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Interest of the D-dimers Assay in the Medical Care of Thromboembolic Disease: Experience of the Hematology Laboratory of the Military Hospital Avicenne of Marrakech

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Abstract: The objective of our study is to show the benefits of D-dimers (DD) dosing in the diagnostic care of thromboembolic disease. A retrospective study conducted over a 2-year period (2016-2017), including all DD dosing requests sent to the hematology laboratory at the Avicenne Military Hospital, excluding patients under 18 years of age. The quantitative assay was performed by an immunoturbidimetric method on STA Compact automaton, (STAGO), with STA®-Liatest® D-Di reagents with respect for the pre-analytical phase. We collected 100 samples over the study's two year period. The requests mainly came from the emergencies and polyvalent intensive care unit. The clinical picture suggested a deep vein thrombosis in 56% of cases and pulmonary embolism in 44% of cases. The search was positive in 78% of cases. Sensitivity and negative predictive value were 100%. Specificity in the ambulatory population was 66.66% vs 28% in the hospital population and also decreased with age.

Keywords: D-dimeres, Veinous Thromboembolic Disease, Age Factor, Inpatient and Outpatient

1. Introduction

D-dimers (DD) are products of fibrin degradation and a major constituent of the blood clot. They were first discovered in 1973 and are now part of the routine tests of hematology laboratories. During the 1980s, DD have been used for the first time as a first exclusion test for deep vein thrombosis (DVT) [1] and pulmonary embolism (PE) [2]. They have, since, been widely studied as a diagnostic tool in venous thromboembolic disease (VTED). Plasma DD measurements were performed either on a slide by agglutination of latex particles sensitized with monoclonal antibodies or by an Elisa (Enzyme Linked Immunosorbent Assay) microplate technique. The lack of sensitivity of latex techniques has limited them to a single use: the aid in the diagnosis of consumption coagulopathies [3]. The Elisa microplate technique showed a marked improvement in sensitivity but the inability to adapt it to the emergency prevented its use in the diagnostic strategy of the VTED.

Today, the hemostasis laboratory can really and effectively contribute to the diagnostic approach of VTED by DD dosing through the introduction of rapid, unitary, semi-quantitative or quantitative dosing techniques.

The objective of our study is to show the interest of the DD dosing and their negative predictive value in the diagnostic management of venous thromboembolic disease.

2. Patients and Methods

This is a retrospective study carried out over a period of two years (2016, 2017), which collected all requests for dosages of DD received at the Hematology Department from the different departments of Avicenne Military Hospital (HMA). We included in our study inpatients in neurology, internal medicine, surgery, cardiology, intensive care units and emergency room patients who had a clinical picture

suggestive of VTED or patients at risk of thromboembolism and who had benefited a dosage of DD during the study period. All patients under 18 years of age were excluded.

The samples were taken on an empty stomach using citrated tube with respect for the steps of the pre-analytical phase. The quantitative assay was performed by immunoturbidimetric method on pure citrated plasma on a calibrated and controlled STA® Compact (STAGO) automated machine with STA®-Liatest® D-Di reagents. This technique is validated by many works that place it in the same way as the ELISA techniques. It is a dispersed solid-phase immunoassay of plasma D-dimer. The measurement zone is 0 to 4000 ng/l FEU without dilution; it is 0 to 20000 ng/ml FEU with dilution.

3. Results

General settings

During the two year's study period (2016-2017), 100 DD dosing requests were processed, 78% of which were positive. The majority of DD samples came from the emergency and intensive care departments (respectively 38.46% and 36.81%). The remaining requests were received from other departments (Medicine Department: 12.73%, Surgical Department: 12%). The sex ratio was at 1.12 with a slight male predominance. Our patients had a 60 years old average age, with extremes ranging from 40 to 80 years old. The symptomatology led to deep vein thrombosis for 56 patients.

Detailed results

Thirty-eight patients were seen in the emergency department, of which 80% were positive (ie>500ng/ml). 78% of hospitalized patients had positive DDs. DD value also varied by age category; with a higher positivity rate for elderly patients (Figure 1).

