

Evidence Suggesting the Beneficial use of Magnesium in Cerebral Ischaemia in an Experimental Model of Cardiac Arrest

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Abstract: *Introduction:* Brain damage is one of the major causes of morbidity and mortality in cardiac arrest victims. The aim of the present study was to determine whether administration of magnesium during cardiopulmonary resuscitation would improve post-resuscitation cerebral injury, as indicated by cerebral ischaemia markers and neurological alertness score.

Methods: Ventricular fibrillation was induced in 24 piglets, left untreated for 5 min before attempting resuscitation. Animals were randomised into 2 groups to receive saline as placebo + adrenaline (Group A) or magnesium sulphate + adrenaline (Group B) during cardiopulmonary resuscitation. Blood samples were collected in the post-resuscitation phase to measure NSE and S-100. Neurological alertness score was assessed 48h after the return of spontaneous circulation.

Results: S-100 and NSE values increased significantly in all resuscitated animals in the observation phase. However, S-100 and NSE values in Group B were statistically lower than those measured in Group A during the whole post-resuscitation period. Neurological outcome was better in Group B animals.

Conclusion: Magnesium may exert neuroprotective effects in cerebral ischaemia, caused by experimental cardiac arrest.

Keywords: Ventricular fibrillation, magnesium, NSE, S-100, neurological outcome.

1. INTRODUCTION

Cardiac arrest (CA) is responsible for 700,000 deaths per year in Europe [1]. Brain damage is one of the major causes of morbidity and mortality in CA victims. The cessation of cerebral perfusion after CA leads to global hypoxic-ischaemic brain damage due to death of neuronal and glia cells and loss of the integrity of the blood-brain barrier.

During recent years, great attention has been given to the levels of two molecular factors: neuron-specific enolase (NSE), and a protein soluble in 100% ammonium sulphate (S-100). These molecular factors correlate with neurological outcome of CA victims [2].

Magnesium has been shown to cause central arteriolar vasodilation and to act against vasospasm in the central nervous system [3]. This effect could be therapeutic against the no-flow phenomenon, often encountered in CA victims [4]. The aim of the present study was to determine whether administration of magnesium during cardiopulmonary resuscitation (CPR) would improve post-resuscitation cerebral injury, as indicated by brain ischaemia markers and by a neurological alertness score.

2. MATERIALS AND METHODOLOGY

The experimental protocol was approved by the General Directorate of Veterinary Services (permit no 445/14-1-2005). Twenty four piglets (*Landrace/Large White*) of both

sexes were included in this study. The experimental protocol has already been described [5].

Briefly, the animals were premedicated with the use of intramuscular injection of 10 mg/kg ketamine hydrochloride, 0.5 mg/kg midazolam, and 0.05 mg/kg atropine sulphate. Anaesthesia was induced with an intravenous bolus dose of propofol (2.0 mg/kg). While the pigs were breathing spontaneously, they were intubated with a 4.5 endotracheal tube. Additional 1mg/kg propofol, 0.15 mg/kg cis-atracurium and 4µg/kg fentanyl were administered afterwards. The animals were then connected to the automatic volume-controlled ventilator (ventiPac Sims pneuPac, Greece) with 21% Oxygen (FiO₂ 21%). End-tidal CO₂ was monitored with a side-stream infrared CO₂ analyzer (Nihon Kohden Corp). The respiratory frequency was adjusted to maintain PETCO₂ 35-40 mmHg. Propofol and cis-atracurium were administered to maintain adequate anaesthetic depth. Fentanyl was administered when the cardiac rate was more than 120 bpm and/or the systolic blood pressure over 130 mmHg.

Electrocardiographic monitoring (ECG) (Mennen Medical, Envoy, Greece) and pulse oximetry (SpO₂) (Vet/Ox Plus 4700, Greece) were performed as previously described [6]. In order to detect changes in cerebral oxygenation, near infrared spectroscopy (NIRS) was utilised (Somanetics INVOS Cerebral Oximeter, Model SPFB Paediatric Somasensor SOMANETICS). The optodes of NIRS were mounted on the intact skin covering each cerebral hemisphere. For optimal spatial resolution, the interoptode distance was set to 5 cm. Data was recorded every 10 seconds after induction of anaesthesia and for the duration of CA and resuscitation. The de-

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vice calculated the regional cerebral oxygen saturation (rSO₂).

