VALUE OF PULMONARY VASCULAR OBSTRUCTION INDEX FOR DETERMINING THROMBOLYTIC THERAPY

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ABSTRACT

***Introduction**: An index for Pulmonary Artery Computed Tomography Index Ratio (PACTOIR) may have important prognostic and therapeutic implications and as well as providing a standard to evaluate thrombolytic therapy response. The aim of this study was to determine whether PACTOIR predict the thrombolytic therapy in the treatment of pulmonary embolism (PE).*

***Materials and methods**: This retrospective study was conducted by reviewing charts of 52 patients (aged ≥18 years) who were admitted to our emergency department (ED) with initial diagnosis of pulmonary embolism and confirmed diagnosis of PE by Computed Tomography Pulmonary Angiography (CPTA). The patients were divided into two groups as follows: Group 1 (n=14) consisted of the patients who received thrombolytic therapy and Group 2 (n=38) consisted of the patients who did not receive thrombolytic therapy. PACTOIR was calculated in both groups to estimate thrombus load. We evaluated the effectiveness of thrombolytic therapy by comparing the levels of D-dimer and Troponin I.*

***Results**: Mean value for PACTOIR, D-dimer and Troponin I levels were 56.4 (%), 6.21 (mg/L) and 0.35 (µg/L) in Group 1 whereas they were 20.46 (%), 2.20 (mg/L) and 0.11 (µg/L) in Group 2, respectively. Significant difference was detected between Group 1 and Group 2 (p<0.001). The sensitivity and specificity values were calculated as 92.9% and 89.5% for PACTOIR, whereas they were 85.7% and 78.9% for D-dimer, respectively. These values were found to be 78.6% and 65.8% for Troponin I, respectively.*

***Conclusion**: Based on our results, sensitivity to show PE severity and to determine thrombolytic therapy was significant when compared to D-dimer and Troponin I. In addition, we concluded that PACTOIR is the parameter with greatest sensitivity in determining the effectiveness of thrombolytic therapy.*

***Key words**: computed tomography pulmonary angiography, pulmonary artery obstruction index, pulmonary embolism, thrombolysis.*

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Introduction

Pulmonary embolism (PE) is a prevalent and potentially lethal condition. Most of the patients who die due to PE die within the first few hours of the event. Although there have been improvements in the diagnosis of pulmonary embolism, delays in diagnosis are still common and they pose an important problem[1]. Massive PE comes right after sudden cardiac death as a cause of sudden death. Timely diagnosis and therapy can prevent recurrent embolism and death in patients who have survived from PE[2]. Randomized and retrospective observational studies conducted in patients with acute PE show that; thrombolytic treatment provides early hemodynamic improvement[3]. The only widely accepted symptom for systemic thrombolysis is; persistent hypotension or shock (i.e. a systolic

blood pressure <90 mmHg or a decrease in the systolic blood pressure by ≥40 mmHg from baseline) caused by acute PE[2,3]. Computed tomography scanning has become an important diagnostic technique in suspected PE as a result of technical advances in CT scanning[4,5]. A majority of previous studies focused on helical CT performance to detect PE and widely described features of arterial embolism. Although the evaluation of the degree of pulmonary arterial obstruction caused by pulmonary embolism may be relevant for patient treatment, it is still not researched enough[6]. An index for CTPA was defined by Qanadli et al[7]. A clot burden index such as this may have important prognostic and therapeutic implications and as well as providing a standard to evaluate thrombolytic therapy response, which may also be reproduced[8].

In this study, we investigated the efficacy of the pulmonary vascular obstruction index ratio in determining thrombolytic therapy.

