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Evaluation The Effect of Sodium Nitroprusside on Cardiopulmonary Resuscitation Outcomes in Guinea Pigs

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ABSTRACT

Background: The success rate of cardiopulmonary resuscitations (CPR) was very low during more than half a century and only a few of them had no neurological complications this study aimed to evaluation the effect of sodium nitroprusside on cardiopulmonary resuscitation outcomes in Guinea pigs.

Methods: In this randomized clinical trial, 22 Guinea pigs randomly were divided in two groups of A and B. The required drugs of standard CPR were prepared and two sample drugs with the names of A (placebo) and B(Sodium nitro perusside) were used for resuscitation. For all samples CPR processes were recorded, but in the samples that reached to ROSC the data related to O2sat, Etco2, HR and type of heart rhythm at the time of ROSC were recorded five and ten minutes after ROSC. At the end, the level of pig brain function was recorded at half, 6, 12 and 24 hours after ROSC.

Results: HR at baseline in controls was higher, after resuscitation, min 5 and min 10 in cases was a little higher but the differences were not statistically significant at baseline, after resuscitation, min 5 and min 10 ($P > 0.05$). Etco2 at baseline, after resuscitation, min 5 and min 10 among controls were higher with no significant difference ($P > 0.05$,). The differences in Spo2 between groups were not significant at baseline, after resuscitation, min 5 and min 10, whereas, after resuscitation and min 5 in controls was a little higher, and in min 10 in cases it was a little higher ($P > 0.05$).

Conclusion: Administration of sodium nitroprusside during standard CPR in animal model after 8 minutes of untreated VF did not improved the rate of ROSC compared to standard CPR and other outcomes.

KEYWORDS Sodium Nitroprusside, Cardiopulmonary Resuscitation,

Introduction

The success rate of cardiopulmonary resuscitations (CPR) was very low during more than half a century and only a few of them had no neurological complications [1]. Under the best possible condition, if the chest pressure is done right it creates less than the 25% of normal spontaneous circulation [2]. During CPR we used various drugs such as epinephrine, which changes Fine VF to Coarse VF [3]. Although Vasoconstrictor medicines improve blood pressure but in long-term have no clear effect and in some cases reduce small blood flows and causes ischemia [2]. Despite the available perceptions high-dose of SNP during CPR does not clearly reduce central aortic pressure. When arterial vascular resistance is reduced by SNP, Forward-vascular flow clearly increases with each chest compression [4]. Previous researches have shown that when ventricular fibrillization (VF) is left untreated over 10 minutes short and long term survival drastically reduces. In animal models the available resuscitation method more than 12 -13 minutes of untreated VF cause lack of neurological improvement in long and short term [5-7]. Successful CPR in untreated VF for more than 12 to 15 minutes as a model for the assessment of right ventricular dysfunction is used after resuscitation as loss of overall movement and average EF reduction clearly in first hours and 4 hours after resuscitation [1]. Sodium Nitroprusside is a potent vasodilator that its activity is depended on the nitric oxide which plays a great role in the relaxation of vascular smooth muscle (VSM) [8]. Reinforced CPR with Sodium Nitroprusside is a method that is consisted of:

1. Active compression and decompression in resuscitation by the device, increases the threshold resistance of blood flow in various organs and increases long and short term survival than the standard cardiopulmonary resuscitation (CPR) in human and animal models.
2. Close the lower part of abdomen due to decreased blood flow in the descending aorta
3. High-dose of bolus in intravenous Sodium Nitroprusside is a vasodilator for coronary and cerebral arteries and reduces peripheral vascular resistance in the brain and heart [1].

Based on the study of Demetris Yannopoulos, recent animal studies have shown that Cardiopulmonary resuscitation (CPR) along with Sodium Nitroprusside can keep brain and heart alive and markedly improves the flow of the carotid artery [1]. SNPe CPR had a significant improvement in the result of animal experiment with the proposed method of AHA 2010 [1, 2].According to the conducted researches due to the positive impact of SNP on improving the results of CPR and lack of researches in this field, we decided to conduct a study to examine the SNP solely in CPR compared with standard in improving symptoms of patients. Also the observational and practical experience of the research conductor on the better ventricular fibrillation accepting of heart during cardiopulmonary pump bypass (CPB) when the cardiac chambers are free of blood is also the main source of the creation of such a hypothesis.

