

USE OF HIGH-DOSE OF UROKINASE DURING CARDIOPULMONARY RESUSCITATION FOR CLINICALLY SUSPECTED MASSIVE PULMONARY EMBOLISM

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Abstract

We are presenting 6 patients who suffered a cardiac arrest (CA) for suspected pulmonary embolism. Before establishing a definitive diagnosis, advanced life support (ALS) algorithm was initiated. Urokinase dosed as 15.000 UI/kg (weight) was administered initially, followed by 4.400 UI/Kg for 12 hours as a continuous intravenous perfusion. Two patients presented absolute contraindications for fibrinolytic therapy, however only one patient presented a major hemorrhagic complication. Global mortality rate was 83%.

Keywords: cardiac arrest, cardiopulmonary resuscitation, pulmonary embolism, reperfusion, thrombolysis.

Introduction

Massive pulmonary embolism (MPE) is a potentially reversible process, which may be responsible for 8-13% of unexplained cardiac arrests (CA). The reported incidence of CA caused by pulmonary embolism (PE) is 2-9% of all out-of-hospital and 5-6% of all in-hospital CA. Right ventricular failure due to pressure overload is considered to be the primary cause of death in severe PE. Patients in CA require immediate resuscitation and since there's no time for specific diagnostic tests a high clinical suspicion of PE as the cause of CA justifies initiating thrombolysis during cardiopulmonary resuscitation (CPR), potentially improving survival. International guidelines no longer consider CPR as a contraindication for thrombolysis as the thrombolytic therapy during reanimation can contribute to stabilization in patients with CA caused by MPE. We present 6 cases of patients with CA due to MPE who were treated with high doses of Urokinase (generalistic product, no specific producer is submitted; we had no laboratory funding) during cardiopulmonary resuscitation and later admitted to the Intensive Care Unit (ICU).

Case Report

We considered that there is no need of informed consent, because we are only using medical parameters, without personal information.

Case 1 A 37-year old female with primary pulmonary hypertension was admitted for elective right heart catheterization. Twenty-four hours after the procedure, she developed progressive cardiac failure that derived into cardiogenic shock and was admitted to the ICU with a presumptive diagnosis of MPE based on clinical findings. She suddenly presented pulseless electrical activity (PEA) hence advance life support (ALS) algorithm was initiated. Ten minutes into reanimation a bolus of 2.000.000 IU of urokinase was administered via a central venous catheter but no response was obtained. After 70 minutes of unsuccessful ALS (60 min after urokinase bolus), resuscitation efforts were stopped. Bleeding complications were not observed during CPR. The patient's autopsy findings were consistent with an MPE.

Case 2 A 70-yr old male with a history of chronic obstructive pulmonary disease (COPD) with dyspnea was admitted to our hospital with a presumptive diagnosis of acute PE that was confirmed by a thoracic scan. Deep vein thrombosis was found with ultrasound. Initial treatment with nonfractionated heparin was started and inferior vena cava filter was placed. On the 12th day after admission, he developed sudden cardiac failure, resistant to treatment. ALS was initiated due to ventricular fibrillation, and a bolus of 1.000.000 IU of urokinase was administered during CPR. The patient did not

respond to resuscitative efforts. Bleeding complications were not observed during CPR.

Case 3 A 63-year old male with a history of deep venous thrombosis of the right leg received treatment with low weight heparin with bad adherence. Three weeks later he presented sudden respiratory distress and syncope and was admitted to the emergency department with a diagnosis of acute PE. Perfusion lung scan showed massive left PE and ultrasound of the limbs confirmed deep venous thrombosis. He was admitted to the ICU and non fractioned heparin was started. After eight days, he suffered a cardiac arrest, ALS was started and intravenous bolus of 1.000.000 IU of urokinase was administered. After 60 minutes of unsuccessful resuscitation, efforts were ended. Bleeding complications were not observed during CPR. The patient's autopsy findings were consistent with an MPE.

Case 4 A 70-yr old female was admitted with a diagnosis of pancreatic adenocarcinoma. A duodenumpancrea-tectomy and a cholecystectomy were performed and she did not received prophylaxis against thromboem-bolic disease in the post operatorly due to severe thrombocytopenia. She developed clinical symptoms suggestive of acute PE which was confirmed with a perfusion lung scan. The patient was admitted in the ICU. She presented abrupt asystole and ALS was started. Presumptive diagnosis of MPE was made and 1.500.000 IU of urokinase was given intravenously. After ten minutes, she recovered spontaneous circulation. Over the next few hours, she developed pulmonary and intra-abdominal bleeding, and a persistent arterial hypoten-sion and anuria. The patient died seven hours after urokinase administration.

