ORIGINAL ARTICLE

Improving D-dimer Positive Predictive Value for Outpatients with Suspected Deep Vein Thrombosis

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Abstract

Context: Sensitive D-dimer assays have been developed to exclude the diagnosis of deep vein thrombosis (DVT) and have exhibited great success when used in conjunction with a diagnostic algorithm, including pretest probability scoring and a compression ultrasound (CUS). Improving specificity of D-dimer assays would significantly improve the utility of CUSs.

Objective: Our objective was to evaluate the ability of a new D-dimer assay to improve specificity, positive predictive ability, and Bayesian probability when compared with an assay previously used in our laboratory.

Methods: We retrospectively reviewed 1015 continuous patients with suspected DVT. All patients were clinically evaluated in our laboratory with a D-dimer assay: 503 were clinically evaluated with a bioMérieux D-dimer test system and 512 were evaluated with a Trinity Biotech D-dimer test system. Outcomes were assessed statistically using sensitivity, negative predictive value, Bayesian negative probability, specificity, positive predictive value, and Bayesian positive probability.

Results: The data for our study showed that with the Trinity Biotech D-dimer assay, specificity increased from 41.3% to 66.9%, positive predictive value increased 2.3 times from 8.8% to 20.0%, and the probability of DVT after positive results on a D-dimer test increased from 25% to 38% when compared with the bioMérieux D-dimer test system. In addition to the improved parameters for clinical performance, a significant number of unneeded CUSs were saved. The number of false positive D-dimer assays significantly decreased and positive predictive ability improved when the Trinity Biotech test system was used in our laboratory.

Introduction

Deep vein thrombosis (DVT) causes thousands of patients in the US to be hospitalized each year, and many more instances of DVT are diagnosed while patients are hospitalized for surgical procedures or medical illness.

Prompt diagnosis of DVT and treatment circumvent the short-term onset of pulmonary embolism and death, the long-term complications of recurring venous thromboembolism, and the complications of post-thrombotic syndrome.[1]

The objective diagnosis of DVT relies on highly sensitive and specific compression ultrasonography (CUS) or ascending venography. The cost of these modalities and the incidence of negative test findings have led to alternative approaches to diagnosis and decision making in suspected cases of DVT. These rely on the use of diagnostic information from clinical history, examination, and assays to detect D-dimers.[2]

Sensitive D-dimer assays have been developed to exclude the diagnosis of DVT and have exhibited great success when used in conjunction with a diagnostic algorithm, including pretest probability scoring and CUS.[2,3] A value of >500 ng/mL has been established by our laboratory as a positive D-dimer result. In conjunction with a low to moderate pretest probability, a CUS is ordered. For those patients with a high pretest probability, a CUS is ordered without the D-dimer assay being done. With the combination of pretest probability and D-dimer assay, both a sensitivity and negative predictive value >96% has been established in the literature[3,4] and has been duplicated by our laboratory.




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The object of this study, approved by the Kaiser Permanente (KP) Southern California Institutional Review Board, was to test whether the positive predictive value, specificity, and Bayesian positive probability of the D-dimer assay was improved by the use of a Trinity Biotech latex-enhanced immunoassay in place of the previous bioMérieux assay used in our laboratory. We also hoped to discover whether improvement in sensitivity, negative predictive value, and Bayesian negative probability occurred when using the new latex-enhanced immunoassay. In addition, we believe that our data will provide a clear understanding of whether the Trinity Biotech latex-enhanced immunoassay enabled a more efficient use of CUS than the bioMérieux did.

Methods

We retrospectively reviewed 1015 continuous outpatients suspected of DVT who were seen in the KP Medical Center in Fontana, CA, between January 2007 and April 2008. We also included in our data a three-month follow-up review of all patients to determine whether any patient presented with a delayed positive DVT. The three-month follow-up assessment involved chart or electronic medical record review for all 1015 patients. We excluded inpatients and residents of skilled nursing facilities for whom the false positive rate of the D-dimer assay was markedly high. The excluded patient population included elderly patients, pregnant patients, and those with cancer or autoimmune diseases. The patients reviewed for this study were referred from primary care clinics, the Emergency Department, surgery clinics, and the Ob/Gyn Department for DVT. For all 1015 patients, we used a diagnostic algorithm including pretest probability scoring to assess clinical likelihood of DVT;[1] those with low to moderate probability scores were deemed candidates for D-dimer analysis. Of the 1015 continuous outpatients suspected of having DVT, 503 patients were tested with the bioMérieux quantitative homogeneous-phase latex D-dimer immunoassay (bioMérieux, Marcy l'Etoile, France) and 512 were tested with the Trinity Biotech immunoturbidimetric latex Auto-dimer immunoassay (Trinity Biotech, Wicklow, Ireland) and an MDA II analyzer (Trinity Biotech). The cost per D-dimer test was the same for both assays.

The bioMérieux assay uses a Mab8-8G monoclonal antibody and a wavelength of 580 nm. The Trinity Biotech latex-enhanced immunoassay combines an MA-8D3 monoclonal antibody and a size-adjusted latex bead so that the 660-nm wavelength used for the assay remains two times the size of the bead. This is reported by the manufacturer to ensure that the particle will have its maximum absorption. The combination of size-adjusted latex bead, MA-8D3 monoclonal antibody, and higher wavelength were reported to increase analytic sensitivity and assay range[2] (Kevin J McGlinchey, MT (ASCP), CLS (CG), Marketing Manager, Instrumentation, Trinity Biotech, personal communication, April 24, 2008).[a] Our study postulated that with the Trinity Auto-dimer assay, there should be an increased level of specificity and positive predictive value and an increased cost efficiency of the assay by reducing the number of negative images.