Materials and Methods:

In this randomized clinical trial, after ethical committee approval of Isfahan University of medical sciences with the code of 393011, 22 Guinea pigs (Cavia porcellus) randomly were distributed in two groups of A and B. The required sample size was estimated using the sample estimation formula and in order to compare the below listed proportions the confidence level was considered 95% ($Z1-a/2 = 1.96$), test power 80% ($Z1-B = 0.84$), incidence of ROSC in the CPR due to the lack of studies was considered 0.5 and the least significant difference between two groups was determined 0.3.

The third person involved in the study, randomly brought a Guinea pig from each of the five cages to the lab for testing,

preparing and coded drugs for CPR.

Inclusion criteria were the lack of heart problem in Guinea pigs and the exclusion criteria included the inability to establish a bone route for injection of drug. All of the samples were approved by a veterinarian who was blinded about the study.

At the beginning, the required drugs of standard CPR were prepared (Ketamine: 2-4 mg /kg) Epinephrine: 0.1 ml/kg: 1: 1000 solution, Atropine: 0.02 mg /Kg, Sodium bicarbonate: 1meq / Kg, Lidocaine: 1 mg/ kg ,Sodium Nitroprusside: 30 micro / kg (high dose, based on available literature) and two prepared sample drugs with the names of A (placebo) and B(Sodium nitro perusside) were used for resuscitation. Research conductors were not aware of the nature of these two types of drug containing syringes. One of them contained placebo and the other contained Sodium Nitroprusside (dose of 30µ/kg) and the third person who cooperated in the project was responsible for the preparation and injection of drug and recording the data during resuscitation, used them randomly during CPR process. When each of the Guinea pigs was brought by the third partner, they were anesthetized with spontaneously breathing by intramuscular ketamine (dose of 2-4 mg /kg) and were placed on the desk. The immediately Nasal Oxygen was placed and Electrocardiography electrodes were connected with hypodermic needles. Capnography probe was placed in the right place. Pulse Oximeter probe was attached to the lower extremities and for this purpose it was placed the intraosseous route with needle of 20 size in the right femur bone. Prior to the induction of arrest, the amount of O2sat, Etco2, HR and type of heart rhythm was recorded by the third person. After this step the AC/DC powered Fibrillators Model Number 302R (80 mA) was used to make Guinea pigs to have cardiac arrest. Then we wait for 8 minutes. Then according to standard CPR and guidelines of Pediatrics (2010) we conducted the stages and in one group of drug A and in another group drug B was used along with Epinephrine. Epinephrine was injected every three to five minutes, To sinus rhythm in Guinea pigs, and If heart rate less than one hundred, atropine would be injected. Then the data of all samples were recorded in the table and for all samples CPR processes were recorded, but in the samples that reached to ROSC the data related to $O2_{sat}$, $Etco_2$, HR and type of heart rhythm at the time of ROSC were recorded five and ten minutes after ROSC. At the end, the level of pig brain function were recorded using Cerebral Performance Categories Scale (CPC Scale) at half, six, twelve and twenty-four hours after ROSC.

The results of reviewed cases including ROSC(The rapid increase in PETCO2 was often the first clinical evidence of restoration of spontaneous circulation), $Etco_2$, $O2_{sat}$, HR, type of cardiac rhythm, time to revive, the level of brain function, ROSC onset, the number of ventricular fibrillation s and doses of medications (epinephrine, atropine, lidocaine, bicarbonate) and other findings were recorded in a particular questionnaire. Obtained data were analyzed by SPSS version 20. Statistical tests used to analyze data included T-test, Chi-square and repeated- ANOVA test.