The right common carotid artery was surgically prepared and dissected. Afterwards, a fluid-filled (model 6523, USCI CR, Bart Inc, Greece) arterial catheter was inserted into the aorta for measurement of the aortic pressure. Mean arterial pressure (MAP) was determined electronically. When the right internal jugular vein was surgically prepared, a Swan-Ganz catheter (Opticath 5.5 F, 75 cm Abbott, Ethicon Mer-silk™, Greece) was inserted into the right atrium and right atrial pressure was measured continuously. Coronary perfusion pressure (CPP) was electronically calculated as the difference between minimal aortic diastolic pressure and the simultaneously measured right atrial diastolic pressure. The left internal jugular vein was also surgically prepared in order to advance a 5F flow-directed pacing catheter (Pacel™; 100cm, St. Jude Medical, Greece) into the apex of the right ventricle.

The animals were randomized into two groups with the use of a sealed envelope, indicating the animal's assignment to 1 of 2 Groups; Group A: saline as placebo (10 ml dilution bolus) + adrenaline (0.02 mg/kg). Group B: magnesium sulphate (0.15 mg/kg/10 ml dilution bolus) + adrenaline (0.02 mg/kg). All the investigators were blinded as to the medication used except the principal investigator who did not take part in any experimental procedure.

Ventricular fibrillation (VF) was induced with a 9V ordinary lithium battery as previously described [7] and the animals were left untreated for 5 minutes. Immediately afterwards drugs according to the animal's Group were injected to the marginal auricular vein and resuscitation procedures started with oxygen (FiO₂100%) and precordial compressions with a mechanical chest compressor (LUCAS™ Chest Compression System, Jolife AB, Mantzaris, Greece) for 2 minutes. Defibrillation was then attempted with a 4 J/kg monophasic waveform shock (PortaPak/90-Medical research laboratories inc., Greece). If the cardiac rhythm was not compatible with a pulse, precordial compression was resumed for 2 min. Successful resuscitation was defined as the return of spontaneous rhythm with a MAP of at least 60 mmHg for a minimum of 5 min.

Endpoints of the experiment were defined as: i) asystole and ii) return of spontaneous circulation (ROSC). The ani-

mals who restored spontaneous circulation were monitored for 240 min, while anaesthesia was maintained. After 4h of post-resuscitation monitoring, the intravenous infusions of cis-atracurium and propofol were discontinued. All catheters were removed using a surgical technique as previously described [6]. The ventilator was switched off and the animals were ventilated by manual squeezing of the reservoir bag (FiO₂ 100%). Atropine 0.2mg/Kg followed by neostigmine 0.05 mg/Kg were administered after the first spontaneous swallowing reflex was detected. The animals were extubated after adequate depth of inspiration was ascertained and the SpO₂ measurement was > 97%. Following the appearance of the righting reflex, each animal was returned to its enclosure. Each parameter of neurological alertness [8] of the surviving animals was scored 48h after ROSC. After the final measurements were completed, the animals were euthanised by a fatal overdose of thiopental.

Blood samples were collected at 60, 120 and 240 min in the post-resuscitation phase in order to measure NSE and S-100. The blood was then centrifuged at 3000 rpm for 10 min and the serum was stored in liquid nitrogen at -70°C. The assessment of S-100 and NSE serum concentrations was performed by an immunolumi-nometric assay, using a LIAISON analyser (LIAISON Sangtec 100^R, Manufacturer. AB Sangtec Medical, P.O. Box 20045, S-16102-BROMMA). All assays were performed in a blinded manner. The total number of ventricular ectopic beats was counted over an interval of 30 min after successful resuscitation as previously described [9].

Measured and derived haemodynamic data over time were analysed, using SPSS 13.0 for Windows. One-sample Kolmogorov-Smirnov Z tests were used to test whether variables within each group are normally distributed. As none of the variables were found to be normally distributed, Mann-Whitney U tests were used in order to test whether the two groups were significantly different at each stage of the experiment. Outcome differences between each sample were analysed with the use of paired t-test. On all tests, p values <0.05 were considered statistically significant.

