CLINICAL REVIEW

Rescue systemic thrombolysis during cardiopulmonary resuscitation

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Abstract

The main goal of the cardiopulmonary resuscitation is good neurological outcome. The primary ischaemic insult initiates a multitude of coagulation and inflammatory cascades resulting in cytotoxic brain oedema, necrosis and apoptosis. Thrombolytic agents may have experimentally and clinically significant beneficial effects in non-traumatic cardiac arrest. Prospective clinical trials show that thrombolytic therapy combined with heparin is feasible, safe and effective during resuscitation. We demonstrate three cases of successful systemic thrombolysis during in hospital CPR in cancer patients. Two patients were successfully resuscitated from cardiac arrest with streptase bolus (500.000 IU) and infusion (100,000/hr). One patient with pulmonary embolism and gynecological bleeding were treated with bolus (10,000 IU) and infusion of heparin (1,000 IU/hr) and successfully resuscitated. We observed a very good neurological outcome in all 3 cases following rescue thrombolysis and standard CPR. Two patients were discharged from hospital in good neurological outcome. One patient died on ICU on 10th day due to myocardial re-infarction and biventricular failure. Systemic thrombolysis is safe and effective treatment modality during resuscitative efforts even in cancer patients. In oncological patients with dissemination and/or bleeding heparin therapy should be considered due to better clinical control. ***(Ref. 17.)***
Key words: systemic thrombolysis, cardiopulmonary resuscitation, heparin, streptase.

The prognosis for patients suffering from cardiac arrest is generally poor: the survival with good neurological outcome after out-of-hospital cardiac arrest and successful resuscitation is only 3–5 %, the survival following in-hospital resuscitation from cardiac arrest with good neurological outcome and hospital discharge is between 5–10 % (Kern, 2001). The main goal of succesful resuscitation is not only the restoration of spontaneous circulation (ROSC), but most of all the restoration and maintaining of normal neurological functions following resuscitative efforts.Injury to the nervous system is characterised by a stereotypical pattern irrespective of the primary injury, which includes trauma, global ischaemia and hypoxemia (cardiac arrest or shock), hypoglycaemia, epidural or subarachnoid haemorrhage. The primary insult initiates a multitude of coagulation and inflammatory cascades resulting in secondary brain injury (Andrews, 1999). Thus, the cardiopulmonary resuscitation (CPR) should integrate following therapeutic interventions: the restoration of spontaneous circulation, haemodynamic support with adequate cerebral perfusion and cerebral protection limiting the secondary brain injury. Brain protection during post-resuscitation period involves pharmacological (Saniova, 1999) and non-pharmacological approach, including local cerebral hypothermia and temperature control of brain (Zahorec et al, 1996).

Approximately 70 % patients who had to be resuscitated after out-of-hospital cardiac arrest, suffered either from acute myocardial infarction or massive acute pulmonary embolism (Silfvast, 1991). The prolonged CPR leads to massive coagulation activation with subsequent cerebral microcirculation disorders and are responsible for cerebral no-reflow and hypoperfusion phenomena during post-resuscitation period and bad neurological outcome (Bottiger and Eike, 2001). Recently many reports show beneficial effects of systemic thrombolysis during CPR on clinical outcome of resuscitated patients from cardiac

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arrest due to acute myocardial infarction, massive pulmonary embolism or after prolonged, initially unsuccessful CPR (Bottiger et al, 2001; Newman, 2000). The prospective clinical trial shows that thrombolytic therapy combined with heparin is feasible, safe and effective during CPR (Bottiger, 2001). Thrombolytic agents may have clinically significant beneficial effects in non-traumatic cardiac arrest (Newman, 2000). We demonstrate three cases of successful systemic thrombolysis during in-hospital CPR.

