MANAGEMENT OF PULMONARY EMBOLISM

LEČENJE PLUČNE EMBOLIJE

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Introduction. Pulmonary embolism is a common condition with high morbidity and mortality, particularly if misdiagnosed or untreated. It has non-specific clinical manifestations, often presenting with symptoms similar to other cardiovascular or common respiratory diseases. Dyspnea is the most common symptom. The main goals of pulmonary embolism therapy are to stop blood clots from getting bigger and prevent formation of new clots. The aim of this article was to review the clinical presentation, incidence, diagnostic algorithms and prevention of pulmonary embolism.

The management of pulmonary embolism depends on patients’ hemodynamic stability (hemodynamically stable and hemodynamically unstable patients), as well as on specific conditions (population who cannot receive the same therapy as the previously mentioned patients). The management is largely focused on medical therapy of pulmonary embolism, as the first line therapy (emergency) and then on medical options for this disease. Special attention was given to urgent intravenous thrombolytic therapy in hemodynamically unstable patients, considering that these patients are the most vitally compromised, in shock and with high mortality rate. The initial treatment in hemodynamically stable patients consists of low molecular weight heparin and unfractionated heparin, which is later replaced by long term oral anticoagulation therapy. Its duration depends on the nature of the basic disease. Some populations cannot receive any thrombolytic therapy (pregnant women, patients suffering from malignant diseases and heparin-induced thrombocytopenia). These patients may receive low molecular weight heparin, unfractionated heparin and warfarin; patients with malignant diseases receive life-long anticoagulation therapy; argatroban or lepirudin are used in the management of heparin-induced thrombocytopenia.

Prevention of pulmonary embolism is lifesaving. It includes prophylactic medical regimens and “mechanical” supportive therapy (elastic graduated compression stockings, inferior vena cava filters).

Key words: Pulmonary Embolism; Thrombosis; Thrombolytic Therapy; Catheterization; Thrombectomy; Anticoagulants; Fibrinolytic Agents; Heparin

Sažetak

Uvod. Plučna tromboembolija je vrlo uobičajeno stanje sa visokim morbiditetom i mortalitetom, naročito ako je pogrešno dijagnostifikovana ili nelečena. Ima nespecifične kliničke manifestacije koje mogu ličiti na druga kardiovaskularna ili respiratorna oboljenja. Otežano disanje je obično vodeći simptom. Glavni ciljevi lečenja plučne tromboembolije su zaustavljanje nastanka krvnog ugruška (tromba) i zaustavljanje formiranja novih. Cilj ovog rada je sumnjacija kliničke prezentacije, incidenca, dijagnostičkih algoritama i naposletku prevencija plučne tromboembolije. Terapija plučne embolije. Terapiju za plučne tromboembolije podelili smo, na osnovu stanja pacijenta, na hemodinamički stabilne i one koji to nisu, kao i na specijalnu populaciju koja ne može da primi istu terapiju kao prethodno navedeni. Osnovni fokus u lečenju plučne tromboembolije stavljamo na terapiju prve linije, tzv. urgentnu terapiju kada se prepozna plučna tromboembolija, a zatim sumiramo sve terapijske (medikamentne) opcije u lečenju ovog oboljenja. Posebno smo obratili pažnju na intravensku tromboličku terapiju, imajući u vidu da su u pitanju pacijenti koji su hemodinamički nestabilni i vitalno ugroženi (prevashodno za neodložnu tromboličku terapiju) i oni koje treba inicijalno stabilizovati i da se na toga leći. Iako dva odvojena entiteta, oba predstavljaju urgentnu terapiju plučne tromboembolije. Inicijalni tretman kod hemodinamički stabilnih pacijenata obuhvata niskomolekularni heparin i nefrakcionisani heparin. Specijalan osvrt dat je i posebnoj populaciji koja nije u mogućnosti da primi standardnu, uobičajenu terapiju za plučna tromboembolija. To su trudnice, osobe sa malignitetom, kao i one kod kojih je heparinom indukovana trombocitiopenija. Ovakvi pacijenti primaju heparin male molekulske težine, kod maligniteta doživotnu antikoagulantu terapiju, a argatroban ili lepirudin se primenjuje kod bolesnika sa indukovanim trombocitopenijom. Zakaženjak. Sprečavanje nastanka plučne tromboembolije je ključno. Ono uključuje profilaktičke medicinske rešetke i mehaničku potporu u vidu elastičnih kompresionih čarapa i postavljanja filtera u v. cava inferior. Ključne reči: plučna embolija; tromboza; trombolitička terapija; kateterizacija; trombektomija; antikoagulanti; fibrinolitički heparin

