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Research Article

Tibial Intraosseous and Intravenous Administration of Epinephrine in Normovolemic and Hypovolemic Cardiac Arrest

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Abstract

Introduction: Cardiac arrests can be classified as either hypovolemic or normovolemic causes. Hemorrhage is the major cause of hypovolemic cardiac arrest. Bleeding can lead to shock with subsequent cardiac arrest. Causes of cardiac arrest in normovolemic scenarios are related to cardiovascular diseases but can include myocardial infarct, blunt trauma, drowning and electrocution. Guidelines for intervention include intravenous (IV) or intraosseous epinephrine administration with repeated dosing every 3 - 5 minutes for patients in arrest. This guideline is based on expert opinion and very little research. No one has investigated the area under the curve (AUC), which is the body's exposure to a drug, or return of spontaneous circulation (ROSC) with tibial intraosseous (TIO) and IV administration of epinephrine in hypovolemic and normovolemic cardiac arrest models.

Aim: Aim of this study were to compare AUC, frequency and odds of ROSC when epinephrine was administered by the TIO and IV routes in hypovolemic and normovolemic models of cardiac arrest.

Methods: This was a prospective, experimental study. 28 adult swine were randomly assigned to 4 groups: TIO Normovolemic Group (TIONG), TIO Hypovolemic Group (TIOHG), IV Normovolemic Group (IVNG) and the IV Hypovolemic Group (IVHG). Pigs were anesthetized. 35% of the pigs' blood volume was exsanguinated in the hypovolemic groups. Pigs were in arrest for 2 minutes; cardiopulmonary resuscitation (CPR) was initiated for 2 minutes. Epinephrine (1 mg) was then administered by either the TIO or IV routes and repeated every 4 minutes or until ROSC. Blood samples were collected over 5 minutes. The serum concentration of epinephrine was determined using high-performance liquid chromatography. Defibrillation was initiated 3 minutes post arrest and repeated every 2 minutes.

Results and Discussion: A Chi-Square indicated that no differences existed among the groups relative to ROSC ($p > 0.05$). Odds of ROSC were higher for the TIONG than other groups. The AUC was higher in the TIONHG vs. the IVHG and IVNG; The IVNG was higher than the TIOHG ($p < 0.05$).

Conclusion: We were able to insert a TIO device in less than 10 seconds and CPR did not have to be interrupted. ROSC was either the same or better in the TIO groups. Because time is of essence to administer epinephrine in a cardiac arrest, perhaps the TIO route should be considered the first-line intervention. This study adds needed empirical data for guidelines for caring for patients in cardiac arrests.

Keywords: *Cardiac Arrest; Epinephrine; Shock; Tibial Intraosseous; Area under the Curve*

Abbreviations

ROSC: Return of Spontaneous Circulation; IV: Intravenous; ERC: European Resuscitation; AHA: American Heart Association; IO: Intraosseous; AUC: Area under the Curve; TIO: Tibial Intraosseous; HIO: Humerus Intraosseous; TIOHG: Tibial Intraosseous Hypovolemic Group; TIONG: Tibial Intraosseous Normovolemic Group; CPR: Cardiopulmonary Resuscitation; MANOVA: Multivariate Analysis of Variance; ANOVA: Analysis of Variance; SEM: Standard Error of the Mean

Introduction

Need for study

The etiology of cardiac arrests can be classified as either hypovolemic or normovolemic causes [1]. The leading cause of cardiac arrest from trauma is haemorrhage in both civilian and military sectors [2-7]. Mortality from bleeding approaches 2 million worldwide. Approximately 5 million individuals die from trauma each year worldwide and it is expected to be over 8 million each year by 2020. [8,9] The bleeding can lead to hemorrhagic shock with subsequent cardiac arrest [10].

The leading cause of cardiac arrest in a normovolemic scenario is cardiovascular disease. Other normovolemic causes of arrest include myocardial infarct, blunt trauma, drowning, electrocution and even psychological stressors [11-16]. In fact, Kiyohara ., *et al*. found that myocardial infarction and cardiac arrest were significantly higher in the first week of an earthquake in Japan [17]. Other investigators have found sudden cardiac arrest during and after a disaster were related to psychological stressors [12-14,17-19].

