CASE REPORT
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Should anti-vitamin K be started on the first day in non-high risk pulmonary embolism?

Da li bi trebalo terapiju antagonistima vitamina K otpočeti prvog dana kod bolesnika sa plućnom embolijom koji nemaju visok rizik?

Goran Koraćević*, Dragana Ilić†

University of Niš, Clinical Center Niš, *Clinic of Cardiology, †Department of Radiology, Niš, Serbia

Abstract

Introduction. Protocols and guidelines have been improving results of our clinical practice. Sometimes there have been differences between guidelines on the same topic, but they have not been so important usually. As far as the start of vitamin K antagonists (VKA) in a non-high risk pulmonary thromboembolism (PTE) patients is concerned, there is global consensus (reflected in all comprehensive guidelines) that it should be on the admission day or a day later. However, there are situations in which this VKA administering from the first (or second) day of hospitalization may actually complicate the treatment. **Case report.** As an illustration, our female, 71 years old patient with second unprovoked, intermediate-high risk PTE was given low-molecular-weight heparin (LMWH) + VKA from the second day. Due to lack of improvement in symptoms, oxygen saturation and D dimer after 9 days, computed tomography pulmonary angiography (CTPA) was repeated and it confirmed minimal advancement. The patient already had achieved target international normalized ratio (INR) and it complicated proceeding to fibrinolytic therapy. **Conclusion.** Correction of the therapeutic approach in the PTE treatment may be needed even if the treatment is completely conducted according to the latest guidelines. We recommend postponing VKA from the first (or second) day of hospitalization (as suggested in all available guidelines for non-high risk PTE patients) until satisfying clinical improvement is reached.

Key words:
pulmonary embolism; anticoagulants; computed tomography angiography; lung; fibrin fragment d; treatment outcome.

Apstrakt

Uvod. Protokoli i smernice poboljšavaju rezultate naše kliničke prakse. Ponekad postoje razlike između preporuka o istoj temi, ali obično te razlike nisu toliko važne. U vezi sa početkom primene antagonista vitamina K (VKA) kod bolesnika sa plućnom tromboembolijom (PTE), postoji globalni konsenzus (prisutan u svim savremenim smernicama) da bi to trebalo da bude na dan prijema ili dan kasnije. Međutim, postoje situacije u kojima davanje VKA od prvog (ili drugog) dana hospitalizacije može, zapravo, komplikovati tretman. **Prikaz bolesnika.** Kao ilustracija, naša 71-godišnja bolesnica, sa drugom neprovociranom PTE srednjeg rizika, je dobila heparin male molekulske težine (LMVH) + VKA od drugog dana hospitalizacije. Zbog izostanka poboljšanja simptoma, saturacije kiseonikom i D dimera nakon 9 dana, kompjuterizovana tomografski pulmonarna angiografija (CTPA) je ponovljena i nalaz je potvrdio minimalan napredak. Bolesnica je već postigla ciljni internacionalni normalizovani odnos (INR) i to je komplikovalo prelazak na fibrinolitičku terapiju. **Zaključak.** Korekcija terapijskog pristupa u lečenju PTE može biti potrebna čak i kad se lečenje sprovodi u skladu sa savremenim preporukama. Predlaže se odlaganje primene VKA od prvog (ili drugog) dana hospitalizacije (kao što se preporučuje u svim raspoloživim vodičima za bolesnike sa PTE koji nisu na visokom riziku), dok se ne postigne kliničko poboljšanje.

Ključne reči:
pluća, embolija; antikoagulansi; angiografija, tomografska, kompjuterizovana; pluća; d dimer; lečenje, ishod.

Correspondence to: Goran Koraćević, University of Niš, Clinical Center Niš, Clinic of Cardiology, 18 000 Niš, Serbia.
E-mail: gkoracevic@yahoo.com

Introduction

Pulmonary thromboembolism (PTE) is the third most important cardiovascular disease (following acute myocardial infarction and stroke), as judged by incidence and mortality. The medical importance of PTE increases due to high chance of misdiagnosis, because PTE often presents with insufficiently specific symptoms and signs.

Excluding cardiac arrest, shock state in PTE carries the highest individual mortality risk and fibrinolysis is (clearly) indicated in this subgroup of patients (encompassing 5%–10% of all PTE patients). Situation about fibrinolysis is far less clear in the intriguing and heterogeneous subgroup with intermediate risk. Although individual mortality risk is not so high in these patients, this subgroup is numerous and therefore it results in large number of fatalities. As an illustration, 22% of patients in the subgroup with high risk died during 30 days of PTE, less in the intermediate–high risk subgroup (7.7%) and the intermediate–low risk subgroup (6.0%) and far less (0.5%) in patients at low risk [1]. Moreover, many of the intermediate–risk PTE patients who survive hospitalization are not completely cured – they can suffer "post-PTE syndrome". The "post-PTE syndrome" means that following PTE, a patient has shortness of breath, fatigue, impaired quality of life and abnormalities in heart and lung findings without any other explanation [2]. The "post-PTE syndrome" is not rare at all – it can be expected in around half of all PTE patients [3].