Case report

1st patient came to the ICU with severe chest pain, hypertension 180/100 mmHg and tachycardia 100 b/min. The infusion with magnesium, Ebrantil and Tenormin iv. bolus transiently improved clinical status. 12-lead ECG did not reveal any acute ischemic changes. 10 minutes after admittance to ICU the ventricular fibrillation abbruptly deteriorated clinical status. The CPR had started immediately including: defibrillation,intubation, breathing with 100 % oxygen and external cardiac massage according ERC guidelines. Electric defibrillation was successful only for short periods 1–2 minutes. The iv. bolus and infusion of antiarytmic drugs (trimecian, bretylium mesylate, amiodaron) did not stabilise cardiac rhytm. The recurrent ventricular fibrillation was treated by repeated external defibrillation (300–360 J) and external cardiac massage. The CPR efforts included: adrenalin, methylprednisolon, cannulation of v. subclavia and a. brachialis, ECG monitoring, ambuing with 100 % oxygen. After 30 minutes we clinically recorded mydriasis and acrocyanosis. ECG (during short periods of sinus tachycardia) showed Pardee wave on lead III, and ST elevation in V4–V5. We decided for systemic thrombolysis with streptase (Streptolysin 500.000 IU/30 min and then continuous infusion 100.000 IU/hr). 10 minutes following the initiation of systemic thrombolysis the spontaneous restoration of circulation was achieved with systemic blood pressure 100/40 mmHg. The hemodynamic support involved noradrenalin and Isoket infusion. No other defibrillation was needed. When blood pressure had reached values 140/70 mmHg the norepinephrine infusion was changed for dobutamin continuous infusion (8 μg/kg/min). The patient was ventilated and brain protection procedures were done: normoventilation, normoxemia, local brain cooling, antiedematous therapy with manitol infusion, enhanced diuresis, corticoids, piracetam and pentoxyphylin adjuvant therapy. ECG and cardiospecific enzymes profile had confirmed successful reperfusion. The streptokinase infusion was stopped after 5 hours and finished with bolus of heparin 5000 IU, when hematoma on upper arm and eyes were observed. The transfusion of fresh frozen plasma and fibrinogen have adjusted coagulation parameters. No bleeding from gastrointestinal tract was detected. The neurological recovery occurred after 12 hours sedation.

The patient was extubated after 48 hours with GOS = 2 (Glasgow outcome score). He was transferred to the cardiac ICU and on day 7th discharged from hospital with normal neurological function (GOS = 1).

2nd patient, 50-years old woman was admitted from Radioterapeutic clinic after brachytherapy with sudden onset of dyspnoe, severe hypoxemia, and shock (blood pressure 70/40 mmHg, tachycardia 120/min). The clinical signs together with diaphoresis, coughing and ECG examination (rSR pattern in V1–V2) support the diagnosis of acute pulmonary embolism. We cannulated vena subclavia and arteria radialis immediately. The hemodynamic status further deteriorated with signs of obstructive shock (low systemic blood pressure and elevated central venous pressure). Electromechanical disociation occurred abruptly with transient loss of consciousness. We started CPR with mask ventilation, bolus of adrenalin and subsequent continuous infusion of noradrenalin (0.09 μg/kg/min). We decided for heparin therapy (10.000 IU i.v. bolus) because this oncological patient had active gynecological bleeding (inoperable infiltrating cancer of cervicis uteri). After the administration of heparin bolus (1–2 minutes) sinus rhythm and blood pressure had restored. The consciousness came back together with spontaneous breathing. No defibrillation and/or mechanical ventilation were needed. We followed with continuous heparin infusion (1.000 IU/hr) and noradrenalin infusion. 15–20 minutes following bolus of heparin the clinical status rapidly improved: the dyspnoe had disappeared and hypoxemia had significantly changed to normoxemia. The perfusion scintigraphy of lungs 6 hours later showed remnant signs of bilateral pulmonary embolism. The heparin infusion lasted 48 hours under the coagulation control and no further bleeding was observed. The patient was transferred to general ward on the 3rd day after heparin treatment of pulmonary embolism with good clinical and neurological outcome.

3rd patient, 75-years old woman was admitted to the ICU with clinical signs of massive pulmonary embolism (dyspnoe, severe hypoxemia, severe hypotension,acrocyanosis, venous extremity edema) from general ward. The ventricular fibrillation abruptly deteriorated hemodynamic status. The CPR started immediately according ERC protocol (intubation, defibrilation, venous and v. subclavia cannulation, adrenalin, trimecain and bicarbonate infusion, manual ambu — breathing with 100 % oxygen). The ROSC was not successful despite repeating and escalating defibrillation. After 15 minutes we decided for systemic thrombolysis with bolus of streptokinase (750.000 IU/hr after hydrocortisone administration) and subsequent Streptase continual infusion (100.000 IU/hr). 25 minutes after the initation of CPR and 5 minutes after systemic thrombolysis the ROSC was successful. The patient was maintained on mechanical ventilation, sedation and cerebral protection. The neurological status improved after 24 hours, however, the weaning from ventilation was not successful due to biventricular heart failure (left ventricle ejection fraction 28–30 %). The tracheostomy was performed on the day 6th and hemodynamic support involved infusion of dobutamine, enhanced diuresis and digitalization, together with complex supportive therapy. The patient died on the day 10th after not-resuscitative ventricular fibrillation. The section had revealed remnant pulmonary embolism and severe ischemic heart disease with subacute myocardial infarction and severe atherosclerotic coronary artery disease.

