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A rapid D-dimer assay in patients presenting at an emergency room with suspected acute venous thrombosis: accuracy and relation to clinical variables

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Background and Objectives. The measurement of D-dimer is claimed to have potential value in excluding deep vein thrombosis (DVT). New rapid methods have been proposed, but few clinical trials have assessed their performance in an emergency context. The different accuracies found between the D-dimer assays have been related to the test used (latex or ELISA), but other variables (such as population investigated, thrombus extension, duration of symptoms or concomitant heparin treatment) may be important, even if not sufficiently investigated.

Design and Methods. We evaluated the accuracy of a rapid semi-quantitative D-dimer test (Dimertest®, Dade Behring), with reference to: a) its use at an emergency unit; b) concomitant heparin administration; c) location of venous thrombosis (VT) (in the deep or superficial venous system limited to the great saphenous vein) and d) symptoms older than 14 days.

Results. Two hundred and ninety-eight patients suspected of having DVT and 116 suspected of thrombosis of the great saphenous vein (GSV) were investigated. In the DVT patients, the sensitivity, specificity, positive and negative predictive values were 77.4% (95% CI 68.9-85.9), 81.4% (95% CI 76.1-86.7), 65.4% (95% CI 56.5-74.3) and 88.8% (95% CI 84.2-93.4), respectively. Excluding patients receiving heparin and those with symptoms older than 15 days, the sensitivity and negative predictive value increased to 86.3% (95% CI 78.4-94.2) and 92.8% (95% CI 88.4-97.2), respectively. In patients with GSV thrombosis, the sensitivity, specificity, positive and negative predictive values were 48% (95% CI 34.5-61.5), 90.6% (95% CI 83.2-97.9), 80.6% (95% CI 66.6-94.6) and 68.2% (95% CI 57.8-78.6), respectively. Excluding patients receiving heparin and those with symptoms older than 15 days, did not change the sensitivity or negative predictive value significantly.

Interpretation and Conclusions. Our results show that previous or concomitant heparin administration, non-acute symptoms and thrombosis localized to superficial veins reduce the clinical usefulness of the D-dimer test as the rate of false negative results is increased.

Key words: D-dimer, venous thrombosis, diagnostic accuracy, clinical variables, emergency room.

Venous thromboembolism (VTE), a life-threatening condition, has a high prevalence in the general population and the prevalence increases with age.[1] Patients with suspected venous thrombosis (VT), involving the deep or the superficial venous system of the lower limbs, are frequently referred to a hospital emergency room (ER). As signs and symptoms of deep vein thrombosis (DVT) are non-specific and found in a variety of non-thrombotic disorders, objective tests must be used.[2,3] In this respect, the measurement of D-dimer is widely claimed to have value in excluding the diagnosis of DVT[4-6] or reducing the need for serial testing.[7,8] As a screening test in an emergency unit, the D-dimer assay should be rapid, sensitive, reasonable specific and easy to perform. The reference method, enzyme-linked immunosorbent assay (ELISA), has a high sensitivity and a high negative predictive value, but it is time-consuming and requires specific equipment and is, therefore, not suitable for use in emergency wards. New rapid methods have been proposed which are

potentially useful in emergencies,[5] but few clinical trials have assessed their performance in this setting.[9,10] Moreover, a wide degree of variability concerning their accuracy has been reported, possibly related to the method used and/or to the population investigated.[6,11] Other variables may be responsible for the low accuracy of D-dimer assay; thrombus load and non-acute symptoms have been also considered as potential causes of a D-dimer false negative result.[12] False negative results may also be due to the fact that the D-dimer concentrations are too low to be detected; this is particularly plausible in patients receiving concomitant heparin or other anticoagulant treatment.[11,13]

Nevertheless, evidence is still lacking; first, there are no data currently available regarding the potential influence of a short-course of heparin on D-dimer results. This may have a clinical impact since it is common practice of general practitioners (GPs) to initiate such as anticoagulant approach when diagnostic imaging for DVT cannot be performed immediately.