Case 5 A 45-yr old male with a history of alcoholic liver cirrhosis received an orthotropic liver transplanta-tion. Forty days after he was admitted with a diagnosis of obstructive cholangitis. Emergent surgery was perfor-med and afterwards he was admitted in the ICU. On the eight day, he presented with acute respiratory distress, raising suspicion of acute PE. He developed ventricular tachycardia and then asystole so ALS was initiated. A bolus of 2.000.000 IU of urokinase was given and 20 minutes later effective rhythm was achieved. Three hours later, he developed massive gastrointestinal bleeding and shock leading to emergency laparotomy and arterial ligation. The following days after the episode progressed to multiorganic failure due to acute liver rejection and infectious complications. He died on

the seventeenth day after admission.

Case 6 A 26-yr old pregnant female was admitted with a presumptive diagnosis of PE. She had a history of bone cancer and multiple interventions related to it. She presented symptoms consistent with deep venous thrombosis of the right leg and later acute dyspnea and syncope. She was admitted in the ICU and non fractio-ned heparin was started. Twelve hours later, she developed pulseless electric activity (PEA). During resuscitation an intravenous bolus of 1.000.000 IU of urokinase was administered and after 30 minutes, she recovered spontaneous circulation. Perfusion lung scan was performed showing lack of perfusion of left lung and inferior right lobule. Venous ultrasonography revealed right femoropopliteal venous thrombosis. Three days later, miscarried due to placental hemorrha-ge. The patient was discharged to home 20 days after admission.

Discussion

Fulminant PE usually manifests as an acute episode characterized by respiratory failure, obstructive shock and/or CA. Around 4.2% of PE patients present with hemodynamic instability or CA; up to 65% of these are fatal. In a prospective registry of patients with PE increased mortality rate of 58.3% was shown in patients with hemodynamic instability compared with a 15.1% rate for their hemodynamically stable controls. PE was the immediate cause of death in 3.5% of the autopsies. In autopsy studies of patients who died in the ICU, PE is reported to be the most frequently missed diagnosis. An acute increase in right ventricular pressure due to pulmonary artery obstruction and liberation of vasoac-tive mediators cause an obstructive shock that may rapidly progress to cardiovascular collapse. In that way, systemic thrombolysis is associated with return of spontaneous circulation and short-term survival in PE-related cardiac arrest. The updated guidelines on management of acute PE indicate that thrombolytics should be considered as it follows: 1. In patients with confirmed PE as the precipitant of CA, thrombolysis is a reasonable emergency treatment option (LE Class IIa); 2. Thrombolysis may be considered when CA is suspected to be caused by PE (LE Class IIb). Furthermore, in a haemodynamically compromised patient with suspec-ted PE unequivocal signs of right ventricle pressure overload and dysfunction justify emergency reperfusion treatment for PE if immediate CT angiography is not feasible.

The usefulness of echocardiography is becoming greater, and bedside echocardiography can often identify signs of PE, such as right ventricle dilation, right ventricle hypokinesia, paradoxical septal wall motion, and an occasionally thrombus itself. Visualizing the mentioned signs with a bedside echocardiogram in a haemodynamically unstable patient or patient in CA could guide further testing and treatment.

Fibrinolytic therapy has demonstrated greater efficacy than heparin in the treatment of MPE. Some studies show the usefulness of high-dose bolus injection of urokinase (15.000 IU/K) for treating MPE. The hemodynamic effects of bolus injection of urokinase (15.000 IU/K) in the right atrium showed that the greatest percentage of the total haemodynamics improvement occurred within the first 3 hours after bolus administration of urokinase. Other authors have reported that it may be possible to stabilize the circulation within 10 to 20 minutes when a bolus of a thrombolytic agent is administered during CPR for suspected PE.

Several risks are associated with thrombolytic therapy: significant bleeding, immunologic complications, hypotension and reperfusion injury. However, in patients with submassive PE, thrombolytic therapy is associated with lower rates of all-cause mortality although with higher risk of major bleeding and intracranial hemorrhage. Some found no clinical significant bleeding complications in the patients with CA and CPR after or before thrombolysis in acute myocardial infarction and authors suggested that the patients requiring CPR during acute myocardial infarction constitute a high-risk group which may particularly benefit from receiving thrombolytic therapy. In addition, patients who have received CPR for less than 10 minutes had no additional complications attributable to thrombolytic therapy.

