Usefulness of Fast ELISA Determination of D-Dimer Levels for Diagnosing Pulmonary Embolism in an Emergency Room

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OBJECTIVE: To determine the sensitivity and negative predictive value of D-dimer levels measured by fast enzyme-linked immunoabsorbent assay (ELISA) in pulmonary embolism.

PATIENTS AND METHODS: Prospective study of consecutive patients with suspicion of pulmonary embolism attended in the Emergency Room of the Hospital de la Princesa in Madrid, Spain. Thromboembolism was diagnosed with an algorithm established in the hospital, and D-dimer levels were determined by fast ELISA (VIDAS D-dimer Assay) in each patient suspected of pulmonary embolism. Patients with negative findings from a test not considered a reference method for thromboembolism were followed for 3 months.

RESULTS: Of 132 patients with clinical suspicion, 28 (21.2%) were positive and 104 (78.7%) were negative for embolism. D-dimer levels were below 0.5 µg/mL in 31 patients, 30 of whom did not have pulmonary thromboembolism whereas 1 did. D-dimer levels were abowe 0.5 µg/mL in 101 patients; thromboembolism did not occur in 74 of these but was reported in the remaining 27. For a value of 1 µg/mL, 66 patients had values below the cut off, 3 of whom presented pulmonary embolism. The remaining 66 patients had D-dimer levels above or equal to 1 µg/mL; 25 of them had a positive diagnosis for embolism and 41 had a negative diagnosis. Sensitivity and negative predictive values were 96.4% (95% confidence interval [CI], 79.8%-99.9%) and 96.8% (95% CI, 81.5%-98.8%), respectively, at a cut off of 0.5 µg/mL; and 89.2% (95% CI, 70.6%-97.2%) and 95.45% (95% CI, 86.4%-98.8%), respectively, at a cut off of 1 µg/mL.

CONCLUSIONS: In an emergency room, thromboembolism can be excluded if plasma levels of D-dimer measured by fast ELISA are below 0.5 µg/mL because of the high negative predictive value at this cut off.

Key words: *Pulmonary embolism. Thromboembolic disease. D-dimer.*

Utilidad del dímero-D por ELISA rápido en el diagnóstico de la embolia pulmonar en un servicio de urgencias

OBJETIVO: Determinar la sensibilidad y el valor predictivo negativo del dímero-D, por enzimoinmunoanálisis (ELISA) rápido, en la embolia pulmonar.

PACIENTES Y MÉTODOS: Estudio prospectivo de pacientes atendidos consecutivamente por sospecha clínica de embolia en el Servicio de Urgencias del Hospital de la Princesa de Madrid. El diagnóstico de tromboembolia se basó en el algoritmo establecido en el hospital, y se determinó el dímero-D por ELISA (VIDAS) en cada paciente con sospecha de embolia pulmonar. A los pacientes con resultado negativo para tromboembolia, establecido por una prueba no considerada de referencia, se les realizó seguimiento clínico a los 3 meses.

RESULTADOS: De 132 pacientes con sospecha clínica, 28 (21,2%) fueron positivos y 104 (78,7%) negativos para embolia. El dímero-D fue < a 0,5 µg/ml en 31 pacientes, de los que 30 no tuvieron tromboembolia pulmonar y 1 sí la tuvo. De los 101 pacientes con dímero-D > 0,5 µg/ml, en 74 no se produjo tromboembolia y en 27 sí.

Si se considera como punto de corte 1 µg/ml, hubo 66 pacientes con valores inferiores, de los que 3 presentaron embolia pulmonar. Otros 66 pacientes mostraron un dímero-D ≥ 1 µg/ml; de ellos, 25 tuvieron un diagnóstico positivo para embolia y 41 negativo. La sensibilidad y el valor predictivo negativo para 0,5 µg/ml fue de 96,4 (intervalo de confianza [IC] del 95%, 79,8-99,9) y 96,8 (IC del 95%, 81,5-98,8), respectivamente; para 1 µg/ml fue de 89,2 (IC del 95%, 70,6-97,2) y 95,45 (IC del 95%, 86,4-98,8), respectivamente.

CONCLUSIONES: Los valores de dímero-D plasmático, determinados por la técnica de ELISA rápido (VIDAS), < 0,5 µg/ml permiten excluir con alto valor predictivo negativo una tromboembolia pulmonar en un servicio de urgencias.

Palabras clave: *Embolia pulmonar. Enfermedad tromboembólica. Dímero-D.*

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Manuscript received September 20, 2004. Accepted for publication January 25, 2005.