Moreover, D-dimer assays have not been sufficiently investigated in patients with thrombosis of the great saphenous vein (GSV); this thrombosis should be considered separately from other superficial venous thromboses because of the possible progression of the thrombus to the deep system[14] and the potential risk of pulmonary embolisation.[15] Because of this risk, we recently suggested that objective criteria should also be applied in suspected GSV thrombosis.[16]

Finally, few data are available on D-dimer accuracy in patients investigated in the ER, a population potentially different from that evaluated in clinics.[17]

In order to provide some of this missing information, we evaluated the diagnostic accuracy of a rapid semi-quantitative D-dimer test (Dimertest®, Dade Behring), with specific reference to: a) its use in an emergency unit; b) concomitant and/or previous heparin administration; c) location of VT (in the deep or superficial venous system limited to the GSV) and d) time elapsed between appearance of the symptoms and patients' referral.

Design and Methods

Patients

Patients presenting spontaneously or referred by a general practitioner (GP) with symptoms of swelling and/or pain and/or inflammation in the lower limbs, and for whom the physician in charge at the ER suspected acute DVT or GSV thrombosis, were considered eligible for the study. Exclusion criteria were 1) signs and/or symptoms of acute pulmonary embolism (PE), 2) previous episode of VT in the same leg and/or objectively documented PE and 3) ongoing oral anticoagulant therapy.

Taking into account the signs and symptoms at presentation,[2] eligible patients were classified as suspected as having 1) DVT, or 2) thrombosis of the GSV, involving at least one vein proximal to the deep system (at the cross or in the popliteal fossa), or 3) both of the previous. After the physical examination, all patients underwent compression ultrasonography (C-US) and blood sampling for D-dimer assay.

Methods

Compression ultrasonography was performed by operators (in charge at the ER or the Vascular Surgery Department) unaware of D-dimer results, using a high-resolution, electronically focused linear array transducer (7.5 MHz probe). The entire deep venous system between the proximal common femoral vein at the cross and the distal veins of the legs was evaluated as was the entire saphenous vein between its junction to the proximal deep venous system and the distal saphenous segment. Ultrasonography was performed using the currently accepted criteria for diagnosing VT;[3] briefly, C-US results were considered abnormal if a vein or venous segment was not fully compressible.

Blood for D-dimer assay was drawn at presentation and tested by technicians unaware of C-US test results. Venous blood (9 vol.), anticoagulated with tri-sodium citrate (1 vol.), was taken in the ER from a forearm vein and sent to the central laboratory; results were available within 30 min. The Dimertest® (Dade Behring) was performed as previously described.[18] Briefly, the test is a semi-quantitative latex assay with a normal value < 200 ng/mL. Latex agglutination is carried out on serial plasma dilutions, the semi-quantitative result reflecting the lowest dilution at which agglutination is observed. This test can detect D-dimer concentrations as low as 200 ng/mL.

The Dimertest® was compared to another agglutination reference method; the correlation was r=0.94 and the regression equation was y=1.19×. Intra-assay (within run) reproducibility was determined for 10 replications of 3 plasma samples that contained different levels of XDP. The results were equivalent for all replicates. Inter-assay (run to run) reproducibility was determined using 10 plasma samples with XDP titers ranging from 1 to 16. In 10 runs, the replications of these specimens did not vary by more than one titer. The correlation

Table 1. Characteristics of patients clinically suspected of having DVT and GSV thrombosis.

Baseline characteristic	*No DVT (n. 205)*	*Confirmed DVT (n. 93)*	*p value*	*No GSV thrombosis (n. 64)*	*Confirmed GSV thrombosis (n. 52)*	*p value*
Age (average)	57.1 (21-81)	67.9 (22-90)	n.s.	58.4 (30-80)	59.9 (26-88)	n.s.
Female (%)	59.4			56.8		n.s.
Active cancer	9 (4.3%)	14 (15%)	$p = 0.03$	4 (4.3%)	2 (3.8%)	n.s.
Beginning of symptoms (days)	9.2 (1-90)	8.6 (1-60)	n.s.	6.9 (1-30)	6.1 (2-20)	n.s.
Concomitant heparin at the referral-time (n. %)	24 (11.7%)	10 (10.7%)	n.s.	8 (12.5%)	12 (23%)	$p = 0.01$
Median days on heparin	2.5			3.4		n.s.

