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Gadofosveset-enhanced Magnetic Resonance Venography in patients with venous pathology of the lower limbs – comparison of diagnostic image quality and inter-rater variability with Gadobutrol Venography and CT Venography

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Abstract

Purpose

This study was performed to compare the diagnostic quality of Gadofosveset-enhanced MR venography (MRV) with Gadobutrol-enhanced MRV and CT venography for the deep veins of the lower extremities in patients with ilio caval venous pathology.

Materials and Methods

Diagnostic capability and image quality was assessed by two independent readers. Inter-reader variability was analyzed by unweighted and quadratic weighted Cohen's kappa values.

Results

The diagnostic capability was equal to or higher in the Gadofosveset group for all examined vessel segments compared with both control groups. The image quality score was significantly higher for the Gadofosveset group compared to both control groups.

Inter-reader variability, expressed by quadratic weighted Cohen's kappa value (k) showed less variability in the Gadofosveset group compared to the control groups.

Conclusion

Our results show that Gadofosveset enhanced MRV is a reliable technique in clinical routine practice, with image quality superior to both Gadobutrol enhanced MRV and CT venography.

Key words: Gadofosveset, Blood-Pool Contrast Agent, Magnetic Resonance Venography, imaging, deep vein thrombosis.

Introduction

Imaging of vascular pathology in the central veins of the lower extremities and the abdomen can be performed using Magnetic Resonance Venography (MRV), Computed Tomography Venography (CTV), Ultrasound (US) and Digital Subtraction Angiography (DSA). In most centers DSA or US is the first choice for the diagnosis of thrombosis in the deep veins of the legs. However, since visualization of the iliac veins and the vena cava is difficult using ultrasound or DSA via a peripheral superficial vein, most centers rely on CTV and/or MRV for these segments [1].

With the advent of novel endovascular interventions such as catheter-directed thrombolysis or recanalization of chronic ilio caval occlusions there is a rising demand for optimal preoperative imaging for patient selection, endovascular planning and follow-up. Recent therapeutic studies show good long-term results suggesting that this treatment may be expanding to a larger patient population in the future [2, 3].

The vast majority of contrast agents used for CT and MRI are rapidly transferred from the blood, resulting in rapidly diminished attenuation/signal in the blood resulting in difficulty to obtain high-resolution images, especially of the central veins, and increased attenuation/signal in many surrounding tissues that may impair the imaging of the vessels.

Gadofosveset (Vasovist[®], formerly supplied by Bayer Schering Pharma AG, Berlin, Germany and Ablavar[®] currently supplied in North America by Lantheus Medical Imaging, North Billerica, MA, USA) is a gadolinium based contrast agent that remains in the blood for a longer time (blood-pool agent) due to its high affinity to serum albumin, allowing longer acquisition time necessary for high resolution images, and the exact timing of the image acquisition is less crucial.

The high affinity for albumin also increases the T1-relaxivity allowing high quality images using relatively low amount of gadolinium [4].

Gadofosveset was rapidly adopted as an angiographic contrast agent for arterial studies [5-11] for thoracic vessels [12] and the heart [13]. Several studies have described the use of Gadofosveset for venous examinations in patients without suspected venous pathology [14, 15] as well as in patients with deep vein thrombosis of the leg [16, 17]. Pfeil and colleagues have showed good inter-rater reliability for MRV on healthy subjects [18]. However few reports are available on patient with severe venous pathology of the ilio caval veins.

This study was performed to compare the diagnostic quality of Gadofosveset-enhanced MR venography (MRV) with Gadobutrol-enhanced MRV and CT venography for the deep veins of the lower extremities in patients with suspected or known ilio caval venous pathology.

