New Technologies, Diagnostic Tools and Drugs

Application of a decision rule and a D-dimer assay in the diagnosis of pulmonary embolism

Nadine S. Gibson¹; Renee A. Douma¹; Alessandro Squizzato²; Maaike Sohne¹; Harry R. Buller¹; Victor E. A. Gerdes¹,³

¹Department of Vascular Medicine, Academic Medical Center Amsterdam, the Netherlands; ²Department of Clinical Medicine, University of Insubria, Varese, Italy; ³Department of Internal Medicine, Slotervaart Hospital, Amsterdam, the Netherlands

Summary

Current strategies for diagnosing pulmonary embolism (PE) include a clinical decision rule (CDR), followed by a D-dimer assay in patients with an unlikely clinical probability. We assessed the implementation of the current guidelines for the diagnosis of PE. A first questionnaire was sent to internists and pulmonologists to assess the proportion of physicians that adequately applied the guidelines. Two versions of a second questionnaire were sent presenting five hypothetical cases of which in two cases with an intermediate clinical probability an abnormal D-dimer test result was added to one version. We assessed the variation of the CDR and compared the proportions of a likely clinical probability between the two versions. A total of 65 physicians responded to the first questionnaire (response rate 75%). Half of the physicians (N=29; 46%) indicated that they use a CDR in all patients and 22 physicians (45%) indicated that they review the D-dimer result after they examined patients. Sixty-two physicians responded on the second questionnaire (response rate 36%). A shift was observed from an unlikely to a likely probability when an abnormal D-dimer test result was added to the clinical information (22% to 41%; p=0.22 and 26% to 50%; p<0.05). Our findings indicate that physicians do not use the guidelines for diagnosis of PE consistently. Furthermore, the knowledge of an abnormal D-dimer test result before seeing the patient leads to a higher CDR score. Physicians should therefore first examine patients before taking note of the D-dimer test result.

Keywords

Pulmonary embolism, thrombosis, venous thrombosis, diagnosis management

Introduction

In the last decade much has changed in the diagnostic work-up of patients with clinically suspected pulmonary embolism (PE). With the introduction of clinical probability assessment and D-dimer assays the proportion of patients in whom PE can be simply and safely excluded has improved significantly (1–4). Current guidelines for venous thromboembolism (VTE) have been adjusted, based on performed studies, and this may have helped physicians in becoming more acquainted with these strategies (5, 6). Although the strategies appear efficient, easy to apply and safe in clinical research settings, it is unknown whether this can be extrapolated to daily clinical practice. To what extent individual physicians are actually using these diagnostic strategies is even less clear. With the popularity of the D-dimer assay, physicians have to be aware of pitfalls that come along with the use of this test. Since an abnormal D-dimer test result is non-specific, it is important that this assay is not used as a screening test (5, 7). The test should also not be performed in patients with a likely clinical probability for PE, since they already need to undergo spiral computed tomography (CT) testing. It has been established that false negative D-dimer test results appear in one per 10 patients with a likely clinical probability (8).

In the emergency room setting the D-dimer test is often ordered before the physician has examined the patient. It is conceivable that knowledge of the D-dimer assay outcome before examining the patient will influence the physician’s clinical probability estimation. In the ‘Wells rule’, a widely accepted clinical decision rule (CDR), the last item (alternative diagnosis less likely than PE) is a subjective element with an important contribution to the overall score, which may be interpreted differently if the physician is aware of a certain D-dimer test result (9).

Therefore, we performed a questionnaire based study to determine the use of CDRs and D-dimer testing in patients with suspected PE. We analysed whether physicians used these tests at all and if so, how consistently. In addition, we determined whether physicians were influenced by the knowledge of a D-dimer test result, when scoring the Wells CDR.

Thrombosis and Haemostasis 103.4/2010

Received: September 11, 2008
Accepted after major revision: February 2, 2010
Prepublished online: February 19, 2010
doi:10.1160/TH08-09-0564
Thromb Haemost 2010; 103: 849–854
Methods

First questionnaire

A first questionnaire was designed to determine which diagnostic strategies for PE were used in daily clinical practice. It specifically contained questions on the use of the clinical probability estimation and D-dimer testing. The responses were classified as using only a CDR, using it alternating with clinical judgement or using only clinical judgement. For the D-dimer assay data were classified as using it never, sometimes, often or always and for the interpretation of the test whether this was done before examining the patient, after or both. A database was formed that contained all Dutch internists (n=1,523) and pulmonologists (n=490) that are listed in the registries for Internal medicine and Pulmonology (Nederlandse Internisten Vereeniging and Nederlandse Vereniging van Artsen voor Longziekten en Tuberculose, respectively). The questionnaire was sent to a randomised sample of the physicians in the database and in case of no response, a reminder was sent.