DVT: deep vein thrombosis; GSV: greater saphenous vein, n.s: not significant.

between the titers obtained with Dimertest® latex assay and the expected titers (based on ELISA XDP values) was r= 0.91 for citrated plasma, r= 0.73 for EDTA samples and r= 0.78 for heparin samples. Citrate is the anticoagulant of choice.

Statistical analysis and ethics

Sensitivity, specificity, positive and negative predictive values for D-dimer were calculated using standard methods (2×2 tables); C-US was considered as the reference test. When indicated, 95% confidence intervals were calculated. Paired t-test and Pearson's χ^2 test were applied when indicated; a p value < 5% (two-tailed) was considered statistically significant. Patients gave oral consent to the study.

Results

Four hundred and seventy-eight consecutive patients were considered during the period February 1999-December 2000. Sixty-four patients were excluded (31 because evaluated in a setting other than the emergency unit, 4 because on oral anticoagulation, 20 because were lacking the D-dimer and 5 the C-US test results, 4 because of a recurrent DVT episode). Thus, 414 patients were considered eligible and included in the analysis. Among these, DVT was clinically suspected in 298 patients (of whom 177 were female [59.4%] and 121 males) and GSV thrombosis in 116 patients (66 female [56.8%] and 50 males). Table 1 shows the clinical characteristics of the two categories of patients.

Among patients on heparin or low molecular weight heparin at the time of referral to the ER, 34 (11.4%) belonged to the DVT group and 20 (17.2%) to the GSV group (Table 1). Twenty-one of the total (38.8%) were receiving low molecular weight heparin (at prophylactic/therapeutic doses) while the remaining were on unfractionated heparin (10,000 IU to 25,000 IU/day). Regarding the time-interval between the beginning of symptoms and the ER referral date, there was not difference between the DVT patients (mean 8.9 days) and the GSV patients (mean 6.5 days) (Table 1).

Among patients clinically suspected of having a DVT, C-US was positive in 93 cases (31.8%, 7 of whom had distal DT [7.5%]), while in those suspected of having GSV thrombosis, C-US was positive in 52 (44.8%); four patients (7.6%) had concomitant involvement of the common femoral vein (CFV) at the cross (Table 2).

The sensitivity, specificity, the positive and negative predictive values of the D-dimer assay in patients with suspected DVT and suspected GSV thrombosis are reported in Tables 3 and 4, respectively. As some variables could affect the accuracy of the D-dimer test,[10,11] separate analyses excluding patients on heparin (either at therapeutic or prophylactic doses) and patients with symptoms older than 14 days were carried out (Tables 3 and 4). In both categories of patients, the exclusion of these potential causes of false negative results improved the sensitivity and increased the negative predictive value of the D-dimer assay.

Table 2. Prevalence of venous thrombosis.

Type of VT	*Patients with confirmed VT (no./total)*	*Prevalence % (95% CI)*
Total DVT	93/298	31.8 (26.2-37)
Proximal DVT	86/93	92.4 (86.9-97.9)
Distal isolated DVT	7/93	7.5 (2.4-12.6)
GSV thrombosis	52/116	44.8 (36.3-53.4)
Involvement of the CFV at the cross	4/52	7.6 (6.9-14.4)

VT: venous thrombosis; CI: confidence intervals; DVT: deep vein thrombosis; GSV: greater saphenous vein; CFV: common femoral vein.

Table 3. Diagnostic accuracy of Dimertest® in DVT patients in relation to clinical variables.

	All patients (no. 298)	*A. Excluding 34 patients on heparin* (no. 264)*	*B. Excluding 42 patients with symptoms > 14 days (n. 256)*	*Excluding A plus B° (no. 69)*
Sensitivity (%) (95% CI)	77.4 (68.9-85.9)	83.1 (75.1-91.1)	81 (72.4-89.6)	86.3 (78.4-94.2)
Specificity (%) (95% CI)	81.4 (76.1-86.7)	81.7 (76.9-86.5)	83 (77.5-88.5)	83.3 (77.5-89.1)
PPV (%) (95% CI)	65.4 (56.5-74.3)	67.6 (58.5-77)	68 (50.6-77.4)	72.4 (63-81.8)
NPV (%) (95% CI)	88.8 (84.2-93.4)	91.3 (86.9-95.7)	90 (85.4-94.6)	92.8 (88.4-97.2)

**Either at therapeutic (25,000 IU/die for more than 24 hours) or prophylactic dose (10,000 to 15,000 IU/die for more than 24 hours or LMWH) at the moment of performing the Dimertest®; °Seven patients had symptoms > 14 days and heparin administration at referral. DVT: deep vein thrombosis; PPV: positive predictive value; NPV: negative predictive value.*

Table 4. Diagnostic accuracy of Dimertest® in GSV patients in relation to clinical variables.