Results:

At the beginning of the project, baseline parameters were similar and there was no statistically significant difference between the two groups for HR, Spo2 and Etco2 (fig 1-3). After cardiac arrest with fibrillator was started, animals went into asphyxia cardiac arrest without group differences. After 8 min of asphyxiation, resuscitation was initiated. Table 1 shows results of resuscitation. As shown in control group four animals could not be resuscitated after 20 min. Six animals in case group could not be resuscitated after 20 min. The number of shocks and injection of epinephrine or atropine were similar in animals that could not be resuscitated in both case and control groups. Also, successful CPR without or with one shock and no use of injection of epinephrine or atropine observed in four animals in control group and in five animals in case group, there was no significant differences in the time of CPR and the number of shocks in animals with successful CPR.

Table 2 shows heart rhythm after shock (defibrillation) in studied animals. As shown, sinus rhythm was observed in eight of animals (four animals in each group), ventricular fibrillation was observed in nine of animals in the two groups, and bradycardia was observed in two animals in control group. CPR in nine animals in both groups was successful. After resuscitation, min 5 and min 10, heart rhythm in all animals in the two groups were sinus rhythm.

The differences in HR, Etco2 and Spo2 between groups are shown in figures 1-3, respectively. HR at baseline in controls was higher than cases, after resuscitation, min 5 and min 10 in cases was a little higher than controls but the differences in HR between groups were not statistically significant at baseline, after resuscitation, min 5 and min 10 ($P > 0.05$, Fig 1). Etco2 at baseline, after resuscitation, min 5 and min 10 among controls were higher than cases, but these differences were not statistically significant in these time point ($P > 0.05$, Fig 2). The differences in Spo2 between groups were not statistically significant at baseline, after resuscitation, min 5 and min 10, whereas, after resuscitation and min 5 in controls was a little higher than cases, and in min 10 in cases was a little higher than controls ($P > 0.05$, Fig 3).

The differences in cerebral performance category (CPC) score between groups at time points (30 min, 6 h, 12 h and 24 h after resuscitation) are shown in table 3. As shown, 30 minutes after resuscitation CPC score in all studied animals was severe deficit, 6 hours after resuscitation in all studied animals was mild deficit. 12 hours after resuscitation in two of animals in control group was mild deficit and in other animals was normal. 24 hours after resuscitation CPC score in all studied animals was normal. There were no significant differences between the two groups for CPC score, 30 min, 6 h, 12 h and 24 h after resuscitation ($P > 0.05$).

Table 1: resuscitation results in studied groups

	Control				Cases			
	CPR, time	Shock(n)	Epinephrine	Atropine	CPR	Shock(n)	Epinephrine	Atropine
Pig 1	+, 5 min	1	-	-	-, 20 min	4	4	-
Pig 2	+, 10 min	0	-	-	-, 20 min	4	4	-
Pig 3	-, 20 min	4	4	-	-, 20 min	2	4	-
Pig 4	+, 4 min	0	-	-	+, 4 min	0	-	-
Pig 5	-, 20 min	3	3	1	-, 20 min	3	2	1
Pig 6	-, 20 min	3	4	-	-, 20 min	2	2	2
Pig 7	+, 6 min	1	-	-	+, 4 min	1	-	-
Pig 8	-, 20 min	0	3	1	+, 4 min	0	-	-
Pig 9	+, 4 min	1	-	-	+, 6 min	1	-	-
Pig 10					-, 20 min	4	3	-

CPR; cardiopulmonary resuscitation. Shocks; first with 2 J/kg, second with 4 J/kg, third with 6 J/kg and fourth shock with 8 J/kg. Epinephrine; 10 mcg/kg in each injection, Atropine; 20 mcg/kg in each injection. +; successful CPR, -; unsuccessful CPR

Table 2: Heart rhythm after shock in studied groups

	After shock (defibrillation)			CPR		After resuscitation		min 5		min 10	
	Sin-R	VF	Sin-B	Successful	Unsuccessful	Sin-R	Other	Sin-R	other	Sin-R	other
Control	4	3	2	5	4	5	0	5	0	5	0
Case	4	6	0	4	6	4	0	4	0	4	0

CPR; cardiopulmonary resuscitation, Sin-R; sinus rhythm, VF; ventricular fibrillation, Sin-B; sinus bradycardia.

