

Levosimendan in Asphyxia-Induced Cardiac Arrest Model

Asfiksiye Bağlı Oluşan Kardiyak Arrest Modelinde Levosimendan

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Submitted / Başvuru tarihi: 26.08.2008 Accepted / Kabul tarihi: 25.09.2008

Objectives: We hypothesized in this study that levosimendan could be used as a single agent in asphyxia-related cardiac arrest resuscitation in experimental rabbit model.

Patients and Methods: Fourteen New Zealand white rabbits were intubated with 3F intubation tube. Pancuronium bromide (0.2 mg/kg) was administered intravenously. The lungs were ventilated with tidal volume 8 ml/kg, frequency 38 /min; PEEP 1 cmH₂O, FiO₂ 0.21. Cardiopulmonary resuscitation (CPR) was carried out after four minutes of cardiac arrest. Animals were randomized to either control or levosimendan groups. Baseline arterial blood gases, heart rates, systolic and diastolic arterial pressures, and post-resuscitation heart rates, systolic and diastolic arterial pressures, blood gas analysis and troponin I levels after 30 minutes of return of spontaneous circulation were recorded.

Results: Baseline data was similar in the groups. There were five animals which responded to CPR in both groups. Blood gas analysis, heart rates in the 30th minute and CPR times of the animals were similar in the groups. Blood pressures were significantly higher in levosimendan-treated group (p<0.05). Myocardial injury demonstrated by troponin I levels was similar in the groups.

Conclusion: Levosimendan alone may not be used as a resuscitation agent in asphyxia-induced cardiac arrest, but it has positive effects on maintenance of arterial pressures.

Key words: Asphyxia; cardiac arrest; cardiopulmonary resuscitation; levosimendan.

Amaç: Bu çalışmada asfiksiye bağlı oluşan kardiyak arrestin deneysel tavşan modelinde resüsitasyonunda levosimendanın tek başına kullanılabileceği hipotezi öne sürülmüştür.

Hastalar ve Yöntemler: On dört Yeni Zelanda türü beyaz tavşan 3F entübasyon tüpüyle entübe edildi. İntravenöz pankuronyum bromid (0.2 mg/kg) uygulandı. Akciğerler tidal volüm 8 ml/kg, frekans 38 /min; PEEP 1 cmH₂O, FiO₂ 0.21 ile ventile edildi. Dört dakikalık kardiyak arresti takiben kardiyopulmoner resüsitasyona (KPR) başlandı. Hayvanlar kontrol ve levosimendan tedavi gruplarına randomize edildi. Arteriyel kan gazı, kalp hızı, sistolik ve diyastolik kan basınçları ve resüsitasyon sonrası spontan dolaşımın dönmesinden 30 dakika sonrası kalp hızı, sistolik ve diyastolik kan basınçları, arteriyel kan gazı ve troponin I düzeyleri ölçüldü.

Bulgular: Baz değerler gruplarda benzerdi. Her iki grupta resüsitasyona cevap veren beş hayvan vardı. Arteriyel kan gazları, kalp hızları ve KPR süreleri iki grupta benzerdi. Kan basınçları levosimendan tedavisi uygulanan grupta belirgin olarak fazlaydı (p<0.05). Troponin I ile gösterilen miyokardiyal hasar her iki grupta benzerdi.

Sonuç: Levosimendan asfiksiye bağlı oluşan kardiyak arrestin resüsitasyonunda tek başına kullanılamaz, ancak arteriyel basınçların idamesinde olumlu etkileri mevcuttur.

Anahtar sözcükler: Asfiksi; kardiyak arrest; kardiyopulmoner resüsitasyon; levosimendan.

Asphyxial causes of cardiac arrest, resulting from airway obstruction or failure of ventilation, account for the vast majority of instances of cardiac arrest in pediatric victims.^[1] Asystole constitutes approximately one-third of arrests in adults, and is more common than ventricular fibrillation in those aged 18-35 years old. Hypoxia is an important and reversible cause of asystole which may lead to death or severe brain injury in case of failure to maintain a patent airway and oxygenation. Hypoxic crises progress through bradycardia and lead to asystole. In emergency practice, data strongly demonstrate that asystole is a resuscitatable dysrhythmia.^[2] Outcome in primary asystolic cardiac arrest is better than when end-stage asystole develops following ventricular fibrillation.^[3]

Levosimendan belongs to a new class of inotropes, which stabilize the interaction between calcium and troponin C, thus improving myocardial inotropic response. In addition to its cardiac effects, levosimendan is also a vasodilator.^[4] It was demonstrated that the vasodilatation by levosimendan may be partially related to a lowering of intracellular free calcium through potential inhibition of phosphodiesterase III, calcium desensitization, or opening of adenosine triphosphate-sensitive potassium channels.^[5,6] It is reported that a single dose levosimendan administration seems to have anti-inflammatory and anti-apoptotic properties, reducing circulating proinflammatory cytokines and soluble apoptosis mediators.^[7] We postulated that levosimendan could be used as a single agent for resuscitation of asphyxia related cardiac arrest because of its myocardial inotropic effects and we designed an experimental study to prove this.