Discussion

The presented case reports demonstrate the safety and effectivness of systemic thrombolysis during in-hospital CPR. Our clinical observation support previous clinical trials that systemic thrombolysis during out-of-hospital CPR (more difficult) is feasible and safe and did not cause CPR-related bleeding complications (Bottiger et al, 2001). Thrombolysis seems to act very quickly and had direct effect not only at the site of pulmonary or coronary thrombosis, but also on the cerebral microcirculation. The experimental and clinical research by Bottiger et al (1995, 2001) shows that this new therapeutic option is safe and can be successfully applied clinically. Although the beneficial effects of systemic thrombolysis in the treatment of acute myocardial infarction and pulmonary embolism are well-known for a long time, the priority of Bottiger research is that systemic thrombolysis can be safely used during CPR and that this treatment option can have beneficial effects on cerebral microcirculation and neurological outcome of resuscitated patients.

The most attractive feature of this therapeutic approach is the adjustment of coagulation activation after cardiac arrest. The imbalance between coagulation and fibrinolysis develops very quickly after cardiac arrest. All patients resuscitated from cardiac arrest, demonstrated markedly increased levels of thrombin-antithrombin complex (Bottiger et al, 1995). The successful resuscitation of the brain requires complete microcirculatory reperfusion. On the cat model of cardiac arrest the investigators demonstrated the beneficial effect of thrombolysis with rtPA 1 mg/kg combined with heparin 100 IU/kg on cerebral perfusion and neurological outcome of cats (Fischer et al, 1996). Other group observed massive fibrin generation with consecutive impairment of fibrinolysis during and after out-of-hospital CPR patients (Gando et al, 1997). They also observed persistent elevation of the tissue factor serum levels, which indicates the activation of extrinsic coagulation pathway, associated with low levels of tissue factor pathway inhibitor in out/of-hospital cardiac arrest patients (Gando et al, 1999). The plasmatic coagulation activation and inhibition of fibrinolysis (elevated tissue factor and very low tissue factor pathway inhibitor) during reperfusion period are both responsible for the microcirculation deterioration in the brain („no-reflow“ or „low-flow“ phenomena). The fibrin formation, endothelial activation and triggering of the inflammatory cascades by ischemia-reperfusion injury seem to be the causal pathogenic processes responsible for prolonged delayed global cerebral hypoperfusion, which lasted 1–4–12 hours following global cerebral ischaemia. Brain-oriented intensive care is very complex and involve many therapeutic approaches including neurocytoprotection (Gustafson, 1992; Saniova, 1999), and patency of brain vessels and cerebral micorcirculation (Sefranek, 1998). The prolonged cerebral hypoperfusion is linked with neuronal and glial cell damage by the process of necrosis or apoptosis and is responsible for further clinical deterioration and bad neurological outcome (Fink and Evans, 2002). The Fas receptor pathway demonstrates the role of extracellular inflammatory ligands in the initiation of programmed cell death. Fas stimulation has been shown to induce apoptosis after brain ischaemia (Felderhoff-Mueser, 2000). The maladaptive (pathological) processes of coagulation system activation, local and systemic inflammation and ischaemia-reperfusion injury are very tightly coupled (Abella and Becker, 2002). The „hyperactivation“ of complement and coagulation system are possible pathogenic factors coupling inflammation cascade, ischemia-reperfusion syndrome and tissue injury (cell necrosis and/or apoptosis).

The most encouring clinical trial by Bernd Bottiger and colleagues (2001) clearly demonstrates clinical efficacy of this treatment option. Patients who had non-traumatic cardiac arrest without signs of bleeding and without ROSC after 15 minutes of resuscitation were given intravenous heparin (1 ml=5.000 IU) and rtPA (50 mg of recombinant tissue plasminogen activator). The study was stopped after an iterim statistical analysis done when 40 patients had been treated, comparing with control patients without systemic thrombolysis. The resuscitative patients with thrombolysis showing significant ROSC (58 % vs 44 %) and improved survival during the hospital stay (15 % vs 8 %). Kern stated that a randomised controlled trial should now be considered ethical (2001).

Systemic thrombolysis during CPR is safe and effective treatment in cases of acute myocardial infarction, acute pulmonary embolism and prolonged CPR (lasted more than 10–15 minutes). Recent experimental and clinical reports show that thrombolytic agents have beneficial effects on cerebral microcirculation and can improve neurological outcome. Systemic thrombolysis and subsequent anticoagulation with heparin may have direct therapeutic and preventive effect during primary and secondary brain injury. Our preliminary data show that this treatment option (in agreement with concept of proactive/preemptive therapy) can be used even in cancer patients without active bleeding or metastatic dissemination. In the cases of active bleeding or metastatic cancer disease we prefer the anticoagulant treatment with heparin, which can be under the better clinical control than systemic thrombolytic agents. Further investigations are expected and conclusive clinical trials should be done.

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