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Case Report

E-CPR in Cardiogenic Shock Following Severe Mix-Intoxication with Beta-Blockers, Angiotensin-Converting Enzyme Inhibitors, Dihydropyridine Type Calcium Antagonist and Allopurinol – ECMO As A Bridge to Recovery

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Abstract

Patient admission to intensive care unit (ICU) due to suggested intoxication either because of suicide or because of accident is not uncommon. We describe the case of a 49-year-old male patient who was admitted to our hospital after ingestion of approximately 75 tablets, consisting of beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, dihydropyridine-type calcium antagonists and allopurinol. Only few hours after ingestion, the patient developed cardiac arrest in presence of preclinical healthcare professionals. Therefore, he was transferred to our heart-catheterization lab under mechanical supported chest compression and we commenced veno-arterial (VA) extracorporeal membrane oxygenation (ECMO) therapy. Heart function almost completely recovered, and finally, after explantation of VA- ECMO, he could be transferred to neurorehabilitation.

Keywords: Intoxication; VA- ECMO; Cardiac arrest; Bridge to recovery

1. Introduction

Admission to ICU following intoxication is an important issue worldwide, e.g. suggested by studies in Europe, the United States (US), India and Iran [1-6]. There are estimations, that in 2007, every 19 minutes one death occurred due to drug overdosing in the US [1], in most cases following intoxication with opioids. Furthermore, intoxications leading to ICU admission are associated with high health care costs [7]. Altogether, approximately 9 to 19% of the ICU admissions worldwide are due to intoxication [5, 6, 8]. Among all patients admitted to ICU following intoxication, suicide attempts account for 12-38%, respectively [5, 6, 8]. In Germany, cardiovascular drugs were shown to be among the top-ten drugs besides antidepressants leading to ICU admission, following suicide attempt [5].

Among cardiovascular drugs, beta blockers are one of the substances most commonly prescribed. Co-ingestion of several cardio depressant drugs, e.g. calcium channel blockers and tricyclic antidepressants were shown to be associated with increased cardiovascular morbidity [9]. In patients with beta- blocker intoxication, current recommendations suggest treatment with glucagon as first-line therapy [10], in addition to circulation support through administration of inotropic agents. When these measures fail, ECMO therapy should be considered as a therapeutic option. The clinical impact of intoxication is often temporary and ECMO can be used as a "bridge to recovery".

2. Case Presentation

A 49-year-old male patient was admitted to our hospital after ingestion of beta- blockers, ACE inhibitors, dihydropyridine-type calcium antagonists and allopurinol. At first medical contact with the paramedics the patient was awake but suffered from dizziness. At his home, there were several blisters consisting of beta-blockers (Metoprolol 200 mg and Metoprolol 47.5 mg), ACE-inhibitor (Ramipril 5 mg), dihydropyridine-type calcium antagonists (Lercanidipine 10 mg and Amlodipine 5 mg) and Allopurinol (Allopurinol 100 mg). He could not exactly report how many tablets he had taken from the respective drugs. However, it was estimated, that he had taken at least 75 tablets, in total. On the way to our hospital the patients' heart rate gradually began to decline as did blood pressure, too. Initial attempts to stimulate the heart rate through administration of atropine and epinephrine were not successful. Therefore, external cardiac pacing was commenced, however, not being successful. Finally, endotracheal intubation was done, and cardiac resuscitation was commenced. Here, the LUKAS-system (Jolife AB, Lund, Sweden) as mechanical chest compression support was applied. After arrival in the emergency room, the patient was transferred immediately to the heart- catheterization lab for implantation of VA- ECMO.

Electrocardiogram (EKG), at the heart- catheterization lab, showed asystole. Arterial blood gas sampling (BGA) showed lactate acidosis with an initial lactate of 10.4 mmol/l. PH was 7.0, pO2 was 60 mmHg, pCO2 was 48 mmHg, base excess -21 mmol/l. Na^+ was 126 mmol/l and K^+ was 6,6 mmol/l. Glucose was 256 mg/dl. Veno-arterial ECMO (Maquet Cardiohelp, Rastatt, Germany) was implanted via right femoral artery and right femoral vein. For

venous drainage, 23 F cannula was used. 19 F cannula was used for arterial cannulation and antegrade leg perfusion was achieved through 6 F cannula.

Coronary angiography which we also did to exclude additional coronary artery pathology as differential diagnosis for cardiac arrest revealed mid-grade stenosis in the distal left circumflex artery (LCX). However, we did not consider the stenosis being responsible for the observed cardiac arrest, and therefore, no stent implantation was done. In addition, transvenous pacemaker was implanted trough left femoral vein. Despite continuous pacemaker stimulation, asystole persisted. Finally, the patient was admitted to our ICU ward for intensive care treatment and therapeutic hypothermia (33°C) for the first following 24 hours after establishing the ECMO circuit.

