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C A S E R E P O R T

High-dose streptokinase in the treatment of acute massive pulmonary embolism complicated with cardiogenic shock, respiratory arrest and ventricular fibrillation

Ratko Lasica*, Jovan Peruničić*, Igor Mrdović*, Radan Stojanović†, Zorana Vasiljević*

Clinical Center of Serbia, *Cardiology Department, Emergency Center, Institute for Cardiovascular Diseases, **Belgrade; School of Medicine,** †Institute for Clinical Pharmacology, Pharmacology and Toxicology, **Belgrade**

Background. *Despite advances in prophylaxis, diagnostic modalities, and therapeutic options, pulmonary embolism remains a commonly undiagnosed entity with lethal outcome. Clinically, pulmonary embolism ranges from massive thromboembolism with cardiogenic shock to asymptomatic, microebolism with anatomically small emboli without hemodynamic, respiratory or other disturbances.* ***Case report.*** *A patient with massive pulmonary embolism complicated with ventricular fibrillation, respiratory arrest and cardiogenic shock was treated with a total dose of 3 750 000 IU of intravenous streptokinase in the 8-hour time period. After successful cardiopulmonary resuscitation, and thrombolytic therapy, the patient regained hemodynamic stability six hours after admission; all clinical and electrocardiographic signs of the right ventricle insufficiency disappeared.* ***Conclusion.*** *This case report suggested that treatment with the high-dose of streptokinase could be beneficial in the patients with massive pulmonary embolism complicated with cardiogenic shock, which must be confirmed by further randomized trials.*

K e y w o r d s : **pulmonary embolism; shock, cardiogenic; ventricular fibrillation; streptokinase.**

Introduction

Massive pulmonary embolism (MPE) is defined by the clinical signs ranging from hypotension to cardiac arrest (1, 2). A meta-analysis of post-mortem studies (1971–1995) showed that massive pulmonary embolism (MPE) was not recognized in more than 70% of the patients (3–6). Pulmonary embolism (PE) was the cause of death in more than 15% of all hospitalized patients (7–9). In the International Cooperative Pulmonary Embolism Registry (ICOPER-study), 2 454 patients with acute massive pulmonary embolism were analyzed, and cumulative mortality in the 3-month period of 17.5% was presented (10, 11). Hospital mortality rate of the patients in the Management Strategies and Determinants of Outcome in Acute Pulmonary Embolism Trial (MAPPET) increased to 31% in those presenting hemodynamic instability (3). In the cases with fatal outcome, it was recognized long time ago that two-thirds of those patients would die within 1 hour of presentation (2). From reported series, it was evident that the combination of voluminous embolus and hemodynamic instability was the most frequent cause of shock, which was associated with mortality rate of approximately 30% (3). The last Guidelines of the European Society of Cardiology for the treatment of massive pulmonary embolism verified thrombolysis as one of the most important therapies in all the patients with massive pulmonary embolism and without absolute contraindications for this therapy, according to the results of major trials that showed better survival rate in the patients treated with thrombolytic therapy (12, 13).

Case report

A 68-year-old woman was admitted to the hospital with shortness of breath, heart palpitations, and recurrent

syncope. Ten days before admission, the patient had clinical signs of thrombophlebitis in the left lower-leg region.

On admission, the patient was somnolent, cyanotic, tachypnoic, with pronounced neck veins. Tachycardia with hypotension (blood pressure value 80/60 mm Hg), with the third heart sound (S3), and the accented second sound over the pulmonary valve, and systolic murmur in the right parasternal region was present on admission. The liver was enlarged (3 cm under the right rib arc). The circumference of the upper-leg and lower-leg regions was larger in the left than in the right leg. ECG on admission showed sinus rhythm with heart deviation of the axis to the right, the heart rate of 140 beats/minute and the expression of S wave in lead I, Q wave in lead III and T wave in lead III, as well as a horizontal type of ST-segment depression in precordial leads V4, V5 and V6 (Fig. 1).