To determine the clinical performance of both assays, we used six statistical assessments: sensitivity, negative predictive value, specificity, positive predictive value, and Bayes's theorem for both positive and negative post-test DVT probability.[4,5]

Results

Table 1 shows the parameters used for evaluating the clinical performance of the D-dimer assays used to exclude the diagnosis of DVT. The 503 patients for whom the bioMérieux test system was used yielded negative findings on 196 D-dimer assays, false nega-

Table 1. Parameters used for clinical performance evaluation

	bioMérieux Mab8-8G monoclonal antibody 580 nm wavelength	Trinity MA-8D3 monoclonal antibody 660 nm wavelength
Sensitivity	96.4%	97.5%
Negative Predictive Value	99.5%	99.7%
Specificity	41.3%	66.9%
Positive Predictive Value	8.8%	20.0%
Bayes Positive Probability	25.0%	38.0%
Bayes Negative Probability	1.8%	0.8%

tive findings on 1 assay, and positive assays of which 27 patients had DVT confirmed by positive findings on CUS. We used these data to calculate sensitivity, negative predictive value, specificity, and positive predictive value. In addition, these four parameters helped us use a Bayesian statistical analysis that estimates the probability of a hypothesis when pretest odds and likelihood ratio are known values.[6] This Bayesian analysis gives us a probability estimate for the presence of DVT when a patient presents with either a positive or a negative D-dimer assay.

The bioMérieux system yielded a sensitivity of 96.4%, a negative predictive value of 99.5%, a specificity of 41.3%, and a positive predictive value of 8.8%. Using a Bayesian analysis, we can estimate that after negative findings on a bioMérieux D-dimer assay, the probability of DVT will be 1.8%; we can estimate the probability after positive findings on a bioMérieux D-dimer assay to be 25%.

... we estimated the probability of DVT after negative findings on a Trinity Biotech D-dimer assay to be 0.8% and after positive findings to be 38%.

For the 512 patients for whom the Trinity Biotech test system was used, there were 316 negative results on D-dimer assays, 1 false negative result, and 195 positive results; 39 of those latter patients had DVT confirmed by positive results on CUS. We used these data to calculate sensitivity, negative predictive value, specificity, and positive predictive value. In addition, these four parameters helped us use a Bayesian statistical analysis that estimates the probability of a hypothesis when pretest odds and likelihood ratio are known values.[4] This gave us a probability estimate for the presence of DVT when a patient presented with either positive or negative results on a D-dimer assay.

The Trinity Biotech system yielded a sensitivity of 97.5%, a negative predictive value of 99.7%, a specificity of 66.9%, and a positive predictive value of 20.0%. Using Bayesian analysis, we estimated the probability of DVT after negative findings on a Trinity Biotech D-dimer assay to be 0.8% and after positive findings to be 38%.

Discussion

The formation of DVT is normally followed by a physiologic fibrolytic response. As a result of this fibrolytic response, plasmin is generated, which causes the release of fibrin-degradation products into the circulation. Because D-dimer is the predominant form of fibrin-degradation product, the absence of a clinically significant rise in circulatory D-dimer implies that thrombosis is not occurring. This is why negative results on D-dimer assays have played such an important role in excluding the diagnosis of DVT. It is therefore most strategic to employ a D-dimer assay that has both a high sensitivity and a high negative predictive value. The specificity and positive predictive value have not been emphasized and have historically produced variable results. False positive results have become common when testing for D-dimer.

Our study compared two D-dimer methodologies, postulating that one of them, the Trinity Biotech immunoturbidimetric latex Auto-dimer immunoassay, would maintain a high sensitivity, an excellent negative predictive value, and Bayesian negative probability while greatly improving specificity, positive predictive value, and Bayesian positive probability. Improving specificity, positive predictive value, and Bayesian positive probability would also significantly decrease the number of false positive D-dimers and decrease unneeded usage of CUS.

Our study showed that with the Trinity Biotech D-dimer test methodology, all parameters for clinical performance improved, including sensitivity, negative predictive value, negative probability, specificity, positive predictive value, and positive probability (Table 1). Greatly significant for our study, when we used the Trinity Biotech D-dimer test, specificity increased from 41.3% to 66.9%, positive predictive value increased a statistically impressive 2.3 times from 8.8% to 20.0%, the Bayesian probability of DVT after positive results on a D-dimer test significantly increased 1.5 times from a 25% probability to a 38% probability, and the Bayesian probability of DVT decreased a statistically impressive 2.3 times from 1.8% probability to 0.8% probability (Table 1).

In addition to the improved parameters for clinical performance, a significant number of unneeded CUSs were saved. The number of false positive results for the bioMérieux system was 279/503; for the Trinity Biotech system, it was 156/512. This was a decrease of 123 unneeded CUSs over a six-month period. With the billable cost for each CUS being $315[7] and our cost per D-dimer test being the same for both the bioMérieux and the Trinity Biotech assays, we calculated that a potential six-month CUS savings of $38,745, or a more significant annual CUS savings of $77,490, could be realized by using the Trinity Biotech D-dimer assay.[4,7]

Future investigations for D-dimer research might

include examining a wider patient source, including inpatients and those suspected of having pulmonary embolism. Much work is still needed to improve the standardization for D-dimer assays, and newer technologies for assay methods that help establish clot age and the probability of DVT recurrence will require thorough assessment. ❖

[a] Trinity Biotech, Wicklow, Ireland

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Keep Moving

Perhaps the secret of avoiding blood clots
lay in the humble admonition of the London bobby: "Keep moving!"

—Alastaire Cooke, KBE, 1908-2004, British-born American journalist and broadcaster