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Department of Imaging Sciences, University of Rochester Medical Center, Rochester, USA

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PICTORIAL ESSAY

Blood Pool Contrast-enhanced Magnetic Resonance Angiography with Correlation to Digital Subtraction Angiography: A Pictorial Review

Martha-Grace Knuttinen, Jillian Karow, Winnie Mar, Margaret Golden, Karen L Xie

Department of Radiology, University of Illinois Hospital and Health Sciences System, Chicago, Illinois, United States

Address for correspondence:
Dr. Jillian Karow,
Department of Radiology, University of Illinois at Chicago Medical Center (M/C 931), 1740 West Taylor Street, Room 2483, Chicago, IL 60612, United states.
E-mail: jkowal9@uic.edu

Dr. Martha-Grace Knuttinen

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ABSTRACT

Magnetic resonance angiography (MRA) provides noninvasive visualization of the vascular supply of soft tissue masses and vascular pathology, without harmful radiation. This is important for planning an endovascular intervention, and helps to evaluate the efficiency and effectiveness of the treatment. MRA with conventional extracellular contrast agents relies on accurate contrast bolus timing, limiting the imaging window to first-pass arterial phase. The recently introduced blood pool contrast agent (BPCA), gadofosveset trisodium, reversibly binds to human serum albumin, resulting in increased T1 relaxivity and prolonged intravascular retention time, permitting both first-pass and steady-state phase high-resolution imaging. In our practice, high-quality MRA serves as a detailed "roadmap" for the needed endovascular intervention. Cases of aortoiliac occlusive disease, inferior vena cava thrombus, pelvic congestion syndrome, and lower extremity arteriovenous malformation are discussed in this article. MRA was acquired at 1.5 T with an 8-channel phased array coil after intravenous administration of gadofosveset (0.03 mmol/kg body weight), at the first-pass phase. In the steady-state, serial T1-weighted 3D spoiled gradient echo images were obtained with high resolution. All patients underwent digital subtraction angiography (DSA) and endovascular treatment. MRA and DSA findings of vascular anatomy and pathology are discussed and correlated. BPCA-enhanced MRA provides high-quality first-pass and steady-state vascular imaging. This could increase the diagnostic accuracy and create a detailed map for pre-intervention planning. Understanding the pharmacokinetics of BPCA and being familiar with the indications and technique of MRA are important for diagnosis and endovascular intervention.

Key words: Interventional radiology, pre-procedural planning, vascular

INTRODUCTION

Over the past decade, magnetic resonance angiography (MRA) has dramatically changed the imaging of blood

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vessels. However, catheter-based digital subtraction angiography (DSA) is still widely accepted as the Gold Standard for the diagnosis of several vascular pathologies with high levels of sensitivity and specificity. DSA is invasive and comes with increased procedural risks including hemorrhage and pain at the catheter site, infection, thrombosis, and possible embolization. In addition, the patient and the provider are exposed to potentially dangerous ionizing radiation during the procedure.[1,2] These limitations have led to an increased interest in exploring new MRA techniques and contrast agents. Contrast-enhanced MRA (CE-MRA) can provide reliable answers to most diagnostic questions including identifying or excluding clinically relevant arterial stenosis in adults with peripheral arterial disease symptoms with a sensitivity of 94.7% and specificity of 95.6%.[3] MRA also is advantageous over angiography due to the concurrent visualization of surrounding tissue and the ability to reconstruct data in any plane.[2]