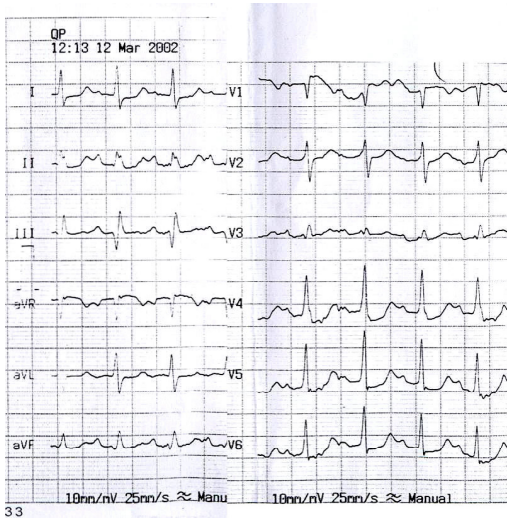

Fig. 1 – ECG on admission: S1Q3T3 pattern as sign of right axis deviation (heart rate 140 bpm)

Echocardiography revealed the enlarged right ventricle (3.4 cm), tricuspid regurgitation (+3) to the right atrium with the indirect estimation of the right ventricle pressure value of 60 mm Hg (Fig. 2).

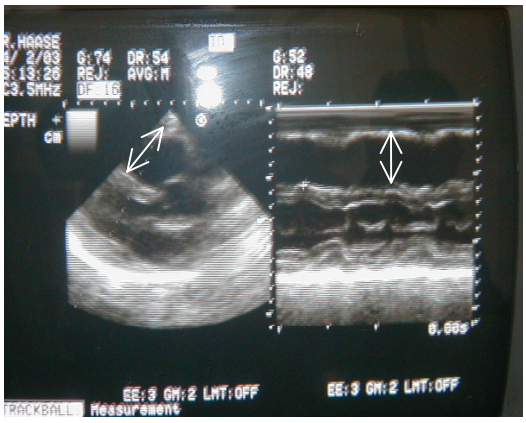

Fig. 2 – Echocardiography showing right ventricular enlargement (arrows)

Arterial blood-gas analysis showed oxygen hyposaturation (88%), with pO_2 of 6.5 kPa. The patient was immediately treated with thrombolytic therapy (1.5 million IU streptokinase intravenously in the 30-minute period). After the first therapeutic bolus of thrombolytic therapy, the patient was still dyspnoic, more tachypnoic (36 respirations/min), without measurable blood pressure, and with the heart rate of 150 beats/minute. ECG showed the recurrence of signs of acute pulmonary heart. Soon, respiratory, and subsequently, cardial arrest ensued. Cardiopulmonary resuscitation (CPR) measures were applied immediately with the endotracheal intubation. During CPR, the repetitive episodes of ventricular fibrillation were registered, and converted by DC shocks. After a successful CPR and defibrillations, the patient restored sinus rhythm. She was conscious and without any neurological disturbances.

Due to prolonged shock despite dobutamine therapy, the patient was treated with another 1 500 000 IU of intravenous streptokinase in the following 30 minutes. After the second dose of streptokinase, the patient became acyanotic, less dyspnoic with the blood pressure of 110/70 mm Hg, and the heart rate of 100 beats/minute. In the ensuing 7 hours, the patient was treated with another 750 000 IU of intravenous streptokinase (100 000 IU/hour). Four hours after the beginning of thrombolytic therapy, there were no S waves in lead I in ECG (Fig. 3), and after 6 hours all signs of the right ventricle overload (S1, Q3, T3) were absent (Fig. 4). The next day, ECG showed the intermediate heart axis with the heart rate of 80 beats/minute. Seven hours after streptokinase therapy, heparin was started intravenously (1 000 IU/hour), with the partial throboplastin time (PTT) monitoring every 6 hours (therapeutic PTT values were 72–118 sec). Oral anticoagulant therapy started on the third day from the admission.

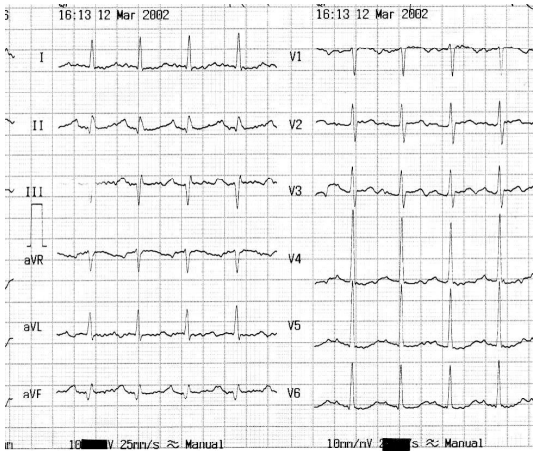

Fig. 3 – ECG 4 hours after the start of thrombolytic therapy; absent S wave in lead I