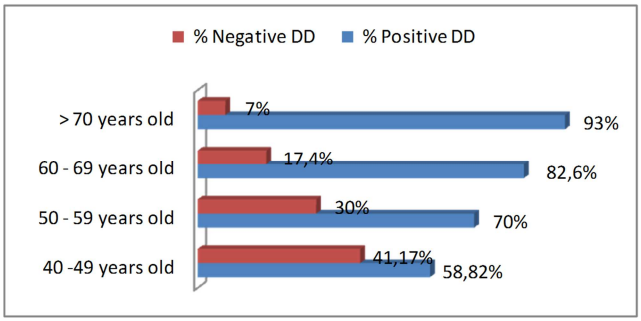

Figure 1. *International Journal of Innovation and Scientific Research (IJISR).*

In the negative DD group (n=22), only 27.27% of the patients (n=6) benefited from imagery examinations without any cases of VTED. In the positive DD group (n=78), 66 patients had radiological examinations (84.61%) amongst which 38 VTED cases were diagnosed (Table 1).

Table 1. *Patients who benefited from imagery examinations.*

	NegativeDD	PositiveDD
Number	22	78
Imaging (échodoppler, angioscanner, echo et angioscanner)	6	66
No Imaging	16	12
Diagnosed VTED	0	38

The statistical endpoint of the study

In outpatients, the sensitivity was 100% while the specificity was 66.6%, the PPV was 86.66% and the NPV 100%. In hospitals, specificity was always 100% and sensitivity 26%, PPV 23.4% and VPV 100%.

For the group of patients over 70 years old, specificity was 28, 57%. In contrast, for patients aged from 60 to 69, the specificity was 47.36% whereas it was 56.25% for the group between 50 and 59 years. (Figure 2)

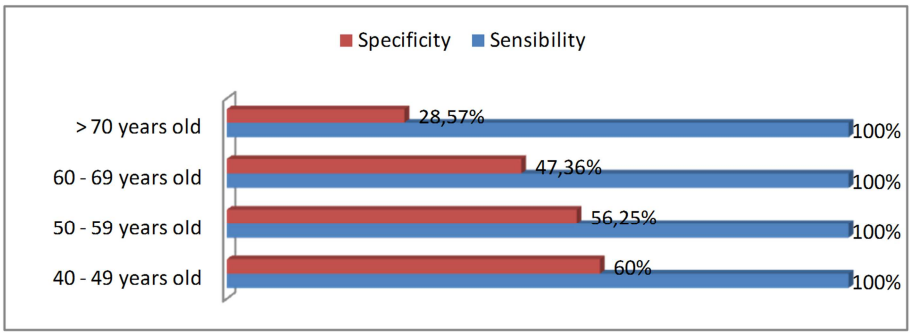

Figure 2. *Sensibility and specificity according to age.*

4. Discussion

The first-line purpose of using DD is to allow the exclusion of a PE or DVT on the basis of a negative test, and thus to avoid imaging tests and their potential adverse effects, to reduce costs and time associated with less diagnostic testing and improve patient satisfaction as a result of more efficient evaluation [4].

Many decision-making algorithms, notably the WELLS score [5], the pulmonary rule-out criteria (PERC)[4] and

revised Geneva score [6], currently used routinely, and offer an adjunct to gestalt clinial assessment to assist in risk stratification and determination of pretest probability. They integrate the DD assay alongside imaging examinations such as pulmonary ventilation or ventilation and perfusion scintigraphy angioscan, or pulmonary angiography which is more invasive. The latter appearing upstream, these exams will be prescribed only in case of DD rate higher than the defined threshold value. Note that in case of high clinical probability, imaging tests are, however, prescribed immediately. Also, an original studie by Kline et al, supported that in patients with low suspicion for PE who are PERC negative, the probability of PE is so low that further testing will not yield a favorable risk-benefit ratio [7], however the 2018 american college of clinical physicians judge that the use of PERC tu exclude PE in low-risk patients is based on a moderate degree of certainty and needs future researchs that focus on defining pretest probability risk cutt offs. [4]

In our study, addressing an ambulatory and hospital population of unselected VTED suspects, the percentage of negative DD is approximately 22%.

In a prospective cohort study conducted to evaluate the clinical utility of a quantitative automated diagnostic DD test in patients with suspected pulmonary embolism, DD was negative for only 11 of 103 hospitalized patients (10.6%; with a 95% confidence interval [CI]; p=0,02) and 7 of 22 outpatients (31.8%; 95% CI; p=0.02) [8].

Another series of 255 patients hospitalized in the general medicine department for various pathologies other than VTED, only 22% of these patients had a DD level below 500 ng/ml [9].

