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Tibial Intraosseous, Intravenous, and Endotracheal Epinephrine Administration in a Hypovolemic Cardiac Arrest Model

Denise Beaumont, CRNA, DNAP*

Director of Program

Michelle Johnson, CRNA, DNP*

Associate Professor

Julie G. Hensler, PhD*

Professor

Dawn Blouin, BS*

Research Assistant

Joe O'Sullivan, CRNA, PhD**

Don Johnson, PhD*

Corresponding author telephone: 210-849-7364

Professor and Director of Research

*US Army Graduate Program in Anesthesia Nursing, Fort Sam Houston, San Antonio Texas and Baylor University

**Retired LTC US Army

Abstract

Introduction: Cardiac arrests are common with over 570,000 reported adult out-of-hospital cardiac arrest just in the United States.

Objective: The aim of this study was to compare tibial intraosseous (TIO), intravenous (IV), and endotracheal (ET) administration of epinephrine relative to area under the curve (AUC), frequency, and odds of spontaneous return of circulation (ROSC) in a cardiac arrest hypovolemic model.

Design: Prospective, experimental, blinded study.

Participants: Adult Yorkshire Swine (n = 7 per group).

Methods: Swine were anesthetized, and each had an IV, ET tube, or TIO inserted. They were exsanguinated 35% of their blood volume and then placed into arrest. After 2 minutes,

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cardiopulmonary resuscitation was initiated. After another 2 minutes, epinephrine (1 mg for IV and TIO groups; 2 mg for ET group) was administered. All subjects were defibrillated every 2 minutes. Blood samples were collected over 5 minutes and analyzed using high performance mass spectrometry. AUC was then calculated.

Main Outcome Measures: AUC, frequency, and odds of ROSC.

Results: AUC in the TIO and ET Groups were significantly lower than the IV Group ($p < 0.05$). ROSC occurred in 4 out of 7 for both the IV and TIO Groups and 2 out of 7 for the ET Group. Odds of ROSC were 3.3 times greater for both IV and TIO groups vs. the ET group.

Conclusions: Chances of survival from arrest are decreased by 9% for every minute delay in administering epinephrine. TIO insertion takes less than 10 seconds and is just as effective as IV. Valuable time can be saved by using this route. ET administration is not as reliable.

Keywords: Intraosseous, Cardiac Arrest, Epinephrine, Resuscitation

Introduction

One of the leading causes of death in the developed world is cardiac arrest.[1] Cardiac arrest can be classified as either hypovolemic or normovolemic causes.[2] The most common cause relative to normovolemia is cardiovascular disease. Other causes include myocardial infarct, blunt trauma, drowning, electrocution, and even psychological stressors.[3-8] Bleeding is a common occurrence and is the leading cause of cardiac arrest from trauma.[9-14] In fact hemorrhage is the leading cause of cardiac arrest from trauma in both civilian and military sectors.[9-14] The hemorrhage can lead to hypovolemic shock and subsequently to cardiac arrest.[15]

Regardless of the cause, investigators have found that time to administration of epinephrine is essential for survival.[16,17] For every minute of delay, chances of survival are decreased by nine percent.[18] Therefore, obtaining vascular access is critical for pharmacological resuscitation efforts. Numerous investigators have found that for both in-hospital and out-of-hospital cardiac arrests, the timing of the first dose of epinephrine was critical for effectiveness.[16,18-21] Patients who are in cardiac arrest have collapsed veins, particularly those in hypovolemic shock. Hence, intravenous (IV) access is very difficult and very time consuming even for the most skilled clinician.

The American Heart Association (AHA) and the European Resuscitation Council state that epinephrine should be administered for victims in arrest. The route in order of preference are IV, intraosseous (IO), or endotracheal (ET).[22,23] Several investigators have found that IO and IV access have similar efficacy.[24-33] However, most of these IO studies have investigated drugs used in a normovolemic model.

