

Diffusion-weighted Imaging Versus Doppler Ultrasound in the Diagnosis of Calf Deep Vein Thrombosis

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Abstract

Objectives: Doppler ultrasound (DUS) is the primary diagnostic tool used in lower extremity deep vein thrombosis (DVT). However, its accuracy may decrease in the calf-located DVT. This study aims to examine the contribution of diffusion-weighted imaging (DWI) to the diagnosis of acute calf DVT (CDVT).

Materials and Methods: Consecutive patients with clinical suspicion of acute onset CDVT, referred to our department between January 1, 2018 and September 1, 2018, were recruited. Patients were initially evaluated with DUS. Same day magnetic resonance imaging (MRI) [axial T1 and T2-weighted, gradient echo, diffusion, and apparent diffusion coefficient (ADC) sequences with 1.5 T MRI] were performed for comparison. The ADC value was measured independently by two radiologists. Second-look DUS was performed as a confirmatory diagnostic method for patients with incompatible MRI and initial DUS findings.

Results: Thirty-four patients were recruited during the study period. Restricted diffusion was defined significantly more often in patients with acute DVT (11/13 vs. 2/21, $p<0.001$). ADC value was $1.08 \times 10^{-3} \text{ mm}^2/\text{s} \pm 0.575$ and $2.7 \times 10^{-3} \text{ mm}^2/\text{s} \pm 0.639$ in patients with and without thrombus ($p<0.001$). Twelve patients had inconsistent results requiring a second look DUS (ultimately 7 false positive, 4 false-negative cases due to initial DUS), and MRI had a false-positive result in 1 patient.



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Abstract

Conclusion: DWI could detect acute DVT with ADC mapping. Diffusion MRI of the lower extremity may contribute to the diagnosis of thrombi isolated to the deep veins of the calf, especially in selected patients with inconclusive or sub-optimal DUS findings.

Keywords: Diffusion-weighted imaging, calf deep vein thrombosis, MRI, apparent diffusion coefficient, Doppler ultrasound

Introduction

Acute deep vein thrombosis (DVT) of the lower extremity is an urgent pathology that can be complicated and has a high mortality and morbidity risk in both the community and in-hospital care and should be treated promptly⁽¹⁾. Although the clinical significance and management of isolated calf DVT (CDVT) are controversial, the blood clot can extend from crural deep veins to proximal (above the knee) and migrate to the lungs causing pulmonary thromboembolism and hence requires an accurate and timely diagnosis for clinical-decision making. Doppler ultrasound (DUS) is a non-invasive, safe, easily applicable, cost-effective primary diagnostic tool used in DVT diagnosis. However, the diagnostic accuracy of DUS may decrease due to secondary factors such as soft tissue edema, obesity, poor patient cooperation, and inexperienced operator as deep crural veins are often thin or have slow flow⁽²⁾. While the sensitivity of DUS diagnosis is lower in distal DVT (71.2%), it is higher in proximal venous thrombosis (96.5%)⁽³⁾.

The use of magnetic resonance imaging (MRI) for direct thrombus imaging and MR venography has been previously documented⁽⁴⁻⁹⁾. Technological advances in fat saturation pulse sequences and surface coils have made DWI applicable to the whole body⁽¹⁰⁻¹²⁾. Most studies evaluating the detectability of acute DVT by diffusion MRI have a limited number of patients or are experimental⁽¹³⁻¹⁵⁾. This study aims to evaluate the capability of echo-planar

diffusion MRI in CDVT detection as a second-line imaging method.

Materials and Methods

Patient Characteristics

Consecutive patients with clinically suspected acute onset CDVT, referred to our department between January 1, 2018 and September 1, 2018, were recruited prospectively. Patient data on age, gender, history of surgery in the lower extremity within the last month, and results of imaging studies were gathered.

Acquisition Protocol

Patients referred to the radiology department with a clinical suspicion of acute CDVT, received a standard of care lower extremity DUS, and then were referred for study protocol MRI after informed consent. A second look DUS was performed as a confirmatory diagnostic method by a different senior radiologist blinded to MRI results but had access to the first study and clinical records, including the ongoing inpatient stay.

