ORIGINAL ARTICLE

Values of D-dimer test in the diagnostics of pulmonary embolism

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ABSTRACT

Aim To establish a value of D-dimer and compare findings of elevated and normal values with the golden standard, computed tomography (CT) of lungs in patients who had symptoms indicating pulmonary thromboembolism (PTE) at admission.

Methods This retrospective/prospective study was conducted at the Department of Internal Diseases of the Cantonal Hospital Zenica, Bosnia and Herzegovina. A sample included 80 patients with symptoms indicating PTE at the time of admission, D-dimers and CT scan of thoracic organs were performed. The patients were divided into two groups: 40 examinees with PTE confirmed by CT scan and 40 patients (control group) whose PTE was not confirmed by the CT scan.

Results Sensitivity of D-dimer according to statistical calculation was 87.5%. Specificity of D-dimer was 57.5%. The chance of a patient to have PTE in case of elevated values of D-dimer was 3.58 higher than in patients with normal D-dimer values. The positive predicative value of D-dimer was 0.54, the negative predictive value was 0.75. Test accuracy was 57.5%. Values of D-dimer >0.83 using a ROC curve and present clinical symptoms of the disease have indicated further diagnostic examination according algorithm and a need for CT scan (of thoracic organs).

Conclusion D-dimer is important in the diagnostics of PTE, high sensitivity and low specificity have been proven. A positive D-dimer test indicates the presence of PTE. However, the test is not reliable. In order to set a diagnosis it is necessary to visualize a blood clot by computed tomography of lungs.

Key words: product fibrin, CT, Wels score
INTRODUCTION

Pulmonary thromboembolism (PTE) is a clinical and pathophysiological condition occurring when a blood clot originating from veins of systemic circulation taken by bloodstream occludes one of the branches of the pulmonary artery and prevents blood to reach a part of lungs (1). Pulmonary thromboembolism is a leading cause of illness and mortality, and it can occur in relation to many clinical conditions (1,2). Pulmonary thromboembolism is on the third place according to prevalence after the ischemic heart disease and cerebrovascular disease with the incidence of 1-2% in the general population and 12-20% in the population of hospitalized patients (2-4). Around 60% of all cases of vein thromboembolism are hospitalized patients, with 5-10% of patients suffering from pulmonary thromboembolism (2,5,6). Epidemiological studies indicate that it is responsible for over 50,000 death cases in the USA (3,7). However, the available data show that less than 10% of all cases of pulmonary embolism end up with death (1,2,8,9). Therefore, the prevalence of fatal embolism cases together with non-fatal embolism is probably higher than 500,000 annually (2,3,5). Researchers from the Duke University have found that the use of automatic, immunoturbidimetric D-dimer assay, in combination with clinical algorithm of risk, favors the assay as the first line in the treatment of patients with a high risk of pulmonary embolism due to a small number of samples available for the analysis from that population (2,3,5). In clinical practice, the biggest problem arises from the question which is the value of D-dimer assay as a marker for further diagnostic algorithm with clinical suspicion of PTE (10,12). The aim of the research was to compare the elevated and normal D dimer test in patients who had clinical suspicion of PTE at admission to hospital and compare the value of D- dimer with the golden standard, CT scan of thoracic organs. Obtained data will help clinicians use the diagnostic algorithm and ensure timely treatment of pulmonary embolism and prevention of death (8,13).

PATIENTS AND METHODS

The clinical retrospective/prospective study was conducted in the periods February-August 2012, and September 2012 -March 2013, respectively, at the Department of Internal Diseases, Cantonal Hospital Zenica, Bosnia and Herzegovina. The research was approved by the Ethics Committee of the School of Medicine in Sarajevo and the Director of the Cantonal Hospital Zenica. The patients in the prospective study were informed about the vital importance of conducting the diagnostic algorithm and timely treatment, for which they gave their consents. The sample included 80 patients with symptoms indicating probable presence of PTE, and consequently D-dimers and computed tomography (CT) of thoracic organs were performed. All the patients were divided into two groups: control group (n=40) included patients with symptoms indicating the presence of PE, who underwent complete diagnostic procedure, and the CT scan excluded pulmonary thromboembolism. The study group (n=40) involved patients with symptoms indicating PTE, who underwent compete diagnostic procedure and the CT scan confirmed PTE diagnosis.