Need for vascular access

Research has consistently demonstrated that return of spontaneous circulation (ROSC) decreases when epinephrine administration is delayed. The chances of ROSC are decreased by 9 percent for every minute of delay in administering epinephrine [20]. Therefore, timely vascular access is necessary in reducing death rates in a cardiac arrest scenario. When patients are in cardiac arrest, their veins have collapsed, particularly in hypovolemic shock, which makes intravenous access (IV) difficult and very time consuming even for the most skilled clinician. Early administration of epinephrine not only increases the chances for ROSC but also decreases neurological complications [20,21]. Furthermore, Donnino., *et al*. found that delayed administration of epinephrine was associated with less chance of ROSC. In addition, they also found that the time to epinephrine administration of 5 minutes or less resulted in a significantly lower rate of death [22]. Likewise, Khera., *et al*. found that delayed epinephrine administration for patients in cardiac arrest was 58% higher than those who received the drug in the first 5 minutes [23]. Zuercher., *et al*. also found that that there were greater odds of ROSC, better neurological outcome and better 24 hour survivability when epinephrine was given earlier [24].

Both the European Resuscitation Council (ERC) and the American Heart Association (AHA) state that 1 mg epinephrine should be administered with repeated dosing every 3 - 5 minutes for patients in cardiac arrest [25,26]. Further, ERC and AHA recommend if IV access is not rapidly obtained, an intraosseous (IO) access should be acquired [25]. Most of studies investigating the efficacy of drugs have demonstrated that the IO and IV access have similar effects [27-36]. However, these IO studies have investigated drugs used in a normovolemic model.

Area under the curve (AUC) reflects exposure of the body to epinephrine. We speculated that epinephrine administration in a hypovolemic compared to a normovolemic scenario may change the volume of distribution ultimately reducing AUC. This in turn may translate into less frequency of ROSC. Only one study has compared the effects of IO epinephrine administration using a hypovolemic and normovolemic model [1]. In that study, Long ., *et al*. found that the humerus intraosseous (HIO) administration of epinephrine was very effective in a normovolemic but not in a hypovolemic model, but they did not investigate the effects of AUC nor the use of the tibia [1].

Aim of the Study

There are no studies comparing tibial intraosseous (TIO) and IV administration of epinephrine relative to AUC and ROSC in hypovolemic and normovolemic cardiac arrest models. The findings of this study give direction for making decisions regarding vascular access for

patients in cardiac arrest, consequently, has the potential of saving lives. The aims of this study were to compare AUC, frequency and odds of ROSC when epinephrine was administered by the TIO and IV routes in hypovolemic and normovolemic models of cardiac arrest.

Materials and Methods

The study was funded by Research Program Grant number (N13-P10) and approved by the Institutional Animal Care and Use Committee (Naval Medical Research Unit, JBSA-FSH protocol 12-01). To avoid as much variability as possible, we purchased the pigs from the same vendor (Oak Hill Genetics, Ewing, IL). All subjects were cared for according to the Animal Welfare Act and the Guide for the Use of Laboratory Animals [37]. This study consisted of 4 groups (N = 28) of adult male Yorkshire-cross, sus scrofa, swine. By use of a random number generator (https://www.random.org/integers), we assigned 7 subjects to each group: TIO Normovolemic Group (TIONG), TIO Hypovolemic Group (TIOHG), IV Normovolemic Group (IVNG) and the IV Hypovolemic Group (IVHG). To avoid any potential hormonal effects, we used all male pigs. Each pig weighed ~70 kg which is approximately the average weight of an adult, male human [38].

The reason for using swine was the cardiovascular, pulmonary and bone physiology are very similar to humans [39,40]. On arrival and right before the study, the resident veterinarian performed a thorough health examination to confirm that each subject was in good health. One potential subject was deleted and replaced because of pneumonia. At midnight the day before the experiment, the subjects were not allowed food but allowed to drink water up until induction of anesthesia. We inserted the EZ-IO device (Teleflex, Philadelphia, Pa) in all animals in the TIO groups. Confirmation of placement was made by aspirating blood and/or bone marrow.

An intramuscular injection of Telazol (4.4 mg/kg), (Tiletamine/Zolazepam, Fort Dodge Animal Health, Fort Dodge, IA, USA) was administer followed by anaesthesia (1 to 2% isoflurane). Each subject in the hypovolemic groups was exsanguinated 35% of his blood volume, which represented a Class III haemorrhage. We sent an electric current through the heart to produce cardiac arrest: A method developed by the investigators [41]. Anaesthesia was discontinued and each animal was left in arrest for 2 minutes without intervention. The rationale for 2 minutes was that we believed this was the minimum amount of time to detect a cardiac arrest. We initiated chest compressions at 100 per minute using the Mechanical Compression Device, Model 1008 (Michigan Instruments, Grand Rapids, MI, USA). The reasons for using the device were to maintain consistency and reproducibility. Ventilation rates of 8 to 10 per minute were used. After another 2 minutes, we administered epinephrine (1 mg) by the TIO and IV routes and blood samples were then collected over 5 minutes. We speculated that a 2 minute time period was the amount of time it would take to initiate cardiopulmonary resuscitation (CPR). The serum concentration of epinephrine was determined for each of the swine by using high-performance liquid chromatography, the industry standard. The investigator performing the calculations was blinded to group assignment.

