Extended Versus Rapid Analysis of the Leg Vein System: a Multicenter Ultrasound Study (The ERASMUS Study)

- An Interim Analysis

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Key Words

Deep vein thrombosis · D-dimer · Echo-colour-Doppler · Compression ultrasonography

Abstract

The reliability of diagnostic strategies based on compression ultrasonography (CUS) for the diagnosis of proximal deep venous thrombosis (DVT) in symptomatic (out)patients is well documented; however these approaches never gained widespread application. Echo-color-Doppler (ECD), is regularly adopted by vascular laboratories as first line test in case of clinically suspected DVT, although the specificity of calf veins imaging is uncertain, as is the negative predictive value of a normal ECD workup. To date, no direct comparison of these strategies is available in the literature. We designed a randomised prospective study to compare the safety and feasibility of two diagnostic approaches: a "rapid" (CUS + D-dimer), and an "extended" strategy (ECD of the whole-leg). All consecutive patients with suspected symptomatic DVT of the legs, if at their first episode, and if not meeting exclusion criteria, will be enrolled in the study. The primary outcome of the study will be the rate of symptomatic VTE during a 3-month follow-up, after a normal diagnostic workup with either of the two proposed strategies. All events will be adjudicated by a blind and

independent committee, based on the results of objective testing. An interim data analysis will be presented during the congress session.

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Introduction

Despite extensive investigation and validation [1-10], serial compression ultrasonography (CUS) and related compound diagnostic strategies (CUS and D-dimer, or CUS and clinical probability) still haven't found a widespread application outside research centres. Instead, in the daily routine of vascular laboratories, echo-color Doppler (ECD) is largely preferred as the first line diagnostic test for patients with suspected deep vein thrombosis (DVT) since, unlike CUS, it is deemed to be accurate in detecting calf vein thrombosis, thus avoiding the need for repeat testing.

To date, no direct comparisons of these approaches are available from the literature, and the diatribe between the supporters of one or the other strategy is growing.

Background

Compression ultrasound virtually eliminated the need of performing venography in symptomatic patients with suspected proximal DVT [1,2]. Serial CUS, implemented to

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overcome the limited accuracy of ultrasonography for the diagnosis of calf vein thrombosis, albeit safe, is not highly effective since up to 98% of the patients have a normal one-week repeat testing; and is also costly, since it has been shown that some \$390.000 are spent per each additional life saved with one follow-up study [1,2,10]. On these premises, several simplified strategies for DVT were evaluated, avoiding repeat testing of patients with either normal D-dimer results, or a low pretest clinical probability [3-8]. These combined diagnostic approaches proved to be comparably safe but more effective than serial CUS, based on the observed reduction of extra hospital visits and additional tests required per initially referred patient (0.8 to 1.6 with serial CUS, versus 0.1 to 0.3 with combined strategies) [6]. Echo-color Doppler, since its introduction in clinical practice, was demonstrated to possess a higher accuracy than CUS for the detection of calf vein thrombosis in symptomatic patients, as shown by studies using venography as the reference standard [11-15]. Due to this features ECD gained a widespread popularity, and is currently employed as standard test in vascular laboratories, albeit no study is available from the literature assessing the incidence of thromboembolic events after a single normal ECD workup in symptomatic patients with suspected DVT.

Aim of the Study

We propose to evaluate the safety and accuracy of two diagnostic approaches: a simplified CUS strategy (subsequently defined as "rapid"), and a thorough ECD evaluation of the whole leg deep-vein system (subsequently defined as "extended"), in a cohort of consecutive symptomatic patients with suspected DVT.

Study Design

Randomised, prospective, multicenter study, with independent and blind adjudication of thromboembolic events. Independent monitoring committee for safety.

Study Objectives

General objectives:

- To evaluate the relative value of the simplified and the extended ultrasound strategy in the diagnostic approach to patients with clinically suspected DVT.

Specific objectives:

- To evaluate the safety of withholding anticoagulant therapy from patients with either normal D-dimer and normal CUS at presentation, or with normal serial CUS;

- To evaluate the safety of withholding anticoagulant therapy from patients with a normal whole-leg ECD workup at baseline.

Patients

All consecutive patients referred to the study centres with clinically suspected DVT, will be eligible for inclusion. Eligible patients fulfilling the inclusion criteria, without exclusion criteria, and signing the informed consent, will be enrolled in the study.