Therefore, PTE patients with intermediate risk can not be considered safe at all. As they can be very heterogeneous subgroup, further refinement in risk stratification is needed. For this purpose, Bova et al. [4] have suggested the score that combines somewhat lower blood pressure (BP), increased heart rate (HR), right ventricle (RV) dysfunction as well as markers of myocardial injury. A non-high risk PTE patient with all above-mentioned has a seven-fold increase in the risk of an adverse 30-day PTE- related outcome predicted. The following criteria are used: systolic BP 90 to 100 mmHg – 2 points; increased cardiac troponin – 2 points; RV dysfunction on echocardiogram or multi slice computed tomography (MSCT) – 2 points and HR $\geq$ 110 beats per minute (b.p.m.) – 1 point. Patients with 0 to 2 points have the first stage, 3 to 4 points the second stage, and with more than 4 points the third stage, with corresponding mortality (30 days following the admission) related to PTE of 1.7%, 5.0% and 15.5%, respectively [4, 5]. Such a score is a certain prerequisite to come closer to the answer to the probably central question in the drug therapy of PTE: whom to thrombolyse among intermediate -risk patients? This remains unresolved issue for decades [6, 7].

To the contrary, the optimal time to start VKA seems to be well-defined, because all available contemporary PTE guidelines suggest it should be on the first or second day, i.e., when the diagnosis is made. For example, the National Institute for Health and Care Exellence (NICE) pathways suggest VKA should be initiated within one day of diagnosis [8]. Similarly, the Anticoagulation Forum recommends that we should start VKA as soon as parenteral anticoagulant's therapeutic concentration is obtained [9]. There are good reasons for such recommendation. One of them is to shorten expensive hospital stay: the sooner we obtain therapeutic INR, the sooner the patient can become an outpatient, with consequent savings. Moreover, the patient may avoid potential in-hospital infection. The reason more is to diminish likelihood of heparin- induced thrombocytopenia (HIT), serious complication of heparin use [10].

However, in PTE patients with an intermediate risk, sudden worsening may occur with hemodynamic compromise, which requires the escalation of therapy. In such situations, already achieved therapeutic level of VKA may increase the bleeding risk and therefore it may complicate an already difficult scenario. As the knowledge of medical community accumulates and new anticoagulants become more widely used, the need for critical evaluation of PTE protocols appears in practice.

Case report

A female patient (71 years old, 70 kg) without any actual medications was admitted because of dyspnea with suspected new PTE. No obvious provoking factor was observed. In the past medical history seven years ago, the patient was hospitalized due to a first recognized unprovoked PTE episode, but she has no medical documentation. Her duplex ultrasound (B-mode imaging and Doppler waveform analysis), and color Doppler of leg veins were then without signs of thrombosis. The patient was treated only by subcutaneous injections at that time. She also had light obstructive lung disease, but no ischemic heart disease diagnosed. Her actual BP was 110/70 mmHg, with diminished respiration sounds at basal part of the right hemithorax on lung auscultation. Her electrocardiogram (ECG) demonstrated sinus rhythm, HR 77 b.p.m., QS in lead III and aVF with ST elevation 0.4 mm in D3 and 0.2 mm in aVF, as well as with negative T in lead III and aVF and Rs in V_2, suggesting recent myocardial infarction; $S_1Q_3T_3$ and negative / biphasic T in V_1–V_4. The absence of negative T in lead I and aVL together with maximal negative T in V_1 (as compared to V_2–V_4) suggested PTE (in differential diagnosis with acute coronary syndrome without ST elevation) [11]. Pathological Q in lead III and aVF resembled description in the American Heart Association statement: "Q in III and aVF (pseudo – infarction)" [12]. Echocardiogram showed dilated RV 34 mm with tricuspid regurgitation 2-3+ (out of 4) with RV systolic pressure 58 mmHg. Vena cava inferior (VCI) was dilated (24 mm), without inspiratory collapse. Left ventricle (LV) diastolic dimension was normal (46 mm), LV ejection fraction was normal (63%), too and regional LV contractility was preserved.