The second day from the admission, d-dimmer value was 1635 μg/L. Color-duplex scan of the leg veins showed the organized and non organized thrombotic masses in the two-thirds of the distal upper-leg region, and in one-third of

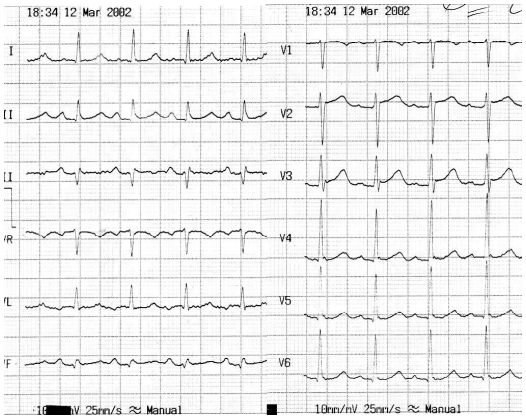

Fig. 4 – ECG 6 hours after the start of thrombolytic therapy; all signs of right ventricular overload were absent

the lower-leg region of the left large saphenous vein, as well as in the expanded upper-leg branch. Perfusion scintigraphy of the lung revealed perfusion defects in the basal and middle regions of the right-lung lobe. Small perfusion defects were recorded in the posterobasal region of the left-lung lobe. On control echocardiography (13th day from the admission), the right ventricle diameter (2.5 cm) was reduced, without regurgitation over the tricuspid valve. On the fourth day from the admission, the value of arterial oxygen saturation was 98%, pO2 11.8 kPa. Ten days from the admission, d-dimmer value was 125 μg/L.

Control color-duplex scan, performed two months later, showed well organized thrombi in the varices of the left large saphenous vein (19 mm in diameter), without other non-organized thrombi. Control perfusion lung scintigraphy two months after the admission, was without any deficiency of lung perfusion. After analysis in the Institute of Genetics, the patient was diagnosed as having factor V Leiden mutation (heterozygote), and the life-time anticoagulant therapy was advised.

Discussion

It was estimated that the hemodynamic instability in MPE accounted for 10% of all PE presentations, although this percentage might be higher (2). A minimal increase in severity produced cardiac arrest with a mortality rate of at least 70% in reported series (3, 4). According to UPET (14), the Urokinase- Streptokinase Embolism Trial (USPET) (15), and the ICOPER (11), 9% (14 of 160 patients), 7% (12 of 167 patients), and 4,2% (103 of 2.454 patients) of all the patients, respectively, initially presented with shock. In the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED), 10% of all patients (38 of 383 patients) presented with circulatory collapse, as defined by the presence of shock or syncope (16). The MAPPET study (3) reported that 59% of the patients had hemodynamic instability on presentation (cardiac arrest – 18%, shock requiring vasopressor therapy support – 10%, and arterial hypotension of < 90 mm Hg not requiring vasopressor therapy – 31%). In the series by Thames et al. (17), syncope was recurrent (35%), and was more prominent in women (82%), and the patients who had not been hospitalized (70%). Recurrent syncope as the sign of massive pulmonary embolism, was also noted in our patient. In the series by Miller et al. (18), of 68 patients without cardiopulmonary disease, and anatomically massive PE (≥ 50% obstruction), cardiac arrest developed in 29% of the patients, and was more common in the group experiencing persistent shock.

Our patient had trombophylia factor V Leiden mutation which was the most common genetic risk factor for deep venous thromboembolism (DVT), with the prevalence ranging between 2% and 15% in general population (19). Over 80% of APCR resistance phenotype could be explained by factor V Leiden mutation (19). Heterozygous factor V Leiden increased the risk of developing the first DVT by 5 to 7 times (or 5 to 7 in 1 000 people each year) (20). If one has a heterozygous form of factor V Leiden, the lifetime risk of developing DVT is 10% or less, but it may be higher if there are close family members who have had DVT (20). The PREVENT, ELATE and THRIVE III trials have demonstrated that the strategy of a long-term anticoagulation in patients with idiopathic DVT, including the isolated calf deep vein thrombosis, was safe and effective (21). Patients with idiopathic DVT or pulmonary embolism had a high risk of experiencing the recurrent event (21).