Defibrillation was administered every 2 minutes and epinephrine was repeated every 4 minutes as recommended by AHA and ERC [25,26]. CPR continued until ROSC or for 30 minutes. The operational definition of ROSC was a mean arterial pressure of at least 60 mmHg and a palpable pulse.

We calculated a large effect size of 0.6 based on previous, similar research [43-45]. Using an α of 0.05, a large effect size of 0.6 and a power of 0.8, we calculated that we needed a sample size of 28 (n = 7 per group). G*Power 3.1 for Windows (Heinrich Heine University, Dusseldorf, Germany) was used for the calculation. Means and standard error of the means (SEM) were calculated for each group. A Multivariate Analysis of Variance (MANOVA) was used to determine if there were any significant differences in the pretest data including weight, cardiac output, stroke volume, systolic blood pressure, mean arterial blood pressure, temperature, heart rate between each group, total blood volume and the amount of blood exsanguination. A Chi-Square was used to determine if there were significant differences in frequency of ROSC by group. All statistics were calculated using SISA (https://www.quantitativeskills.com/sisa/index.htm). We used an odd sratio calculator to compare the odds of ROSC by group (https://www.medcalc.org/calc/odds_ratio.php).

The major limitation of this study was a small sample size. Nevertheless, we had enough power to find significance. Also, not all the investigators were blinded to group assignment although they meticulously adhered to the procedures of this study. As with all animal studies, the findings may not be generalizable to humans; however, cardiovascular, bone and respiratory systems of swine are very similar to humans [39,40].

Results and Discussion

A MANOVA indicated that there were no significant differences in the pretest data ($p > 0.05$) indicating that the groups were equivalent on these parameters. A Chi-Square indicated that there were no significant differences in ROSC between the groups ($p > 0.05$). However, the odds of ROSC were higher for the TIONG than any other group (See table 1 and figure 1 for a summary). An ANOVA indicated there were significant differences in the groups relative to AUC (See table 2 for Summary and figure 2 for a Summary of the means and SEM.

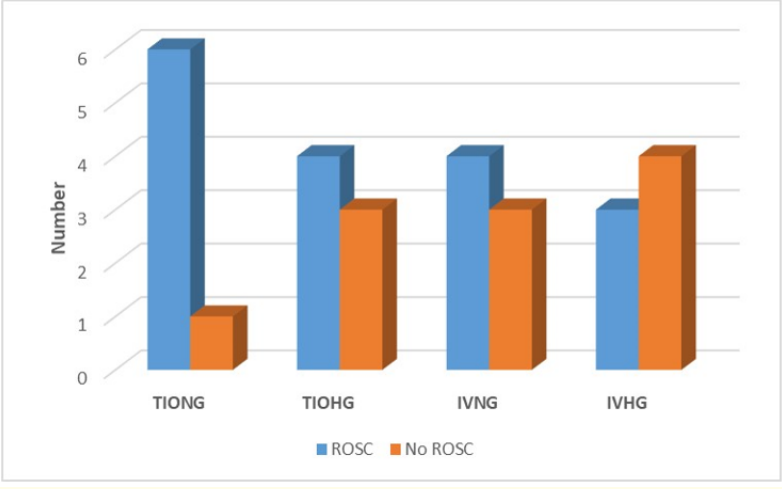

Figure 1: *Comparison of return of spontaneous circulation by group.*

Group	ROSC	No ROSC	Comparison
TIONG	6 (85.7%)	1 (14.3%)	TIONG 4.5 X > TIOHG TIONG 4.5 X > IVNG TION 8 X > IVHG
TIOHG	4 (57.1%)	3 (42.9%)	TIOHG = IVNG TIOHG 8 X > IVHG
IVNG	4 (57.1%)	3 (42.9%)	IVNG 1.78 > IVHG
IVHG	3 (42.9%)	4 (57.1%)	Covered above

Table 1: *Group comparison of odds of return of spontaneous circulation.*

Comparison of Groups	P value
TIONG no difference than TIOHG	P = .375
TIONG greater than IVHG	P = .003*
TIONG greater than IVNG	P = .037*
IVNG no difference than IVHG	P = .291
IVNG greater than TIOHG	P = .005*