	All patients (no. 116)	*A. Excluding 20 patients on heparin* (no. 96)*	*B. Excluding 10 patients with symptoms > 14 days (no. 106)*	*Excluding A plus B° (n. 87)*
Sensitivity (%) (95% CI)	48 (34.5-61.5)	42.5 (77.3-57.7)	48.9 (35-62.8)	44.7 (29-60.4)
Specificity (%) (95% CI)	90.6 (83.2-97.9)	94.6 (88.4-100.8)	91.2 (83.8-98.6)	95.9 (89.8-102)
PPV (%) (95% CI)	80.6 (66.6-94.6)	85 (69.4-100.6)	82.7 (60.8-96.6)	89.4 (75.4-103.4)
NPV (%) (95% CI)	68.2 (57.8-78.6)	69.7 (59.4-80)	65 (54.4-75.6)	69.1 (58.2-80)

**Either at therapeutic (25,000 IU/die for more than 24 hours) or prophylactic dose (10,000 to 15,000 IU/die for more than 24 hours or LMWH) at the moment of performing the Dimertest®. °One patient had symptoms >14 days and heparin administration at referral. DVT: deep vein thrombosis; PPV: positive predictive value; NPV: negative predictive value.*

Discussion

Many, if not most of the patients clinically suspected of having DVT or SVT are referred to the ER. In this setting, physicians are asked to i) confirm the clinical suspicion, ii) initiate appropriate therapy and, finally, iii) discern whether hospitalization is needed. Although objective non-invasive tests for diagnosing VT have been extensively evaluated in a clinical setting, their usefulness and feasibility in the emergency unit lack such validation.

The D-dimer assay is a relatively new tool. In combination with other diagnostic tests (such as C-US) or standardized pre-test clinical probability, this assay can be effectively used for refuting acute VTE at referral.[6-8] Several D-dimer assays have become available including classical ELISAs, latex agglutination tests, immunofiltration assays and whole blood D-dimer tests. These assays are useful if the results are rapidly available and the test has a high sensitivity with a reasonable specificity. These two characteristics vary widely in the published reports.[11] This heterogeneity can be explained by methodologic differences between studies (study design, selected cut-off value and diagnostic reference standard used) as well as clinical differences (study population and indication for D-dimer testing). Therefore, it is essential that each D-dimer assay is evaluated in the local setting and the specific population for which the test is proposed. In this respect, it appeared appropriate to us to set up diagnostic strategies suitable for the particular setting of an emergency unit.

The results of our investigation permit us to make some considerations; first of all, although the overall accuracy of the Dimertest® is almost equivalent to that of other latex assays,[11] it appears slightly lower that that reported in recent investigations.[19-20] This relatively low diagnostic accuracy could be mainly due to i) technical reasons (selected cut-off value and/or not automated performance), ii) the population investigated, and/or iii) the study design.

Regarding the first issue, we used the D-dimer assay currently employed in our Institution, a semi-quantitative latex assay, without an automated method for measurement; specifically, we did not evaluate the diagnostic accuracy of the test at cut-offs different from those suggested by the manufacturer.[18] Another reason for the discrepancy may lie in the population investigated. Our patients, in fact, may differ from those investigated in clinics, as the prevalence of VT in the emergency room is higher than that reported in patients evaluated in clinics and there is a shorter time interval between appearance of symptoms and patients' referral.[17] These differences may affect the diagnostic accuracy of the D-

dimer assay.[21] Taking in consideration the study design, two characteristics makes our investigation original from previous reports: the complete screening of the deep venous system (including the distal veins) and the careful distinction between patients suspected of having DVT from those suspected of having GSV thrombosis.