Material and Methods

Patients

The Radiology Information System (RIS) was used to retrospectively identify all 34 examinations using Gadofosveset for MRV of the lower limbs in as many patients between January 2007 and August 2009. For comparison 14 consecutive patients examined according to the same protocol on the same MR scanner using Gadobutrol were identified. Another 16 consecutive CTV referred by senior consultants in vascular medicine were also used for comparison. The majority of cases were referred for chronic ilio caval occlusions, and less common reasons for referral included acute ilio caval thrombosis, pelvic varices and venous vascular malformations. All patients examined were considered for endovascular treatment. Age, gender, weight and creatinine levels as well as immediate adverse reactions and technical problems were registered from RIS data. Clinical patient records were scrutinized for potential

adverse events with a follow-up time of 2-5 years (mean follow-up time 3.1 years). For the majority of patients the serum creatinine was not measured after the examination, thus any analysis of potential renal damage indicated by serum creatinine increase was impossible. Table 1 summarizes the patient data. Because this was a register study as part of the hospital's quality assurance program, no informed consent was needed and the local ethics committee waived ethical approval for publication of the results.

Magnetic Resonance and Computed Tomography Imaging

MRI was performed with a 1.5 T scanner (Symphony, Siemens Healthcare/Medical Solutions, Erlangen, Germany). Matrix coils covering the upper leg and the abdomen were used for signal reception. Similar sequences were used for all MRI examinations. Angiographic sequences (FI3D) were performed in the coronary projection with slice thickness of 0.7 mm, repetition time of 5.6, echo time of 2, number of averages 1, number of phase encoding steps 461, 100% sampling, 70% field of view, acquisition matrix of 832x576 and a flip angle of 15. The infrarenal caval vein, the iliac and femoral veins were examined. Additional sequences such as T1 TSE and TIRM were not evaluated in this study.

Contrast medium was administered using a peripheral venous access and a power injector (Spectris Solaris, Medrad, Pittsburgh, US) in all patients. The Gadofosveset trisodium dose was aimed at 0.12 ml/kg bodyweight (Vasovist® 0.25mmol/ml, Bayer Schering Pharma AG, Berlin, Germany) ranged from 5.0 to 10.0 ml, with an average dose of 8.7 ml. The Gadobutrol doses in the control population (Gadovist® 1mmol/ml, Bayer Schering Pharma AG, Berlin, Germany) ranged between 18-30 ml with an average dose of 22 ml.

CT venography was performed from below the knees to the heart on 16- or 64-channel multidetector CT (Somatom, Siemens Healthcare/Medical Solutions, Erlangen, Germany) at

120kV and 140mAs, collimation of 16x0.75mm or 64x0.75mm, pitch of 1.2 and rotation time of 0.5 seconds. The scanner was started manually based on Hounsfield unit-monitoring at the level of the infrarenal caval vein. Monitoring was started 90 seconds after injection of contrast medium and scanning was started manually or at the latest 150 seconds after contrast medium injection. Patients were administered 150 ml of Omnipaque 300 (n=11), Visipaque 270 (n=1), or Visipaque 320 (n=3). One patient was administered 75 ml of Visipaque 270 due to impaired renal function.

Image analysis

Images were analyzed in a Sectra PACS (IDS7, Sectra Medical Systems, Sweden) by two independent radiologists (JW and LL). Image settings were adjusted to make identification and image data unavailable during the reading. Assessment was made on whether the examination was good enough for radiological diagnosis for a number of previously defined vessel segments; the suprarenal caval vein, infrarenal caval vein, common, external and internal iliac veins, common, superficial and deep femoral veins and popliteal veins. The overall quality of the examination was also assessed on a four-grade scale (0= non diagnostic, 1=acceptable, 2=good, 3=excellent). Maximal diameter was measured in coronal images for MRV and coronal reconstructed images for CT of the infrarenal caval vein and the common and external iliac veins. For those patients that had undergone DSA within one month of the examination, the diameter measurements were compared in an open analysis to those at the same level on DSA images.

Statistical methods

Data were analyzed using standard statistical methods (SPSS version 20, IBM Corporation NY) including two-tailed Mann-Whitney U-test to compare data between the study groups. A p-value <0.05 was regarded as significant. For the scoring of the overall image quality the inter-reader variability was analyzed using degree of agreement and Cohen's kappa coefficient (un-weighted

and quadratic weighting). For the weighted Kappa analysis quadratic weighting was chosen and the relative distances between all steps in the image-quality scale were set to 1.

