

D-DIMER RELEVANCE IN THROMBOEMBOLIC SYNDROMES

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Keywords: D-dimers, pulmonary embolism, deep vein thrombosis, predictive value

Abstract: D-dimer marker analysis is relatively inexpensive, simple to perform, done at the bedside together with other manoeuvres and not requiring any special preparation. We aimed at demonstrating diagnostic effectiveness of D-dimers as a method of first choice in the diagnosis of thrombotic events. We conducted a retrospective descriptive epidemiological study over a period of 3 years. Patients were selected from all the cases that were presented in the Emergency Unit within the Clinical County Emergency Hospital of Sibiu in whom D-dimer markers were harvested. Of the initial batch of 310 people who had D-dimer testing, we selected a group of 193 patients who had positive D-dimer results. Of the 193 patients with positive D-dimer results, 22 were confirmed with TEP (12%) and 12 with TVP (7%) and a total of 7 patients presented both disorders simultaneously. A percentage of 81% of the total patients with positive D-dimer results were diagnosed with conditions in which the value of D-dimers could increase non-specifically. 15% of all cases of TVP resulted in death. For TEP, there were 37% patients who died; in 55% of the cases the values of D-dimers were > 1600ng/l and 37.5% had values > 3200ng/l. TEP diagnosis was confirmed in D-dimers negative values (below 200 ng/l) in 2 cases in the study group. Conclusions: The high negative predictive value of D-dimers (between 0, 98-1.00) reveals that a value of D-dimers below 200 ng/l excludes in over 98% of cases the thrombotic syndrome. Very high negative predictive value of D-dimers indicates an important role, especially in the diagnosis of exclusion of the thrombotic syndromes (TEP and TVP) than in the positive diagnosis.

INTRODUCTION

Cardiovascular and thromboembolic accidents in particular represent a pathology of extreme emergency, whose approach faces the clinician with two major issues: the need to set the diagnosis and the therapeutic intervention. In developing this study, we had in view to demonstrate the effectiveness of D-dimers in the diagnosis of thromboembolic diseases and especially, in the diagnosis of pulmonary embolism (PE) and deep vein thrombosis (DVT). Quantitative latex-derived assays and integral blood agglutination have a diagnostic sensitivity of 95% and thus are often referred to as moderately susceptible. Within research studies in safe conditions, these tests have proved to exclude pulmonary thromboembolism in patients with improbable PE. Pulmonary angiography can definitively diagnose PE, but it is too expensive and invasive to be used in every patient, as compared to D-dimer testing.(1)

D-dimer testing, coupled with a pre-test clinical assessment can safely exclude pulmonary embolism and deep vein thrombosis in almost half of patients with symptoms in the emergency department, according to two studies developed on July 17, 2014 by Annals of Medicine - Dr. Philip Wells (Ottawa Hospital, Ontario, Canada) and Dr. Clive Kearon et al (McMaster University Clinic, Hamilton, Ontario, Canada). PE is usually suspected in patients in the emergency room, but it is actually present in only 25-35% of potential cases.(2)

Several studies have shown the main usefulness of measuring D-dimers, which is the high negative predictive value of the test in the diagnosis of deep vein thrombosis in an appropriate clinical setting. Clinically, (pre-test) probability (Wells score) in DVT is determined by evaluating multiple factors, such as recent or on-going therapy for cancer, lower extremities immobilization, recent major surgeries, tenderness, swelling and a history of DVT. Based on this score, the

likelihood of developing DVT is categorized as low (unlikely to develop) or high (likely to develop).(3)

In a study that analysed data from 10 academic medical centers and two community hospitals in the United States, negative predictive value of D-dimer testing was of 99% among patients aged 60-80 years old, dropping to 21%-31% in the case where the patient was older than 80 years of age.(4) Similarly, D-dimer testing was considered to be very valuable in pregnant patients; if a pregnant woman had a low pre-test probability of DVT, the negative predictive value of D-dimer negative value testing was of 100%.

Taking into account that D-dimer assay involves activation of coagulation and of fibrinolytic systems, it is valuable in the diagnosis and monitoring of disseminated intravascular coagulation (DIC) in combination with other parameters. A study conducted in 2010 showed that low level of D-dimer in plasma in children and adolescents correlates well with the lack of traumatic brain injury.(5)

PURPOSE

The main objective of this study is to achieve an accurate picture of the role played by D-dimer markers in the diagnosis of thrombosis, based on the diagnostic effectiveness of this method, as well as taking into consideration the accessibility and the time needed for examination, the possibility of repeating the analysis when needed and the costs.