The major advantage of using both the TIO and ET routes is time, and the time saved may translate into return of spontaneous circulation (ROSC). Few studies have studied the effectiveness of the ET route. In one of the few studies addressing the ET route of administration of epinephrine, Burgert, et al. found that the route was not reliable and not effective in achieving ROSC in a hypovolemic cardiac arrest adult model.[34] Conversely, Kertes, et al. found the use of the ET route to be very effective for a hypovolemic pediatric cardiac arrest model but not for a

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hypovolemic adult cardiac arrest model.[35] Niemann et al. found that IV epinephrine was more effective than the ET route but emphasized that cardiopulmonary resuscitation (CPR) studies have not adequately addressed the use of ET epinephrine in doses recommended.[36]

Area under the curve (AUC) reflects the body's exposure to epinephrine after administration. We reasoned that epinephrine administration in a hypovolemic compared to a normovolemic model may change the volume of distribution ultimately reducing AUC that may translate into less frequency of ROSC. Only one study has compared the effects of IO epinephrine administration using hypovolemia and normovolemia subjects.[2] In that study, Long, et al. found that the humerus IO administration of epinephrine was very effective in a normovolemic model but not in a hypovolemic model. They did not investigate the effects of AUC.[2]

There are no studies comparing TIO, ET, and IV administration of epinephrine relative to AUC, frequency, and odds of return of spontaneous circulation (ROSC) in a hypovolemic cardiac arrest model. The findings of this study may give direction for making decisions regarding vascular access for patients in cardiac arrest, hence, 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 TIO, IV, and ET routes in a hypovolemic model of cardiac arrest.

Methods and Procedures

Design

This study was a prospective, randomized, between-subjects, experimental design. The Institutional Animal Care and Use Committee approved the investigation, and the research took place at the Naval Medical Research Unit-San Antonio, an approved laboratory facility.

Subjects

We used 21 adult male Yorkshire-cross, *sus scrofa*, swine. By using a random number generator (https://www.random.org/integers), we assigned 7 swine to each group: TIO group (TIOG), ET group (ETG), and IV group (IVG). Male pigs were used to avert possible hormonal effects from the female hormones. The swine weighed 60 to 80 kg which approximates the average weight of an adult, male human.[37,38] The rationale for using pigs was because the cardiovascular, pulmonary, and bone physiology are very similar to humans.[39,40] To avoid as much variability as possible, we purchased swine from the same vendor (Oak Hill Genetics, Ewing, IL). Male swine were used to avoid any potential hormonal effects.

Veterinary Care and Housing

Care of the swine was in accordance with the Animal Welfare Act and the Guide for the Use of Laboratory Animals.[41] The facility veterinarian preformed a comprehensive health assessment to confirm that each swine arrived and remained healthy throughout the study. All swine could eat antibiotic-free food until midnight of the study and were allowed unlimited water access up until induction of anesthesia. For safety reasons the pigs were kept in separate enclosures but housed in the same room to allow for social interaction.

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Animal Preparation

Swine were injected with an intramuscular dose of Telazol (4.4 mg/kg), (Tiletamine/Zolazepam, Fort Dodge Animal Health, Fort Dodge, IA, USA). General anesthesia was induced via inhalation of isoflurane (2% to 5%) and 100% oxygen. Once tracheal intubation was confirmed, we decreased the isoflurane concentration to deliver a dose between 1% and 2%. Swine were ventilated at a rate of 10-14 breaths per minute with 8-10 mL/kg of tidal volume with an Aestiva 5 anesthesia machine (Datex-Ohmeda, Madison, WI, USA). The swine's heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), electrocardiography (ECG), oxygen saturation (SpO_2), body temperature (ºC), and end-tidal capnography ($ETCO_2$) (Datex-Ohmeda Cardiocap 5 monitoring system GE Healthcare, Helsinki, Finland) were continuously monitored.

The left carotid artery and left femoral artery were exposed for the cannulation of both arterial catheters with an 8.5 French x 10 cm central venous catheter (Arrow International, Reading, PA, USA). The carotid arterial line was for continuous arterial blood pressure monitoring, and the femoral arterial line was for exsanguination and blood specimen collection. The femoral arterial line was also used for the continuous monitoring of cardiac output (CO) and stroke volume (SV) using a Vigileo hemodynamic monitor (Edwards Lifesciences, Irvine, CA, USA). Each of the swine's body temperature was warmed to ≥ 36°C using a forced-air warming system (3M Inc., St. Paul, MN, USA) and an under-body circulating water blanket (Gaymar Industries, Orchard Park, NY, USA).