MRA and contrast agents

Non-contrast MRA sequences are currently being developed;[4] however, in daily practice, CE-MRA still provides a higher contrast-to-noise ratio, higher spatial resolution, more rapid speed of acquisition, less artifacts, and higher diagnostic accuracy compared to non–CE-MRA techniques. Therefore, CE-MRA is heavily favored in clinical practice. These contrast agents are formed by chelation of the gadolinium (Gd) ion to prevent cellular uptake and decrease acute toxicity. Free Gd has an ionic radius similar to calcium and acts as an inorganic blocker of many types of voltage-gated calcium channels, inhibiting many calcium-dependent physiological processes. Therefore, ligands are utilized to encapsulate the Gd ion in order to increase thermodynamic stability allowing the contrast agents to be excreted intact. Different agents contain different ligands which create compounds that have varying pharmacokinetic properties and biodistributions. These differences are the basis for the classification and target of Gd-contrast agents (Gd-CA).[5,6]

The first approved agents are classified as conventional extracellular fluid (ECF) agents. After intravenous injection, these agents occupy the intravascular and interstitial space which is collectively known as the ECF. The volume of distribution (V_D) of these agents ranges from 0.21 l/kg to 0.28 l/kg, which is consistent with the V_D of ECF agents. Blood pool contrast agents (BPCAs) which largely remain in the vasculature were recently introduced. The V_D of these agents is 0.148 l/kg ± 0.016 l/kg, which is lower than that of ECF agents, but also indicates these agents are not 100% confined to the vasculature (V_D of pure intravascular agents is 0.07 l/kg). BPCAs contain a lipophilic biphenylcyclohexyl group that reversibly binds human serum albumin. This bond does not allow the BPCA to rapidly extravasate from the vessel into the interstitial space, as occurs with unbounded conventional ECF agents. BPCAs exhibit a prolonged plasma half-life and, therefore, a longer imaging window unlike conventional agents which are restricted to a short imaging window during the first pass.[6] BPCA also allows for steady-state imaging from 5 min up to 60 min post injection, if needed.[7]

The mechanism of action for all Gd-CA can be explained by the difference in T1 relaxation times of blood and surrounding tissue when the contrast is injected intravenously. In general, these agents also shorten T1, T2, and T2* relaxation time constants of adjacent water molecules. The shortened T1 generates a high intravascular signal-to-noise ratio. The binding of albumin by BPCA further increases the relaxivity compared to conventional agents, and thus further improves the image resolution and vascular enhancement. These properties allow for a lower dose of BPCA needed for quality image acquisition.[5,8] The recommended dose for gadofosveset is 0.03 mmol/kg compared to a dose of 0.1 mmol/kg for all other conventional agents. This could potentially decrease the risk of nephrogenic systemic fibrosis (NSF). There are several indications for using MRA in clinical practices, including known or suspected vascular pathology, cardiac congenital anomalies, treatment planning, and postoperative follow-up of vascular pathology or cardiac congenital anomalies. All of these indications could benefit from the improved image resolution, increased vascular enhancement, and decreased dose of contrast needed when utilizing BPCA.

Gadofosveset trisodium

Gadofosveset trisodium, marketed as Ablavar® (Lantheus Medical Imaging, N. Billerica, MA, USA) is the first clinically approved BPCA available in the United States for use in aortoiliac occlusive disease (AIOD). Phase III trials showed a reduced rate of non-interpretable imaging and improved diagnostic confidence compared to unenhanced two-dimensional time-of-flight MRA. The agent was proven safe with low incidence of severe and serious adverse events. Therefore, overall, gadofosveset was determined to be safe and effective for the MR evaluation of patients with AIOD.[7] An additional phase III trial of 145 patients with known or suspected renal artery stenosis demonstrated an increased specificity (23–29%), sensitivity (25–42%), and accuracy of diagnosis (23–29%) of gadofosveset-enhanced MRA compared to non–CE-MRA. The same study demonstrated a decrease of uninterpretable images from 30% to less than 2% when utilizing gadofosveset.[9] Gadofosveset has also

been shown to decrease the number of uninterpretable images when evaluating peripheral arterial disease affecting the pedal arteries. Bosch et al., showed a decrease in uninterpretable images from 16% to 2% when utilizing the BPCA.[10]