Second questionnaire

In a separate second questionnaire, sent several months later, physicians were randomly assigned to two versions of this questionnaire in which five hypothetical patient cases with a clinical suspicion of PE were presented. The clinical probability of the cases varied from unlikely to likely. To assess the influence of the a-priori knowledge of the D-dimer test result, two versions were prepared for cases with an intermediate clinical probability of PE. In Case 2 the D-dimer result was left out in version A and in version B the clinical information included an abnormal D-dimer result of 1.8 mg/l. In the fourth case it was the other way around; version A was the version with an abnormal D-dimer result of 2.4 mg/l and it was left out in version B. Physicians received one of the two versions, and were not informed that there were two versions and they were told that the goal of this project was “to further evaluate the clinical decision rule”. The cut-off value for an abnormal D-dimer test result of > 0.5 mg/l was added to this questionnaire together with an example of a CDR, the ‘Wells rule’, illustrating the seven items of the rule and the cut-off value of 4 points (Table 1).

Statistical analysis

In the first questionnaire, the proportions of physicians that applied evidence based diagnostic strategies were analysed. We assessed the proportions of physicians that were aware of a CDR, that used it and that used it consistently. The same was done for the D-dimer test. These data were also analysed for several subgroups of physicians (field of specialisation, working in a tertiary centre, number of patients with PE seen per month).

For the second questionnaire, we analysed the variation of the CDR score in the five cases, using descriptive statistics. An independent two sample t-test was used for the comparison between the two versions of Cases 2 and 4. We compared the proportion of physicians that scored the cases as ‘pulmonary embolism likely’ between the versions A and B (physicians that were informed about an abnormal D-dimer and those who were not). Since we wanted observe a difference we have sent the second questionnaire to more physicians. Statistical analyses were applied using SPSS version 14.0.2.

Results

First questionnaire

Of the first questionnaire 87 copies were sent out to a randomised group which represented 4% of the 2,013 physicians, of which 65 (75%) were completed and returned, including the reminder. The practice characteristics of the physicians are detailed in Table 2; 68% were internists, 32% were pulmonologists and the majority was male (86%). The practice characteristics of the 22 physicians that did not return the questionnaire did not differ from those included in this analysis (male gender n=19 (86%); academic centre n=8 (36%); internists n=14 (64%); pulmonologists n=8 (36%)). All but two physicians indicated that they regularly examine patients with a clinical suspicion of PE, hence 63 questionnaires were analysed.

Almost all physicians used a clinical probability test (N=60; 95%) to assess the clinical probability in patients with suspected PE, as is depicted in Figure 1. These physicians were divided equally in those using a CDR in all patients, or using it alternating with clinical judgement (N=29 and N=31, respectively). The remaining three physicians always used clinical judgement. Upon the question which CDR was used, the Wells rule was the only rule that was referred to by 46 physicians (71%), whereas the others could not report a specific decision rule.

All physicians indicated that they use a D-dimer test of whom 53 (84%) indicated that they used this test always or very often. Four physicians (6%) reported to be always aware of the D-dimer
result before they were seeing their patients. Half of the remaining physicians (N=22; 45%) reported to be aware of the result only after they examined the patients whereas the others (N=27) reported that it varied between before and after.

When we compared the use of these tests among several subgroups (internists vs. pulmonologists, academic vs. non academic work settings and those physicians who see more than five patients with suspicion of VTE a month vs. those who see fewer), only small differences were observed, which were not clinically relevant (data not shown).

Second questionnaire

The second questionnaire was sent to 172 physicians (representing 9% of the 2,013 physicians) of whom 62 (36%) returned a completed questionnaire. The practice characteristics were as follows: 65% were internists, the remaining 35% were pulmonologists and 75% of the physicians were male. The practice characteristics of the non-responding physicians did not differ from those included in this analysis (data not shown). Case 1, 3 and 5 were similar for all physicians, whereas for the second and fourth case there were two different versions with respect to knowledge of D-dimer result.

The CDR score per physician varied, although most physicians agreed on the scores of the first case (69% of the physicians scored 10 points) and the third case (89% scored 1 point), as is depicted in Figure 2. For Cases 2, 4 and 5 with an intermediate clinical probability more variability in the CDR score was observed.

Furthermore, a shift was observed between the two versions of cases 2 and 4 from an unlikely clinical probability to a likely clinical probability when an abnormal D-dimer test result was added to the information. A total of 22% of physicians calculated a score > 4 (PE likely) without the knowledge of an abnormal D-dimer vs. 41% if the abnormal D-dimer was added to the information (p=0.22). For Case 4 these percentages were 50% vs. 26% with or without information of an abnormal D-dimer test result, respectively (p<0.05; Fig. 2).

Discussion

This survey shows that the majority of responding internists and pulmonologists operate to a large extent according to the guidelines for diagnosing PE. However, the guidelines are not used consistently, since only half of the physicians indicate that they use a
CDR in all patients. While clinical judgement is a respected method of clinical probability estimation, it is less efficient in withholding patients from additional imaging tests, and may be less safe in inexperienced physicians (10, 11). In this study the scoring of the CDR was clear in those patients with a low or a high clinical probability, but variable and therefore arguably the same as one's clinical judgment, in the cases in which diagnostic uncertainty for VTE was the greatest. While literature indicates that the inter-observer variability of clinical judgment is inadequate if compared to explicit CDRs it is unclear whether this counts for all clinical probability groups (12).

Although guidelines advise assessing the clinical probability before performing the D-dimer test, about one third of the responding physicians were already aware of the D-dimer result before they examined the patient. And even more important, physicians were influenced in scoring the CDR by the knowledge of an abnormal D-dimer test result.

Figure 2: Distribution of the CDR score for the five hypothetical cases. Case 1 was a patient with a high clinical probability for PE; 69% of the physicians scored 10 points with the decision rule. Case 3 was a patient with a low clinical probability; 89% scored 1 point. Case 5 was a patient with a moderate clinical probability; 26% scored 2.5 points and 55% scored 5.5 points. There were two versions of the cases 2 and 4: version A and B. The vertical dotted line stands for the cut-off value of the CDR for ‘pulmonary embolism unlikely’ (≤ 4) or ‘likely’ (> 4). When an abnormal D-dimer test result was added to the patient information, it was clear that a higher proportion of the patients was scored as ‘pulmonary embolism likely’ (2B and 4A).
What is known about this topic?
- Recent studies have shown that clinical probability assessment and D-dimer assays are safe and useful tools for the diagnostic work-up of pulmonary embolism.
- An abnormal D-dimer test result is non specific, therefore it is important that this assay is not used as a screening test.

What does this paper add?
- The guidelines for diagnosing pulmonary embolism are not used consistently, since only half of the physicians indicate to use a clinical decision rule in all patients.
- The knowledge of an abnormal D-dimer test result influences physicians when scoring the clinical decision rule.

There is no information on which items contributed to the total score of the Wells rule, but the influence of the D-dimer test on the physician’s clinical probability estimation is probably caused by the subjective element of the Wells rule ‘alternative diagnosis less likely than pulmonary embolism’. It appears that physicians may have more confidence in an objective blood test than in their own expertise. Due to its moderate specificity the D-dimer assay could also be abnormal in several other situations, and the influence on the CDR is therefore not justified. Furthermore, only a minority of the D-dimer tests have been evaluated in appropriate clinical trials concerning the exclusion of PE (13). Moreover, it has been shown that false negative D-dimers appear in almost 10% of the patients with a likely clinical probability, and physicians should therefore always first assess the clinical probability before taking notice of the D-dimer test result (8). Taken together, adherence to the guidelines was observed in less than a third of the physicians, which is in agreement with the literature, and this may result in unnecessary testing and a less safe strategy (14, 15).

When we focus on the study restrictions, a questionnaire based survey will always have certain limitations, for example the retrospective character and that those that did not answer the questionnaire may have influenced the data. However, the characteristics of these physicians did not differ from those that participated. The response rate of 75% on our first questionnaire was higher than we had expected from response rates of other questionnaires sent to physicians (16, 17). The lower response rate of 36% on the second questionnaire can be explained by the fact that no reminder was sent. It is plausible that those physicians that are familiar with diagnostic strategies would be more inclined to return the questionnaire. It can therefore be hypothesised that those who did not return the questionnaire are even less familiar with the diagnostic strategies for PE. Furthermore, the percentage of physicians represented in the first and second questionnaire of 4% and 9%, respectively, is just a small proportion of the total database, which may affect the generalisability of the study. Finally, physicians may act in clinical practice different from what they report in a questionnaire. Despite these limitations, we believe our results are a good reflection on how diagnostic strategies for PE in the Netherlands are applied.