Wells score was 4.5 (previous PTE 1.5 point + alternative diagnosis less likely than PTE 3 points) and Revised Geneva score was 7 (previous PTE 3 points + HR 75–94 b.p.m. 3 points + age > 65 years 1 point). Both scores suggested intermediate clinical probability for PTE. Multislice computed tomography pulmonary angiogram (CTPA) showed the presence of thrombotic

masses in the lobar branches of the pulmonary arteries bilaterally (Figure 1).

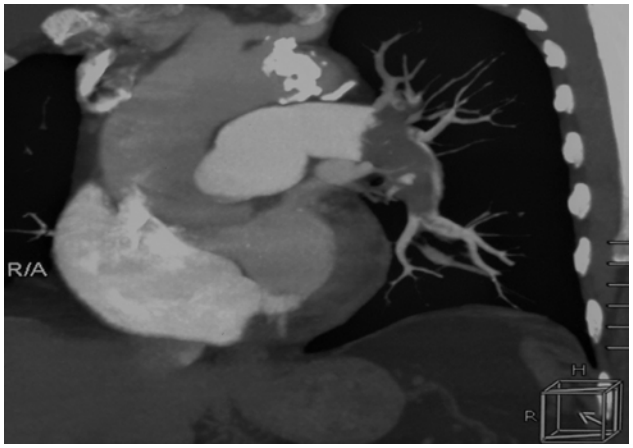

Fig. 1 – Computed tomography pulmonary angiogram (CTPA) shows the central embolic material in the left pulmonary artery (coronal plane). Thrombotic masses were seen in the segmental arteries of the lower lung lobes. There was only a marginal flow of blood in these arteries. There was a small pleural effusion (2cm) on the right side. There was no consolidation of lung parenchyma. Right ventricle end-diastolic diameter/left ventricle end-diastolic diameter (RVEDD/LVEDD) ratio was 1.6 (cut-off value 0.9), as measured 1 cm above and parallel to the annular line in the four chamber view.

D-dimer was high, 3,383 μg/L (age-adjusted cut-off was for her 710 μg/L, using latex method), high sensitive troponin I was 40 ng/L (borderline, normal values < 40 ng/L), brain nariuretic peptide (BNP) was 807 ng/L (normal values < 30 ng/L in chronic and < 100 ng/L in acute setting). Her oxygen saturation was 88% while breathing room air, C-reactive protein was 16.2 mg/L (3.2 times upper normal limit of 5 mg/L), procalcitonin 0.03 ng/ml (in the normal range). A hematologist excluded antiphospholipid syndrome and systemic lupus erythematodes. Neither gynecologist nor gastroenterologist have found carcinoma. Her duplex ultrasound and color Doppler of veins of lower extremities showed no signs of thrombosis, just with small localized dilatation. Pulmonary embolism seventy index (PESI) score was 91 (age in years 71 + arterial oxyhaemoglobin saturation < 90%, 20 points), i.e. Class III, moderate mortality risk (3.2%–7.1%).

Repeated unprovoked PTE of the patient was classified as intermediate-high risk (no hypotension, PESI III–V, present RV dysfunction and cardiac biomarker). Our patient had no hypotension at admission. Therefore, she was treated without fibrinolytic. She received enoxaparin, 1 mg per kg of body weight two times a day (b.i.d.) subcutaneously (s.c.) and warfarin from the second day, according to the guidelines, including the latest 2014 European Society of Cardiology (ESC) Guidelines and 2016 Anticoagulation Forum Pulmonary Embolism Guidelines [13, 14].

Anti-Xa was 0.76 IU/mL on the 5th day and enoxaparin dose was raised to 80 mg b.i.d. International normalized ratio (INR) reached a therapeutic level (≥ 2) on the ninth day – it was 2.2. On the 10th day of hospitalization, the patient was still dyspnoic, her oxygen saturation was 93%, D-dimer was 2,346 μg/L, i.e. three markers of no clinical improvement with the usual protocol. High D-dimer in PTE patients on anticoagulant therapy usually means residual thrombosis [15]. Therefore, we repeated CTPA which showed the continued presence of a thrombotic mass in the pulmonary arteries, predominantly of the lower lobe on both sides, but with a discrete mass reduction. No pleural effusion was seen (Figure 2).