3. RESULTS

Baseline haemodynamic measurements did not differ between the two groups, as shown in Table 1. By the end of the 5th minute of VF, MAP decreased from 89.3±7.6mmHg

Table 1. Baseline Hemodynamic Measurements; SpO₂=Saturation of Peripheral Oxygenation, rSO₂= Regional Cerebral Oxygen Saturation

	Group A	Group B	P
Heart Rate (bpm)	108.4±17.5	111.4±13.4	NS
Systolic Blood Pressure (mmHg)	104.3±8.0	110.4±18.3	NS
Diastolic Blood Pressure (mmHg)	77.6±11.6	86.0±13.7	NS
Mean Arterial Pressure (mmHg)	89.3±7.6	94.9±8.8	NS
Mean Right Atrial Pressure (mmHg)	11.1±1.4	10.7±2.2	NS
SpO ₂ (%)	91.1±3.9	94.0±1.9	NS
Coronary Perfusion Pressure (mmHg)	67.2±11.1	76.9±14.5	NS
rSO ₂ (%)	61.1±2.5	61.2±2.0	NS

Table 2. Post-Resuscitation Dysrhythmias; PVC = Premature Ventricular Contractions, VT = Ventricular Tachycardia

	PVC	Salvos	Episodes of VT
Group A	76±25	16±4	22±7
Group B	24±23	8±5	8±2
P	<0.05	<0.05	<0.05

to 22.5±3.3 mmHg in group A, and from 94.9±8.8mmHg to 21.8±2.4 mmHg in Group B (p=NS). CPP declined rapidly and remained between 0 and 3mmHg in both Groups.

All animals, but one in Group A, were successfully resuscitated. The deceased animal was excluded from further statistical analysis. Just before the first defibrillation attempt, no significant differences in haemodynamic parameters between the 2 groups were observed. However, there was a trend toward lower aortic systolic pressure (Group A: 76.5±13.0, Group B: 70.9±11.3), aortic diastolic pressure (Group A: 36.5±4.5, Group B: 31.2±6.8) and CPP (Group A: 19.7±7.0, Group B: 16.7±9.0) in Group B.

All animals were monitored for 4 hours. Post-resuscitation heart rate, blood pressures and right atrial pressure of both groups did not differ significantly during the whole post-resuscitation phase. However, ventricular ectopy was minimized in Group B, as shown in Table 2. rSO₂ values in Group B were significantly higher at the 2nd min of CPR and remained significantly higher during the first 5 min of ROSC (Fig. 1). S-100 and NSE values increased significantly in all resuscitated animals in the observation phase. However, S-100 and NSE values in Group B were statistically lower than those measured in Group A during the whole post-resuscitation period (Fig. 2, 3). Furthermore, a significant negative correlation was found between rSO₂ and S-100 (r=-0.71, p<0.05) and NSE (r=-0.64, p<0.05) respectively, during the whole post-resuscitation phase. Finally, animals in Group B scored higher in a neurological assessment scale than animals in Group A (p<0.05) (Fig. 4).

4. DISCUSSION

Global interruption of the cerebral circulation causes general brain oedema and selective neuronal death in vulnerable areas of the brain, whereas a period of extended anoxia time leads to infarction in the cortical and subcortical regions [2, 10]. Meanwhile, ischaemic reperfusion injury in patients resuscitated after CA is known to damage organs subsequently, as neutrophils, activated by proinflammatory cytokines, infiltrate visceral interstitial spaces and occasionally damage visceral tissues and cells [11-13]. It is thus conceivable that organ damage by reperfusion injury influences the outcome of resuscitated patients [14]. During cerebral ischaemia, there is also excessive activity of amino acids, especially glutamate. When the glutamate receptors are activated, the intracellular calcium increases. This leads to activation of intracellular enzymes and neuronal death [15].

NSE is a dimer intracellular enzyme of glucose metabolism and occurs as $\gamma\gamma$ -enolase in neurons and as $\alpha\gamma$ -enolase in neuroendocrine cells and in small lung cancer cells [16]. Several authors have demonstrated that different cerebral diseases such as ischaemic stroke, meningoencephalitis and head injury cause an elevation in the serum concentration of NSE [17, 18]. Measurement of NSE may supplement clinical cerebral assessment after CA and successful resuscitation [19]. Even though its prognostic value in the assessment of comatose patients recovering from CA is still under debate, several studies have concluded that a NSE rise usually occurs early in victims of CA.