Experimental Procedures

Anesthesia was induced and then a 15-minute stabilization period was allowed. After the stabilization period, we created a Class III hemorrhage by exsanguinating 35% of each swine's blood volume via suctioning from the femoral artery catheter. The amount of hemorrhage was calculated by using a factor of 70 mL/kg of body weight. We calculated the standard one ml of blood weighs one gram. Therefore, if the pig weighed 70 kg, we calculated that he would have 4900 ml of blood; 35 % of volume is equal to 1470 ml or 1470 grams. The rate of hemorrhage was approximtely100 mL of blood per minute. An electronic scale (Thermal Industries of Florida, Owatonna, MN, USA) was used to measure the amount of bleeding. The scale is accurate and precise within 0.5%. The scale was zeroed according to the manufacturer's instructions before each pig was exsanguinated. Once the hemorrhage was accomplished, an electric current was sent through each of the swine's heart to produce cardiac arrest, a procedure developed by the investigators.[42] Anesthesia was discontinued, and each animal was left in arrest for two minutes. The rationale for waiting two minutes after the arrest was to mimic the minimum amount of time to initiate CPR in a real-life scenario. Mechanical chest compressions at 100 per minute were initiated using the Mechanical Compression Device, Model 1008 (Michigan Instruments, Grand Rapids, MI, USA). The rationale for using the device was to maintain consistency and reproducibility. Ventilation rates were 8 to 10 per minute. After two minutes of CPR, we administered epinephrine (1 mg for TIOB and IVG and 2 mg for ETG) and repeated every four minutes. Blood samples were then collected over five minutes from the femoral artery with 10 mL discarded right before each sample to avoid any residual of

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epinephrine from the previous collection. The femoral artery was then irrigated with 5 mL of normal saline to maintain patency. The samples were analyzed using high performance liquid chromatography with mass spectrometry (HPLC-MS/MS).

A biphasic defibrillator was used to administer a 200-J electrical pulse at three minutes after epinephrine administration and repeated by every two minutes. Both defibrillation and epinephrine administration were continued until ROSC or for 30 minutes. After 15 minutes post arrest, we administered the exsanguinated blood. The rationale for 15 minutes was this would be the amount of time to acquire blood for transfusion. If an animal achieved ROSC, we monitored all the hemodynamic parameters for an additional 30 minutes. If no ROSC was achieved, we continued the resuscitation for twenty minutes. All procedures followed the guidelines of AHA.[23,43] For the purposes of this study, ROSC was defined as a MAP of at least 60mm/Hg and a palpable pulse for at least 10 minutes.

Statistical Analyses

We calculated a large effect size of 0.6 based on previous, similar research.[44-46] 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). We performed a power analysis using G*Power 3.1 for Windows (Heinrich Heine University, Dusseldorf, Germany). For the statistical analyses we used IBM® SPSS® v.22 Software (Chicago, IL). Means and standard error of the means were calculated for AUC. We used a multivariate analyses of variance (MANOVA) to analyze the pretest data. We used a univariate ANOVA to determine if there were significant differences between the groups relative to the AUC epinephrine. When statistical significance was achieved, we used a Least Significant Difference post-hoc test. A Chi-Square Test was used to determine if there were differences in the frequency of ROSC between the groups. We calculated and compared the odds of achieving ROSC by each group.

Findings

A MANOVA indicated no significant differences in the pretest data including HR, SBP, DBP, MAP, ECG), SpO_2, body temperature (ºC), and $ETCO_2$, weight, CO, SV, SBP, DBP, MAP, oxygen levels, body temperature, $ETCO_2$, blood volume, and the amount of exsanguination indicating the groups were equivalent on these variables ($p > 0.05$).

There were significant differences in the AUC by group. The AUC in the TIOG was significantly lower than both the ETG ($p = 0.021$) and IVG ($p = 0.019$). There was no significant difference between the ETG and TIOG ($p = .98$) (See Figure 1). However, only two subjects in the ETG had any measurable serum levels of epinephrine, and five had none. Those two had high AUC which artificially increased the means of that group.