The PE is a relatively common acute cardiovascular disorder associated with high early mortality rates that have not changed significantly despite advances in diagnosis and treatment over the past 30 years [3, 4]. Due to pulmonary bed obstruction, PE may result in acute right ventricular failure, a life-threatening condition. Due to the fact that most
Acute pulmonary embolism (PE) is a common and sometimes fatal condition with a highly variable clinical presentation. It is critical for the therapy to be administered in a timely fashion so that recurrent thromboembolism and death can be prevented [1, 2]. The PE is a relatively common acute cardiovascular disorder associated with high early mortality rates that have not changed significantly despite advances in diagnosis and treatment over the past 30 years [3, 4]. Due to pulmonary bed obstruction, PE may result in acute right ventricular failure, a life-threatening condition. Due to the fact that most patients ultimately die within the first hours after the onset of symptoms, early diagnosis is of paramount importance. Depending on PE presentation, the initial treatment is primarily focused on restoring adequate blood flow through the pulmonary bed and preventing PE recurrence. Appropriate therapy is best selected using risk stratification by assessing hemodynamic impact as the strongest marker of short-term prognosis, morphological extent of PE, the patient’s cardiovascular and pulmonary system status, the degree of neurohumoral adaptation and potential risks of the therapy [5, 6]. Since no exact epidemiological data are available, the incidence of PE is estimated to be approximately 60 to 70 per 100,000, and that of venous thrombosis approximately 124 per 100,000 of the general population [7, 8]. The European guidelines for the diagnosis and management of PE report annual incidence rates of venous thrombosis and PE of approximately 0.5 to 1.0 per 1,000 inhabitants [8, 9]. However, the actual figures are likely to be substantially higher because silent PE can develop in up to 40% to 50% of patients with deep vein thrombosis (DVT) [10]. In addition, autopsy studies have shown that PE had been diagnosed before death in 30% to 45% of patients [9, 10]. After coronary artery disease and stroke, acute PE ranks third among the most common types of cardiovascular diseases. While clinical data indicate that most cases of PE occur at 60 to 70 years of age, autopsy data show the highest incidence among individuals aged 70 to 80 years. If untreated, acute PE is associated with a significant mortality rate (as high as 30%), whereas the death rate of diagnosed and treated PE is 8%. Up to 10% of acute PE patients die suddenly. Two of three patients dying from PE die within 2 hours after the onset of symptoms [11].

The accuracy of diagnosis decreases as the patient age increases. The diagnosis is difficult due to comorbidities, such as bronchopneumonia, chronic obstructive pulmonary disease, asthma or chronic fibrotizing pulmonary processes. In contrast, PE is easily diagnosed in patients with DVT. The most common sources of PE (up to 85% of cases) include DVT followed by thrombosis of iliac and renal veins, and the inferior vena cava. The upper limbs are not usually identified as a source of major PE [11, 12].

The risk of PE can be assessed based on hemodynamic stability (systolic blood pressure (BP) > 90 mmHg or systolic BP < 90 mmHg), and high (> 4 points) or low (< 4 points) probability according to the original modified Wells’ criteria [12]. Due to high mortality in the early stages of PE, [13] aggressive treatment is necessary in high-risk patients (modified Wells’ score > 4, systolic BP < 90 mmHg). Hypoxemia with systolic BP < 90 mmHg suggests massive PE with high mortality [13].

All patients being evaluated for PE should receive supportive therapies and empirical anticoagulation (unless contraindicated) should be initiated without delay [14]. The data on exclusive outpatient management of acute symptomatic PE are limited, but the existing evidence supports the feasibility and safety of this approach in carefully selected low-risk patients.

The first line PE therapy is supportive therapy including [15]:

- **Respiratory support**
  - Supplemental high-flow oxygen should be administered;
  - Mechanical ventilation may be necessary for patients with severe hypoxemia/respiratory failure.

- **Intravenous fluids**
  - If systolic BP is < 90 mmHg, intravenous fluids should be given. Acute right ventricular failure with resulting low systemic output is the leading cause of death in patients with PE.
  - Studies indicate that aggressive volume expansion is of no benefit, and may even impair right ventricular function by causing mechanical overstretch, or by reflex mechanisms that depress contractility. However, modest fluid challenge (i.e., 500 mL) may help to increase the cardiac index in patients with PE, low cardiac index, and normal BP.
  - Local resuscitation protocols should be followed.

- **Vasopressors**
  - If systolic BP is < 90 mmHg, vasopressors should be given. They are often necessary in association with (or while waiting for) pharmacological, surgical, or interventional reperfusion treatment.
  - Noradrenaline (norepinephrine) appears to improve right ventricular function via a direct positive inotropic effect, while also improving right ventricular coronary perfusion by peripheral vascular alpha-receptor stimulation and the increase in systemic BP. However, its use should probably be limited to hypotensive patients.
  - Dobutamine may be considered for patients with PE, low cardiac index, and normal BP; however, raising the cardiac index above physiological values may aggravate the ventilation-perfusion mismatch by further redistributing flow from (partly) obstructed to unobstructed vessels.
– Adrenaline (epinephrine) combines the beneficial properties of noradrenaline and dobutamine, without the systemic vasodilatory effects of the latter.