The non-contrast MRI protocol consisted of T1 and T2 weighted, gradient-echo, diffusion-weighted sequences, and ADC map were applied to the patients with a 12-channel body-phased array coil on a 1.5 Tesla scanner (Magnetom Symphony, Siemens, Germany) in axial and coronal sections, including both lower extremities. MRI parameters are listed in Table 1.

Ethics

This study was approved by Acibadem University Faculty of Medicine Ethics Committee (decision no: 2018-18/17, date: 22.11.2018).

Image Analysis and Patient Records

The region of interest was drawn on ADC maps corresponding to T1-weighted, T2-weighted, gradient-echo, and diffusion-weighted sequences from the thrombus level and the regular vessel, which was the equivalent of the same vessel in the other extremity, and ADC values were measured independently by two radiologists. Other sequences were evaluated with consensus. In MRI, additional findings (increased vessel diameter, subcutaneous and muscular edema) were evaluated.

Statistical Analysis

The data was analyzed using SPSS 26.0 (IBM Corp, Armonk, NY, USA). Chi-square test and Fisher's exact test were used to evaluate the factors associated with acute DVT and the relationship between the history of surgery and the presence of acute DVT.

Table 1. Magnetic resonance imaging (MRI) parameters

Cor TIRM	TR/TE, 4960/63; TI, 230 ms; slice thickness/gap, 5 mm/1; FOV, 500 mm; matrix, 448x336; Average 1; scan time, 3 min
TSE-T2WI-FS	TR/TE, 4420/109, slice thickness/gap, 7 mm/2.5; FOV, 430 mm; matrix, 320x180; average 3; scan time, 2.5 min
TSE-T1WI	TR/TE, 400/11, slice thickness/gap, 7 mm/2.5; FOV, 430 mm; matrix, 320x180; average 2; scan time, 2 min
T2 FL2D	TR/TE, 500/12.5; slice thickness/gap, 7 mm/2.5; FOV, 380 mm; flip angle 20°, matrix, 320x195; scan time, 1.5 min
Ep 2d-diff	TR/TE, 9300/81; slice thickness/gap, 7 mm/2.5; FOV, 500 mm; flip angle 20°, matrix, 320x195; b-values, 0, 400, and 800 s/mm ² ; scan time, 5 min
The total scanning time	14 min

Turbo inversion recovery magnitude (TIRM), inversion time (TI), field of view (FOV), Fat-suppressed turbo spin-echo T2-weighted imaging (TSE-T2WI-FS), Turbo spin-echo T1-weighted imaging (TSE-T1WI), T2 fast low angle shot two-dimensional sequence (T2 FL2D), Two-dimensional echo planar-diffusion (Ep 2d-diff)

Kappa test was used to evaluate the compliance between MRI and DUS in diagnosing acute DVT. The interclass correlation coefficient was used to evaluate the compliance between radiologists.

In evaluating the relationship between the standard or pathological status of the measurement results, the distribution characteristics of the measurement values were determined by the Shapiro-Wilk test; then, the intergroup difference was evaluated with the Mann-Whitney U test.

Results

Thirty-four patients (male: 16, female: 18) were included in the study. The mean age was 46.3±14.1 (20-77). Six patients had a history of lower extremity surgery within the last month.

During the initial scans, 16 and 14 patients had positive findings for CDVT in DUS and MRI, respectively. Of those patients, nine had concurrent positive findings per both modalities (Figures 1-3). The result breakdown of the initial scans is provided in Table 2.