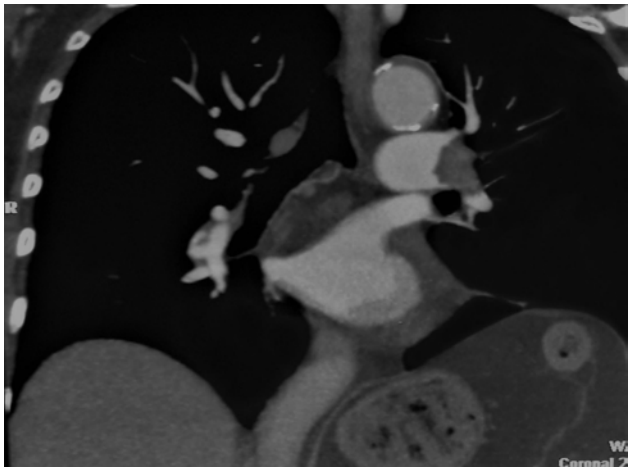

Fig. 2 – Computed tomography pulmonary angiogram (CTPA) in coronal plane shows shows a small reduction of the thrombotic mass in the left pulmonary artery.

We recognized that the effect of previous treatment was minimal and decided to proceed with more effective therapy, according to guidelines [12]. In order to prepare our patient for thrombolysis, we stopped VKA and introduced fondaparinux 2.5 mg next day. When INR dropped below two, we started fondaparinux 7.5 mg once-daily. Unfractionated heparin was not given because frequent activated partial thromboplastin time (aPTT) measurements, e.g. every two hours (when fibrin-selective thrombolytic is applied) was not possible at our institution. The day after beginning treatment with fondaparinux 7.5 mg once-daily, fibrinogen was 4.8 g/L (upper limit of normal 4.6 g/L) and we gave 50 mg of tissue plasminogen activator (TPA) and continued fondaparinux. The rapid clinical improvement was observed: dyspnea disappeared, oxygen saturation increased to 96%, D-dimer decreased to 813 μg/L, RV dimensions and RV systolic pressure got normalized, VCI decreased toward normal (24 mm) and inspiratory collapse appeared. Magnetic resonance pulmonary angiography (MRPA) was done to evaluate eventual residual thrombosis in pulmonary arteries (Figure 3). It showed significant reduction of thrombotic masses in pulmonary arteries. Thrombus was seen in the main artery of the left lung, the diameter was 12 x 10 mm. The reduction of flow through this artery was 30%. Also, the diameters of

both pulmonary arteries were reduced to 20 mm. Color Doppler ultrasound showed no thrombus in her deep leg veins. Her *Clostridium difficile*-induced enterocolitis was well-controlled. Next ECGs showed the presence of r in lead III and aVF. On the day of discharge, D-dimer was 505 μg/L, fondaparinux was ceased and rivaroxaban 15 mg b.i.d. was introduced. The rivaroxaban dose was decreased to 20 mg once daily on the 21st day from the hospital admission. The ergometer bicycle graduated exercise test was negative a month later. In the 5th month following hospitalization, the patient requested the switching from rivaroxaban to VKA (due to financial reasons). Two years from the hospitalization, the patient is without complains, including dyspnea, chest pain, and bleeding. Echocardiography demonstrated normal RV dimensions and pulmonary artery (PA) systolic pressure.

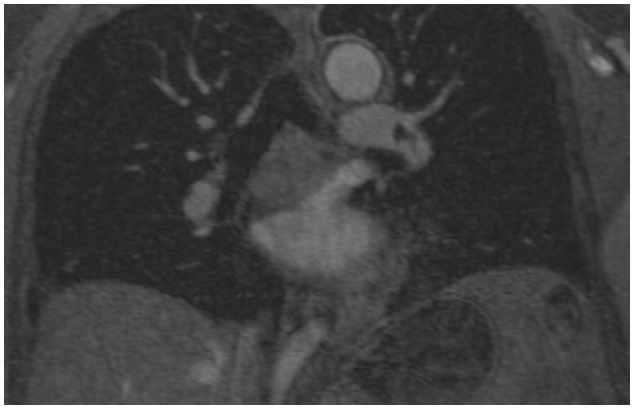

Fig. 3 – Magnetic resonance angiography of pulmonary arteries (MRPA) shows reduced thrombotic mass in the left pulmonary artery.

Diagnostic tests for the detection of the antiphospholipid syndrome were performed with negative result, e.g., Anticoagulant Dilute Russell Viper Venom Test (DRVVT) and silica clotting time (SCT), as well as anticardiolipin antibodies and antibodies to β2-glycoprotein I. Furthermore, in the DNA analysis, Factor V Leiden, FII 20210A, methylenetetrahydrofolate reductase (MTHFR) variant C677T, antithrombin (AT) III, but also Factor XIII were all negative. On the other hand, the patient was found to be heterozygot for plasminogen activator inhibitor-1 (PAI-1) [high risk "4G" for polymorphysm 4G/5G in the position – 675 was present in one gene copy (heterozygot) for PAI-1 (SERPINE1)].