Results

The study population contains all 34 Gadofosveset-enhanced MRV in as many patients all performed on the same scanner at our hospital. In one case the abdomen was excluded in the examination and in two cases the upper legs were excluded due to specified instructions in the referrals. In all other cases the examination covered the upper part of the legs and the abdomen. There were no early reactions or other adverse events related to the contrast medium and no major technical problems were reported. No long-term complications related to the contrast media, including Nephrogenic Systemic Fibrosis (NSF) was seen in any of the patient groups during follow-up (19).

The results from the assessment of the diagnostic ability of the images for venous segments are shown in table 2. The Gadofosveset group had the highest portion of diagnostic examinations for all analyzed vessel segments, however for one segment the numbers were equal also for the control groups. Figure 1 shows examples of the images in the Gadofosveset group.

Both reviewers rated the Gadofosveset MRV considerable higher on the subjective image quality scale compared to the MRV control group and also compared to the CTV group (table 3). The quality score for both control groups were significantly lower ($p < 0.001$). The weighted Kappa values are lower for both control populations (MRV control $k = 0.59$, and CTV control $k = 0.44$) compared to the Gadofosveset group ($k = 0.68$).

Seventeen of the patients in the Gadofosveset group (50%), 3 of the MRV control group (21%), and 7 of the MRV control group (44%) underwent a subsequent angiography (DSA) within one

month of the examination. The subsequent DSA did not always include all vessel segments analyzed in this study. Tables 4 and 5 summarize the results of the diameter measurements. For the Gadofosveset group the mean diameter difference between MRV and DSA (n between 6 and 13) was 1.1 mm or less for all segments. In both control populations there were relatively few patients who had undergone a subsequent DSA, and only for the inferior caval vein were 3 or more DSA measurements available. The mean diameter difference between MRV and DSA were 5 mm for the MRV group and 4 mm for the CTV group.

Discussion

This is a retrospective study of 34 consecutive MRV of the lower limbs using Gadofosveset that were compared with 14 consecutive MRV of the lower limbs performed using Gadobutrol. These examinations are all done on the same MR scanner and for the same clinical indications. As a second comparison we used 16 consecutive CTV referred for suspected ilio caval pathology by senior consultants in vascular medicine.

There were no technical problems or early adverse events related to the contrast medium according to the RIS-documentation for any of the examinations.

The proportion of vessel segments that were assessed as diagnostic by both readers was higher for the Gadofosveset group for all examined segments except one where all groups were equally high. The difference between Gadofosveset- and Gadobutrol-enhanced images may be due to the higher T1-signal enhancing the signal, and the blood-pool effect allowing much longer acquisition time and also making acquisition-time point less important when using Gadofosveset [4]. This is more pronounced for the vena Cava and the iliac veins than for the femoral veins, probably due to slower uptake in surrounding tissues for blood-pool agents compared to conventional gadolinium based contrast media, thereby providing higher contrast to noise ratio

for the vessels.

The significant difference in image quality between the Gadofosveset MRV and the control groups may to some extent also be due to the difficulties in timing the start of image acquisition in relation to the contrast medium administration, since it is not readily possible to rely on bolus-tracking techniques. Exact timing is even more challenging in patients with severe venous pathology in the lower limbs since the optimal timing may differ between left and right side. The blood-pool characteristics of Gadofosveset on the other hand make it virtually insensitive to the timing between administration and image acquisition.

Furthermore, there is an observed difference in diagnostic capability between left and right side in both control groups, which is not present in the Gadofosveset group. This may be due to a higher prevalence of venous pathology on the left side due to May Turner syndrome, i.e. compression of the left common iliac vein between the right common iliac artery and the vertebral bodies, which is an underlying condition in a large portion of left iliac vein thrombosis. The results suggest that image quality with Gadofosveset MRV is to a higher degree maintained even when there is severe venous pathology.

It is possible for all MRV to obtain a first-pass (arterial) dataset that can be subtracted from the late (venous, or steady-state) dataset to produce images where the contrast in the arteries is subtracted, however such subtraction may also induce artifacts and in our experience it is more advantageous to assess the venous pathology on unsubtracted images.

