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THE CUTTING EDGE: RESEARCH UPDATE

Effect of the Pulmonary Embolism Rule-Out Criteria on subsequent thromboembolic events among low-risk emergency department patients: the PROPER randomized clinical trial

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Background

The diagnostic strategy for pulmonary embolism (PE) endorsed by the European guidelines recommends an assessment of the clinical probability of PE using a structured score (Geneva score or Wells score) or an unstructured estimation of probability (referred as clinical gestalt) [1]. In patients with low to moderate pre-test likelihood of PE, the D-dimer test should be carried out, and, if positive, follow-up should be done with a computed tomography pulmonary angiogram (CTPA) [2].

Due to high mortality rate if left untreated, emergency physicians often feel compelled to order a D-dimer test for patients complaining of dyspnea, chest pain or both. However, the D-dimer test has low specificity, resulting in more than 50% of false-positive patients undergoing the CTPA confirmatory test [3], which has significant clinical and biological contraindications, as well as cost implications.

Consequently in 2004, Kline et al. developed the PERC score (Pulmonary Embolism Rule-out Criteria) to reduce the use of the D-dimer test [4].

The PROPER trial (PERC Rule to Exclude Pulmonary Embolism in the Emergency Department) [5] is the first randomized clinical trial that has its objective to prospectively validate the safety of PERC in ruling out PE by assessing the percentage of failures of this diagnostic strategy.

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Summary

This is a non-inferiority, crossover cluster-randomized clinical trial carried out in 14 France emergency departments (ED) during the period August 2015–September 2016. The follow-up period ended in December 2016. Patients with a low clinical probability of PE were included. Each center was randomized for a sequence of two periods of 6 months (the control period and the PERC period with a washout interval in between of 2 months). In the PERC period, the diagnosis of PE was excluded without conducting any other diagnostic test when the eight items of PERC score were all negative. Inclusion criteria were new onset or worsening of dyspnea or chest pain, and a low clinical probability of PE (estimated by the treating physician's gestalt evaluation as below 15%). Exclusion criteria were an obvious etiology presentation different from PE, an acute severe presentation ($SpO_2 < 90\%$, respiratory distress, and hypotension) or a contraindication to CTPA, pregnancy, and the impossibility to follow-up with anticoagulant therapy.

The primary endpoint was the number of thromboembolic events during the 3-month follow-up period that were not initially diagnosed. The noninferiority threshold was set at 1.5%. Secondary endpoints included patients undergoing CTPA, adverse events related to this diagnostic technique, length of stay in the ED, hospital admissions and re-admission, anticoagulant therapies prescribed and related major hemorrhages, and all-cause mortality at 3 months.

Results

Of the 1916 patients initially enrolled (ITT population), only 1749 completed the trial: 847 in the PERC group and 902 in the control group with a mean age of 44 years and 51% women. PE was diagnosed at the initial presentation in

14 patients in the PERC group (1.5%) vs 26 patients in the control group (2.7%) [difference 1.3% (95% CI − 0.1% to 2.7%), $p = 0.052$].

One PE (0.1%) was diagnosed during the follow-up period in the PERC group compared with none in the control group: the difference of proportion between the two groups was 0.1% [95% CI $-\infty$ to 0.8%].

The proportion of patients who underwent CTPA in the PERC was 13% while it was 23% ($p < 0.001$) in the control group. In the PERC group, there was a significantly lower hospital stay in the ED (average reduction 36 min), and a lower number of admissions (13% vs 16% in the control group). There was no significant difference in the rate of all-cause mortality at 3 months: 0.3% (3 patients) in the PERC group and 0.2% (2 patients) in the control group [difference 0.1% (95% CI −0.5 to 0.7%), $p > 0.99$]. The five deaths were reviewed by an adjudication committee and none was considered likely to be linked to a PE. There was no severe hemorrhage or any severe adverse events following CTPA.

The authors conclude that in very low-risk patients with suspected PE, the randomisation of patients to a PERC strategy versus a conventional diagnostic strategy did not result in an inferior rate of missed diagnosis of thromboembolic events over 3 months. Moreover, they conclude that a PERC strategy is associated with various benefits in terms of reduced use of CTPA, shorter ED length of stay, and lower likelihood of initial hospital admission.

Strengths of the study

- This study focuses on clinically relevant issues: the D-dimer test has very low specificity and subsequent CTPA is expensive and may be harmful.
- The study design and methodology: the primary and secondary noninferiority endpoint margins are in line with the previous studies focused on this topic.

Weaknesses of the study

Low gestalt probability should describe a population where the prevalence of PE is below 15%. In this study, the actual prevalence of PE is 1.5% in the PERC group and 2.7% in the control group. Using the PERC score in a population with very low PE probability could overestimate the sensitivity of the test.

Question mark

- Even though the study population was large in size and included 14 participating EDs in France, 167 patients (8.7%) were included in the full analysis set and later excluded (withdrew consent, lost to follow-up, protocol deviation, and wrongly included). We wonder if this dropout could have affected the results.
- The two groups differ significantly for certain baseline characteristics, such as prevalence of women, shortness of breath, heart rate, estrogen use, and clinical signs of deep venous thrombosis, suggesting a lower risk in the PERC group. Similarly, the rate of PE is different between the two groups. We wonder if these differences could have influenced the results of the study.

Sponsorship: None.

Clinical bottom line

This study provides evidence that in a very low risk PE population, use of PERC scoring in ruling out PE could significantly and safely reduce the use of CTPA. The PERC strategy can be useful in the very low risk population; however, there is still no evidence that it can be useful for patients who are not at very low risk.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Statement of human and animal rights This article does not contain any studies involving human participants or animals performed by any of the authors.

Informed consent None.

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