Discussion

As many as 1/4 of all venous thromboembolism (VTE) episodes may occur in patients with malignant neoplasm [16]. An occult cancer was found in as many as 7.6% of 5,863 VTE patients of the large *Registro Informatizado Enfermedad TromboEmbólica* (RIETE) registry. Independent predictors were chronic pulmonary disease, male gender, age over 70 years, anemia, previous episode of VTE, recent operation and increased platelet count [17]. In PTE patients detailed medical history, physical examination as well as usual laboratory analyses are important [14]. If we do sputum cytology plus pelvic and MSCT of abdomen and pelvis, as well as mammography, it is probable that we might not improve survival of the whole group tested [14], but we can double the cancers diagnosed (as judged by meta-analysis of 2287 VTE patients) [16] and early-stage cancers [18]. On the other hand, extensive screening has significant psychological and financial consequences [18]. As a kind of balance, one may follow the NICE guidelines, i.e. add sputum cytology plus pelvic and MSCT of abdomen and pelvis, as well as mammography in patients who are > 40 years old [18]. Other way, we can proceed with tumor marker screening which is adjusted to sex and age (colon, prostate, breast and cervix) [18].

It is also important to decide how long we should recommend oral anticoagulant therapy (OAC) following VTE event. Mostly, it depends on whether the first VTE episode is provoked. In patients with unprovoked VTE longer OAC administration is generally needed. To refine the risk stratification following interruption of OAC, adequate scores were developed, e.g., DASH, Vienna prediction model and HERDOO2 score. For example, the DASH score incorporates high D-dimer concentration (2 points), being ≤ 50 years old (1 point), male gender (1 point) and the use of hormone (-2 points). If the score is >1 it is recommended to proceed with OAC due to high risk of rethrombosis (over 5% a year) [19, 20]. In parallel, it is also important to evaluate patient's risk of bleeding, as the decision to continue OAC or not has to be a balance of both risks (for rethrombosis and for hemorrhage). For bleeding prediction we have several options: RIETE, VTE-BLEED, the Kuijer, mOBRI, Shireman, ATRIA, HEMORR2HAGES, HAS-BLED, modified HAS-BLED, ACCP scores, EINSTEIN model, Hokusai model, ACCP scheme, Outpatient Bleeding Risk Index, etc. [21–24].

The most important reason for guideline authors to recommend VKA from the beginning of PTE treatment has been presumably an intention to avoid both prolonged hospitalization and HIT. This suggestion has not been changed for years, meaning that it has functioned correctly. PTE patients with intermediate risk at admission usually react favorably to anticoagulant therapy and LMWH or fondaparinux are the drugs of choice for most of them [25]. The drawback with starting VKA early arises when such patients during hospitalization experience hemodynamic compromise with the need for therapy escalation, including often "secondary" thrombolysis [25]. Reasons for this hemodynamic worsening are numerous: progression of RV dysfunction, new thromboembolism from concomitant deep venous thrombosis, additional damage to cardiopulmonary function from comorbidities (e.g., infection, anemia, ischemia, arrhythmias), etc. To our opinion, another reason for "secondary" thrombolysis are persistent

symptoms (e.g., severe dyspnea) despite anticoagulant treatment [13].

Half-dose (50 mg) of recombinant tissue-type plasminogen activator (rtPA) is safe in patients with 'moderate' PTE [14] and efficient comparably to 100 mg rtPA [26], which led to the name "safe-dose thrombolysis", as originally suggested by Sharifi et al. [27]. Administration of fibrinolytic agent, while the patient is on VKA and has therapeutic INR, may lead to excessive bleeding. Therefore, it is wise to avoid VKA until it becomes obvious that fibrinolytic treatment will not be needed.

We believe that the right time to start OAC in intermediate-risk PTE patients is when symptoms, ECG, echocardiographic findings, O_2 saturation, etc. get under control [28]. MRPA was useful in our patient for targeted evaluation of particular pulmonary artery to analyze eventual thrombus burden reduction following anticoagulant / thrombolytic therapy. In contrast to CTPA, MRPA can help us to individualize therapy without the risk of excessive radiation.

Conclusion

This case report suggests that even if the treatment of PTE has completely been conducted in accordance with the latest guidelines, the outcome of the treatment may be suboptimal

As our case report illustrates, with VKA from the first day of admission, it is somewhat complicated to administer thrombolytic later during the clinical course (if there is no improvement in dyspnea, ECG, echo, oxygen saturation, etc). We suggest postponing VKA from the first (or second) day of hospitalization (as suggested in all available guidelines for non-high risk PTE patients) until satisfying clinical improvement is reached.

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