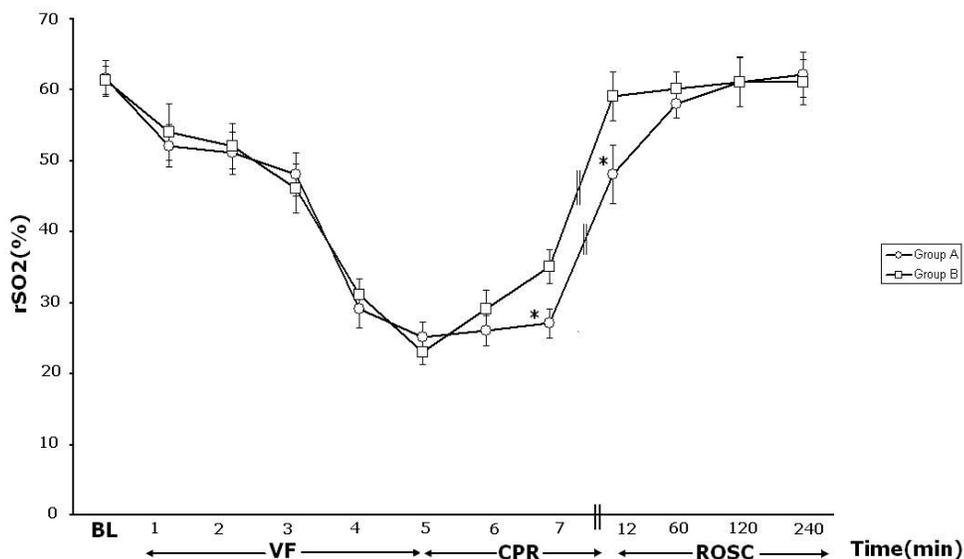


Fig. (1). rSO₂ fluctuation during the experiment. *= $p<0.05$ Group A versus Group B. VF= ventricular fibrillation, CPR= cardiopulmonary resuscitation, rSO₂= regional cerebral oxygen saturation.

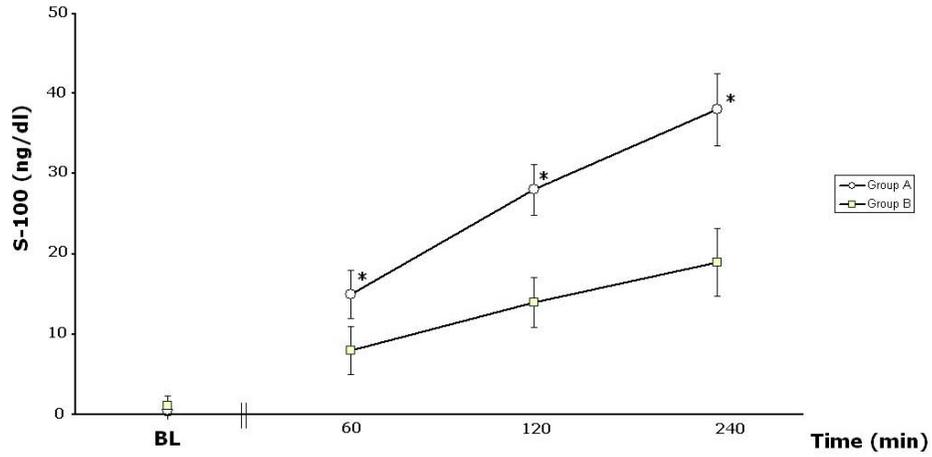


Fig. (2). S-100 fluctuation in time. *=p<0.05 Group A versus Group B. BL=baseline.

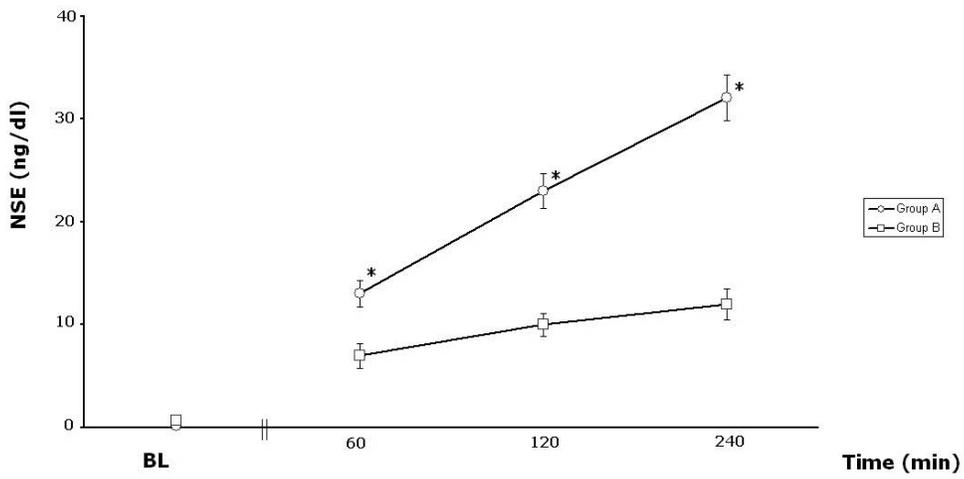


Fig. (3). NSE fluctuation in time. *=p<0.05 Group A versus Group B. BL=baseline.