PATIENTS AND METHODS

The investigation conforms with the Guide for the Care and Use of Laboratory Animals published by the US National Institutes of Health (NIH Publication No. 85-23, revised 1996). The study was approved by the Animal Research Ethics Committee.

Animals and instrumentation

Experiments were performed on 14 New Zealand white rabbits of both sexes, each weighing about

3 kg. Anesthesia was induced by intramuscular ketamine (50 mg/kg) and xylazine. A catheter (24 gauge) was placed in an ear vein to give maintenance fluid of 0.9% NaCl (20 ml/h). An arterial catheter (20 gauge) was placed in an ear artery to monitor blood pressure (Petaş Kma 375). The animals were intubated with a 3F intubation tube. The depth of anesthesia was confirmed by the absence of response to paw clamp.

Limb lead II electrocardiograms were recorded with subcutaneous limb electrodes (right and left upper, right lower). Pancuronium bromide (0.2 mg/kg) was administered intravenously. The lungs were ventilated (Tidal volume (VT): 8 ml kg⁻¹, frequency: 38 min⁻¹; PEEP: 1 cmH₂O; FiO₂: 0.21) using a time-cycled, volume-cycled ventilator (Galileo Hamilton Medical). Ringer's lactate of 20 ml min⁻¹ was given. Experimental animals were randomized to either control (saline solution) or levosimendan-treated cardiac arrest groups.

Baseline arterial blood gases were measured (Cobas B221) after 10 minutes of ventilatory support. Heart rates, systolic and diastolic arterial pressures, pCO₂, PO₂, pH, O₂ saturation and lactic acid levels were recorded.

Cardiac arrest and resuscitation

Cardiac arrest was induced by disconnecting the intubation tube from mechanical ventilation. Cardiac arrest was defined by a mean arterial pressure of 10 mmHg measured. Time to loss of aortic pressure waveform fluctuation (pulseless electrical activity or asystole) was defined as the period between ventilator disconnection and cardiac arrest. Cardiopulmonary resuscitation (CPR) was carried out after 4 minutes of cardiac arrest by turning on the ventilator (FiO₂: 1.0; tidal volume: 8 ml.kg⁻¹; rate: 38 min⁻¹), manual antero-posterior compression of the animal thorax (150 min⁻¹) and levosimendan infusion with a loading dose of 20 microgram.kg⁻¹ in 10 minutes and maintenance dose of 0.4 microgram.kg⁻¹ in levosimendan-treated group and normal saline solution in control group. Maintenance doses were continued throughout the experiment. Successful resuscitation was defined as the period from commencement of resuscitation

Table 1. Baseline blood gas analysis and other data of the animals

	Levosimendan group #7	Control group #7	<i>p</i>
Heart rate (beat.min ⁻¹)	131±3	130±7	0.654
Systolic TA (mmHg)	85±5	82±5	0.275
Diastolic TA (mmHg)	54±3	50±5	0.110
PCO ₂ (mmHg)	35±3	34±3	0.367
PO ₂ (mmHg)	73±8	71±8	0.701
PH	7.38±0.03	7.39±0.03	0.796
O ₂ saturation (%)	93±2	92±2	0.437
Lactic acid (mmol/L)	1.63±0.56	1.54±0.56	0.749
PEA time (min)	1.4±0.5	1.4±0.5	1.000
Successful CPR	5	5	1.000

PEA: Pulseless electrical activity.

to achieving a mean arterial pressure of at least 50 mmHg. Resuscitative efforts were discontinued if spontaneous circulation did not occur within 5 minutes of commencement of chest compressions. Time of CPR was noted.