Use of high doses of urokinase have also been tested previously. Authors described a case of administration of 1.500.000 UI of urokinase, and mechanical thrombectomy afterwards, without any complications. References described 17 patients with MPE who received high dosage of thrombolytic therapy before or after (less than 24 hours) undergoing resuscitation. Others reported two patients with PE and CA which 2.000.000 UI of UK were given during ALS with cardiovascular stabilization and without any bleeding complications. This suggests that if chest compressions become necessary, specific therapy should be initiated immedia-

tely on suspicion of PE based on the patient's history and clinical picture. Even if myocardial infarction is misinterpreted as PE, a bolus injection of a thrombolytic agent during ALS might be an appropriate therapeutic statement.

In our patients, bleeding complications occurred only in those with contraindications for the use of fibrinolytic agents particularly postoperative patients and pregnancy. Although these patients had contraindications for fibrinolytic treatment, their immediate life-threatening condition justified overriding the bleeding risk factors. Although recent major surgery is considered to be a contraindication for the use of fibrinolytic therapy, several authors have questioned this view for life-threatening patients. Thus, we believe that a greater tolerance towards the established contraindications for fibrinolytic treatment should be assessed according to the risk-benefit evaluation when confronting with a serious life threat of imminent death without any confirmed diagnosis.

Our approach shows well that urokinase was not associated with severe hypotension during resuscitation (in contraposition with the effects of common allergic reactions of streptokinase). Urokinase was not associated with a high rate of intracerebral bleeding when compared with rt-PA. In addition, the early recanalization of the obstructed pulmonary artery has been definitively established. If the strategy with high-dose bolus of urokinase is used, CPR should be prolonged for a longer interval than is classically recommended. There are reports of success in PE when CPR continued for more than one hour and recommendations have favored a prolongation of the ALS time of up to 1.5 hours. Metanalysis aimed to identify differences among thrombolytic regimens didn't show any statistically significant differences related to efficacy.

In conclusion, our observations suggest that the clinical suspected MPA with CA can also be one of the recommended applications of thrombolysis with high-dose bolus injection of thrombolytic with efficacy.

References

1. Hess EP, Campbell RL, White RD. Epidemiology, trends, and outcome of out-of-hospital cardiac arrest of non-cardiac origin. *Resuscitation* 2007; 72: 200–6.
2. Pokorna M, Necas E, Skripsky R, Kratochvil J, Andrlík M, Franek O. How accurately can the aetiology of cardiac arrest be established in an out-of-hospital setting? Analysis by “concordance in diagnosis crosscheck tables”. *Resuscitation* 2011; 82: 391–7.
3. Bergum D, Nordseth T, Mjølstad OC, Skogvoll E, Haugen BO. Causes of in-hospital cardiac arrest- incidences and rate of recognition. *Resuscitation* 2015; 87: 63–68.
4. Konstantinides SV, Torbicki A, Agnelli G, Danchin N, Fitzmaurice D, Galiè N, et al. Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology (ESC). 2014 ESC Guidelines on the diagnosis and management of acute pulmonary embolism. *European Heart Journal* 2014; 35: 3033–3080.
5. Böttiger BW, Arntz HR, Chamberlain DA, Bluhmki E, Belmans A, Danays T, et al. TROICA Trial Investigators; European Resuscitation Council Study Group. Thrombolysis during Resuscitation for Out-of-Hospital Cardiac Arrest. *N Engl J Med* 2008; 359: 25.
6. Antman EM, Anbe DT, Armstrong PW, Bates ER, Green LA, Hand M, et al. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction-- executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 1999 Guidelines for the Management of Patients With Acute Myocardial Infarction). *Circulation* 2004; 110: 588-636.
7. Tejerina E, Esteban A, Fernández-Segoviano P, María Rodríguez-Barbero J, Gordo F, Frutos-Vivar F, et al. Clinical diagnoses and autopsy findings: Discrepancies in critically ill patients. *Crit Care Med* 2012; 40: 842–846.
8. Neumar RW, Shuster M, Callaway CW, Gent LM, Atkins DL, et al. Part 1: Executive Summary: 2015 American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation*. 2015 Nov 3; 132 (18 Suppl 2) : S315-67. M F Hazinski MF, M Shuster M, et al. 2015 American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation* 2015; 132: S313-S314
9. Borloz MP, Frohna WJ, Phillips CA, Antonis MS. Emergency department focused bedside echocardiography in massive pulmonary embolism. *J Emerg Med* 2011; 41: 658–660.
10. Chatterjee S, Chakraborty A, Weingberg I, Kadakia M, Wilensky RL, Sardar P, et al. Thrombolysis for Pulmonary Embolism and Risk of All-Cause Mortality, Major Bleeding, and Intracranial Hemorrhage. *JAMA* 2014; 311: 2414- 2421.