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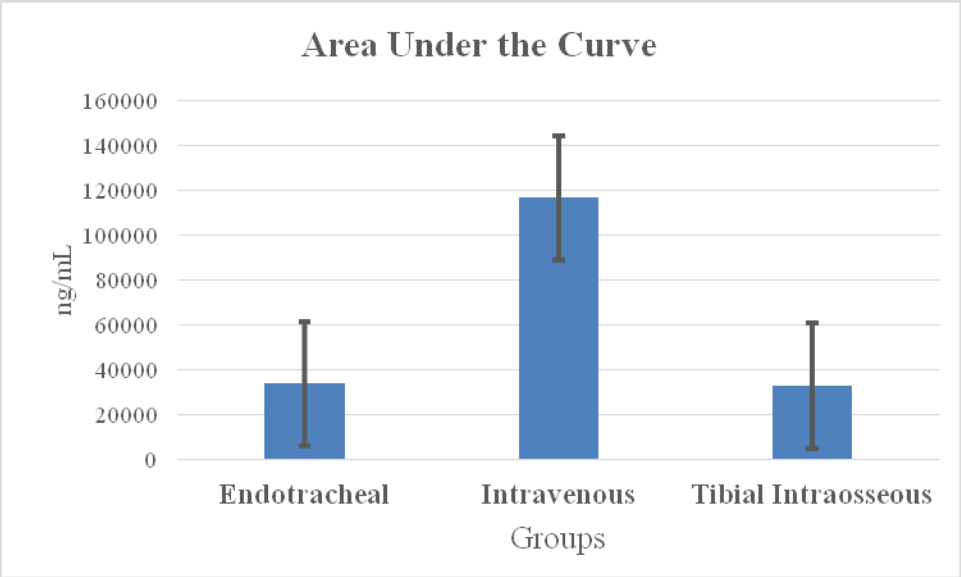

Figure 1 Means and standard errors by group

There were no significant differences in time to ROSC between groups: TIOG vs. IV (p = .92) or ETG (p = .48); IVG vs. ETG (p = .53). The means and standard error of the means were as follows: TIOG: 476 ± 79, IVG: 465 ± 79, and ETG: 376 ± 57. The reader is cautioned that the results for the ETG group was based on only 2 subjects that had ROSC.

A Chi-square indicated that there was no significant difference in frequency of ROSC between the TIOG and IVG (p = 1), IVG and ETG groups (p =.28), or TIOG and ETG (p = 0.28). (See Figure 2)

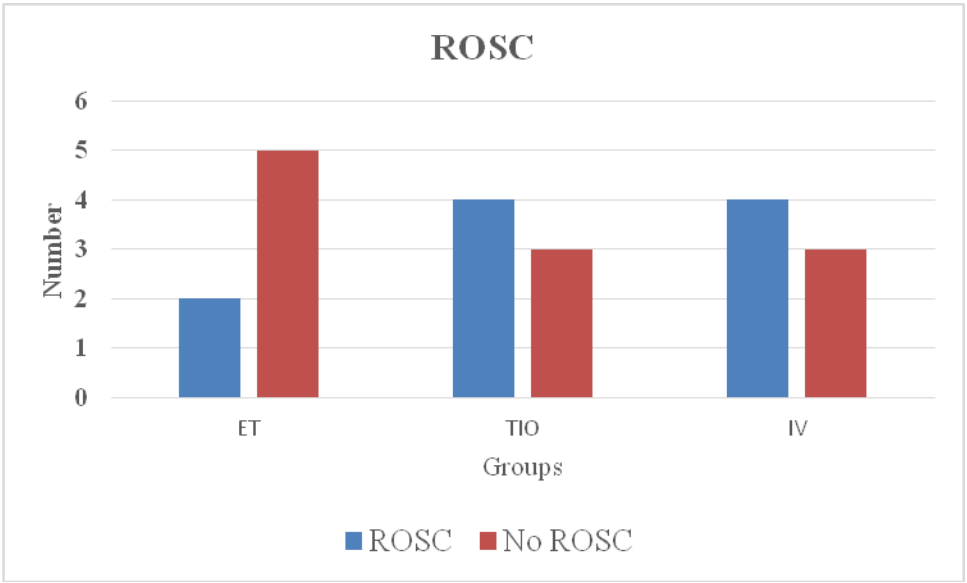

Figure 2 Number Achieving ROSC or No ROSC

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The odds of ROSC were the same for both the TIOG and IVG. Both had 3.3 times greater chance of achieving ROSC than the ETG.