Norepinephrine treatment had already been started in the emergency room. On ICU, high- dose norepinephrine support was necessary (5.7 mg/h). ECMO flow, initially, was 5.2 L/min and FiO_2 on ECMO was 0.6. Lactate level after arrival on ICU was 4,8 mmol/l. Pressure controlled ventilation was performed with 12 mbar positive end expiratory pressure (PEEP) and 22 mbar peak inspiratory pressure. FiO_2 at the ventilator was 0.25. Antibiotic therapy with Ampicillin/Sulbactam was started due to possible aspiration following emergency intubation and also resuscitation.

Blood sampling showed significant leukocytosis (18.880/µl), however neither CRP (0,78 mg/l) nor PCT (0.23 µg/l) were tremendously increased. Hemoglobin (13.9 g/dl) was within the normal range, platelet count was reduced (89.000/µl). Both creatinine (202 µmol/l) and creatinine kinase (202 µmol/l) were increased. In addition, GOT (447 U/l), GPT (446 U/l) and LDH (621 U/l) all were elevated above the cutoff values. Bilirubin (40.6 µmol/l) was elevated, too.

The next day, norepinephrine treatment had to be further increased (6.5 mg/h) due to hemodynamic instability. Epinephrine therapy was added (2.8 mg/h). At the ECMO, flow remained unchanged and FiO_2 could be decreased to 0.4. Lactate, despite hemodynamic instability, further dropped to 2.5 mmol/l. Both leukocytes (26.350/µl) and creatinine (214 µmol/l) were increasing. Creatinine kinase (556 U/l) was further elevated, too. In addition, LDH (1985 U/l), GOT (1604 U/l) and GPT (1208 U/l) further increased, as did bilirubin (59.9 µmol/l).

The third day after admission, again norepinephrine support had to be further increased, finally reaching 8,5 mg/h. Then, both norepinephrine and epinephrine support could be gradually reduced from day to day. Finally, on day eight norepinephrine therapy could be discontinued. Discontinuation of epinephrine therapy was already possible on day four after admission. Concomitantly, electric heart activity began to recover.

The following days, GOT, GPT, LDH began to decline. In contrast, creatinine, creatinine kinase and bilirubin were further increasing, before they finally started to decline again.

Initially, the ECMO flow was 5.2 L/min and remained unchanged until day three after admission. The following days, reduction of ECMO flow was possible, too. On day six, FiO_2 at the ECMO had to be increased step by step, finally reaching 1.0. Chest X-ray showed signs of pneumonia on both sides. Therefore, antibiotic therapy was escalated to Piperacillin/Tazobactam, which we continued the following nine days. Tracheal suctioning revealed infection with Klebsiella pneumonia, Serratia marcescens and Pseudomonas aeruginosa. Antimicrobial diagnostics showed that Piperacillin/Tazobactam had antimicrobial activity against all three bacteria, therefore, we continued the antibiotic regimen we had started after escalation for 10 days in total. Blood culture sampling, which had been done, too, didn't show septicemia. Finally, on day eight after admission ECMO explantation was done. Here, the Manta® system (Teleflex, Fellbach, Germany) which seals the puncture site from the inside of the vessel was used for vascular closure.

Since weaning from the respirator was prolonged and the patient didn't show sufficient awake reaction, we performed cerebral CT scan. Here, embolic stroke in the right anterior cerebral media artery territory could be observed. Therefore, we consulted our colleagues from neurology. EEG showed general abnormalities. Sensory evoked potentials could be recorded bilateral. NSE was 72 µg/l after 24 hours and 62 µg/l after 72 hours, respectively. Finally, after successful weaning from ECMO and after successful treatment of ventilator associated pneumonia, the patient was transferred to neurorehabilitation for further recovery.

3. Discussion

With this case, we want to present our experience regarding the feasibility of ECMO support in a patient suffering from cardiogenic shock after severe mix intoxication consisting of cardio- depressant drugs. Beta blockers, one very important group of cardio-depressant drugs, exert their effect through competitive blockade of beta- adrenoreceptors [11]. Furthermore, calcium antagonists and ace inhibitors are important substances for the management of arterial hypertension [12], either acting on the renin angiotensin aldosterone system in the course of ACE inhibitors [13], or on calcium channels that can be found on vascular smooth muscle cells [14] in the course of dihydropyridine calcium channel antagonists. For some drugs, e.g. digitoxin, specific antidots are available [15]. Other drugs might be eliminated through dialysis [16, 17]. Unfortunately, with the drugs that our patient used for self-intoxication, neither an antidot-infusion, nor dialysis were feasible. Therefore, vasopressor therapy through application of catecholamines and, also, application of atropine was used as first line symptomatic therapy. However, since refractory cardiac arrest persisted, therapy was escalated to ECMO. Additional measures that might be used have been described in the literature, too (Table 1).