In summary, although diagnostic strategies for PE have found wide implementation, there still are some pitfalls. Physicians assessing patients in emergency room settings should be cautious when requesting D-dimer assays and should always examine patients first before reviewing the D-dimer result. This will prevent physicians being influenced by a non specifically elevated D-dimer result.

Appendix

Case 1
You are paged by an emergency room physician, who has just seen a 68-year-old woman who had a curative hemicolectomy four weeks earlier because of a Dukes B colon carcinoma. She now complains of a swollen left leg and shortness of breath. Upon the physical exam, the respiratory rate was 24/minute, the tension 110/75 mmHg, heart rate was 108/minute and the left leg looked very suspect for deep-vein thrombosis. The EKG shows a new right bundle branch block and on the chest X-ray some pleural effusion can be seen in the right pleural cavity.

CDR score: .......................... points
A. You perform an ultrasound of the leg. If positive for thrombosis, you perform no further diagnostic tests.
B. You ask for a D-dimer test and let further diagnostic actions depend on the outcome of this test.
C. You perform a CT scan to exclude or diagnose pulmonary embolism.

Case 2 – version A
You see a 63-year-old Indian man. His medical history contains a knee operation in 1980, complicated by deep vein thrombosis of that leg. He also has diabetes and mild hypertension. The patient explains he’s been having a severe flu for almost a week, but that he now also has shortness of breath and chest pain. Upon physical examination you find his body temperature is 37.7°C, the blood tension is 145/90 mmHg, he has an elevated heart rate (110/minute), his respiratory rate is 20/minute. The chest X-ray is normal. Besides tachycardia, the ECG shows no abnormalities.

CDR score: .......................... points
A. You do not perform diagnostic testing for pulmonary embolism, because you believe this diagnosis is unlikely for this patient.
B. You ask for a D-dimer test and let further diagnostic actions depend on the outcome of this test.
C. You perform a CT scan to exclude or diagnose pulmonary embolism.

Case 2 – version B
Same case as version 1, only ‘D-dimer 1.8 mg/l’ was added to the information.

A. You request a troponin assay and ask the cardiologist to examine the patient.
B. You perform a CT scan to exclude or diagnose pulmonary embolism.
C. You perform an ultrasound of the leg. If this is negative for thrombosis, you perform a spiral CT-scan.
Case 3
A man, 68 years old, who has an active carcinoma of the prostate, comes to see you in the outpatient clinic complaining of chest pain, cough, shortness of breath and a cold. With physical examination you find the following parameters: body temperature 37.5°C, tension 120/60 mmHg, heart rate 88/minute. Auscultation of the lungs is normal and so are the chest X-ray and the EKG. Laboraroty test: D-dimer 0.3 mg/l.

CDR score: ……….. points
A. You do not perform diagnostic testing for pulmonary embolism, because you believe this diagnosis is unlikely for this patient.
B. You ask the patient to come back in two days, because you do not fully trust the D-dimer and the clinical decision rule with his underlying malignancy.
C. You perform a CT scan to exclude or diagnose pulmonary embolism.

Case 4 – version A
You see a woman aged 61 years who stopped smoking two years ago. After her second pregnancy she had a DVT in the left leg. During the following three years she used oral contraceptives without any complications. The patient reports she has been coughing a lot more than usual during the past week. Five days ago, she had a fever when she measured her body temperature at home (38.4°C), but this was gone soon afterwards. Since one day, she has shortness of breath and a mild pain on the lateral side of the left thorax. With physical examination you find a body temperature of 37.2°C, her blood tension is 151/94 mmHg, the heart rate is 108/minute, the respiratory rate is 22/minute, on auscultations of the lungs no abnormalities. Both the chest X-ray and the EKG are normal. The D-dimer test is 2.4 mg/l.

CDR score: ……….. points
A. You thoroughly re-examine the patient and the chest X-ray to exclude a rib fracture or pneumothorax.
B. You perform a CT scan to exclude or diagnose pulmonary embolism.
C. You refer the patient to a cardiologist.

Case 4 – version B
Same case as version 1, except for leaving out the D-dimer result.

A. You thoroughly re-examine the patient and the chest X-ray to exclude a rib fracture or pneumothorax.
B. You perform a CT scan to exclude or diagnose pulmonary embolism.
C. You refer the patient to a pulmonologist to perform a bronchoscopy.

Reference

Downloaded from www.thrombosis-online.com on 2018-03-09 | ID: 1001066444 | IP: 54.70.40.11
For personal or educational use only. No other uses without permission. All rights reserved.