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ORIGINAL ARTICLE

Levosimendan Improves Neurological Outcome in a Swine Model of Asphyxial Cardiac Arrest

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Background In asphyxial cardiac arrest, the severe hypoxic stress complicates the resuscitation efforts and results in poor neurological outcomes. Our aim was to assess the effects of levosimendan on a swine model of asphyxial cardiac arrest.

Methods Asphyxial cardiac arrest was induced in 20 Landrace/Large White piglets, which were subsequently left untreated for four minutes. The animals were randomised to receive adrenaline alone (n=10, Group A) and adrenaline plus levosimendan (n=10, Group B). All animals were resuscitated according to the 2010 European Resuscitation Council guidelines. Haemodynamic variables were measured before arrest, during arrest and resuscitation, and during the first 30 minutes after return of spontaneous circulation (ROSC), while survival and neurologic alertness score were measured 24 hours later.

Results Return of spontaneous circulation was achieved in six animals (60%) from Group A and nine animals (90%) from Group B (p=0.303). During the first minute of cardiopulmonary resuscitation, coronary perfusion pressure was significantly higher in Group B (p=0.046), but there was no significant difference at subsequent time points until ROSC. Although six animals (60%) from each group survived after 24 hours (p=1.000), neurologic examination was significantly better in the animals of Group B (p<0.01).

Conclusions The addition of levosimendan to adrenaline improved coronary perfusion pressure immediately after the onset of cardiopulmonary resuscitation and resulted in better 24-hour neurological outcome.

Keywords Cardiac arrest • Cardiopulmonary resuscitation • Asphyxia • Levosimendan • Neurological outcome

Introduction

Asphyxia is one of the major causes of cardiac arrest in adults and the most common cause in children. Asphyxial cardiac arrest (ACA) differs from ventricular fibrillation (VF) in the progression to complete ischaemia; it is gradual in asphyxia and sudden in VF. In ACA, anoxia results in more severe myocardial injury and diffuse microcirculation disturbances,

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complicating the resuscitation efforts and aggravating post-resuscitation myocardial dysfunction [1].

Until now, the evidence on the pathophysiology and treatment of ACA has remained scarce. As no specific guidelines exist, immediate restoration of ventilation with supplemented oxygen is the most important therapy. Of note, the role of current inotropic/vasopressor administration during CPR is increasingly challenged. Although the International Liaison Committee on Resuscitation recommends adrenaline as the main vasopressor during cardiopulmonary resuscitation (CPR) and vasopressin as an alternative option, their combination has been associated with better outcomes than epinephrine alone [2–4]. However, the limited success in the treatment of ACA and the poor neurological outcomes attributed to post-cardiac arrest brain injury suggest that more effective treatment is required [5].

Levosimendan is a calcium sensitiser developed for intravenous use in hospitalised patients with acutely decompensated heart failure. Clinical data show that levosimendan improves haemodynamics, exerts cardioprotective effects on cardiomyocytes, and decreases mortality rates [6–9]. Moreover, this agent has been used in combination with adrenaline in experimental VF, improving initial resuscitation success [10], while the combination of adrenaline, atenolol, and levosimendan was shown to improve 48-hour survival and post-resuscitation cardiac function in a swine model of cardiac arrest [11]. Although levosimendan has shown promising results in VF cardiac arrest, its effect on ACA has not been studied. The aim of the present study was to assess whether the combination of adrenaline and levosimendan would improve initial resuscitation success, 24-hour survival, and neurologic outcome compared with adrenaline alone in a swine model of ACA.

Material and Methods

The study was approved by the General Directorate of Veterinary Sciences (permit no K/309/8-3-2011) according to Greek legislation regarding ethical and experimental procedures, while the work described has been carried out in accordance with the EU Directive 2010/63/EU for animal experiments. The experimental protocol has been previously described [12]. In brief, 20 healthy male Landrace/Large-White piglets, with an average weight of 19±2 kg, aged 12 to 15 weeks comprised the study population. The animals were fasted overnight but had free access to water.