Inclusion criteria:

- Outpatient with symptoms and signs of DVT
- First episode of clinically suspected DVT

Exclusion criteria:

- Age < 18 years
- Previous (objectively documented) episodes of venous thromboembolism
- Predominant symptoms of (referral for) pulmonary embolism
- Pregnancy (certain or suspected)
- Life expectancy < 3 months
- Ongoing mandatory anticoagulant treatment for other reasons
- Symptoms lasting for more than 2 weeks
- Geographic inaccessibility for follow-up
- Anticipated low-compliance

Methods

Study flow-chart (refer to Figure 1)

At referral all included patients will first undergo a clinical PTP assessment, that will not influence their subsequent management, and will be randomised to undergo either of the two proposed diagnostic strategies, the rapid CUS, and the extended ECD.

Pretest Probability

The clinical pre-test probability will be assessed according to the simplified clinical score described by Wells and others [5]. Briefly, the items evaluated in this clinical model fall into three groups: a) signs and symptoms of venous thrombosis, b) risk factors for venous thromboembolism and c) alternative diagnosis. The clinical model stratifies patients with suspected DVT into groups with high (3 points), moderate (1 or 2 points), or low (0 points) probability for DVT.

Fig. 1. Flow-chart of the study

Fig. 2. Rapid CUS strategy

Symptomatic leg

Irrespectively of the test randomisation arm, only symptomatic limbs should be objectively evaluated for the presence of thrombotic vein involvement. Should a patients present with bilateral leg symptoms, then objective tests will be mandatorily performed in both lower extremities.

No asymptomatic leg DVT is to be considered a potential event for the Erasmus study.

Rapid CUS (refer to Figure 2)

This strategy is described in detail elsewhere [3]. Briefly, all patients will be first evaluated with CUS. Patients with abnormal ultrasound results will be considered to have DVT, and administered anticoagulant therapy according to standard protocols. Patients with normal ultrasound results will undergo SimpliRED testing, and subsequently be managed according to the results of SimpliRED, as follows: patients with normal SimpliRED will be discharged from the centre, and followed-up for three months; those with abnormal SimpliRED will be scheduled for repeat CUS after one week.

Patients with abnormal repeat CUS will be administered anticoagulant treatment according to current practice, while those with repeatedly normal ultrasound results will not be considered to have DVT, will not receive anticoagulant therapy, and will be followed-up for three months.

All patients with a normal diagnostic workup will be scheduled for clinical and instrumental evaluation after 3 months, and instructed to immediately contact the study centres should symptoms of venous thromboembolism manifest themselves in the meantime. Patients presenting with suspected venous thromboembolism during the follow-up period or at the three months visit, will undergo objective testing to confirm or refute the disease. Patients with abnormal (positive) testing will be treated according to current standards.

Patients failing to attend the scheduled visit will be contacted by telephone to assess their status, and will be invited to attend a clinical and instrumental evaluation at the study centre as soon as possible.

D-dimer

A rapid whole blood bedside D-dimer assay (SimpliRED® D-dimer assay, AGEN Biomedical Ltd., Brisbane Australia) will be used [8]. The assay is based on autologous red cell agglutination, using a chemical conjugate of a monoclonal antibody specific to human D-dimer (DD-3B6/22) linked to a monoclonal antibody which binds to the surface of human red blood cells (RAT-1C3/86) as active agent. The test can be performed either on capillary or on citrated venous blood. Agglutination occurs at D-dimer concentrations above 0.2 mg/L. The SimpliRED® outcome will be categorised as normal or abnormal.

CUS

Compression ultrasonography will be performed and interpreted as described elsewhere [2], with slight modifications. Briefly, the common femoral (at the groin), and the popliteal vein (in the popliteal fossa), down to the branching of the calf veins, will be examined in the transverse plane only. The test results will be categorised as normal (compressible vein), abnormal (non-compressible vein), or non interpretable.