The research examined the following parameters taken at the onset of the disease (risk factors): trauma, fractures (especially large bone of lower limbs), orthopedic surgery (especially hip and knee), major abdominal, gynecological, and vein surgery, cardiovascular diseases accompanied by cardiac decompensation and arrhythmias, septic conditions, malignant diseases, miscarriage, childbirth.

D-dimers were determined by a new method of immunoturbidimetry (BCSX System, hemostasis testing, Siemens Healthcare Diagnostic, Erlangen, Germany) and interpreted as elevated above the reference values (<500 ng/L) in the Biochemical Laboratory of the Cantonal Hospital Zenica. Computed tomography was performed (Siemens Somatom definition 44 slice device, Erlangen,Germany) immediately after the admission to hospital. The Ultravist 300 mg/ml iopromide (Bayer Pharma AG, Berlin,Germany) radiological contrast agent was used. Interpretation of the scan was done by an experienced radiologist of the Cantonal Hospital Zenica.

Nominal and ordinal variables were analyzed using the χ² test, and in case of a lack of expected frequency, Fisher exact test was applied. For continuous variables symmetry of their distribution was first analyzed with the Kolmogorov-Smirnov test. When the distribution of continuous variables was symmetric, arithmetic mean and standard deviation were used to show mean values.
and dispersion measure. To compare variables parametric tests were applied (Student’s t test and ANOVA). Significance level was at p<0.05.

RESULTS

The average age of the control group and the study group was 61.07±14.44 (22-84) and 58.60±16.40 years (21-80), respectively. Average age of the patients involved in the research was 59.83±15.40 years (21-84) (p=0.476) (Figure 1).

The analysis of average values of coagulation factors in the study and control group has shown significantly elevated levels of D-dimer in the study group (p=0.002). In the analysis of the average values of D-dimer test, we found that the value of D dimer was statistically higher in the study group patients (p = 0.002). The values of D-dimer varied from physiological values and they were significantly higher in the study group (p=0.002). Average values of activated partial thromboplastin time (APTT) and international normalized ratio (INR) were not statistically different (Figure 2).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Study group</th>
<th>Control group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased D-dimer values</td>
<td>37 (92.5%)</td>
<td>31 (77.5%)</td>
</tr>
<tr>
<td>Within normal physiological values</td>
<td>3 (7.5%)</td>
<td>9 (22.5%)</td>
</tr>
</tbody>
</table>

Table 2. Prevalence of physiological and pathological values of D-dimer within the examined groups

The analysis of average values of coagulation factors in the study and control group has shown significantly elevated levels of D-dimer in the study group (p=0.002). The values of D-dimer varied from physiological values and they were significantly higher in the study group (p=0.002). Average values of activated partial thromboplastin time (APTT) and international normalized ratio (INR) were not statistically different (Figure 2).

The analysis of symptoms indicating pulmonary thromboembolism has shown that 25 (62.5%) patients from the control group and 23 (57.5%) from the examined group were coughing, equal percentage of the examinees in both groups, 29 (72.5%), had difficulties breathing and suffocation; however, when it comes to the presence of pain, 36 (90%) patients from the study group experienced pain as compared with 29 (72.5%) from the control group (p=0.045) (Table 1).

Analyzing the values of coagulation factors in the control and study group we found that the elevated D-dimer was more present in the patients from the study group (n=37), as compared with the examinees from the control group; there is a statistically significant difference in the prevalence of pathological findings of D-dimer between the groups (p=0.047) (Table 2).