– Bed rest - systematic recommendation of bed rest, as part of the early management of patients with DVT, PE, or both, is not supported by available evidence.

Initial anticoagulation

Anticoagulation should be initiated immediately in all patients who present with suspected PE, unless contraindicated [16]. If PE is subsequently excluded, anticoagulation can be discontinued. In patients with confirmed PE, anticoagulation should continue for at least 3 months [16].

Therapeutic anticoagulation can be achieved with dabigatran, rivaroxaban, apixaban, or edoxaban, which are recommended over vitamin K antagonist (VKA) therapy (usually warfarin), which is in turn recommended over low-molecular weight heparin (LMWH) [17]. Fondaparinux is generally reserved for patients with heparin-induced thrombocytopenia (HIT) or those with a history of this condition.

In hemodynamically stable patients, direct-acting oral anticoagulants (i.e., apixaban, edoxaban, rivaroxaban, dabigatran) are considered to be an acceptable therapeutic intervention. Dabigatran is a direct thrombin inhibitor, while apixaban, edoxaban, and rivaroxaban are selective factor Xa inhibitors. The advantage of these agents is that they require no monitoring, have a rapid onset of action, and are short-acting. They also do not interact with food; however, they do undergo drug interactions and have limited reversibility, although dabigatran can be reversed with idarucizumab. Randomized clinical trials have demonstrated non-inferiority of efficacy and safety in patients with hemodynamically stable PE [18]. Rivaroxaban and apixaban are used as monotherapy, whereas dabigatran and edoxaban require lead-in therapy with a parenteral anticoagulant for 5 to 10 days before they are initiated. Because of this, rivaroxaban and apixaban are often the preferred treatments in hemodynamically stable patients.

If a patient has started taking warfarin, it is usually appropriate to discontinue the parenteral anticoagulant once a therapeutic international normalized ratio of 2.0 to 3.0 has been established.

Fondaparinux is generally not recommended in hemodynamically unstable patients. LMWHs can be used interchangeably, in accordance with local protocols [19]. No difference in thromboembolism recurrence, hemorrhage, or overall mortality has been found between the different drugs in this class.

Unfractionated heparin (UFH) is recommended in cases where primary reperfusion is being considered, as well as in those with serious renal impairment (i.e., creatinine clearance < 30 mL/min), or severe obesity. The majority receives intravenous UFH administered as a bolus followed by continuous infusion titrated to a target activated partial thromboplastin time of 2 to 3 times the upper limit of normal (approximately 60 to 80 seconds). Weight-based nomograms may achieve therapeutic range faster. UFH, which can be rapidly reversed, is preferred in patients undergoing fibrinolysis or embolectomy. These recommendations are based on the short half-life of UFH, the ease of monitoring, and its rapid reversal by protamine [19, 20].

On the other hand, LMWHs, such as enoxaparin have been shown to be as safe and effective as intravenous UFH [20, 21]. LMWHs offer several advantages over UFH, including a longer half-life, increased bioavailability, and a more predictable dose response. In addition, LMWHs are dosed by weight, administered subcutaneously, and usually do not require dose adjustments or laboratory monitoring. Besides, UFH is largely hepatically cleared and LMWHs are renally cleared. Patients with chronic kidney disease, massive obesity, pregnancy, or anticipated bleeding or thromboembolism despite correct weight-based dosing of LMWH may benefit from laboratory monitoring. However, the utility of anti-Xa testing continues to be the subject of debate because the correlation of anti-Xa levels to antithrombotic effect and risk of bleeding has been questioned [21, 22].

Thrombolytic therapy

In hemodynamically compromised patients (shock or systolic BP < 90 mmHg) or right-sided heart strain (assessed by transthoracic echocardiography), thrombolytic treatment is recommended, as these patients have a high mortality rate. Primary therapy with fibrinolysis or embolectomy is generally considered for patients presenting with either massive or submassive PE. However, because of a relative paucity of randomized controlled trials, the use of primary therapy in the treatment of massive and submassive PE remains controversial [21].

Choice of intervention varies depending on the local provision: systemic thrombolysis [21] or catheter-directed thrombolysis [22], although current guidelines of the American College of Chest Physicians recommend systemic thrombolytic therapy using a peripheral vein over catheter-directed thrombolysis. Whenever technique is employed, a delay in treatment can be life-threatening [23].