MATERIALS AND METHODS

We performed a retrospective descriptive study over a period of 3 years, respectively between 01.01.2013 and 12.01.2015. Patients were selected from all the cases who were presented in the Emergency Unit within the County Clinical Emergency Hospital of Sibiu during this period and who had D-

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Article received on 20.03.2016 and accepted for publication on 16.09.2016
ACTA MEDICA TRANSILVANICA September 2016;21(3):76-78

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dimer testing. Of these, we selected the patients who required follow-up and care for more than 24 hours, being admitted to one of the departments of the Hospital.

Therefore, the study included all patients who had D-dimer markers testing and who were hospitalized in one of the Hospital departments: Cardiology, Internal Medicine, Hematology, Oncology, Neurology, Orthopaedics Surgery I and II, Gynecology. Additional data were obtained from the patient's clinical record. For statistical processing of the data, we used SPSS software, version 10, and Windows operating system.

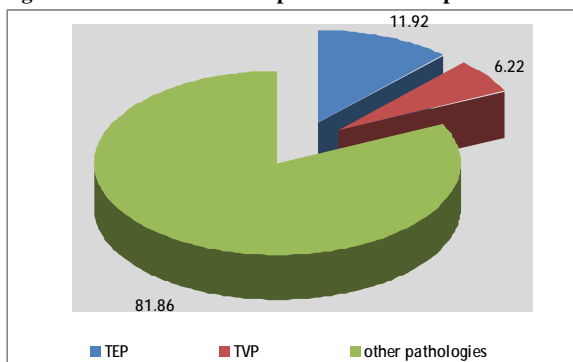
Of the initial batch of 310 people, who had D-dimer testing, we selected a second batch of 193 patients who had positive D-dimers and we analysed this batch in more details. We obtained three groups of patients with high values of D-dimers presenting: pulmonary thromboembolism, deep vein thrombosis and a group of patients with other pathologies.

RESULTS AND DISCUSSIONS

Of the 310 patients who had D-dimer testing, in only 193 patients, the value of these markers was high, representing about 62%, in remaining 117, the values were normal

Comparing D-dimer testing with CT, which is also used in the diagnosis of venous thromboembolism, we note that the analysis of these markers is cheaper, easier to perform, can be achieved in 15 minutes at the bedside, together with other manoeuvres, requiring no special preparation. Of the 193 patients with positive D-dimer, 22 were confirmed with PE (12%) and 12 (7%) with DVT, of which 7 patients had both diseases simultaneously.

Figure no. 1. Distribution of positive D-dimer patients



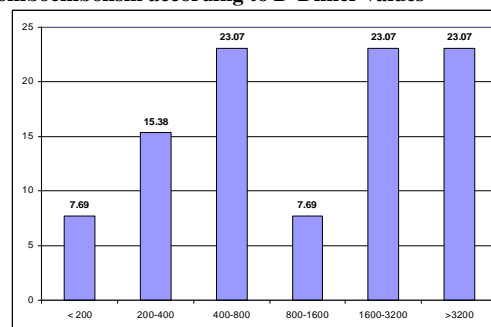
A percentage of 81% of all patients with positive D-dimers have been diagnosed with other diseases in which the value of D-dimers can increase non-specifically (figure no. 2). D-dimers pathological variations can occur in other diseases as well, leading to the activation of coagulation induced by the formation of thrombin, fibrin and reactive fibrinolysis:

- Surgery,
- Liver diseases,
- Myocardial infarction, angina, heart failure,
- Disseminated intravascular coagulation,
- Sepsis,
- Neoplasms,
- Blood diseases,
- Ischemic stroke,
- Thromboembolic treatments,
- During pregnancy - very high levels are associated with complications.

In the group of patients with PE, 55% of cases registered values of D-dimers > 1600 ng/l and 37.5% had

values > 3200 ng/l.

Figure no. 2. Distribution of patients with pulmonary thromboembolism according to D-Dimer values

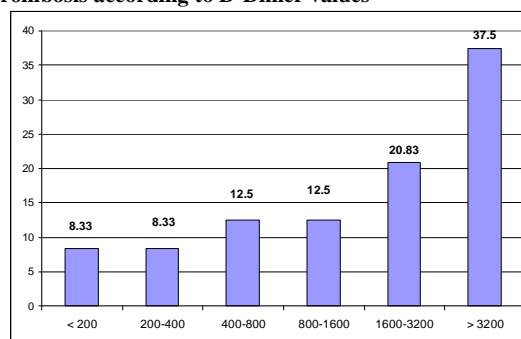


For PE, there is a significantly higher percentage of patients who died, 37%. P value level of significance obtained by Chi Square Person's test is 0.005, which shows that the number of patients with improved health, 58%, is significantly higher than the number of deceased patients, 37% or healed, 4%.