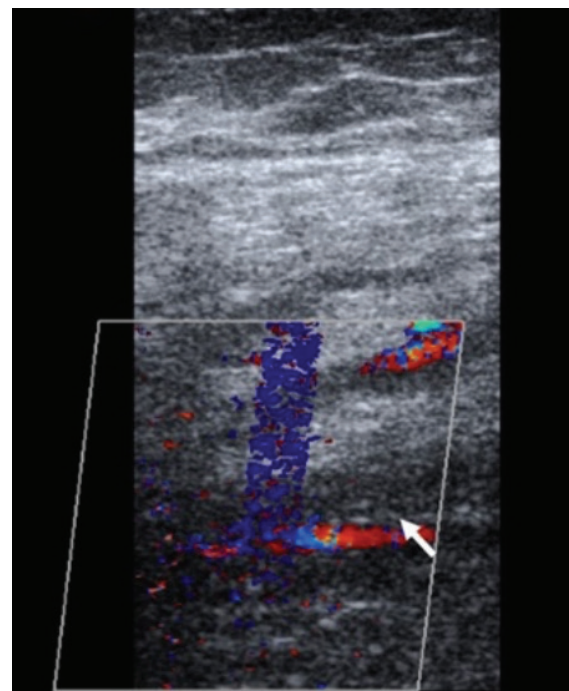


Figure 1. Doppler US of a recently operated 48-year-old female with deep venous thrombosis of the posterior tibial vein
US: Ultrasonography

Twelve out of 34 patients had inconsistent results between DUS and MRI and thus required a second look DUS per the study protocol (Table 3). In seven cases where DUS was compatible with CDVT but had negative findings on MRI, a second look DUS confirmed MRI



Figure 2. In the same patient, T2-weighted image (a) shows hyperintense signals compatible with extensive edema, and T1-weighted image (b) reveals surgery material on the left cruris

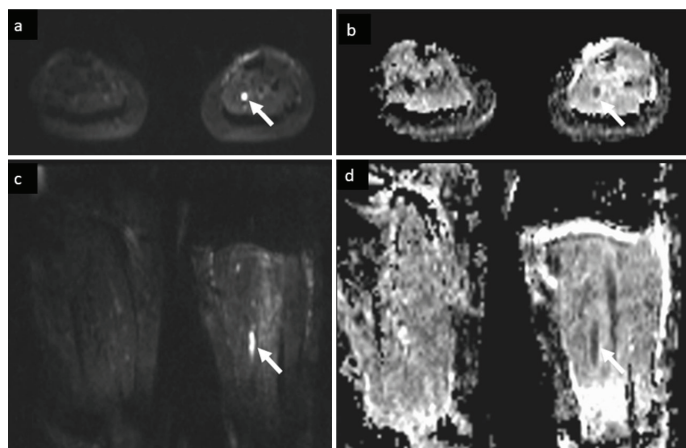


Figure 3. DWI (b=800) with ADC map defines acute thrombosis of posterior tibial vein as restricted diffusion on axial (a,b) and coronal (c,d) images

DWI: Diffusion-weighted imaging, ADC: Apparent diffusion coefficient

Table 2. The result breakdown of the initial scans

	DUS (+)	DUS (-)	Total
MRI (+)	n=9	n=5	n=14
MRI (-)	n=7	n=13	n=20
Total	n=13	n=18	n=34

DUS: Doppler ultrasound, MRI: Magnetic resonance imaging, n: Number

results. Slow flow (n=3) and partial subacute-chronic thrombus formation (n=4) were detected in the second look DUS, partially explaining the false-positive results of the initial DUS.

Five patients had negative DUS results but positive findings in the study MRI protocol. Four of those patients did have evidence of acute CDVT in the second-look DUS. Three of those patients had extensive subcutaneous tissue and muscle edema, partially explaining the missed diagnosis. The remaining one patient did have positive findings in DWI and ADC map, which was evaluated as leveling secondary to slow flow in the vessel lumen in the T2-weighted sequence in MRI.

Ultimately 13 patients were found to have acute CDVT at the completion of the second look DUS. Three out of six patients who had lower extremity surgery within the last month were diagnosed with acute CDVT.

Of 13 patients with acute DVT, affected veins were popliteal vein (n=2), anterior tibial vein (n=2), peroneal vein (n=11), posterior tibial vein (n=13) and gastrocnemius veins (GV) (n=4). Acute DVT was observed in both the medial and lateral GV in two of the cases with acute DVT in the GV and only in the medial GV in two of them.