Post-resuscitation ventilatory support and monitoring

The lungs were ventilated (VT: 8 ml.kg⁻¹; frequency: 38 min⁻¹; PEEP: 1 cm H₂O; FiO₂: 1.0), and the animals received a maintenance infusion of either saline or levosimendan. Heart rates, systolic and diastolic arterial pressures, pCO₂, PO₂, pH, O₂ saturation and lactic acid levels and

Table 2. Data of the animals which responded to CPR

	Levosimendan group #5	Control group #5	<i>p</i>
Heart rate (beat.min ⁻¹)	142±14	144±13	0.834
Systolic TA (mmHg)	76±4	66±5	0.016*
Diastolic TA (mmHg)	43±3	36±4	0.021*
PCO ₂ (mmHg)	35±4	37±5	0.462
PO ₂ (mmHg)	118±13	117±11	0.917
PH	7.33±0.04	7.33±0.03	0.753
O ₂ saturation (%)	99±1	98±1	0.511
Lactic acid (mmol/L)	4.10±1.08	3.80±1.27	0.675
CPR time (min)	3.2±1.3	3.6±1.1	0.590
Troponin I (ng/ml)	0.98±0.23	1.03±0.19	0.753

**p*<0.05; CPR: Pulseless electrical activity.

troponin I levels were recorded after 30 minutes of return of spontaneous circulation.

Statistical analysis

Results were presented as mean ± standard deviation. Statistical analysis was performed using the Mann-Whitney U test. Probabilities of 0.05 or less were considered to be statistically significant. Response to CPR between the groups was analyzed by Fischer's exact test.

RESULTS

Baseline blood gas analysis of the animals, heart rates, and arrest times were similar in the groups. Hemodynamic parameters (systolic and diastolic arterial pressures) did not differ between the groups. Response to CPR was also similar in the groups (Table 1).

There were five animals which responded to CPR in each group and this was not statistically significant. The unsuccessful CPR animals were excluded from the groups and the remaining five animals' post manipulation data were analyzed. Blood gas analysis of the animals in the 30th minute did not differ in the groups. Heart rates and CPR times were similar in the groups. The systolic and diastolic arterial pressures were significantly higher in the levosimendan-treated group (*p*<0.05) (Table 2). Myocardial injury which was demonstrated by troponin I levels was also similar in the groups.

DISCUSSION

The primary postulation of the study was not proved with the data gathered which meant that resuscitation of the asphyxia-induced cardiac arrest with only levosimendan was not superior to normal saline solution in case of CPR success, blood gas analysis, myocardial injury and CPR times. On the other hand, the present study proved that maintenance of arterial pressure was better with levosimendan, that is, post-CPR systolic and diastolic arterial pressures were higher in the levosimendan-treated group. The asphyxial model which resulted in cardiac arrest simulated the cardiac arrests in most of the airway-associated cardiac arrests.^[8] The quality of organ function following successful cardiopulmonary resuscitation can be related to an inter-

action of several factors: the type of arrest, e.g. primary ventricular fibrillation versus asphyxia, pre-existing disease, injury incurred during the arrest (duration of no flow) and the direct effects of resuscitative interventions, i.e. catecholamines and defibrillation. 4-min versus 8-min asphyxial cardiac arrest has shown comparable degrees of early left ventricular systolic dysfunction, but better early systolic recovery following the less protracted asphyxial period. On the other hand, 8 min of asphyxial arrest has shown in more pronounced diastolic pathology.^[2] In our study 4-min asphyxia was used on the animals. Catecholamines were not used in the CPR medications. The only agent was levosimendan. Epinephrine was reported to impair hemodynamics, cause myocardial damage, and worsen survival in an in vivo rat model. However, resuscitation was commenced 1 minute after onset of cardiac arrest in that study.^[9] Therefore we did not use epinephrine or other catecholamines in our study. The results demonstrated similar survivals after CPR. However arterial pressures were higher in levosimendan group.

There is limited number of studies concerning the effects of levosimendan in CPR. Levosimendan has improved post-resuscitation myocardial function in pig model and is reported to serve as an alternative to dobutamine as an inotropic agent for management of post-resuscitation myocardial dysfunction.^[10] Our study showed a better cardiac function after CPR with levosimendan. It has positive effects on maintenance of arterial pressure in case of successful CPR. The systolic and diastolic arterial pressures were significantly higher in the levosimendan-treated group although response to CPR was similar. However, myocardial injury marker did not show a significant difference with levosimendan. The present study is the only study which concerns the effects of levosimendan in asphyxia-induced cardiac arrest.

In conclusion, the data gathered in the present study may not have significant implications

for resuscitative therapeutics. But it may be concluded that levosimendan may not be used alone as a positive inotropic agent in asphyxia-induced cardiac arrest; however, it has positive effects on maintenance of arterial pressure probably in case of successful CPR.

Limitations

The investigators were not blinded to whether the infusion was saline or experimental drug.

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