Table 1. Prevalence of clinical symptoms in patients with clinical suspicion of pulmonary thromboembolism

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Control group</th>
<th>Study group</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cough</td>
<td>25 (62.5)</td>
<td>23 (57.5)</td>
<td>0.803</td>
</tr>
<tr>
<td>Pain</td>
<td>29 (72.5)</td>
<td>36 (90.0)</td>
<td>0.045</td>
</tr>
<tr>
<td>Difficult breathing and suffocation</td>
<td>29 (72.5)</td>
<td>29 (72.5)</td>
<td>1</td>
</tr>
</tbody>
</table>

The patients had 76.2% higher chance of getting PTE if the values of D-dimer were higher than 0.83 (p<0.05; cut off >0.83; CI95% 0.653 – 0.850). The sensitivity of D-dimer of 87.5% (CI95% 73.2 – 95.8), and increased values of D-dimer obtained by the immunoturbidimetry method occurred in 87.5% patients with the symptoms of PTE, whose diagnosis was confirmed by the CT scan. D-dimer specificity was 57.5% (CI 95% 40.9–73.0), e.g. 57.5% patients D-dimer obtained by immunoturbidimetry was increased with no presence of pulmonary thromboembolism (it was not proven by the CT scan) (Figure 3).
Determining D-dimer concentration is one of the basic tests used for exclusion of the diagnosis of thromboembolic diseases, deep vein thrombosis and pulmonary embolism (11-13). Testing of plasmatic D-dimers in the patients in this research admitted to the Department for Internal Diseases, the Cantonal Hospital Zenica, proved to be an excellent non-invasive triage test in patients with suspected PTE (10,14,15). The age difference of both studied groups was not statistically significant. Average age in this study was 59.83 years. A number of studies showed that the incidence of PTE is higher in the middle and old age, and significantly higher in patients over 45 (7,11). In our study we analyzed the symptoms that indicated pulmonary thromboembolism and it was found that 62.5% of the patients of the control group and 57.5% of the test group had had cough, equal percentage of respondents in both groups (72.5%) had experienced wheezing and choking, and 90% and 72.5% of the patients from the studied and control group, respectively, had felt pain. D-dimer has a significant place in the diagnostic algorithm of the acute PTE (6,16,). Our results showed high sensitivity of D-dimer test. D-dimer test is sensitive, but it is not a specific marker for pulmonary thromboembolism (13,17). It has a low level of false negative results (15,18). Our results showed that from the study group only 3.75% of patients had a negative value of D-dimer and the risk of pulmonary thromboembolism was high, which is the reason why CT of thoracic organs was performed thus proving PTE. The negative value of D-dimer test in combination with low risk by Wells score can effectively eliminate the need for expensive diagnostic imaging methods, which is confirmed by the references (13,15). Researchers at Duke University have found that the use of automatic immunoturbidimetric D-dimer test is useful in combination with certain risk factors through Walls, as the first-line screening test for diagnosing pulmonary thromboembolism (19,20).

This study suggests that a negative D-dimer test with a little pretest is likely exclude the presence of venous thromboembolism, which was shown by Bates and his associates (7).

Based on the obtained values of D-dimer test in the present study, the negative predictive value of D-dimer was 0.75, which means that in case patients had physiological values of D-dimer with unclear clinical presentation of PTE, the probability that they had no PTE was 75%.

Carrier et al. discovered that among the patients aged 60-80, a low to negative Wells score in combination with a negative D-dimer test occurred in 99% of the negative predictive value (NPV), indicating the probability that patients have pulmonary thromboembolism is 99%. (7,10). However, in patients older than 80 with low negative Wells score in combination with the negative D-dimer test, 21-31% resulted in a negative predictive value (15). A study by Wels, Carries et al. indicated that the use of a manual D-dimer test of blood agglutination in combination with the grading system for clinical pretest probability known as the Wells score resulted in the significant decrease of number of patients who had undergone the diagnostic method of compression ultrasound (7,20).