Interventional radiology and pre-procedural planning

The use of pre-treatment imaging is becoming increasingly important to reduce procedure time, decrease exposure to ionizing radiation, and decrease the time the patient is sedated. The Trans-Atlantic Intersociety Consensus Group (TASC) concluded that CE-MRA is the ideal imaging modality in predicting which patients require conservative management versus interventions such as angioplasty or surgical revascularization,[11] leaving angioplasty for use in targeted therapy. CE-MRA has been shown to adequately demonstrate vascular anatomy and identify the lesions responsible for patient symptoms, making it sufficient for planning and therapy in many cases.[8] Pre-procedural MR images can be reconstructed in any plane and can be viewed from many angles creating a "roadmap" of potentially complicated vasculature. The use of BPCA can further enhance the detail of these roadmaps. In this article, we illustrate through case presentations the clinical and promising future applications for gadofosveset-enhanced MRA in the evaluation of peripheral vascular disease and abdominal and pelvic pathology.

CLINICAL CASES

Imaging of aortoiliac occlusive disease

Precise anatomic arterial mapping is essential for endovascular treatment of patients with peripheral arterial disease. Although DSA has been considered the Gold Standard, its invasiveness can lead to significant morbidity and mortality. The steady-state imaging that is possible with gadofosveset allows for greater spatial resolution at the cost of acquisition time; this, in turn, allows for detailed visualization of the degree of stenosis and mural abnormalities [Figure 1a–d]. Hadizeh et al., compared the accuracy of steady-state imaging with first-pass gadofosveset MRA against DSA that included a subset of patients with known peripheral arterial disease. Their results found 100% concordance of stenosis grade between the steady-state images and the DSA images. This improved accuracy was attributed to the higher spatial resolution which can be obtained because of the longer intravascular contrast time of the steady-state images.[12]

A 64-year-old woman with a 2-year history of progressive bilateral lower extremity claudication presented with bilateral leg rest pain. Gadofosveset CE-MRA was performed to confirm the diagnosis of AIOD, grade the stenosis, and determine appropriate treatment plan. First-pass MRA revealed localized atherosclerotic disease of the infrarenal abdominal aorta [Figure 1a–d].

Imaging of venous thrombosis

Gadofosveset is also effectively applied to venous imaging. Hansch et al., demonstrated an increased detection of thrombus in the pelvic region, upper leg, and lower leg when utilizing gadofosveset-enhanced MRA over Doppler ultrasound.[13] Its high signal intensity venous enhancement relative to non-vascular structures during steady-state imaging allows for a broad coverage and high contrast evaluation of deep venous structures. This difference in signal is attributed to the higher signal intensity of contrast-enhanced venous blood compared to extracellular agents.

A 44-year-old man with a history of recurrent deep venous thrombosis (DVT) and pulmonary embolisms (PEs) status post inferior vena cava (IVC) filter placement at an outside hospital presented to the emergency room (ER) with chest pain. Computed tomography (CT) scan for work-up of PE revealed two small possible chronic PEs in the right lower lobe and apical right upper lobe. Lower extremity duplex