Among patients with isolated distal DVT (7/93, 7.5%), in two cases the Dimertest® furnished false negative results. Nevertheless, even excluding these patients from the analysis (as cause of false negative D-dimer), the overall accuracy of the Dimertest® only improved slightly (sensitivity 79.1%, negative predictive value 89.7%). One can argue the utility of performing D-dimer assays in the case of extensive ultrasonographic evaluation;[22] however, the best management of patients clinically suspected of calf vein thrombosis is still controversial,[7] even though recent reports have stated the danger associated with distal, isolated DVT and the need for treatment.[23]

As reported above, we distinguished between patients clinically suspected of having DVT from those suspected of having GSV thrombosis and found that the D-dimer assay had a different diagnostic accuracy between these two categories of patients. A number of studies have pointed out the potential danger associated with GSV thrombosis[14,15] and we recently suggested that objective criteria for confirming the clinical suspicion of these VTs and evaluating their progression to the deep system should be used.[16]

We further investigated potential causes of false negative D-dimer results. Theoretically, a lower than expected D-dimer plasma level may occur in various clinical situations: an old, occlusive thrombus may generate insufficient D-dimer concentrations[9] and heparin treatment may also cause a decrease in D-dimer level.[13] In a previous analysis, an association was found between a low thrombus load and a *false normal* D-dimer;[12] it is difficult, however, to evaluate the thrombus load in patients with VT. Our results clearly showed that D-dimer accuracy was lower in superficial thrombosis than in DVT, even when patients on concomitant heparin treatment/prophylaxis were excluded. The possible explanation for these findings is that the thrombus load in SVT is lower than that in DVT and, therefore, SVT does not generate a sufficient concentration of D-dimer to be detected.

The situation is clearly different in patients with DVT, when the exclusion of the aforementioned variables improved the diagnostic accuracy of the assay, thus increasing the negative predictive value to 92.8%.

Although anticoagulant therapy has been proven to be associated with low D-dimer concentration,[13] no data are currently available on the effect of a short-course of heparin on D-dimer accuracy. The role of a few days of heparin (2.5 days, median in our DVT patients) in reducing D-dimer levels can be debated; moreover, dosage and type of heparin widely varied among our patients. Nevertheless, taking into account these limits, our study demonstrated that even this anticoagulant approach may affect D-dimer results. Because the common practice of initiating heparin treatment if diagnostic imaging for acute venous thromboembolism is not immediately available, this information may have considerable clinical impact both on the first diagnosis of the diseases and, particularly, on the prospective of reducing the need for C-US in patients with a low suspicion of DVT and a negative D-dimer assay.[24]

What are the clinical implications of our findings? In the specific setting of the emergency unit, important clinical variables, such as ongoing heparin administration, late referral and localization of thrombosis to superficial veins only may reduce the usefulness of the D-dimer assay as a screening tool for VT.

Therefore, although the D-dimer assay may help ER physicians to make a diagnosis in patients with recent DVT, as a sole and simple laboratory assay, the test cannot absolutely exclude VT. At the present, the D-dimer test must be part of a combined approach that requires standardized evaluation of clinical probability along with objective tests (such as C-US) for confirming or refuting the clinical suspicion of VT.[25]

Contributions and Acknowledgments

SS was responsible for the conception and the design of the study, data handling and writing the manuscript. He also performed the statistical analyses. CP, FF contributed to the design, data handling and writing of the paper. VT was responsible for the laboratory analysis procedures. RA contributed to data handling and collection of clinical data. SP, RG, MS, MAB contributed to the collection of clinical data. AO contributed to the paper revision and furnished logistic support. The order of the names of the Authors reflects the time, work and scientific contribution of all the authors.

Disclosures

Conflict of interest: none.

Redundant publications: yes, <50%.

Manuscript processing

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paper was taken jointly by Prof. Vicente and the Editors. Manuscript received April 18, 2001; accepted July 24, 2001.

Potential implications for clinical practice

This study furnishes important messages for correctly evaluating the value of the D-dimer assay (a widely used test in patients clinically suspected of having acute venous thromboembolism) in relation to clinical variables that significantly reduce the diagnostic accuracy of the test.

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