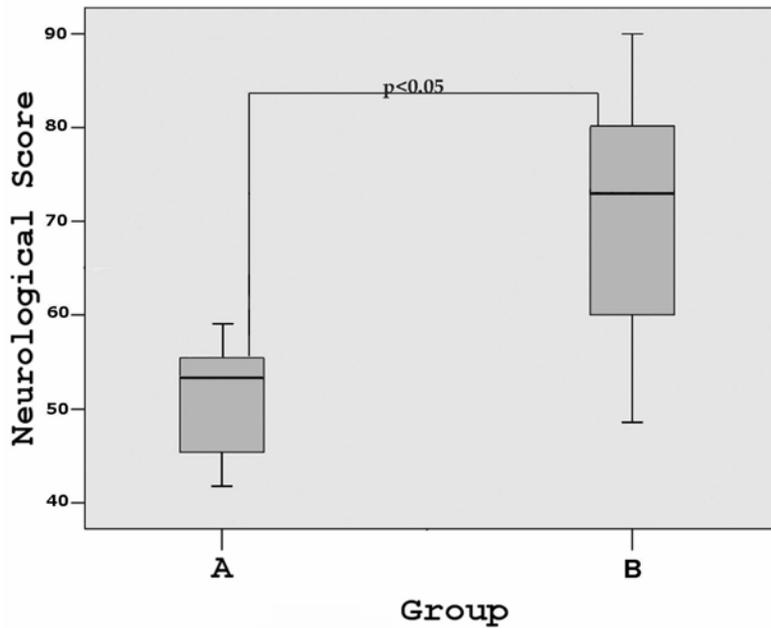


Fig. (4). Neurological alertness score in both Groups.

S-100 is a dimer intracellular calcium-binding protein with the heterodimer S-100a occurring in melanocytes and glia cells and the homodimer S-100b in glia and Schwann's cells [20]. Elevated serum levels of S-100 have been observed after ischaemic stroke, meningoencephalitis and head injury. Several clinical studies have shown that increased serum concentrations of protein S-100 predict ischaemic brain damage after cardiac surgery. S-100 may also be released from the heart or other injured tissue, indicating that S-100 has a heterogeneous cerebral and extracerebral release pattern [21]. The implication of the protein in CA patients has been recently pointed out, as a rise in S-100 indicated severe cerebral damage and poor neurological recovery [22]. Our study has confirmed that NSE and S-100 rise occur early in the post-resuscitation phase and continue to rise 4 hours after CA.

NIRS is a non-invasive and easily applicable technique that might help to prognosticate outcome and offers new insights into monitoring cerebral oxygenation after CA. A clinical study by Mullner *et al.* has shown that low rSO₂ readings after CA are associated with a higher mortality [23]. In another clinical study, rSO₂ appears to be correlated to electroencephalogram (EEG), in patients undergoing surgery for cardioverter-defibrillator implantation. When circulatory arrest occurred, rSO₂ measurements decreased rapidly, following the changes of the EEG waveform. After recovering from circulatory arrest, EEG waveform normalized and rSO₂ turned to baseline values [24]. In addition, Shahand *et al.* concluded from their study in volunteers that rSO₂ may serve as a reliable indicator of changes in brain oxygenation induced by hypoxaemia [25]. Furthermore, there is great evidence that the use of NIRS is essential to detect malperfusion of the frontal lobes of the cerebral hemispheres [26]. These are in accordance with our findings, where rSO₂ values decreased rapidly in the course of VF and rose during CPR, reaching baseline values early in the post-resuscitation phase.

Magnesium has a voltage-gated antagonist action on the N-methyl-D-aspartate (NMDA) receptor. Interest has focused on the role of NMDA receptor antagonists in the protection of the central nervous system from ischaemic damage [27]. There has been keen interest in the use of magnesium as a potential neuroprotective intervention. In a study in newborn piglets, magnesium preserved NMDA receptor binding properties and maintained ionic homeostasis by attenuating the reduction in Na⁺/K⁺-ATPase activity [28].