Table 3: The differences in cerebral performance category score between studied groups

		Control	Case	P-value
30 min after resuscitation	normal	0	0	n.s
	mild deficit	0	0	
	severe deficit	5 (100)	4 (100)	
6 h after resuscitation	normal	0	0	n.s
	mild deficit	5 (100)	4 (100)	
	severe deficit	0	0	
12 h after resuscitation	normal	3 (60)	4 (100)	n.s
	mild deficit	2 (40)	0	
	severe deficit	0	0	
24 h after resuscitation	normal	5 (100)	4 (100)	n.s
	mild deficit	0	0	
	severe deficit	0	0	
Data are number (%), n.s; no significant				

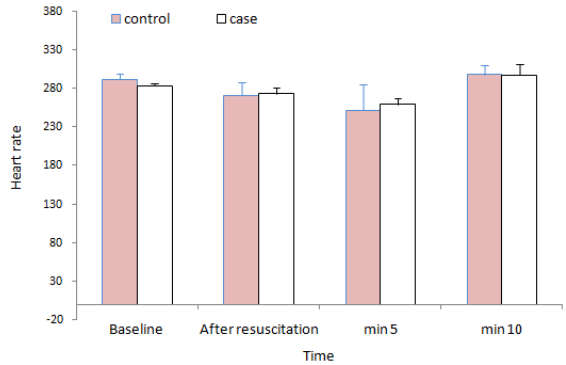

Figure 1: The differences in Heart rate between studied groups

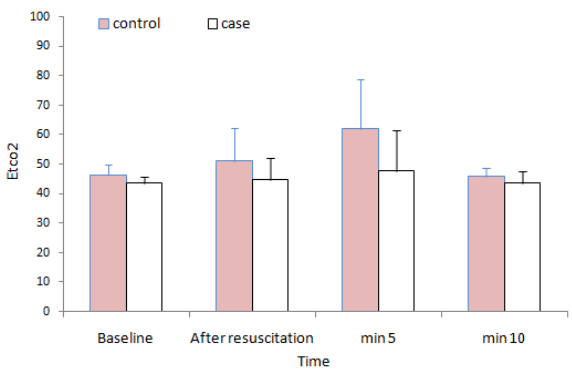

Figure 2: The differences in Etco2 between studied groups

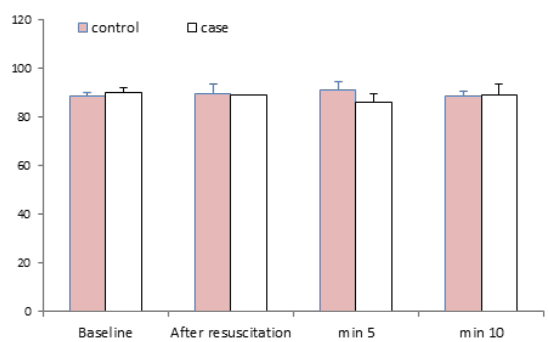

Figure 3: The differences in Spo2 between studied groups

Discussion

The capability to perform high-quality CPR is the first intervention, among the interventions directed to improve outcome of cardiac arrest. Consequently, chest compression potentially reestablishes some organ blood flows and cardiac output, accounting for tissue oxygen delivery and reducing thereby the ischemic injuries to the heart and brain [1]. In this investigation the effect of sodium nitroprusside in CPR was assessed in pigs after 8 minutes of untreated ventricular fibrillation. Our results show that the frequency of resuscitated animals after injection of sodium nitroprusside was similar to standard CPR. There was no significant difference in the time of CPR and the number of ventricular fibrillation s in animals with successful CPR. HR, Etco2, Spo2 and CPC score during 24 hour follow-up in both groups were similar and CPR with sodium nitroprusside was not more effective than CPR without sodium nitroprusside. No effective benefits of sodium nitroprusside than standard CPR can be explained by selected animals whereas typically studies were conducted on healthy young animals with no atherosclerotic disease that did not need additional myocardial blood flow enhancement in order to survive from cardiac arrested.