The significantly higher image quality scoring for the Gadofosveset group compared to the control groups is perhaps the most important finding. The results strongly favor Gadofosveset with significantly higher average scoring by both reviewers. The absence of any scoring lower than 2, on a scale between 0 and 3, also suggests that the technique is robust and relatively

insusceptible to technical errors and artifacts. This is further underscored by the high Kappa value of 0.68 suggesting a good inter-reader agreement. Figure 1 illustrates Gadofosveset-enhanced images. The sharp reproduction of the vessels including small details is probably the reason for the large differences in image quality scoring although the difference in diagnostic ability for the various venous segments is less pronounced.

The mean difference in diameter for the inferior caval vein was only 1.1 mm for the portion of patients (50%) of patients that had a subsequent DSA within 1 month of the MRV. This difference was significantly lower compared to the MRV control population ($p=0.004$), as well as compared to coronal reconstructed images from the CTV control group ($p=0.016$). This difference further underscores the superior image quality of Gadofosveset MRV compared to the alternatives. If the differences in images quality influences the decision to perform endovascular treatment remains to be studied, but in our material it is evident that the number of patients with a subsequent DSA within one month is higher for the Gadofosveset group than for the control groups although the demographic data are similar.

All MRV in this material were done at 1.5T and it is possible that examination at 3T may provide better results that could to some extent improve the results for the MRV with conventional gadolinium-based contrast media. CT is generally more readily available and less expensive compared to MR. Recent development of CT including dual-energy acquisition and dedicated protocols for CTV may also improve the results, as have been shown for example using pedal cannulation and contrast injection [20].

For clinically relevant doses the price/examination is approximately 25% lower for Gadofosveset compared to Gadobutrol (based on the official prices provided by the manufacturers for the doses used in our patient material).

Gadofosveset has been widely used as an angiographic agent for MRA [5-13]. For venous imaging there are studies on healthy subjects or patients with no venous pathology, including inter-reader variability with generally good results [14, 15, 18]. A couple of studies have been done on patients with deep vein thrombosis of the leg in 6 cases [16] and 8 cases [17]. But we have not been able to find reports on imaging of the caval vein and the iliac veins in consecutive series of patients with acute thrombosis or chronic thrombotic occlusions using blood-pool agents.

Conclusions

In this report we show that Gadofosveset provides high-resolution MRV in clinical routine practice with a good success-rate and superior image quality in a series of patients with high prevalence of venous pathology affecting the ilio caval veins. Imaging of advanced pathology in the deep veins can be a valuable application of blood-pool contrast agents.

Authors 1-5: no conflict of interest

For this type of study formal consent is not required.

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Table 1

	Gadofosveset MRV	Control (Gadobutrol MRV)	Control (CTV)
Number of patients (n)	34	14	16
Male/female (p-value)	15/19	7/7 (p=0,76)	7/9 (p=0,99)
Age (mean, p-value)	12-71 (42)	23-79 (47, p=0,34)	20-83 (51, p=0,09)
Weight kg (mean, p-value)	39-104 (75)	45-112 (78, p=0,61)	52-118 (74, p=0,50)
Reason for referral			
Chronic occlusion caval/iliac	23	7	6
Acute thrombosis caval/iliac	5	3	10
Venous malformation	4	2	0
Pelvic varices	2	2	0

Table 1: Patient characteristics (gender, age and bodyweight) and the primary reason for referral for the three groups. No significant differences were found between the groups by Mann Whitney test.

Table 2

Reader 1/Reader 2 (%)	Gadofosveset MRV	Control (Gadobutrol MRV)	Control (CTV)
Infrarenal inferior caval vein	100/97	86/71	94/100
Suprarenal inferior caval vein	100/100	79/86	94/100
Right common iliac vein	100/100	86/100	88/94
Right external iliac vein	100/97	100/93	88/94
Right internal iliac vein	100/100	86/100	94/100
Right common femoral vein	100/100	100/100	100/94
Right superficial femoral vein	100/97	86/100	100/88
Right deep femoral vein	100/100	100/100	100/100
Right popliteal vein	100/97	86/100	100/94
Left common iliac vein	100/94	86/57	94/81
Left external iliac vein	100/91	100/71	88/63
Left internal iliac vein	100/97	93/57	88/81
Left common femoral vein	100/97	100/57	94/81
Left superficial femoral vein	100/97	86/64	88/69
Left deep femoral vein	100/100	100/79	88/81
Left popliteal vein	100/94	86/57	88/75

Table 2: Assessment diagnostic ability for all previously defined vessel segments made by the two independent readers (reader 1/reader 2).