Animals were premedicated with intramuscular injection of 10 mg/kg ketamine hydrochloride, 0.5 mg/kg midazolam, and 0.05 mg/kg atropine sulfate, as previously described [13]. The marginal auricular vein was catheterised and anaesthesia was induced with an intravenous bolus dose of propofol 1% (2 mg/kg) and fentanyl (2 μg/kg). Animals were intubated with a 5.0 endotracheal tube (MLT^{TM} 5.0 Oral, 27 mm, Mallinckrodt Medical, Athens, Greece). Animals were immobilised in the supine position on a surgical table and connected to a ventilator (Alpha Delta lung ventilator; Siare, Bologna, Italy). All animals were volume controlled, ventilated with 21% oxygen and a total tidal volume of 15 ml/kg. End-tidal CO_2 ($ETCO_2$) pressure was monitored (Nihon Kohden Corp., Italy), and the respiratory rate was adjusted to maintain an $ETCO_2$ of 35 to 40 mm Hg. Anaesthesia was maintained with continuous infusion of propofol (5 mg/kg/hour) and remifentanyl (20 μg/kg/hour), while muscle relaxation was achieved with rocuronium (0.3 mg/kg/hour). Non-invasive monitoring (Datascope Expert DS-5300 W ECG; Fukuda Denshi, Tokyo, Japan) also included electrocardiogram and pulse oximetry.

For measurement of aortic pressures, an arterial catheter (Model 6523, USCI CR; Bart Inc, Papapostolou, Athens, Greece) was inserted into the aorta via the right common carotid artery. Mean arterial pressure (MAP) was determined by the electronic integration of the aortic blood pressure waveform and was calculated electronically. The internal jugular vein was surgically prepared and a Swan-Ganz catheter (Opticath 5.5 F, 75 cm; Abbott, Ladakis, Athens, Greece) was inserted into the right atrium, for continuous measurement of right atrial pressure. Coronary perfusion pressure (CPP) was electronically calculated as the difference between minimal aortic diastolic pressure (DAP) and the simultaneously measured right atrial diastolic pressure. After surgical preparations, the animals were observed for 20 minutes.

Before the experimental procedure, the piglets were randomly assigned to two different groups of 10 subjects each, according to the agents used, by means of a sealed envelope. At the onset of CPR, the control group (Group A) would receive an IV push of epinephrine (0.02 mg/kg) plus 10 mL saline as placebo, whereas the levosimendan group (Group B) would receive an IV push of epinephrine (0.02 mg/kg) plus levosimendan (0.012 mg/kg) [11].

Asphyxial cardiac arrest was induced by endotracheal tube clamping, as previously described, while cardiac arrest was defined as a MAP of less than 10 mmHg and by the absence of aortic pulsations [12]. At the onset of cardiac arrest, infusion of drugs was discontinued. After four minutes of ACA, the endotracheal tube was unclamped and cardiopulmonary resuscitation (CPR) was immediately initiated according to the 2010 European Resuscitation Council Guidelines on resuscitation with ventilation in 100% oxygen and 10 breaths delivered asynchronously with chest compressions at a rate of 100/min (LUCAS; Jolife, Lund, Sweden) [14,15]. A 20-mL flush of isotonic sodium chloride solution was followed after each drug administration. In case of VF or pulseless ventricular tachycardia, defibrillation was attempted with a 4 J/kg monophasic waveform shock delivered between the right infraclavicular area and the cardiac apex (Primedic Defi-B Defibrillator; Metrax GmbH, Rottweil, Germany). The investigators involved in data recording, data entry, and data analysis were blinded to each animal's allocation, while the resuscitation team was blinded to placebo versus levosimendan interventions.

Successful resuscitation was defined as return of spontaneous circulation (ROSC) with a MAP of at least 60 mm Hg for a minimum of 10 minutes. When ROSC was achieved,