Thrombolytic treatment of acute PE restores pulmonary perfusion more rapidly than anticoagulation with UFH alone. The Food and Drug Administration has approved t-PA (alteplase) 100 mg administered as a continuous infusion over 2 hours for the fibrinolysis of massive PE. Every patient being considered for fibrinolysis requires meticulous screening for contraindications, because the bleeding risk may be as high as 3.0% for intracranial hemorrhage [24, 25]. Although fibrinolysis is generally considered to be a lifesaving intervention in patients with massive PE, the extent of the clinical benefit remains unclear [26]. In a recent analysis of the International Cooperative Pulmonary Embolism Registry, fibrinolytics did not reduce the mortality rate or recurrent PE at 90 days. In submassive PE, the Management Strategies and Prognosis of Pulmonary Embolism-3 Trial demonstrated a reduction in the need for escalation of therapy among patients receiving alteplase [26, 27].
In patients with massive or submassive PE, in whom fibrinolysis is contraindicated or has failed, surgical embolectomy may be considered. Additional indications include paradoxical embolism, persistent right heart thrombi, and hemodynamic or respiratory compromise requiring cardiopulmonary resuscitation. In specialized centers caring for patients with massive PE, surgical embolectomy has been demonstrated to be a safe and effective treatment technique [28].

The early resolution of pulmonary obstruction leads to a prompt reduction in pulmonary artery pressure and resistance, with a concomitant improvement in right ventricular function. The hemodynamic benefits of thrombolysis are confined to the first few days; in survivors, differences are no longer apparent at 1 week after treatment [21, 22]. With thrombolysis, risk of major bleeding is 22%. In the case of thrombolysis, intracranial hemorrhage risk is 1% to 3% compared to 0.3% with heparin alone [21].

Absolute contraindications for thrombolysis include [22, 23]:
- Hemorrhagic stroke or stroke of unknown origin at any time
- Ischemic stroke in the preceding 6 months
- Central nervous system damage or neoplasms
- Recent major trauma/surgery/head injury (in the preceding 3 weeks)
- Gastrointestinal bleeding within the last month
- Known bleeding risk.

Relative contraindications for thrombolysis include [24]:
- Transient ischemic attack in the preceding 6 months
- Oral anticoagulant therapy
- Pregnancy, or within 1 week postpartum
- Traumatic resuscitation (in relation to this episode of PE)
- Refractory hypertension (systolic BP >180 mmHg)
- Advanced liver disease
- Infective endocarditis
- Active peptic ulcer.

When patients are excluded based on these criteria, the incidence of intracranial hemorrhage in the remaining treated patients has been shown to be negligible [24, 25]. In patients with confirmed PE, deciding whether to initiate thrombolysis or to continue with anticoagulation should be made on a case-by-case basis according to clinical presentation and pre-existing morbidity. This tends to vary according to local expertise and center provision.

**Treatment of pulmonary embolism in special populations**

- In general, the initial approach to the treatment of PE as well as the treatment of life-threatening PE in special populations is similar to that in the general population. However, definitive therapy may differ in hemodynamically stable patients with malignancy, pregnancy, and heparin-induced thrombocytopenia. Patients with malignancy: in hemodynamically stable
the risk of VTE in patients undergoing hip replacement, major knee surgery, and hip fracture repair [37, 38]. Abdominal or pelvic surgery for malignancy is associated with an elevated risk of postoperative VTE. The Enoxaparin and Cancer II study demonstrated that extended prophylaxis with enoxaparin reduced the risk of VTE in those patients [31].

Elastic graduated compression stockings

Elastic graduated compression stockings are not routinely used in patients with DVT to prevent post-thrombotic syndrome [38].

Inferior vena cava filters

The primary indication for inferior vena cava filter placement is contraindicated anticoagulation and recurrent PE despite anticoagulation therapy. However, it may be appropriate as an adjunct to anticoagulation in patients in whom another embolic event would be poorly tolerated (i.e. poor cardiopulmonary reserve, or severe hemodynamic or respiratory compromise), although clinical data are lacking. Filters are not routinely placed as an adjunct in patients with PE. Filter placement is also sometimes used in patients at high risk of recurrence in whom it is anticipated that anticoagulation may need to be discontinued because of bleeding. Examples include patients at moderate risk of bleeding who cannot receive fresh frozen plasma or red blood cells (i.e. due to religious preference), and patients with metastatic malignancy who are at a high risk for both recurrence and bleeding. Although filters are not routinely placed as an adjunct in patients with PE, some experts place them in patients at risk for decompensation due to cardiopulmonary compromise. We agree that the adjunct use of filters should not be a routine and placement should be individualized taking into consideration the risk of recurrence and bleeding, patient preferences, institutional expertise, medical morbidities, and surgical complications [31, 39].

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