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DA LI BI TREBALO POČETI ANTI-VITAMINOM K PRVOG DANA NEVISOKORIZIČNE PLUĆNE EMBOLIJE?

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SHOULD ANTI-VITAMIN K BE STARTED ON THE FIRST DAY IN NON-HIGH RISK PULMONARY EMBOLISM? – A CASE REPORT

DO ANTI-VITAMINOM K PRVOG DANA NEVISOKORIZIČNE PLUĆNE EMBOLIJE?

– Prilaz bolesnika

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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 antagonist (VKA) in a non-high risk pulmonary thromboembolism (PTE) patient 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 administering VKA 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, Computerized tomography pulmonary angiography (CTPA) was repeated and it confirmed minimal advancement. She already had achieved target international normalized ratio (INR) and it complicated proceeding to fibrinolytic therapy. Conclusion. Therefore, correction of the therapeutic approach may be needed even if the treatment is completely according to the latest guidelines. 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.

Key words: pulmonary thromboembolism, anticoagulant therapy, computed tomography pulmonary angiography, D-dimer.

Apstrakt

Uvod. Protokoli i smernice poboljšavaju rezultate naše kliničke prakse. Ponekad postoje razlike između preporuka o istoj temi, ali te razlike obično nisu toliko važne. Što se tiče početka primene antagonista vitamina K (VKA) u PTE pacijenta sa visokim rizikom, postoji globalni konsenzus (koji se ogleda 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 pacijentka, sa drugom neprovociranom PTE srednjeg rizika, je dobila LMVH + VKA od drugog dana. Zbog izostanka poboljšanja simptoma, saturacije kiseonikom i D dimera nakon 9 dana, ponovljen je CTPA i on je potvrdio minimalan napredak. Ona je već postigla ciljni INR i to je komplikovalo prelazak na fibrinolitičku terapiju. Zaključak. Stoga, korekcija terapijskog pristupa može biti potrebna čak i kad je lečenje potpuno u skladu sa savremenim preporukama. Sugerišemo odlaganje VKA od prvog (ili drugog) dana hospitalizacije (kao što se preporučuje u svim raspoloživim vodičima za pacijente sa PTE koji nisu na visokom riziku), dok se ne postigne kliničko poboljšanje.

Ključne reči:
plućna tromboembolija, antikoagulantna terapija, pulmonalna angiografija kompjuterizovanom tomografijom, D-dimer.

**Introduction**

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

Therefore, PTE patients with intermediate risk can not be considered safe at all. As it has been very heterogeneous subgroup, further refinement in risk stratification is needed. For this purpose Bova et al. suggested the score that combines somewhat lower blood pressure (BP), increased heart rate (HR), 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 MSCT) 2 points and HR ≥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. 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 thrombolysate among intermediate-risk patients? This remains unresolved issue for decades.

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, NICE pathways suggest VKA should be initiated within one day of diagnosis. Similarly, the Anticoagulation Forum recommends that we should start VKA as soon as parenteral anticoagulant’s therapeutic concentration is obtained. 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.\(^\text{10}\)

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 appear 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 she 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. She 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 ECG demonstrated sinus rhythm, HR 77 b.p.m., QS in lead III and aVF with ST elevation 0.4mm in D3 and 0.2mm in aVF, as well as with negative T in lead III and aVF and Rs in V\(_2\), suggesting recent myocardial infarction; S,Q,T; 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)\(^\text{11}\). Pathological Q in lead III and aVF resembled description in the American Heart Association statement: “Q in III and aVF (pseudo - infarction)”\(^\text{12}\). Echocardiogram showed dilated RV 34 mm with tricuspid regurgitation 2-3+ (out of 4) with RV systolic pressure 58 mmHg. Vena cava inferior 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. Multi-slice computed tomography pulmonary angiogram (CTPA) showed the presence of thrombotic masses in the lobar branches of the pulmonary arteries bilaterally (Figure 1).
Fig. 1 – CTPA shows the central embolic material in the left pulmonary artery (coronal plane). There was only a marginal flow of blood in these arteries. Thrombotic masses were seen in the segmental arteries of the lower lung lobes. There was a small pleural effusion (2cm) on the right side. There was no consolidation of lung parenchyma. RV end-diastolic diameter –to –LV 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 3383 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), 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). Hematologist excluded antiphospholipid syndrome and systemic lupus erythematoses. 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. 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%).

Her repeated unprovoked PTE 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 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 fifth day and enoxaparin dose was raised to 80mg b.i.d. International normalized ratio (INR) reached a therapeutic level (≥ 2) on a ninth day – it was 2.2. On the 10th day of hospitalization, she was still dyspnoic, her oxygen saturation was 93%, D-dimer was 2346 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 (Figure 2).
Fig. 2 – CTPA in coronal plane 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. In order to prepare our patient for thrombolysis, we stopped VKA and introduced fondaparinux 2.5mg next day. When INR dropped below two, we started fondaparinux 7.5 mg once-daily. Unfractionated heparin was not given because frequent aPTT measurements, e.g. every two hours (when fibrin-selective thrombolytic is applied) is 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 TPA and have 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).

Fig. 3 – MR angiography of pulmonary arteries (MRPA) shows reduced thrombotic mass in the left pulmonary artery.
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 have shown 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 21\textsuperscript{st} day from the hospital admission. The ergometer bicycle graduated exercise test was negative a month later. In the fifth month following hospitalization she 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 PA systolic pressure.

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 FXIII were all negative. On the other hand, she 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 VTE episodes may to occur in patients with malignant neoplasm \textsuperscript{16}. An occult cancer was found in as many as 7.6% of 5,863 VTE patients of the large RIETE (Registro Informatizado Enfermedad TromboEmbólica) registry. Independent predictors were chronic pulmonary disease, male gender, age over 70 years, anemia, previous episode of VTE, recent operation and increased platelet count \textsuperscript{17}. In PTE patients detailed medical history, physical examination as well as usual laboratory analyses, are important \textsuperscript{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 \textsuperscript{14}, but we can double the cancers diagnosed (as judged by meta-analysis of 2287 VTE patients) \textsuperscript{16} and early-stage cancers \textsuperscript{18}. On the other hand, extensive screening has significant psychological and financial consequences \textsuperscript{18}. As a kind of balance, one may follow The National Institute for Health Care Excellence (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 \textsuperscript{18}. Other way, we can proceed with cancer screening which is adjusted to sex and age (colon, prostate, breast and cervix) \textsuperscript{18}.

It is also important to decide how long we should recommend 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, 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 re-thrombosis (over 5% a year) \textsuperscript{19,20}. In parallel, it is also important to evaluate patient’s risk of bleeding, as the
The decision to continue OAC or not has to be a balance of both risks (for re-thrombosis 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 DVT, 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 (50mg) recombinant tissue-type plasminogen activator (rtPA) is safe in patients with ‘moderate’ PTE 25 and efficient comparably to 100 mg rtPA 26, which led to the name “safe-dose thrombolysis”, as originally suggested by Sharifi et al. 25, 27. Administration of fibrinolytic, 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, O2 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 treatment of PTE which is completely according to the latest guidelines can be obviously 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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References:


