level of stenosis.

Table 4 Stenosis scores between first pass (FP) and steady-state (SS) imaging techniques

Stenosis		SS						Total
		None	Mild	Mild-Moderate	Moderate	Severe	Total	
FP	None	167	0	0	0	0	0	167
	Mild	4	1	0	0	0	0	5
	Mild-moderate	4	0	2	0	0	0	6
	Moderate	0	3	2	1	0	0	6
	Severe	1	0	0	1	8	3	13
	Total	4	0	0	1	6	40	51
Total		180	4	4	3	14	43	248

Table 5 shows the results between the two imaging techniques in assessing thrombosis. The proportion of images with no discrepancy was 97% with a 95% confidence interval of 94% to 99%. Therefore, as with assessment of stenosis, there was again very little discrepancy

between the two techniques. The two techniques never disagreed by more than one level (i.e. "none" was never paired with "complete" thrombosis).

Table 5 Assessment of thrombosis

Thrombosis	N	No discrepancy	Thrombosis lower according to SS by 1 level	Thrombosis higher according to SS by 1 level
SVC	29	29 (100%)	0	0
RB	27	26 (96%)	1	0
RS	26	24 (92%)	2	0
RA	23	21 (91%)	1	1
RI	27	27 (100%)	0	0
LB	28	27 (96%)	0	1
LS	24	24 (100%)	0	0
LA	22	21 (95%)	0	1
LI	26	26 (100%)	0	0
Total	232	225 (97%)	4	3

Table 6 shows the SS thrombosis scores against the FP thrombosis scores. The table suggests that agreement appeared to be fairly good between SS and FP. Indeed, the kappa coefficient was 0.77, indicating good agreement between SS and FP. A McNemar's test was performed

on the reduced table of counts with "Partial" and "Complete" combined to form a single category. The p-value was calculated to be 1.00, so there was no significant difference in thrombosis assessment between the two techniques.

Table 6 Thrombosis scores between FP and SS imaging techniques

Thrombosis		SS			Total
		None	Partial	Complete	
FP	None	212	3	0	215
	Partial	4	10	0	14
	Complete	0	0	3	3
Total		216	13	3	232

Table 7 shows the discrepancies between the two techniques in terms of the presence of artefacts. The proportion of images with no discrepancy in assessment of artefacts was 64% with a 95% confidence interval of 58% to 70%. Therefore, the SS and FP imaging techniques did not agree for a reasonably high proportion of images. In 2 venous segments, the SS imaging suffered major artefacts while the FP imaging suffered no artefacts. However overall, where discrepancies occurred, the SS technique usually concluded a lower level of artefact compared to the FP technique