Restricted diffusion was observed significantly more often in patients with acute DVT (11/13 vs. 2/21, $p<0.001$). Findings of T1-weighted, T2-weighted, and gradient-echo

Table 3. Inconsistent results between DUS and MRI required a second look DUS, including possible reasoning

	Second look DUS (n)	Results of second look DUS
DUS (+) MRI (-)	7	DVT (-) n=7: n=3; slow flow n=4; partial subacute-chronic thrombus formation
DUS (-) MRI (+)	5	DVT (+) n=4: n=3 extensive subcutaneous and muscle edema 1 DVT (-)
Total (n)	12	

DUS: Doppler ultrasound, MRI: Magnetic resonance imaging, DVT: Deep vein thrombosis, n: Number

sequences were comparably distributed in DVT and non-DVT groups (Table 4).

Mean ADC values were significantly lower in patients with acute DVT when compared to those without ($1.08 \times 10^{-3} \text{ mm}^2/\text{s} \pm 0.575$ vs. $2.7 \times 10^{-3} \text{ mm}^2/\text{s} \pm 0.639$, $p < 0.001$). All ADC value measurements were 93.6-100% compatible between the two radiologists.

Discussion

DVT is a common condition that can be seen both de novo and as a complication due to various factors (surgery, prolonged immobilization, trauma) and may cause death due to pulmonary embolism or result in post-thrombotic syndrome due to long-term sequelae^(16,17). Whereas clinical significance and management of distal DVT are more controversial compared to proximal DVT, in order to initiate appropriate treatment, the acuity of the thrombus needs to be known⁽¹⁸⁾. DUS is a practical, non-invasive, safe, easily applicable, and cost-effective primary diagnostic tool with high diagnostic accuracy in lower extremity DVT⁽¹⁹⁾. However, since it is an examination depending on the radiologist's experience and the patient's physical condition, false negative and positive results may occur⁽²⁾.

MRI has the potential to be safely used in the diagnosis of acute DVT, even in cases of renal insufficiency or contrast allergy. Although DUS and MR venography are widely used as non-invasive diagnostic methods, DWI can provide information about thrombus age that DUS and MR venography cannot provide^(13,20).

We showed that DWI is a useful tool in CDVT diagnosis together with ADC mapping in cases of either inconclusive or sub-optimal DUS findings. As evidenced by smaller case series^(13,14) and our prospective study, DWI and ADC mapping findings were significantly different in DVT patients. Those were used as an indicator of the need for a second look DUS, were involved in both rule out and rule in situations.

DUS may be more susceptible to either patient factors (poor cooperation, muscle-soft tissue edema, DVT in

Table 4. MRI findings of patients with and without acute DVT

	Acute DVT (+) (n=13)	Acute DVT (-) (n=21)	p*
T1			NS
Isointense	4	5	
Hypointense	0	1	
Hyperintense	9	15	
T2			NS
Isointense	0	1	
Hypointense	5	5	
Hyperintense	7	14	
Periphery hyperintense center hypointense	1	0	
Slow flow	0	1	
Gradient-echo			NS
Hypointense	2	1	
Hyperintense	1	16	
Periphery hyperintense center hypointense	9	0	
Periphery hypointense center hyperintense	1	2	
Slow flow	0	2	
DWI			<0.001
Hypointense	2	19	
Hyperintense	11	2	
ADC			<0.001
Hypointense	13	1	
Hyperintense	0	20	
Vascular diameter			NS
Normal	4	17	
Increased	9	1	
Decreased	0	3	
Subcutaneous edema			0.002
-	1	13	
+	12	8	
Muscle edema			<0.001
-	1	16	
+	12	5	

NS: Not significant, DWI: Diffusion-weighted imaging, ADC: Apparent diffusion coefficient, DVT: Deep vein thrombosis, MRI: Magnetic resonance imaging

crural veins, obesity) or operator inexperience⁽²⁾. Twenty out of 34 of our study patients had subcutaneous edema, and 17 had muscular edema complicating the conduction of optimal imaging. While subcutaneous and muscle edema was observed in eight and five of those without acute DVT, respectively, were present in 12 patients with acute DVT ($p=0.002$, $p<0.001$). Since factors that may result in a suboptimal study is found more frequently in CDVT patients, diffusion MRI of the lower extremity may contribute to the diagnosis, especially in patients with thickened extremities and edema where the calf deep venous system cannot be optimally evaluated sonographically.