However, the non-specificity of an increase in DD is to be taken into account when interpreting their dosage, especially in hospitals with patients with many underlying defects. Their elevation can be seen in many physiological and pathological situations; hence the difficulties of interpretation in the hospital population and the usefulness of the test becomes limited [3].

In our study, 38.46% were outpatients, 8 of which had a dosage of negative DDs (20%); this result is lower than that found by Siman et al. (31.8%) [8], the rest of the patients in this study were hospitalized in different departments (intensive care unit, cardiology, surgery department, other).

We also observed a gradual rise of the DD level with age. This elevation is usual in the course of life [10] but is amplified by the co-morbid conditions frequently encountered in the elderly.

We found 2 negative DD tests out of 30 performed on our patients over 70 years of age, an exclusion rate of 7% while it is over 17% for 23 patients under 70 years of age. A retrospective study of Petitot and al [11] showed 8 cases of negative DD assay in 49 tests performed on patients over 80 years of age with an exclusion rate of 16.3%, while it is over 35% for 70 patients under 80 years of age and even reaches more than 50% for patients under 70 years of age. They found that the usefulness of the test is correlated with the age of the population to which it is applied. Its efficiency decreases as age increases. In the same way, a Righini and al study also showed that the measurement of DD levels made it possible to exclude pulmonary embolism in nearly 60% of patients under 40, but less than 20% in the group between 70-79 years old and only 5% of those over 80 [12].

In light of these results, it appears that when one addresses a geriatric population, the sensitivity of the test is not affected by age, only its specificity is, making it less interesting because of the proportionally growing false positives. Therefore, several scientific studies proposed an age-adjusted DD cut-off [13], and a recent metaanalysis [4] supported that using a strategy of adjusting the DD for age modestly increases the proportion of patients with a negative DD result, which may reduce the need for advanced imaging in approximately 5% to 10% of patients, without a significant increase in missed cases of PE.

On the other hand, DD dosing has allowed a clear improvement in the management of VTED. Indeed, the clinical diagnosis is particularly difficult because of the low sensitivity and specificity of the clinical manifestations and many complementary examinations, notably phlebography in DVT and angiography in PE, which are invasive and carry a risk of morbidity and mortality. Other less invasive exams that often allow them to be overlooked; the venous Doppler ultrasonography in DVT, helical CT and pulmonary scintigraphy in PE; which are not always easily accessible for all care facilities and require significant infrastructure in terms of equipment and staff [14].

In this work, the DD assay excluded the suspected diagnosis for 22 patients with negative assay results. Patients who had a high DD level, 78 cases, almost all had appropriate additional tests to confirm the diagnosis of DVT or PE and to retain it in 38 cases with low specificity and low positive predictive value of the test, with in return a significant save of medical care; which implies the benefit of integrating this test into a decision tree.

The integration of the DD assay, as a screening step, into the diagnostic strategy of VTED has been suggested in the outpatient known cause of DD elevation by Bounameaux [15] and Perrier [16]. By excluding a substantial proportion of ambulatory patients suspected of VTED, the dosage of low-cost DD would reduce the need for unnecessary or expensive investigations. The value of the DD assay in the evaluation of venous thromboembolic disease lies in its high negative predictive value and its high sensitivity, which makes it possible to avoid costly or invasive tests for PE, such as pulmonary perfusion scintigraphy and angiography with negative DD test results.

The majority of published studies on the use of DDs have been limited for the most part to preselected emergency department (outpatient) patients for whom the prevalence of VTED is the lowest and the negative predictive value (NPV) the highest. Bed rest, and therefore hospitalization, is a risk factor for VTED. The incidence of DVT and PE increases with the presence of risk factors for VTED, which explains its high prevalence in hospital inpatients [17]. Unfortunately,

the profitability of the use of DDs in the hospitalized population is classically mediocre, given the numerous pathological situations leading to the synthesis of low levels of fibrin that disrupt the assay and thus to exclude the VTED in less than 10% of cases against 30% for ambulatory patients [17]. Prescription criteria for DDs such as: age<80 years, absence of surgery, absence of cancer, hospitalization time of less than 3 days, would make it possible to increase the profitability of DDs without restricting their use to ambulatory patients only [18]. It has indeed been shown that after 3 days of hospitalization, the specificity of the dosage is only of 15% [19].