Both insulin and glucagon infusion therapy in the course of severe beta-blocker and calcium channel intoxication have been proposed [18] and regarding insulin application no severe adverse effects have been observed [19]. The beneficial effects of insulin might be due to positive inotropic effects which have been described both in vitro [20] and in vivo [21]. Glucagon can exert chronotropic, dromotropic and inotropic activities on the myocardium

independent of beta- blockade [22]. These activities are believed to be due to increased cAMP production [23]. To our knowledge, so far, there are no randomized clinical studies comparing the use of glucagon in the course of beta-blocker or calcium antagonist intoxication and evidence comes either from preclinical studies with animals [24] or from reported cases that were successfully treated with glucagon application [25].

In addition, use of lipid emulsions has been proposed in intoxicated patients for increased clearance of the respective toxic substance [26, 27], however with conflicting evidence [28]. Indeed, the use of lipid emulsion was first suggested in case of intoxication with local anesthetics [29] by Weinberg et al. [30]. Several beneficial effects have been attributed to lipid emulsions, e.g. a redistributive effect for lipophilic drugs in the lipid phase of the emulsion, and an effect on metabolism and organ function [31]. In ECMO therapy, there is increasing evidence, that lipid emulsions might have detrimental effects on ECMO circuit, finally leading to failure of the oxygenator [32]. Therefore, using both, lipid emulsions and ECMO in conjunction require alertness for this dangerous potential complication.

Charcoal might be used in intoxicated patients to hinder enteric resorption [33], however, in shock, there is concern that adverse effects might occur due to impaired bowel peristaltic [34]. In addition, timing is critical, too, and with delayed administration of charcoal, enteric resorption might not be impaired sufficiently [35]. There have also been several reports of intestinal complications after administration of charcoal, e.g. small bowel obstructions [36-38] and aspiration with subsequent ARDS [39].

ECMO therapy has been just recently suggested as a possible treatment option in a position statement of the ESC for patients suffering from persistent cardiogenic shock [40]. In the US, the use of ECMO with respect to intoxication was investigated by the American College of Medical Toxicology (ACMT) Toxicology Investigators Consortium (ToxIC) in a registry from January 2010 till December 2013. In total, only 10 cases of 26,000 could be identified where ECMO was used. Fortunately, overall survival rate was 80% in these cases [41]. Furthermore, 46 papers beginning from 1966 till 2012 describing ECMO use in poisoned patients either published in Pubmed/Toxnet/Cochrane or Embase could be identified [42]. These published cases and our case clearly demonstrate that ECMO can serve as a bridge-to-recovery enabling clearance of ingested drugs by renal or hepatic metabolization until recovery of cardiovascular function, especially in previously healthy young people.

We could demonstrate, that cardiac arrest, following intoxication can be successfully treated through ECMO therapy. Therefore, ECMO is an interesting option, especially in young patients with no or minor preconditions. Finally, charcoal, insulin, glucagon, lipid emulsion, antidot or dialysis might offer therapeutic options, too, depending on the respective substances used for intoxication.

Drug	Action	CAVE	Dose	References
Charcoal	Scavenging effect	Aspiration/ARDS [39], Bowel obstruction [36-38]	50 g was used in most studies [33]	[33, 36-39]
Atropine	Positive chronotropic	Arrythmias, Anticholinergic syndrome	According to effect, 1.5 mg every 4-6 hours	[18]
Insulin	Positive inotropic	Hypoglycemia, Hypokalemia	Loading dose 0.5-1 IU/Kg followed by infusion of [18] (0.5 - max. 10 IU/kg) * and corresponding glucose substitution	[18-21]
Glucagon	Positive inotropic, chronotropic, dromotropic actions	Nausea, Vomiting, Hypoglycemia	Adult: 5-10 mg loading dose followed by infusion of 1 mg to 10 mg per hour [18]	[18, 22, 23]
Norepinephrine	Positive inotropic and vasoconstrictive actions, higher effect on vasoconstriction	Arrythmias, intestinal ischemia, limb ischemia, unpredictable doses	According to effect	[18]
Epinephrine	Positive inotropic and vasoconstrictive actions, higher effect on inotropy	Arrythmias, intestinal ischemia, limb ischemia, unpredictable doses	0.05-1 µg/Kg/min	[18]
Lipid emulsion	Scavenging effects, metabolic effects, organ protective effects	Failure of ECMO oxygenator has been described [32]	20% emulsion: 1.5 ml/Kg loading dose followed by infusion of 0.25 ml/Kg/min to a total volume of 10 ml/Kg (max.: 12.5ml/kg/24h) [29]	[18, 27, 29-32]

Table 1: Drugs available for intoxication with beta- blockers and calcium antagonists.

4. Conclusion

ECMO therapy might be considered, not only for patients with either heart or pulmonary failure, waiting for organ- or LVAD implantation, but also for patients suffering from severe intoxication, especially in case that resuscitation becomes necessary in previously healthy people. Here, early admission to a tertiary hospital where ECMO can be provided, is important to improve patient survival.

Disclosures

The authors declare that they have no conflict of interest.

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