In an effort to enhance perfusion during resuscitation and to improve survival, over the past decades, a variety of alternatives to conventional CPR have been developed. Though, in routine use, none has consistently been shown to be superior to conventional CPR [2]. Continuously, clinical demonstration of survival benefits from administration of a specific vasopressor or combination of vasopressors during CPR, at either standard or higher doses are rare [3-5] and poor outcomes have also raised the question of the optimal pharmacologic approach to augment circulation during CPR.

The administration of sodium nitroprusside as a new and quite provocative drug intervention to be used during CPR has introduced by Yannopoulos et al [6]. They reported improved CPR, without need for epinephrine after repeated administration of sodium nitroprusside, combined with mechanically enhanced venous return. The rate of ROSC reported by Yannopoulos et al. [6] was 88% (7/8) in pigs, after 15 minutes of untreated VF, which received sodium nitroprusside during CPR and survived during 24 hours follow-up though in standard CPR 63% (5/8) animals achieved ROSC, and 25% (2/8) animals survived 24 hours. In our study the rate of ROSC in sodium nitroprusside animals after 8 minutes of untreated VF was 40% (4/10) and in standard CPR was 56% (5/9), also all animals achieved ROSC in both group survived during 24 hours follow-up. Etco2 and cerebral performance in our study were not different between animals but in Yannopoulos et al. [6] study in sodium nitroprusside animals was better than standard CPR. The differences between these results can be explained by the different method, different dose of sodium nitroprusside and minutes of untreated VF.

Yannopoulos et al. [7] in other study show that standard CPR followed by active compression–decompression, inspiratory impedance threshold device with administration of sodium nitroprusside (1 mg) in isoflurane anesthetized pigs, after 6 minutes of untreated VF, significantly improved hemodynamic parameters compare to standard CPR. In sodium nitroprusside animals the rate of ROSC was 100% (7/7) and in standard CPR was 25% (2/8). Also, in this study ETCO2 was significantly higher in sodium nitroprusside animals during CPR than standard CPR animals. So they concluded that the mechanical components of sodium nitroprusside CPR act synergistically to significantly improve ROSC rates, vital organ perfusion pressures and carotid blood flow compared to standard CPR. The rate of ROSC in the present study in sodium nitroprusside animals was 40% and in standard CPR was 56%, also Etco2 in both groups were similar and CPR with sodium nitroprusside was not more effective than CPR without sodium nitroprusside. The rate of ROSC in sodium nitroprusside animals in Yannopoulos et al. [7] study was higher than our study (100% vr. 40% respectively), this can be explained by the different method and dose of sodium nitroprusside whereas we added sodium nitroprusside to standard CPR but Yannopoulos et al. [7] added sodium nitroprusside to standard CPR followed by a mechanical platform. Synergy between the pharmacological agents and the mechanical intervention is possible.

This study has some limitations. First relates to the doses of drugs used, surely, multiple different drug combinations are possible. In our study because of the lacks dose-response data selected sodium nitroprusside dose was considered as high dose in this model and was chosen because previously significant responses in animal cardiac arrest models have been reported. Second, it was conducted on apparently healthy animals, and cannot be direct application to human victims of cardiac arrest. Furthermore, the applicability of sodium nitroprusside in an ischemic model of cardiac arrest needs to be further investigated because our models used open coronary arteries without stenosis.

Conclusion: The findings of this experimental study indicate that administration of sodium nitroprusside during standard CPR in animal model after 8 minutes of untreated VF did not improved the rate of ROSC compared to standard CPR alone and other outcomes. The underlying mechanisms of the effect of sodium nitroprusside during standard CPR are not fully understood, and this study warrants further large randomized trials focusing on clinical outcomes to better assess the effect of this drug.