D-dimer test is not a specific marker for PTE, however, it serves as an accessory test in the diagnostic protocol for the exclusion of pulmonary thromboembolism. In our study a positive predictive value of the D-dimer implied that the CT confirmed PTE in 54% of patients corresponding to the results in the reviewed literature (11,21).

Many factors are associated with positive D-dimer (16). D-dimer test can be elevated in a range of non-thrombolytic disorders including recent surgeries, bleeding, injuries, pregnancy, postpartum period, age older than 80 years, malignity
and septic condition (7,15). In clinical practice the biggest problem arises from the question which value of D-dimer test is to serve as a marker for further diagnostic algorithm in case of clinical suspicion of PTE (17). Application of cut-off values significantly increases specificity without changing the sensitivity of the test thereby improving clinical benefit of D-dimer in the diagnosis of PTE (10,22). In this study we found that in case of clinical suspicion of pulmonary thromboembolism, and D-dimer values higher than 0.83, further diagnostic algorithm needed to include CT thoracic organs (23). Based on AUC ROC curve, we can conclude that respondents have 76.2% greater risk of developing PTE if they have D-dimer values higher than 0.83. Increased limits on the values of D-dimer can reduce false positivity, and increase the false-negative results in older patients (11,22,23).

In conclusion, we found that D-dimer test was a valuable tool in the evaluation of patients with suspected PTE, and it may help physicians with further diagnostic algorithm and eliminate the need for radiological tests, but only in combination with clinical presentation, associated risk factors and the possible presence of other diseases, which can give similar symptoms of pulmonary thromboembolism.

ACKNOWLEDGEMENT

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TRANSPARENCY DECLARATION

Competing interests: none to declare.

REFERENCES


Vrijednost D-dimer testa u dijagnostici akutne plućne tromboembolije

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SAŽETAK

Cilj istraživanja je utvrditi vrijednost D-dimera i uporediti nalaz povišenih i normalnih vrijednosti sa „zlatnim standardom“ kompjuterizovane tomografije pluća (CT) kod pacijenata koji su pri prijemu imali simptome koji ukazuju na plućnu tromboemboliju (PTE).

Metode U retrospektivno-prospektivnoj studiji, provedenoj na Internom odjelu Kantonalne bolnice Zenica, uzorak je sačinjavalo 80 bolesnika sa simptomima koji su, pri prijemu u bolnicu, ukazivali na moguću PTE. Određena je vrijednost D-dimera i utvrđena CT torakalnih organa. Pacijenti su podijeljeni u dvije grupe: 40 ispitanika kojima je prema CT-u dokazana PTE i 40 ispitanika kojima to nije dokazano (kontrolna grupa).

Rezultati Osjetljivost D-dimer testa iznosila je 87.5%, a specifičnost 57.5%. Izračunavanjem omjera izgleda ustanovljeno je da se šansa za PTE kod povišenih vrijednosti D-dimera 3,58 puta veća nego kod ispitanika koji su imali normalne vrijednosti D-dimera. Pozitivna prediktivna vrijednost D-dimera iznosila je 0.54, a negativna 0.75. Tačnost testa iznosila je 57.5%. Vrijednosti D-dimera >0,83 primjenom ROC krive i prisutni klinički simptomi bolesti, ukazuju da su u daljem dijagnostičkom algoritmu obavezno urađeni CT torakalnih organa.

Zaključak Određivanje vrijednosti D-dimer testa u dijagnostici PTE-a je značajno. Pozitivan D-dimer ukazuje na plućnu emboliju, ali test nije pouzdan. Za postavljanje dijagnoze PTE-a potrebna je vizualizacija tromba putem kompjuterizovane tomografije pluća.

Ključne riječi: produkt fibrina, CT, Wels-scor