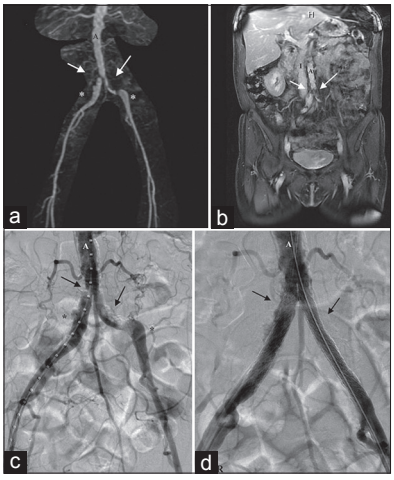

Figure 1: 64-year-old woman with 2-year history of progressive bilateral lower extremity claudication presented with bilateral leg rest pain and was diagnosed with localized atherosclerotic disease of the infrarenal abdominal aorta. Gadofosveset contrast-enhanced magnetic resonance angiography (CE-MRA) (a) First-pass MRA images show high-grade stenosis of right common iliac and long segment stenosis of the left common iliac artery (white arrow). There is also associated post-stenotic dilatation as indicated by the asterisks (A = aorta). (b) High-resolution steady-state image provides further detail of the atherosclerotic plaque (white solid arrows), which is significantly worse on the left (I = inferior vena cava, A = aorta). (c) Digital subtraction angiography performed prior to endovascular intervention reveals 100% correlation to the stenosis identified on MRA as shown by the black arrows, with post-stenotic dilatation as indicated by the asterisks (A = aorta). (d) Covered stents were placed in a kissing fashion at the common iliac arteries extending to the distal aorta with improved patency. The black arrows demonstrate the area of previous bilateral stenosis (A = aorta).

ultrasound revealed a subacute DVT of the right distal external iliac and common femoral veins and chronic DVT of the left distal external iliac, left common femoral, left profunda femoris, bilateral femoral, right popliteal, right gastrocnemius, right posterior tibial, and right peroneal veins. Gadofosveset CE-MRA of the abdomen and pelvis was performed to further assess the venous system. The scan showed a metallic artifact secondary to IVC filter with associated thrombus. The thrombus was noted to extend superiorly to the level of the renal vein inflows [Figure 2a–c].

Imaging of malformations

When assessing for vascular malformations and deciding on appropriate interventional therapies, magnetic resonance imaging (MRI) is essential for differentiating between high-flow vascular malformations and low-flow venous malformations. Utilization of the time-resolved first-pass effect of gadofosveset allows for this distinction, and can effectively be a roadmap for interventional treatment. This time-resolved first-pass effect can assess arteriolar feeders, and/or venous drainage, while the steady-state high-resolution imaging can assess the surrounding vascular structures.[14]

A 37-year-old woman with history of trauma to left knee in 2000 underwent three surgeries to help with swelling and pain presented with continued left lower extremity pain and swelling which was significantly limiting her lifestyle. On examination, a bruit was appreciated over the left patellar area. Previous MR imaging in 2008 revealed

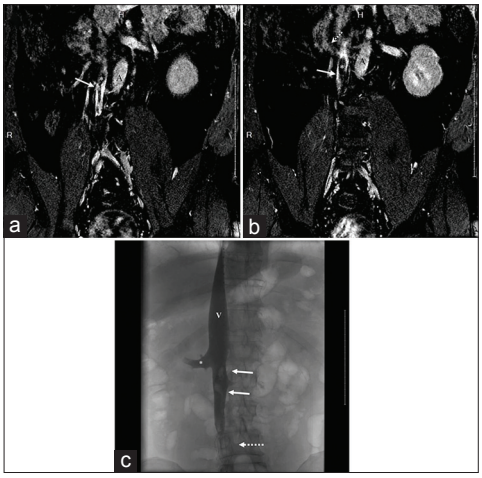

Figure 2: 44-year-old man with history of recurrent deep venous thrombosis (DVT) and pulmonary embolisms (PEs) post inferior vena cava (IVC) filter placement presented to the emergency room (ER) with chest pain. Gadofosveset contrast-enhanced magnetic resonance angiography (CE-MRA) of the abdomen and pelvis, coronal MR venograms: (a) shows a metallic artifact secondary to IVC filter with associated thrombus (*) and (b) shows the thrombus extends superiorly to the level of the renal vein inflows (dotted white arrow) (white solid arrow denotes the IVC, A = aorta). (c) Transcatheter IVC venogram prior to therapeutic thrombolysis demonstrates IVC filter (dotted white arrow) within the infrarenal IVC and filling defects (white solid arrows) consistent with thrombus extending superiorly to the level of the renal inflows (*) (V = IVC).

arteriovenous malformation (AVM). Gadofosveset CE-MRA was performed to re-evaluate the extent of her AVM and determine appropriate treatment plan. MRA showed a large AVM with dominant arterial feeders from the left superficial femoral artery. This was confirmed by DSA [Figure 3a–g]. Endovascular treatment of AVM was performed with Onyx resulting in decreased flow through treated portions of the AVM [Figure 3h–j].