Discussion

The purposes of this study were to compare AUC of plasma epinephrine concentration, frequency, and odds of ROSC following TIO, ET or IV administration of epinephrine in a hypovolemic of cardiac arrest model. The AUC of plasma epinephrine concentration was significantly greater when epinephrine was administered by the IV compared to either ET or TIO routes. The frequency of ROSC was not statistically significantly different when comparing the IV, ET and TIO routes of administration. However, perhaps if we had had a larger sample, we would have had enough power to detect a difference in ROSC between the ETG compared to both TIOG and IVG. We want to emphasize the clinical significance in that we found that both the IVG and TIOG had 3.3 times greater odds of achieving ROSC compared to the ETG.

Only two subjects in the ETG group had a detectable AUC epinephrine. One had a concentration much higher than all the other subjects at 218,116 ng/mL. The ETG had double the dosage (2 mg vs. 1 mg) which may help explain the higher AUC in the one subject; however, five others had no detectable levels. ET epinephrine may not distribute in the lower areas of the bronchial tree. The non-uniform distribution may decrease the availability of epinephrine to the vasculature. A mismatch between the distribution in the lung and those areas of the lung being perfused may also cause less drug to be absorbed. In addition, significant right-to-left shunting may occur after an arrest, and the vasoconstrictive effects of epinephrine may impede absorption and shunting the pulmonary blood.

We speculate the reason for less AUC in the TIOG and ET compared to the IVG is that with hypovolemia there is release of endogenous epinephrine because of the shock. Both endogenous and the exogenous administered catecholamines have an additive effect causing vasoconstriction. Both IO and ET routes of administration require passage of epinephrine across a permeable tissue barrier to enter the systemic circulation in contrast to direct access provided by the IV route. The significantly lower AUC values for epinephrine following ET and TIO administration compared to IV indicates relatively poor systemic distribution of epinephrine from bone or lung during hypovolemia. Changes in circulation as a result of hemorrhage, which include reductions in circulating blood volume, peripheral vasoconstriction because of sympathetic nervous system activation and decreased pulmonary blood flow to less than 20% would be expected to negatively affect the absorption of epinephrine following ET or TIO administration.[36,47,48] In fact, Voelckel et al. found that hemorrhage along with epinephrine administration reduces flow to the bones to almost zero.[49] Consistent with this idea, Burgert et al. found that the maximum plasma concentration was significantly lower following TIO epinephrine administration when compared with IV in hypovolemic subjects.[34] In addition, they found the time to maximum plasma epinephrine concentration was significantly greater following TIO administration when compared with IV.[34] They also found that following ET administration, epinephrine plasma concentrations peaked immediately although at a significantly lower level than following IV administration, and then there was a steady decline.[34]

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The advantage of the ET route is that it can be placed in less than 30 seconds by an experienced provider, but one of the disadvantages is that CPR has to be interrupted.[50] In this study, we found that the ET could be inserted in 20 seconds. However, our findings indicate that the ET route was highly variable and unreliable and supports the conclusion by other investigators.[34,51,52] Orlowski et al. found that the ET route of administration was unreliable and not reproducible in either the normotensive or shock animals.[53] Likewise, Burgert et al. concluded that the ET route was not reliable in a hypovolemic model.[34]

Conclusion

Although the AUC for the TIOG was significantly less than the IVG, the ROSC was the same. Therefore, the TIO route may be considered first-line intervention saving valuable time to administer epinephrine. In this study the TIO and IV lines were already in place when we initiated cardiac arrest, but in a real-life scenario, probably neither would be in place. Studies show that it may 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.[54] More time would be needed for a patient in hypovolemic arrest. In this study, we were able to insert a TIO device in less than 10 seconds, and CPR did not have to be interrupted. The ET is highly variable, and our data suggest that it is not a viable option for administration of epinephrine in an adult hypovolemic cardiac arrest model. Future studies should include a pediatric model whereby the epinephrine administration by the ET route is 0.1 mg/Kg of body weight. The larger dose may result in higher AUC levels and ROSC occurrence.

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