Materials and methods

This retrospective study was conducted at the Emergency Department of Samsun Training and Research Hospital between January, 2014 and July, 2015. Institutional Ethics Committee approval was obtained for the study protocol. Exclusion criterias were being under 18 years old and a contraindication for thrombolytic therapy such as; any prior intracranial hemorrhage, known structural intracranial cerebrovascular disease (eg, arteriovenous malformation), known malignant intracranial neoplasm, ischemic stroke within 3 months, aortic dissection, active bleeding or bleeding diathesis, recent surgery encroaching on the spinal canal or brain, and recent significant closed-head or facial trauma with radiographic evidence of bony fracture or brain injury. The charts of 88 patients (aged ≥ 18 years) who were admitted to emergency department with initial diagnosis of pulmonary embolism reviewed retrospectively. Fifty-two of those, who underwent CT angiography and diagnosed PE were included in the study. Twelve of the remaining 28 patients were excluded from the study due to insufficient image quality while 16 patients were excluded due to lack of pulmonary embolism diagnosis. The patients included in the study were assigned into 2 groups as follow: group 1; 14 patients who received thrombolytic therapy and group 2; 38 patients who received anticoagulant therapy.

Alteplase (ACTILYSE® 50 mg) was given as follow: 10 mg bolus intravenous (i.v) followed by 90 mg i.v over 2 hours. Anticoagulant therapy with low molecular weight heparin (Clexan® Enoxaparin sodium) was applied to the patients who inappropriate to receive thrombolytic therapy.

Radiological imaging

All CT scans were obtained by using a multidetector row CT scanner (Philips Brilliance® CT 64-slice). Final diagnosis of PE was made by an experienced radiologist on thoracic CT. Degree of occlusion was determined by amount and localization of clot on CT images. Vascular obstruction index proposed by Quanadli et al.[7] was used for this purpose; Σ (percentage of vascular obstruction)=n (number of segmental branches from the most proximal part to the distal part of clot) x d (degree of obstruction; 1 if partial and 2 if complete). In this equation, n values range from 1 (obstruction in only one segment) to 20 (bilateral main pulmonary arteries were occluded). To determine percentage of obstruction, the scores found were divided by maximum values, which were next multiplied by 100 (Σ [(n x d) / 40] x 100).

Biochemical analysis

On admission to emergency department, arterial blood gas analysis of the patients were performed by using GEM® Premier™ 4000 device. D-dimer was measured by using The Sysmex® CA-1500 and Troponin I levels were measured by using The Advia Centaur® CP. Laboratory results were extracted by reviewing patient charts retrospectively.

Statistical analysis

Statistical analyses were performed by using SPSS 22.0 (serial number 10240642, IBM© NewYork, USA) for Windows. Data were presented as; mean ± standard deviation (SD), median (min-max) and frequency (%). The Shapiro-Wilk test was used to analyze normal distribution assumption of the quantitative outcomes. To compare two independent groups, we used Student's t test for normal data, and Mann-Whitney U test for non-normal data. Continuity Correction Chi-Square test was used to compare percentages. Receiver operating characteristic (ROC) curve was used to illustrate and evaluate the diagnostic performance of PACTOIR, D-dimer and Troponin I. The area under the ROC curve (AUC) was evaluated as the measure of a diagnostic test's discriminatory power.

Confidence intervals were computed for AUC. Sensitivity, specificity, positive predictive and negative predictive values were evaluated. A p value less than 0.05 was considered as statistically significant.

Results

	Thrombolytic(+)		Thrombolytic(-)		
n; 52	Mean±SD	Median (Min-Max)	Mean±SD	Median (Min-Max)	p
Age (year)	64.92±13.66	61.50 (39.00-88.00)	60.60±15.52	59.00 (35.00-87.00)	<0.001
PACTOIR (%)	56.4±9.13	55 (42.5-75.0)	20.46±15.61	15.00 (5.00-55.00)	<0.001
D-dimer (mg/L)	6.21±4.75	4.66 (0.88-20.00)	2.20±2.93	0.79 (0.00-12.4)	<0.001
Troponin I (µg/L)	0.35±0.33	0.23 (0.00-1.03)	0.11±0.22	0.01 (0.00-1.25)	0.001
RR/Minute	30.14±5.33	30.00 (20.00-40.00)	19.68±4.06	19.00 (14.00-30.00)	<0.001
Pulse rate/Minute	124.14±8.98	124.5 (106.0-144.0)	94.28±15.49	100.0 (70.0-121.0)	<0.001
SBP (mm/Hg)	71.42±8.64	61.50(39.00-88.0)	120.0±20.40	115.0 (80.0-180.0)	<0.001
PaO_2 (mm/Hg)	58.71±5.63	60.0(49.0-65.0)	73.94±8.55	77.0(41.0-82.0)	<0.001
$PaCO_2$ (mm/Hg)	26.5±3.18	26.0(20.0-30.0)	36.23±5.30	35.0(30.0-50.0)	<0.001