Imaging of pelvic pathology

Chronic pelvic pain is a common health problem that affects millions of women worldwide, but can be a difficult condition to address. Pelvic congestion syndrome (PCS) is a diagnosis that should be considered in many women after other pelvic pathologies have been ruled out. Given its vague symptomatology, PCS is often underdiagnosed. Many of these patients undergo an MRI which offers improved diagnosis and allows for more precise pre-procedural treatment planning.

The incompetent ovarian veins in this syndrome can be identified with gadofosveset imaging. Specifically, the steady-state imaging can allow a clear depiction of the ovarian veins at high resolution. Furthermore, the time-resolved first-pass images are equivalent to a Gold Standard transcatheter venogram in depicting retrograde flow within the ovarian veins.[15]

A 41-year-old woman presented with worsening intermittent pelvic pain that had persisted for several years. Gadofosveset CE-MRA of her abdomen and pelvis was performed to assess underlying pathology. MRA revealed a dilated left gonadal vein (white solid arrow) coursing inferiorly to the pelvic area. The patient was treated with coil embolization of left gonadal vein [Figure 4a–e].

DISCUSSION

The role of minimally invasive imaging techniques has risen in the past several years in order to aid in clinical decision-making and determine appropriate treatment strategies in patients with various diseases. MRA is less invasive than diagnostic angiography without associated complications or radiation exposure. Contrast enhanced -MRA (CE-MRA) has a higher contrast-to-noise ratio, higher spatial resolution, more rapid speed of acquisition, and less artifacts when compared to non–CE-MRA; however, conventional extracellular agents provide limited imaging window for MR angiogram and is highly dependent on the skill of the technologist/operator to scan with the right timing. Blood pool contrast agents (BPCAs) such as gadofosveset have the added advantage of prolonged intravascular time, allowing for a longer