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REFERENCES

1. Mangus DB, Huang L, Applegate PM, Gatling JW, Zhang J, Applegate RL 2nd. Asystematic review of neuroprotective strategies after cardiac arrest: from bench to bedside (Part I - Protection via specific pathways). Med Gas Res. 2011;4:9. doi: 10.1186/2045-9912-4-9. | 2.Schultz J, Segal N, Kolbeck J, McKnite S, Caldwell E, Yannopoulos D. Sodium nitroprusside enhanced cardiopulmonary resuscitation (SNPeCPR) improves vital organ perfusion pressures and carotid blood flow in a porcine model of cardiac arrest. Resuscitation. 2012;83(3):374-7. | 3. Otto CW, Yakaitis RW, Ewy GA. Effect of epinephrine on defibrillation in ischemic ventricular fibrillation. The American journal of emergency medicine. 1985;3(4):285-91. | 4.Yannopoulos D, Matsuura T, Schultz J, Rudser K, Halperin HR, Lurie KG. Sodium nitroprusside enhanced cardiopulmonary resuscitation improves survival with good neurological function in a porcine model of prolonged cardiac arrest*. Critical care medicine. 2011;39(6):1269-74. | 5. Högler S, Sterz F, Sipos W, Schratter A, Weihs W, Holzer M, et al. Distribution of neuropathological lesions in pig brains after different durations of cardiac arrest. Resuscitation. 2010;81(11):1577-83. | 6. Janata A, Bayegan K, Sterz F, Weihs W, Holzer M, Sipos W, et al. Limits of conventional therapies after prolonged normovolemic cardiac arrest in swine. Resuscitation. 2008;79(1):133-8. | 7. Janata A, Weihs W, Schratter A, Bayegan K, Holzer M, Frossard M, et al. Cold aortic flush and chest compressions enable good neurologic outcome after 15 mins of ventricular fibrillation in cardiac arrest in pigs*. Critical care medicine. 2010;38(8):1637-43. | 8. Su Q, Li L, Naing KA, Sun Y. Safety and Effectiveness of Nitroprusside in Preventing No-Reflow During Percutaneous Coronary Intervention: A Systematic Review. Cell biochemistry and biophysics. 2013:1-6. | 9. Berg RA, Hemphill R, Abella BS, et al. Part 5: Adult basic life support: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation 2010;122:685-705. | | 10. Cave DM, Gazmuri RJ, Otto CW, et al. Part 7: CPR techniques and devices: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation 2010;122:720-728. | 11. Brown CG, Martin DR, Pepe PE, et al. A comparison of standard-dose and high-dose epinephrine in cardiac arrest outside the hospital.The Multicenter High-Dose Epinephrine Study Group. N Engl J Med 1992;327:1051-1055. | 12. Gueugniaud PY, David JS, Chanzy E, et al. Vasopressin and epinephrine vs. epinephrine alone in cardiopulmonary resuscitation. N Engl J Med 2008;359:21-30. | | 13. Wenzel V, Krismer AC, Arntz HR, et al. A comparison of vasopressin and epinephrine for out-of-hospital cardiopulmonary resuscitation. N Engl J Med 2004;350:105-113. | 14. Yannopoulos D, Segal N, McKnite S, Aufderheide T, Lurie G. Controlled Pauses at the Initiation of Sodium Nitroprusside Enhanced CPR Facilitate Neurological and Cardiac Recovery after 15 Minutes of Untreated Ventricular Fibrillation. Crit Care Med 2012;40(5):1562-69. | | 15. Schultz JC, Segal N, Caldwell E, Kolbeck J, McKnite S, Lebedoff N, Zviman M, Aufderheide T, Yannopoulos D. Sodium nitroprusside enhanced CPR improves resuscitation rates after prolonged untreated cardiac arrest in two porcine models. Crit Care Med 2011;39(12):2705-10. |