Table 1: The baseline clinical and biochemical characteristics of study population.

A value of p < 0.05 was accepted as statistically significant. PACTOIR ; Pulmonary Artery Computed Tomography Index Ratio, RR; Respiratory Rate, SBP; Systolic blood pressure, PaO_2; Partial pressure of oxygen , $PaCO_2$; Partial pressure of carbon dioxide.

	Sensitivity (%)	Specificity (%)	NPV (%)	PPV (%)	OR (95%CL)	p
PACTOIR	92.9	89.5	97.1	76.5	0.961(0.914-1.007)	<0.001
D-dimer	85.7	78.9	93.8	60	0.838(0.730-0.946)	<0.001
Troponin-I	78.6	65.8	89.3	45.8	0.788(0.653-0.9229)	<0.001

Table 2: Receiver operating characteristic curve analysis of study predicting thrombolytic therapy.

p< 0.05 was accepted as statistically significant. CI; Confidence interval, OR: odds ratio, NPV; Negative Predictive Value, PPV; Positive Predictive Value, PACTOIR; Pulmonary Artery Computed Tomography Index Ratio.

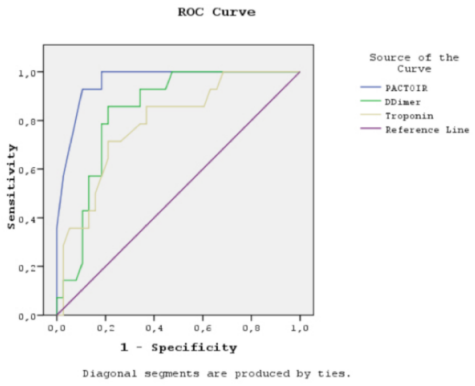

Fig. 1: Receiver operating characteristic curve analysis of study patients for predicting thrombolytic therapy. AUC (Area under the Curve) value was 0.961 (p< 0,.001) for PACTOIR, 0,838 (p< 0,001) for D-dimer (p<0.001) and 0,788 (p<0.001).

Fourteen patients (26.9%) received thrombolytic therapy while 38 patients (73.1%) did not receive thrombolytic therapy. Twenty-three 44.2% were men and 55.8% (n=29) were women. In group 1; 57.1% (n=8) of the patients were men and 42.8% (n=6) were women, while 39.4% (n=38) were men and 60.5% (n=13) were women in group 2 (Table 1).

Median age was 61.5 years in the patients who received anticoagulant therapy whereas 59 years in the patients who received thrombolytic therapy. Significant difference was detected between groups in terms of age distribution (p<0.001) (Table 1). The groups were compared in terms of PACTOIR and biochemical parameters. Similarly, significant differences were detected in PACTOIR, Troponin I, D-dimer, PaO_2, $PaCO_2$ levels, systolic blood pressure, pulse rate and respiration rates between groups (p<0.001) (Table 1). Receiver operating characteristics (ROC) curve analysis was used to assess sensitivity of PACTOIR, D-dimer and Troponin I in determining thrombolytic therapy. The sensitivity, specificity, negative predictive value (NPV) and positive predictive value (PPV) values were calculated for PACTOIR, D-dimer and Troponin I (Table 2). PACTOIR was found to have the greatest sensitivity in determining thrombolytic therapy. AUC value was calculated as 0.961 for PACTOIR (p<0.001), 0.838 for D-dimer (p<0.001) and 0.788 (p<0.001) for Troponin I (Figure 1). Only 2 patients died due to intracranial hemorrhage among the patients who received thrombolytic therapy while no death occurred among those who did not receive thrombolytic therapy.