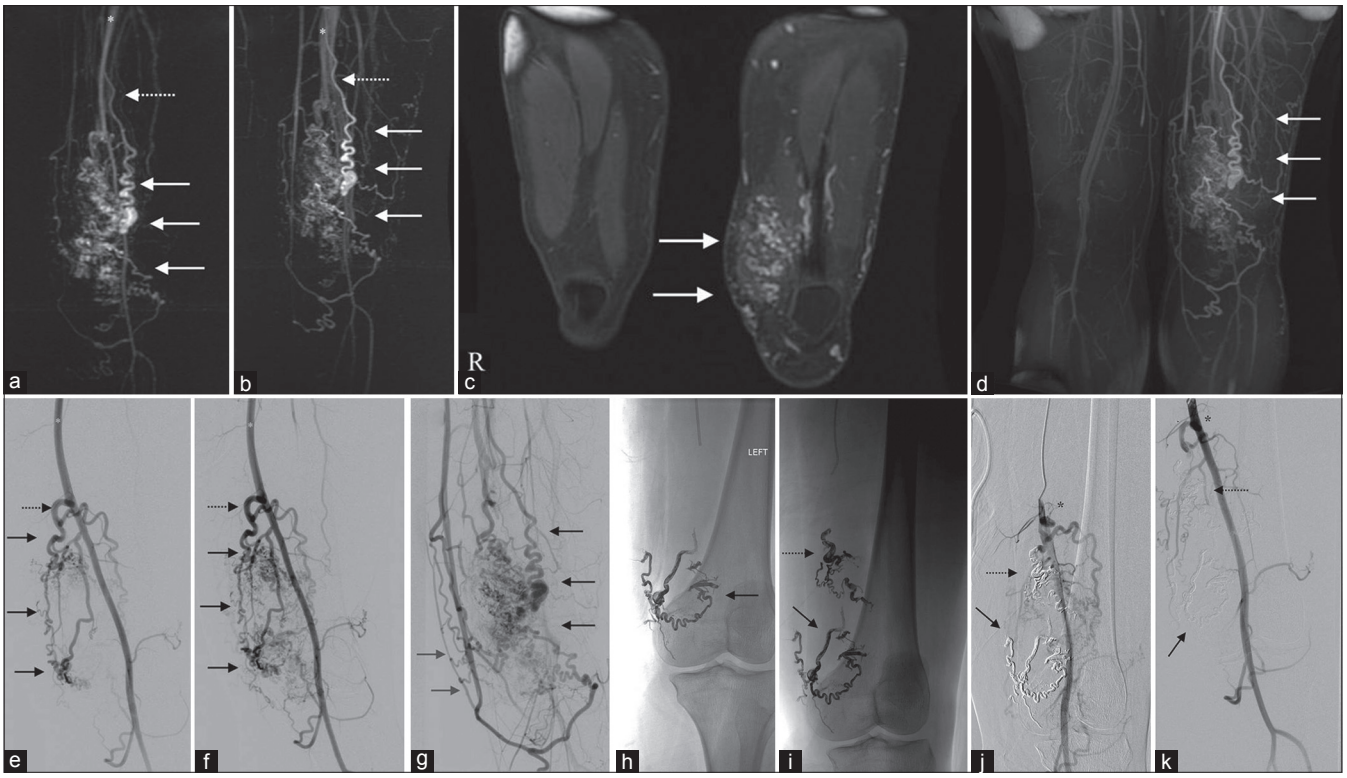

Figure 3: 37-year-old woman with history of trauma to left knee presented with continued left lower extremity pain and swelling with a bruit over the left patellar area. Gadofosveset contrast-enhanced magnetic resonance angiography (CE-MRA) (a) First-pass and (b) steady-state MRA images demonstrate large AVM (white solid arrows) with dominant arterial feeders (white dotted arrow) from the left superfi cial femoral artery (SFA, * = SFA). Steady-state (c) magnetic resonance imaging (MRI) and (d) MRA high-resolution images demonstrate the vasculature in more detail. (AVM is denoted by white solid arrows.) Corresponding digital subtraction angiography (e and f) arterial and (g) venous phase images demonstrate a large AVM (black solid arrows) with a predominant arterial feeder (black dotted arrow) arising from the SFA confirms the MRA findings. Early venous filling is demonstrated by the solid gray arrows (* = SFA). (h-i) Fluoroscopic images show staged endovascular treatment of AVM performed with Onyx (solid black arrow denotes the Onyx placed first, dashed black arrow is the Onyx placed second). (j) Digital subtraction angiogram (DSA) image shows decreased flow through treated portions of the AVM (Onyx is subtracted out in DSA image, but is still faintly visible). (k) Final angiographic result reveals significant decrease in fl ow to the AVM (* = SFA).

steady-state imaging time for higher resolution acquisition and improved overall image quality. However, since gadofosveset remains in the vascular system for up to an hour, caution must be used in rare cases where a second injection is required as there is the possibility of residual venous contamination from the initial examination. In addition, during the steady-state imaging phase, venous enhancement may be perceived as "venous contamination," as often seen in conventional extracellular contrast agents, especially when 3D maximal intensity projection (MIP) images are generated and viewed. To overcome this issue in our practice, we routinely review the high-resolution images in sequential slices and in multiple planes as this will help delineate the venous and arterial vasculatures easily, given the higher imaging contrast and spatial resolution.