Introduction

Pulmonary embolism is a common condition whose diagnosis in emergency rooms remains problematical.[1] Clinical data and conventional chest x-rays are usually

not sufficiently specific for diagnosis. Lung scintigraphy has been one of the imaging techniques most widely used in patients with clinical suspicion of pulmonary embolism,[2] but although the technique is highly sensitive, it lacks specificity. In the last 10 years, spiral computed tomography (CT) has become an alternative in view of the problems of specificity of ventilation-perfusion scintigraphy.[3] The sensitivity and specificity of spiral CT range from 53% to 100% and from 81% to 100%, respectively, when lung scintigraphy or pulmonary arteriography are used as reference methods.[4-6] Spiral CT has been included in a number of diagnostic protocols that combine a series of tests in cases of clinical suspicion of thromboembolism. These protocols involve stratification of clinical risk, and also measurement of D-dimer plasma levels, Doppler ultrasound of lower limbs, and pulmonary arteriography.[7-9]

The negative predictive value of D-dimer levels has been reported to be high for ruling out a diagnosis of thromboembolic disease,[3,7] but the positive predictive value is very low as D-dimer levels can also be elevated in venous thromboembolic disease and other disease processes such as heart failure, surgery, infections, connective tissue disorders, and cancer.[10,11] The diagnostic value of D-dimer measurement is affected by many variables (particularly comorbidity, sedentary lifestyle, outpatient or hospital patient, thrombus size, anticoagulant therapy, and time between the event and D-dimer measurement) and the type of D-dimer assay used.[7] The traditional latex agglutination assay has fallen into disuse because of its lower sensitivity compared to other methods; turbidimetric techniques and enzyme-linked immunoabsorbent assay (ELISA) techniques are the most sensitive, whereas the usefulness of the SimpliRED assay is still under debate.[11] Our study aims to establish the sensitivity and negative predictive value of D-dimer levels measured by a fast ELISA assay for diagnosis of pulmonary thromboembolism in the emergency room.

Patients and Methods

A prospective study of consecutive patients attended between September 2002 and July 2003 in the Emergency Room of the Hospital de la Princesa in Madrid with clinical suspicion of pulmonary embolism was conducted.

Study Design

The study included patients who presented with symptoms suggesting pulmonary embolism. Inclusion criteria were as follows: clinical suspicion of thromboembolism in patients attended in the emergency room, age over 18 years old, and measurement of D-dimer levels at the time of admission. Patients were excluded in the following instances: pregnancy, age under 18 years old, anticoagulant therapy, 3-month clinical follow-up not possible, and refusal to give informed consent for the tests or withdrawal of informed consent. The treating physician classified each patient according to pretest clinical probability (low, medium, high)[8] and requested diagnostic tests for pulmonary thromboembolism according to the workup established at the Hospital de la Princesa by the Venous Thromboembolic Disease Working Group (Figure 1). The diagnostic tests included in this workup were chest x-ray, perfusion scintigraphy, venous ultrasound of lower limbs, spiral CT, and pulmonary arteriography.

Patients diagnosed with pulmonary embolism by any of these tests were put on anticoagulant therapy. Those with negative findings in tests not considered a reference method (negative on venous ultrasound of the lower limbs combined with low clinical probability, low-probability lung perfusion scan, or a negative spiral CT) were observed for 3 months. The patient was considered as positive for pulmonary embolism if thromboembolic venous events occurred in this period. If the findings of the perfusion scan or pulmonary arteriography were normal, diagnosis of pulmonary embolism was ruled out, and patients neither received treatment nor were scheduled for further follow-up.

The protocol for this study was approved by the ethics committee of our hospital. Informed consent was not required, except for normal diagnostic procedures (spiral CT, lung scintigraphy, and arteriography).

D-Dimer Measurement

Plasma D-dimer levels were determined initially in all patients by the VIDAS® D-dimer technique (bioMérieux, Lyon, France), a double-sandwich enzyme-linked fluorescent assay. Concentrations were expressed in micrograms per milliliter of equivalent units of fibrinogen. The time between determination of D-dimer levels and imaging tests did not exceed 24 hours in any patient.

Clinical Follow-up

Patients who were considered negative for pulmonary embolism based on ultrasound images of the lower limbs, had a low-probability in lung perfusion scan or spiral CT, and those who were not put on anticoagulant therapy were assessed after 3 months. In this assessment, the medical history of the patient was recorded, and if this was not possible, the patient's family physician was contacted or the patient or family members were called by telephone. The appearance of possible signs and symptoms of venous thromboembolic disease or initiation of anticoagulant therapy was investigated. Other authors have described the same approach or a similar one for clinical follow-up in other studies.[12,13]

A patient was considered to have thromboembolic disease when deep vein thrombosis was diagnosed in individuals with symptoms of pulmonary embolism, when the perfusion scan, spiral CT, or pulmonary arteriography was positive, or when events related to thromboembolic disease were reported during the 3 months of clinical follow-up (venous thrombosis or pulmonary embolism).

A patient was considered free of thromboembolic disease when the perfusion scan was normal or indicated low probability in patients with low clinical probability and with negative clinical follow-up, when 2 venous ultrasound examinations (initially and at 7 days) were negative in patients with low clinical probability and clinical follow-up at 3 months was negative, or when spiral CT was negative and clinical follow-up at 3 months was also negative, or when pulmonary arteriography was negative. When CT was inconclusive, the patient was reassessed and further diagnostic tests were requested. Clinical follow-up of 3 months was done in cases where the patient was considered