Table 2: *Summary of area under the curve by group.*

**Significant at the 0.05 level*

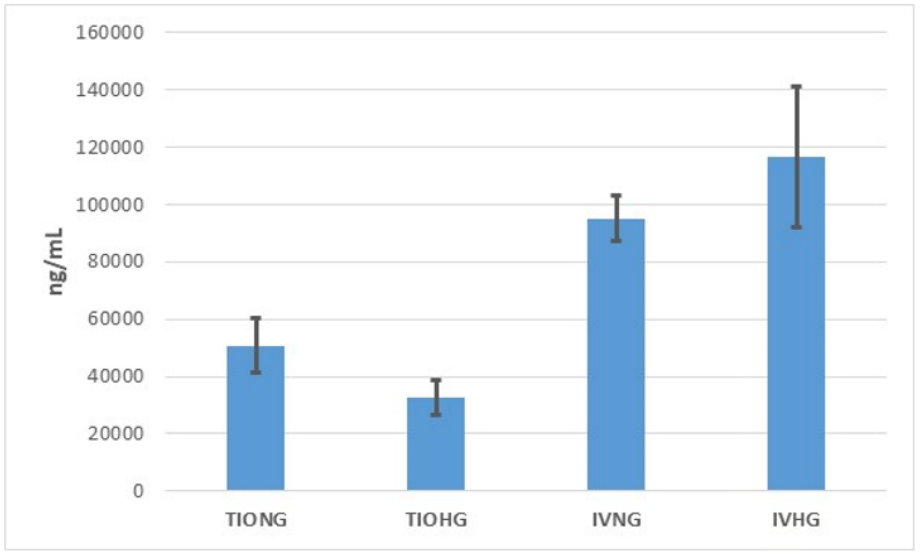

Figure 2: *Comparison of area under the curve by group.*

We found that the AUC of epinephrine and ROSC were higher in the TIONG compared to the TIOHG. We reasoned that when an arrest occurs with hypovolemia there is release of endogenous epinephrine. An additive effect occurs with the endogenous and exogenous administered epinephrine causing vasoconstriction to the bones. Subsequently, there is less delivery of epinephrine from the bone into the systemic circulation [46]. This idea was supported by Voelckel., *et al*. who found that hemorrhage along with epinephrine administration reduces flow to the bones to almost zero [46]. This study expands the study by Neill., *et al*. by investigating TIO epinephrine administration in an adult cardiac arrest model and analyzing the effect of hypovolemia and normovolemia on AUC and ROSC in an adult arrest model. Neill, ., *et al*. found that the humerus intraosseous (HIO) was not effective in a Pediatric hypovolemic cardiac arrest model. They found that the concentration maximum, mean concentration and ROSC were significantly higher in the IV group compared to the HIO group [47].

Only one study has compared the effects of IO epinephrine administration in a hypovolemia and normovolemia cardiac arrest model. In that study Long., *et al*. found that all the swine achieved ROSC in the HIO normovolemic model and 3 out of 7 in the hypovolemic model. Our study expands their investigation in that we compared a normovolemia and hypovolemia in a TIO model of an adult cardiac arrest with the addition of AUC.

Conclusion

The findings of this study support that the TIO administration of epinephrine can be used in both normovolemic and hypovolemic cardiac arrest models. Although there were not significant differences, ROSC was higher or the same in the TIO groups compared to the IV groups. The recommendation to use IO route of epinephrine if an IV route is inaccessible is based primarily on expert opinion [25,26]. This study adds research findings to substantiate that the TIO can be used in both hypovolemic and normovolemic cardiac arrest scenarios. In this investigation both the TIO and IV lines were already in place when we initiated cardiac arrest. However, in a real life scenario, probably neither would be in place. Investigators have found that it can take as much as 49 minutes to start an IV. Leidel., *et al*. found IV failure rates were from 10 to 40% in patients not in arrest with an average time to obtain IV access was 2.5 to 16 minutes. In extreme cases, it took as long as 55 minutes in critically ill patients who were not in arrest [48]. More than likely additional time would be needed for a patient in a hypovolemic arrest. Also, to start an IV, CPR would have to be interrupted. In this study, we were able to insert a TIO device in less than 10 seconds and CPR did not have to be interrupted. Further, because time is of essence to administer epinephrine in a cardiac arrest, perhaps the TIO route should be considered first-line intervention.

Conflict of Interest

None of the authors have a conflict of interest.

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