The time-resolved first-pass effect and the steady-state imaging together paint a picture useful to provide a detailed assessment and diagnosis of various pathologies. In our experience, the imaging quality and diagnostic capability of CE-MRA with gadofosveset closely correlates with DSA and decreases the amount of uninterpretable images which is a common issue with non-CE-MRA. Moreover, if CE-MRA provides sufficient explanation/diagnosis for a patient's symptoms that do not require intervention, then traditional angiography can be avoided. However, if the findings are inconclusive, then further detailed anatomical imaging can be obtained from traditional angiography. In addition, those patients who are diagnosed with a condition treatable by intervention on the basis of MRA will be treated accordingly, and will have the pre-treatment roadmap information available from the MRA. In our institution, the interventionalists have benefited from the improved image quality for pre-procedural planning and the subsequent decreased procedure time and dose of contrast needed when performing the procedure.

CONCLUSION

Gadofosveset-enhanced MRA proves to be a good diagnostic tool with accurate correlation to DSA without the risks of invasive angiography. The clear and precise images generated when using gadofosveset also create a detailed roadmap for pre-procedural planning which can reduce the

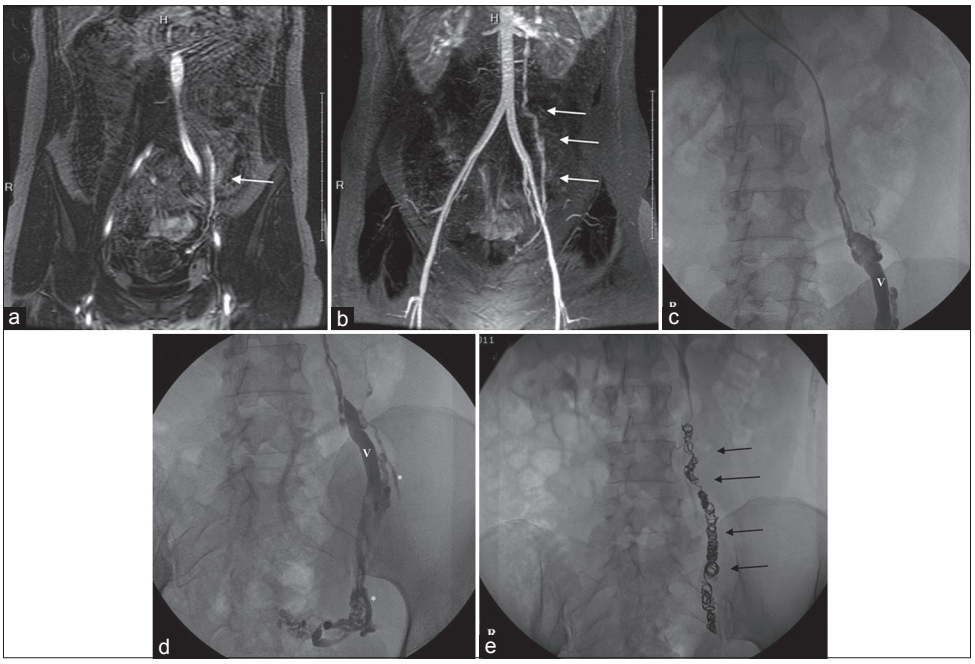

Figure 4: 41-year-old woman presented with worsening intermittent pelvic pain over several years. Gadofosveset contrast-enhanced magnetic resonance angiography (CE-MRA) performed of her abdomen and pelvis to assess for underlying pathology. (a) Venous phase image shows a dilated left gonadal vein (white solid arrow) coursing inferiorly to the pelvic area. (b) Maximum intensity projection (MIP) image demonstrates enlarged gonadal vein (white solid arrows) supplying several pelvic collaterals confirming the presence of pelvic venous insufficiency. (c and d) Conventional transcatheter venography following catheterization of the left renal vein demonstrate the dilated left gonadal vein (V) supplying several pelvic collaterals (*), confirming MR findings. (e) Post-therapeutic venography demonstrates coil embolization of left gonadal vein (black solid arrows).

procedural time. This subsequently results in a decreased radiation dose to the patient and a potential decrease in sedation time which translates into improved patient safety.

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