In our work the goal was to confirm these data, and thus specify the type of population in which the dosage of DD would be useful and efficient; keeping in mind that in our study, the specificity in the outpatient population was 66.66% and 28% for the inpatient population.

The DD assay is performed, most often on plasma, by immunological methods, based on the use of monoclonal antibodies recognizing different epitopes present solely on the D-fragment dimers. These neo-antigens are absent from the molecule native fibrinogen, fibrinogen degradation products, or soluble fibrin monomers [20]. They therefore have good analytical specificity (no cross reaction), but DD being only the result of an activation of fibrinolysis secondary to the activation of coagulation, their plasma level is not associated with good diagnostic specificity. It is thus necessary to distinguish the situations where the activation of the clotting remains localized (for example: venous or arterial thrombosis, pulmonary embolism...), of cases where it is more generalized (for example: disseminated intravascular coagulation (CIVD) of the septic shock...). This difference will have an importance on the choice of test to use for their dosage. In case of systemic activation, DD levels are generally very high and a semi-quantitative assay method, such as slide agglutination of latex particles, may be perfectly sufficient. This is not the case in the case of more localized activation of coagulation, where a quantitative and very sensitive dosage will be essential [21]. As a result, the different tests available do not all have the same performance.

Although it represents the gold standard, conventional Elisa (enzyme linked immunosorbent assay) techniques are of little interest in routine, given their technical implementation constraints (production time, not adapted to unit dosage, etc.). Also, and to meet a growing demand, new rapid tests, based on different principles, have been developed and marketed in recent years. Among these, we mention the Elfa (enzyme linked fluorescent assay), close to the classic ELISA but automated and therefore faster (result made in less than 35 minutes) and suitable for unit dosages. Nevertheless, most kits marketed today are based on the principle of agglutination of latex microbeads coated with a monoclonal antibody with satisfactory sensitivity. Their main interests lie in their speed of execution (a few minutes), in their automation on the same analyzer as standard hemostasis balances, or even in their lower cost than the Elisa. In preliminary studies, these techniques seem to have, in the diagnosis of exclusion of PE, performances comparable to those of Elisa techniques [21].

The STA®-Liatest® D-Di (Diagnostica Stago, Asnieres), which is the method used at the Avicenna Military Hospital in Marrakech, is part of this new generation of tests whose sensitivity is comparable to that of the ELISA method and whose performance has been assessed and approved [22]. The LIATEST D-Di has a sensitivity and a 100% NPV in our study. These same values were found in 3 other studies. [22, 23]

Therefore, the dosage of DD integrates, today, into the diagnostic strategy of pulmonary embolism and more generally of VTED. Only a low level of DD, that is to say less than the threshold value (a result often misinterpreted as "negative") can be interpreted, and excludes the diagnosis of pulmonary embolism. The NPV of DD levels measured by a sensitive technique is generally greater than 98% [21]. For lack of specificity, a level of DD higher than the threshold value would not allow the diagnostic of an acute thromboembolic process. We deduce the need to integrate the DD assay into a multidisciplinary diagnostic approach that compares the results of this assay with clinical and radiological data.

5. Conclusion

Although PE due to thrombotic occlusion of the main or branching pulmonary arteries is common, it remains difficult to diagnose owing to the nonspecific signs, symptoms, and risk factors with which it is associated [24]. Acute PE can lead to significant morbidity and mortality, and patients presenting to their physicians or to an emergency department with cardiopulmonary symptoms are often evaluated for the disease. Because no individual risk factor, patient symptom, or clinical sign can definitively diagnose or exclude PE, clinical decision tools have been developed to help guide clinicians during their evaluation of patients with suspected acute PE. These decision tools are meant to help physicians stratify patients into groups for whom different diagnostic strategies are appropriate: those for whom PE is so unlikely that they need no further testing, those for whom plasma DD testing can provide additional risk stratification, and those who are at high enough risk that imaging is indicated.

Highly sensitive plasma D-dimer tests (those that measure the level of this fibrin degradation product by using enzyme-linked immunosorbent assays) can be used to rule out PE in patients with low or intermediate pretest probability of PE.

DDs, using an analytically efficient technique validated by well conducted bioclinical studies and when integrated into a complete diagnostic approach and at a variable level according to the clinical probability, have shown their greatest interest essentially in the exclusion of thromboembolic disease in order to spare patients the use of invasive examinations and the health system a significant cost of care.

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