The advantage of thrombolytic therapy in patients with massive pulmonary embolism, compared to heparin, was observed in multiple studies (22, 23). Thrombolytic therapy for massive pulmonary embolism reduced mortality, the number of relapses and improved survival rate (24). In PIOPED study, thrombolytic therapy was considered a standard in the treatment for patients with “shock or major disability”. The investigators considered it “unethical” to treat this group with heparin alone (25). The application of thrombolytic therapy in patients with massive pulmonary embolism had to be imperative (26), because the waste of time might be the most important factor for higher mortality and more frequent hemorrhage (27). Similar to “golden hour” of trauma, myocardial infarction, and stroke, there was a “golden hour” for MPE during which a timely-approach to diagnosis and therapy could affect the outcome. Despite better effects of TPA in relation to streptokinase (28), streptokinase was used more often in our country for the economic reasons. On the other hand, streptokinase as one of the most commonly used thrombolytic drugs in large clinical trials, is non fibrin-specific and brought about a lytic state with the potential for hemorrhage (29). Bolus therapy with a recombinant tissue-type plasminogen activator (rt- PA) [0.6 mg/kg/15 min] was equivalent to the traditional 100 mg/2 h. Intravenous application of rt-PA appeared to be equivalent to intrapulmonary rt-PA(30). Few studies suggested 2-hour intravenous injection of 1.5 million IU of streptokinase for the therapy of massive pulmonary embolism (13, 28). Could we use a higher dose of streptokinase in a shorter time interval if hemodynamic pa-

rameters of patients were the same or worse after the recommended dose of streptokinase? In this case, we decided to use a dose of 1 500 000 IU of intravenous streptokinase for 30 minutes, followed by another 1 500 000 IU of intravenous streptokinase for the next 30 minutes. Some authors recommended the use of 1 500 000 IU of intravenous streptokinase in the 30-minute time period for the PE therapy, followed by 1 500 000 IU of intravenous streptokinase in the next 2–3 hours (31).

Early recognition of PE is important for the prompt medical or surgical life-saving interventions (1). The last Guidelines of European Society of Cardiology for the treatment of massive pulmonary embolism, verified thrombolytic therapy as one of the most important therapies, for all the patients with massive PE and without absolute contraindications for this therapy.

Conclusion

Our case report suggested that higher doses of streptokinase in a shorter time interval could be beneficial for patients with massive pulmonary embolism and cardiogenic shock. This remains to be be tested by randomized trials.

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A p s t r a k t

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VISOKA DOZA STREPTOKINAZE U LEČENJU PLUĆNE EMBOLIJE KOMPLIKOVANE KARDIOGENIM ŠOKOM, RESPIRATORNIM ARESTOM I VENTRIKULARNOM FIBRILACIJOM

Uvod. I pored napretka u profilaksi, dijagnostičkim modalitetima i terapijskim mogućnostima, plućna embolija je i dalje često nedijagnostikovan entitet sa letalnim ishodom. Kliničke manifestacije plućne embolije kreću se od masivne tromboembolije sa kardiogenim šokom do asimptomatske mikroembolije sa anatomski malim embolusima bez hemodinamskih, respiratornih i drugih komplikacija. **Prikaz slučaja.** Prikazan je bolesnik sa masivnom plućnom embolijom koja je bila komplikovana ventrikulskim fibrilacijom, respiratornim zastojem i kardiogenim šokom. Lečen je ukupnom dozom od 3 750 000 IJ streptokinaze datom intravenski tokom 8 sati. Nakon uspešne kardiopulomonalne reanimacije i primenjene trombolitičke terapije već 6 sati nakon prijema bolesnik je bio hemodinamski stabilan i bez kliničkih i elektrokardiografskih znakova insuficijencije desnog srca. **Zaključak.** Ovaj prikaz slučaja sugeriše da lečenje velikom dozom streptokinaze može biti korisno kod bolesnika sa masivnom plućnom embolijom komplikovanom kardiogenim šokom, što mora biti dokazano daljim randomizovanim studijama.

K lj u č n e r e č i : **pluća, embolija; šok, kardiogeni; fibrilacija komora; streptokinaza.**

Correspondence to: Ratko Lasica, Clinic Center of Serbia, Cardiology Clinic, Dr Subotića 6, 11 000 Belgrade, Serbia and Montenegro, Tel: +381 11 1777 081. E-mail: lratko@ptt.yu