Table 3

Reader 1/Reader 2	Gadofosveset MRV	Control (Gadobutrol MRV)	Control (CTV)
Quality score range (0-3)	2-3/2-3	0-3/1-3	0-3/1-2
Quality score mean (p)	2,8/2,7	1,4/1,6 (p<0,001)	1,6/1,7 (p<0,001)
Degree of agreement	88%	50%	50%
Unweighted Kappa	0,68	0,25	0,22
Quadratic weighted Kappa	0,68	0,59	0,44

Table 3: Subjective image quality score range and mean by the two independent readers (Reader 1/Reader 2) for the three groups (Gadofosveset MRV, Gadobutrol MRV and CTV), and inter-reader variability measured by the degree of agreement defined as the degree of identical scores from both readers, and by Cohen's Kappa value unweighted and quadratic weighted. The difference in kappa-values between the Gadofosveset group and the control groups was significant according to two-tailed Mann-Whitney U-test.

Table 4

Gadofosveset	Mean \varnothing MRV (mm)	Mean \varnothing DSA (mm)	Max MRV-DSA (mm)	Mean \varnothing dif. (mm)
Inferior caval vein	22,8 (n=25)	21,1 (n=13)	3	0,8
Right common iliac vein	14,7 (n=27)	15,6 (n=10)	4	1,1
Right external iliac vein	13,1 (n=29)	13,1 (n=9)	3	1
Left common iliac vein	17,6 (n=18)	16,7 (n=6)	2	0,3
Left external iliac vein	14,1 (n=22)	13,3 (n=6)	4	1,1

Table 4: Comparison of diameter between the preoperative examination (Gadofosveset-MRV) and the subsequent angiography (DSA). The mean diameter of the vessels in each group are shown, and the maximal and mean difference between the preoperative examination and subsequent DSA. The number of patients that underwent a subsequent DSA including the specific vessel segment is indicated.

Table 5

Group	Mean ø MRV (mm)	Mean ø DSA (mm)	Max MRV-DSA (mm)	Mean ø dif. (mm)
Gadofosveset - Inferior caval vein	22,8 (n=25)	21,1 (n=13)	3	0,8
Control Gadobutrol MRV - Inferior caval vein	21,1 (n=11)	16 (n=3)	7	5 (p= 0.004)
Control CTV - Inferior caval vein	22,7 (n=16)	21,1 (n=7)	6	4 (p= 0.016)

Table 5: Comparison of the diameter of the inferior caval vein in all three groups (Gadofosveset-MRV, Gadobutrol-MRV and CTV) and the subsequent angiography (DSA). The number of patients that had a subsequent DSA including the caval vein is indicated. The mean diameter of the caval vein is shown, as well as the maximal and mean difference between the preoperative examination and the subsequent DSA. The mean difference was significantly lower for the Gadofosveset group compared to the MRV control group (p=0.004) and the CTV control group (p=0.016).

Figure 1

Figure 1: Examples of Gadofosveset MRV images. Panel A is a MIP-image showing the deep veins of the abdomen and pelvis. Panel B is a magnification of the bifurcation area, showing the aortic (A) and caval (C) bifurcations. Panel C is a MIP-image showing the veins and arteries of the upper part of the legs. Panel D is a MIP-image showing the deep veins of the abdomen and pelvis in a patient with a post-thrombotic syndrome and occlusion of the vena cava and the iliac veins, illustrating the extensive collateral vasculature typical of such cases. Panel E is magnification of the upper part of a leg showing the relationship between the superficial artery (a) and vein (v) and details of the vein such as valves (arrowhead) and small branches (arrow). Panel F is magnification of the pelvis in a patient with a post-thrombotic syndrome following a thrombotic occlusion of the left common and external iliac veins. The image shows an example of a spontaneously partially recanalized vein with membranous septa, typical of such cases.