DEM Journal Club

Article Appraisal

Article: Effect of the Pulmonary Embolism Rule-Out Criteria on Subsequent Thromboembolic EventsAmong Low-Risk Emergency Department Patients: The PROPER Randomized Clinical Trial

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Background and Study Objective(s):

Overtesting for Pulmonary Embolism (PE) accelerated in emergency departments across the world after the introduction of D-dimer assay and CT Pulmonary Angiogram (CTPA) imaging for PE came into 'usual care' after 2001. The PERC rule was introduced in 2004 (Kline et. al.) and was intended to decrease overtesting for PE, and specifically, to minimize unnecessary CTPA. The PERC rule uses the physicians' overall gestalt to identify a group of patients that have less than a 15% probability of PE. In order for the PERC rule to be negative, it requires the absence of all 8 criteria. In the US, a negative PERC rule has shown to have lower than 2% false-negative failure rates; this is generally considered less than the risks (mortality & morbidity) associated with the workup for PE, has been recommended by several practice guidelines. However, Righini et al. (2005) and Hugli et al. (2011) independently performed 2 retrospective studies that caused controversy about the performance of the PERC rule among patients evaluated for PE in European emergency departments. In both reports, PERC had shown a higher failure rate of 6% and 7% (false negative) rate. These two reports raised concerns that perhaps the PERC rule would not be applicable in Europe, or other regions where the prevalence of PE is greater.

The PROPER trial is the first to compare the use of PERC to standard practice in an RCT, and does so in the European population with the purpose of demonstrating that PERC is not inferior to standard practice (D-Dimer followed by CTPA) in low-risk populations.

Study Design:

This was a cluster randomized non-inferiority trial of fourteen emergency departments in France that included 1916 patients. Each of fourteen emergency departments were randomized such that half of them underwent a "PERC-based strategy", and the other half, the "usual strategy", was the control group who proceeded with the standard diagnostic protocol. After a 2 month washout period, the 2 arms crossed over. In the PERC protocol, if all 8 items were negative then no further investigations were necessary, otherwise they would undergo standard of care. In the control group, the standard of care was D-dimer with additional CTPA if age adjusted D-dimer was positive. The primary endpoint was occurrence of VTE during 3 month follow up. The delta for the endpoint was 1.5%. The group also contacted patients and their

clinicians by phone and supplemented with medical records information.

Results:

The trial completed a per-protocol assessment of 1749 patients from 15 Emergency Departments who had a low clinical probability for PE as per physician gestalt. Control arm consisted of 902 patients compared to 847 patients that underwent the PERC intervention arm. Out of the 847 patients in the PERC group, 459 (48%) were PERC negative. It is this group that directly addresses the controversy of whether PE can be safely excluded without lab tests or imaging; only 1 patient (0.1% [95% CI, 0%, 0.9%] was found positive for a PE -- this patient had an inconclusive CTPA, and was diagnosed using V/Q scan. If the true failure rate is in the upper limit of the 95% CI (~0.9%) this estimate would approximate the 1% failure rate that is expected of tests such as pulmonary vascular imaging.

Secondary outcomes included comparison of frequency of PE diagnosis at initial presentation with the control group 26 patients (26/902 [2.7%]) and the PERC intervention arm with 14 patients (14/847 [1.5%]) This revealed that the PERC group had a 1.3% (95%CI [-0.1% to 2.7%] p=0.052) absolute difference lower initial PE diagnosis rate. However, both groups had similar 3 month outcomes, raising the concern whether the PERC strategy facilitated the failure to diagnose some patients with mild PE, whether some isolated PE's even warrant anticoagulation, and if these missed diagnoses helped or harmed these patients in the long run.

CTPA imaging was performed in 23% of patients in the control group, versus 13% of PERC group patients, resulting in an 10% (95 CI -13% to -6% p<0.001) difference. These 10% of patients may benefit from avoiding harm by not being submitted to risk of unnecessary radiation exposure, contrast induced acute kidney injuries, and risk of false-positive PE diagnosis due to small or vaguely defined filling defects.

Finally, PERC group rates were significantly reduced for median length of emergency department stay, with mean reduction time of 36 minutes (95%CI 4min to 68min) and hospital admission difference of 3.3% (95% CI 0.1% to 6.6%).

Validity of Results:

The results appear valid as the primary outcome of VTE occurred in 0.1% (1 patient) in the PERC group, with a point estimate for the difference in proportions favoring control. However, the upper bound of the 95% CI does not cross the delta margin of noninferiority, and therefore the PERC strategy is considered non-inferior.

It is important to consider whether a 2 month washout period is sufficient to confer sufficiently "randomized" results. Within the study it was mentioned that some patients were not included in the study, despite being candidates, some patients crossed over getting D-dimers, and some patients did not undergo CTPA despite positive D-dimers. This brings into question whether the preceding 6 month treatment arm potentially influenced the subsequent 6 month arm, despite the washout period.

It is also important to note that the prevalence of PE in this study (2.3%) was much less than previous studies, particularly amongst the European population.

As the authors point out, the sample size calculation was not accurate due to an inaacurate estimation of maximal failure rates.
Furthermore, the loss of 54 patients, if included in ITT analysis, may have resulted in a failure to show non-inferiority.

Finally, the PERC protocol may have allowed PERC negative patients with mild PE (i.e. subsegmental PE) to never present to subsequent visits to a health care professional or receive testing for PE, and therefore being counted as true negatives.

Generalizability of Results:

The population studied were 1916 patients from France. These emergency departments were mostly urban hospitals, with the exception of 1 rural hospital that had both learners and staff emergency physicians. The controversy behind this original study was the higher incidence of PE/VTE in Europeans, however this study demonstrated low incidence of the disease in the population studied. The mean age of the group studied was also found to be young, with mean age of 44, and this is something to consider when applying this rule broadly to our population.

The Bottom Line:

Overall, this study shows that PERC rule may be useful for clinical decision making involving patients with low risk of PE, and may help to reduce over investigations, ED LOS and hospital admission in this subgroup of the population.