Extended ECD (refer to Figure 3)

All patients will be imaged starting from the proximal deep venous system of the leg. The only accepted criterion to adjudicate a proximal DVT will be the finding of a non-compressible venous segment(s). Patients with abnormal ECD results will be considered to have DVT, and will be administered anticoagulant therapy according to standard protocols. Subsequently, the calf deep-venous system will be investigated, from the popliteal vein downwards. The accepted criterion to adjudicate a DVT will be the detection of non-compressible venous spots. Patients with abnormal results will be considered to have calf DVT, and will be treated according to local protocols. Then the muscular veins of the calf (gastrocnemial and soleal sinusoids) will be examined. In this case, criteria for venous thrombosis will be the finding of non-compressible venous segment(s), and / or lack of intraluminal color filling or reverse color filling after augmentation manoeuvres (squeezing of the distal calf or of the foot). Patients with a normal whole-leg ECD workup will not be further investigated, will not be given anticoagulant treatment, will be discharged from the hospital (unless admission will be deemed mandatory for other reasons), and followed-up for three months.

Fig. 3. Extended ECD strategy

Patients will be instructed to immediately return to the study centres, should symptoms suggesting venous thromboembolism arise during the follow-up period. Patients presenting with suspected venous thromboembolism during the follow-up period or at the three months visit, will undergo objective testing to confirm or refute the disease. Patients with abnormal (positive) testing will be treated according to current standards. Patients failing to attend the scheduled visit will be contacted by telephone to assess their status, and will be invited to attend a clinical and instrumental evaluation at the study centre as soon as possible.

Echo-color-Doppler

Echo-color-Doppler will be performed and interpreted according to described methods [14,15], with slight modifications. Briefly, the proximal venous system will be examined first, with the patients laying supine. The common femoral vein, the great saphenous vein junction, the profunda femoris, and the superficial femoral vein down to the distal part of the thigh will be scanned along their length on a longitudinal plane, with a 7.5 MHz linear transducer. The popliteal vein to its trifurcation, the lesser saphenous vein junction and muscular veins (gastrocnemial and soleal sinusoids) will be evaluated with the patients in the prone position or in a (left or right) lateral decubitus, employing augmentation manoeuvres to enhance vessel visualisation. In case of Doppler-flow pattern abnormalities at the common femoral site, the iliac vessels and the inferior vena cava should also be scanned, possibly with a curvilinear 3.5 MHz probe.

Subsequently, having the patient sitting with his/her legs hanging over the edge of the bed, the calf veins will be evaluated. Starting from the most proximal point downwards, the posterior tibial and common peroneal veins will be visualised on a longitudinal plane along their length, with a 7.5 MHz linear transducer, employing augmentation manoeuvres to enhance vessel visualisation. Albeit strongly encouraged, anterior tibial vein visualisation will be optional, since occurrences of isolated DVT of the anterior tibial vein are not reported in the literature [12,13,16].

Sample-size

The observed cumulative incidence of symptomatic venous thromboembolic events during follow-up, after a normal workup with the rapid CUS strategy, is around 1% [3]. To our knowledge, no data are available from the literature regarding the incidence of venous thromboembolic events after a normal extended workup with ECD. To be conservative, we assume that both strategies are equally accurate and safe. Based on previous studies, we took an

increase of 1.5 percentage points as indicating clinical equivalence [1-4]. From these assumptions, a study enrolling about 3000 patients (i.e.: 1500 patients per arm) would provide an 80% probability (Type II error = 20%) of rejecting, with a one-side test at a significance level of 0.05 (Type I error = 5%), the hypothesis of a higher than 1.5% excess incidence of venous thromboembolism during the three months follow-up in the extended ECD group as compared with the rapid CUS group.

Outcomes

Primary outcome

- Prevalence of venous thromboembolism during a three months follow-up, after a normal diagnostic workup with either of the two proposed strategies.

Secondary outcomes

- Cost-efficacy and feasibility of the two strategies;
- Time elapsed to perform the rapid and the extended strategy.

Venous Thromboembolic Complications

All deaths and suspected venous thromboembolic complications will be reviewed by an independent blinded adjudication committee, and adjudicated as follows:

and adjudicated as follows:

- In case of suspected symptomatic DVT the diagnosis will be ruled in by either a new incompressibility on CUS, ECD or by an intraluminal filling defect on ascending venography.
- In case of suspected symptomatic pulmonary embolism the clinical suspicion will be confirmed by a high probability ventilation-perfusion lung scan, or an abnormal (helical) spiral CT scan, or an abnormal pulmonary angiography.
- In case of death, fatal pulmonary embolism will be adjudicated on the finding of autopsy or on clinical grounds, according to the opinion of an independent physician.

Results

An interim data analysis will be presented during the congress session.

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