Furthermore, administration of magnesium to newborn piglets prevented hypoxia-induced modification of neuronal nuclear membrane function that leads to intranuclear Ca²⁺ dependent transcription of apoptotic proteins leading to hypoxic neuronal programmed cell death [29].

According to a systematic review of currently available pharmacological neuroprotective agents in CA, the use of magnesium seems to be effective in global and focal cerebral ischaemia, both in animal studies and in clinical trials. Amighi *et al.* investigated the prognostic impact of magnesium serum levels with respect to the occurrence of neurological events in patients with advanced atherosclerosis and found that low magnesium serum levels indicate an increased risk for neurological events in patients with symptomatic peripheral artery disease [30]. Also, magnesium ther-

apy might be efficient as a prophylactic adjacent therapy in acute lacunar stroke syndrome and after aneurismal subarachnoid haemorrhage to reduce the risk for poor outcome [31, 32]. Moreover, several animal studies have demonstrated a protective effect of magnesium in focal ischaemia after temporary or permanent cerebral artery occlusion [33, 34]. In a trial of Lee *et al.* male rats (*Sprague-Dawley*) were subjected to right middle cerebral artery occlusion for 90 minutes followed by 72 hours of reperfusion. Administration of magnesium at the commencement of reperfusion enhanced electrophysiological and neurobehavioural recovery and reduced brain infarction after cerebral ischaemia-reperfusion [35]. This is in agreement with our study that demonstrated that magnesium may have some neuroprotective effect following CA, as indicated by biochemical markers of cerebral ischaemia, supported further by rSO₂ values and by the neurological alertness score.

There are some studies that question routine use of magnesium in resuscitation. In the study of Thel *et al.* there was no improvement in survival or hospital discharge in patients with in-hospital cardiac arrest who were treated with magnesium supplementation compared to placebo. However, if the quality of life in survivors was specified as the primary endpoint, this trial would have had a positive result, which suggests that magnesium may have a protective cerebral effect [36]. Regarding out-of-hospital CA, 3 randomized studies failed to prove any beneficial outcome in survival and/or neurological outcome in patients who received magnesium sulphate [37-39]. However, in these studies the quality of chest compressions was not standardized adding a significant bias in their results. The use of magnesium has not been proven to exert any marked effects on diastolic aortic pressure and CPP [40]. This was further confirmed by this experimental model where no significant difference was marked with the addition of magnesium.

Furthermore, magnesium has been safely applied to patients with a compromised left ventricular pump function [41]. In addition, it has been shown to act favourably against a number of ventricular arrhythmias [38]. Several studies have also shown that an infusion of magnesium can reduce the incidence of arrhythmias occurring after acute myocardial infarction [42]. This swine experimental model demonstrated that the incidence of ventricular ectopy was significantly lower in the magnesium-treated group.

The authors recognise several limitations in this preliminary experimental study. The number of animals is relatively small, and the experiment was conducted on apparently healthy pigs. Furthermore, in this experimental model, no neurological deficit score was assessed, and the ischaemic cerebral damage was mainly based on indirect markers and measurements.

Within these limitations, the authors conclude that magnesium may exert neuroprotective effects in cerebral ischaemia, caused by CA. However, more research is essential to further clarify the potential beneficial effects of magnesium.

5. CONCLUSIONS

Magnesium sulphate, when administered during CPR, does not adversely affect ROSC, minimizes ventricular ectopic beats, increases rSO₂ values and exerts some neuroprotective effect as evidenced by decreased values of ischaemia

cerebral markers and by the improved neurological alertness score in this swine model of CA.

6. LIST OF ABBREVIATIONS

CA	=	Cardiac Arrest
NSE	=	Neuron Specific Enolase
S-100	=	protein soluble in 100% ammonium sulphate
CPR	=	Cardiopulmonary Resuscitation
ECG	=	Electrocardiogram
SpO ₂	=	Pulse Oximetry
NIRS	=	Near Infrared Spectroscopy
rSO ₂	=	Regional Cerebral Oxygen Saturation
MAP	=	Mean Arterial Pressure
CPP	=	Coronary Perfusion Pressure
VF	=	Ventricular Fibrillation
ROSC	=	Return of Spontaneous Circulation
EEG	=	Electroencephalogram
NMDA	=	N-methyl-D-aspartate

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