DVT is a severe condition, the analysis conducted, showing that 15% of cases resulted in death. P value level of significance, obtained by Chi Square Pearson's test is 0.005, which shows that the number of patients with improved health status (70%) at discharge is significantly higher ($\chi^2 = 7.538$, $p = 0.023$) than those cured (15%) or deceased (15%). There are no patients discharged with worsened DVT.

It can be noticed that in the case of DVT, in about 45% of cases, the values of D-dimers were up to 800ng/l and in about 45%, values higher than 1600ng/l ($\chi^2 = 2$, $p = 0.736$) so, in case of DVT, D-dimer values can be both normal and elevated. There is also a confirmed case of DVT with negative D-dimers <200 ng/l in a percentage of 8.33%.

Figure no. 3. Distribution of patients with deep venous thrombosis according to D-Dimer values



TEP diagnosis was confirmed at negative values of D-dimers below 200 ng/l, in 2 cases in the study group (8.33%) both patients received anticoagulation therapy prior to the thrombotic event.

One can say with 99% accuracy that there is an association between D-dimers value and PE diagnosis ($p = 0.002$). D-dimers sensitivity to detect thrombotic syndromes was of 0.90-1.00 and the specificity was of 0.42 to 0.43, which shows that D-dimers are sensitive but not specific; they can increase in other diseases mentioned in this paper. D-dimers high negative predictive value (between 0, 98 to 1.00) reveals that a value below 200 ng/l excludes in over 98% of cases a thrombotic syndrome. Low positive predictive value (0.04-0.05) demonstrates that high D-dimers do not confirm the diagnosis of DVT.

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Table no. 1. D-dimers sensitivity in thrombotic syndromes

Indicators	PE	DVT	PE+DVT
Sensitivity	0.9	0.9	1
Specificity	0.43	0.42	0.42
Positive predictive value	0.10	0.05	0.04
Negative predictive value	0.98	0.99	1

DISCUSSIONS

D-dimer testing coupled with a pre-test clinical evaluation may safely exclude pulmonary embolism (PE) and deep vein thrombosis (DVT) in almost half of patients with symptoms within the emergency department, according to two studies conducted on 17th July 2014 by the Annals of Medicine - Dr. Philip Wells (Ottawa Hospital, Ontario, Canada) and al, Dr. Clive Kearon et al (McMaster University Clinic, Hamilton, Ontario, Canada). Pulmonary embolism is usually suspected in patients in the emergency room, but is actually present in only 25-35% of potential cases.(6)

Several studies have shown that the usefulness of measuring D-dimer is the high negative predictive value of the test in the diagnosis of deep vein thrombosis in an appropriate clinical setting. Clinically (pre-test), probability (Wells score) of DVT is determined by evaluating multiple factors, such as recent or on-going cancer therapy, lower extremity immobilization, recent major surgery, tenderness, swelling and history of previous DVT. Based on this score, the likelihood of developing DVT is categorized as low (unlikely to develop) or high (likely to develop).

In a study that analysed data from 10 academic medical centers and two community hospitals in the United States, the negative predictive value of D-dimer test is 99% among patients aged 60-80 years, but it drops to 21% -31% when the patient is older than 80 years. Similarly, D-dimer is considered to be a very valuable test in pregnant patients; if a pregnant woman has a low pretest probability of DVT, the negative predictive value of a negative D-dimer test is 100%. Because D-dimer assay involves activation of coagulation and of fibrinolytic systems, it is valuable in the diagnosis and monitoring of DIC in combination with other parameters. A 2010 study showed that D-dimer low levels in plasma in children correlates well with the absence of traumatic brain injury.(6)

CONCLUSIONS

Comparing D-dimer testing with CT, which is also used in the diagnosis of venous thromboembolism, we note that the analysis of markers is cheaper, easier to perform, being achieved in 15 minutes at the bedside, together with other manoeuvres and requiring no special preparation.

Of the 193 patients with positive D-dimers, 22 were confirmed with PE (12%) and 12 with DVT (7%) and a total of 7 patients had both disorders simultaneously.

A percentage of 81% of the total patients with positive D-dimers were diagnosed with other diseases, cases in which D-dimers value can increase non-specifically.

Evaluation of D-dimers can be used as a method of first choice in the diagnosis of thrombotic events demonstrating increased sensitivity. Due to reduced specificity of this method, it is mandatory to correlate clinical data with the results and confirm the diagnosis by imaging methods (Doppler ultrasound, computed tomography with contrast agent). In terms of diagnosis importance, very high negative predictive value of D-dimers indicated a significant role played rather in the diagnosis

of exclusion of the thrombotic syndromes (PE and DVT) TEP and DVT) than in positive diagnosis.(6)

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