Acute thrombi in the lower extremity deep veins⁽¹³⁻¹⁵⁾ were usually shown as hyperintense on DWI as in cerebral vein and portal vein thrombi^(14,21,22). However, tumors and inflammatory lesions, normal structures such as peripheral nerves in the lower extremities, lymphatic system, and bone marrow may show similarly restricted diffusion⁽¹⁰⁾. Therefore, evaluating DWI in combination with other sequences and clinical and laboratory findings will prevent false-positive cases. Multiparametric MRI (combined T2-weighted sequence and ADC) was also shown to be an effective method for distinguishing venous thrombus and acute and chronic pulmonary thromboembolism in autopsy samples⁽²³⁾. We used T1-weighted and gradient-echo sequences in addition to DWI, ADC, and T2-weighted sequences to double-check for false positivity. Acute thrombus signal intensity was observed as restricted diffusion in DWI, and factors that could cause other sequences accounted for false positivity. In our study, false positivity secondary to slow flow (leveling in T2-weighted sequence in MRI) was observed in only one patient. However, T1-weighted, T2-weighted, and gradient-echo sequences were comparable among those with and without DVT.

Phinikaridou et al.⁽²⁰⁾ conducted a mouse model of DVT in the inferior vena cava and reported that *in vivo* magnetization transfer and DWI could be useful in thrombus staging. The study mentioned above showed that

ADC values were the highest on the 7th and 14th days of thrombus and were lower in erythrocyte-rich and collagen-rich thrombi. Also, Wu et al.⁽¹⁵⁾ compared acute DVT (≤ 14 days) and nonacute DVT (>14 days), they found ADC values lower in acute DVT than non-acute DVT. In our study, ADC values were important in discriminating false positivity for acute DVT in the initial DUS also (Table 3).

In the study of Bendick et al.⁽²⁾, involving 112 patients, compared DUS and MR venography and revealed the necessity of questioning the results of DUS in case of suspicion of a thrombus in the crural deep veins. In their study, they mostly attributed the false-negative results of DUS to the thrombus's location (crural veins), presence of either non-occlusive thrombus or acute thrombus masked by severe chronic thrombus and operator dependency. In our study, four patients were evaluated as false negative in the first DUS. We attributed this to the localization of the thrombus in the crural deep veins and the presence of extensive edema.

ADC measurement results in our study showed superior operator correlation than DUS in the detection of thrombus in the crural deep veins. Non-senior radiologists and resident doctors who are expected to evaluate under emergency conditions can easily differentiate acute DVT in DWI in suspicious cases. Our study revealed that DWI in the lower extremity is more effective than DUS in evaluating proximal crural deep veins.

This study is limited since MRI is sensitive to flow artifacts caused by slow flow and relatively small case size. DWI, which is a rapid, non-contrast, and non-invasive examination in diagnosing acute DVT in selected cases or in hospitals where MRI appointment density is not high, can be used as a second-line imaging method. However, future studies in larger patient groups are needed to support our study results.

Conclusion

DWI can detect acute DVT with ADC mapping. Diffusion MRI may contribute to the diagnosis of CDVT as an alternative or complementary diagnostic tool in specific patient populations with inconclusive results or

high clinical suspicion where optimal visualization and evaluation cannot be achieved in the DUS of calf deep venous system.

Ethics

Ethics Committee Approval: This study was approved by Acıbadem University Faculty of Medicine Ethics Committee (decision no: 2018-18/17, date: 22.11.2018).

Informed Consent: Informed consents were obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and/or Medical Practices: Bilgi Z, Concept: Tekin ZN, Türk A, Barutçu Ö, Design: Tekin ZN, Türk A, Barutçu Ö, Data Collection and/or Processing: Tekin ZN, Türk A, Barutçu Ö, Analysis and/or Interpretation: Tekin ZN, Türk A, Bilgi Z, Literature Search: Tekin ZN, Türk A, Bilgi Z, Barutçu Ö, Writing: Tekin ZN, Bilgi Z.

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