Discussion

The question of ideal treatment strategy for acute PE is still under discussion. Numerous factors such as clinical scenario, hemodynamic variables, PE location, and availability of personnel trained in advanced PE management therapies influence the type of strategy to be used[9]. The role of thrombolytic therapy in the management of acute PE will continue to be controversial especially in the management of intermediate-risk patients, until randomized clinical trials show a clear morbidity or mortality benefit.

Hemodynamic instability (systolic blood pressure < 90 mm Hg) or a clinical risk factor evaluation suggesting the likelihood of hypotension development are currently accepted symptoms for thrombolytic therapy[10-12]. In the present study, we determined clot load (PACTOIR) with the method proposed by Qanadli et al[7] and investigated its sensitivity to predict thrombolytic therapy by comparing D-dimer and Troponin I levels in patients' diagnoses with PE at CT angiography. CTPA quantification of PACTOIR is a potentially useful tool to predict mortality severity in patients with PE[7,8,13]. Collomb et al. concluded that in determining patients who needed thrombolytic therapy or surgical treatment and also as a sign of PE severity, degree of pulmonary artery obstruction could be used[14].

In patients with acute PE, although the localization of emboli assessed at CTPA could be used for risk stratification, no association was found between prognosis and obstruction index[15]. In our study, significant difference was detected in PACTOIR values between patients who received or didn't receive thrombolytic therapy ($p<0.001$). In addition, sensitivity of PACTOIR in determining thrombolytic therapy was found to be 92.9%. A considerable association was found between degree of obstruction in vascular bed and blood gas values[16, 17]. Metafratzi et al. indicate that PaO_2-PaO_2 and PaO_2, which can be found available in the primary evaluation of suspected PE in combination with other clinical parameters, is helpful in making the primary care physician suspect about severe acute PE[16].

In our study, significant difference was detected in PaO_2 values in blood gas analysis regarding hypoxemia caused by PE ($p<0.001$). PaO_2 values were found to be significantly lower in the patients who received thrombolytic therapy. Regarding hemodynamic instability (systolic BP<90 mmHg), significant difference was detected between groups. By these results, we think that there is a relationship between PACTOIR level and PE severity. Levels of D-dimer are positively associated with right ventricle dysfunction on CTPA and PE burden. They are also helpful in monitoring the therapeutic response. The large thrombosis and/or emboli demonstrate higher D-dimer levels which decrease in time[18,19]. High plasma troponin concentrations detected on admission have been reported together with PE and they have been reported to be associated with worse prognosis. A meta-analysis conducted with 1985 patients showed high cardiac troponin I or -T concentrations in approximately 50% of the patients who had acute PE[20]. Five honderd twenty-six normotensive patients with acute PE were studied in a prospective, cohort which measured troponin T concentrations (14 pg/mL) by a high-sensitivity assay. The results showed a negative predictive value of 98% with reference to a complicated clinical course and this value was similar to that of the simplified pulmonary embolism severity index[21]. In parallel with literature, significant differences were detected in D-dimer and troponin I levels between our study groups ($p<0.001$). However, we determined cut-off values for PACTOIR, D-dimer and Troponin I by using ROC analysis. The highest AUC value was detected for PACTOIR in ROC analysis (Figure 1).

Based on our results, sensitivity to show PE severity and to determine thrombolytic therapy was significant when compared to D-dimer and Troponin I (Table 2).

In conclusion, our results reveal that PACTOIR is a more effective parameter than Troponin I and D-dimer levels; however, further clinical studies with larger sample size are needed in this topic.

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