Comparison of Adult and Child Endotracheal Administration of Epinephrine in a Normovolemic Cardiac Arrest Model

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Abstract

Background: Maximum concentration (Cmax), Time to maximum concentration (Tmax), Mean Concentration over time (MC), Area under the Curve (AUC), and return of spontaneous circulation (ROSC) were compared between endotracheal epinephrine pediatric (ET Epi Peds) and endotracheal epinephrine adult (ET Epi Adult) groups in a swine cardiac arrest model.

Methods: Pigs were placed in arrest for 2 minutes, CPR was initiated for 2 minutes, and epinephrine was then administered. Blood samples were collected over 5 minutes. Epinephrine was repeated every 4 minutes until ROSC. Defibrillation began at 3 minutes and was repeated every 2 minutes until ROSC. Cardiopulmonary + defibrillation (CPR+Defib) and CPR Only groups were control groups.

Results: For the ET Pedi Group, the mean ± standard error of mean (SEM) were as follows: Cmax = 204 ± 35 ng/mL; Tmax = 142 ± 9 seconds; and AUC = 35,245 ± 7,133 ng/mL. Because only one subject had one measurable epinephrine level in the ET Adult group, we did not compare Cmax, Tmax, or AUC between the groups. The MC of the ET Pedi Group was significantly higher than the ET Adult Group over 5 minutes (p < 05). ROSC frequencies were 8 out of 8 in the ET Pedi Group and 1 out of 7 achieve ROSC. None in Pedi CPR Only or Adult CPR Only achieved ROSC. The mean times in seconds ± SD were as follows: ET Pedi Group, 372 ± 163; ET Adult Group, 490 (only 1 subject); ET Pedi CPR+Defib Group, 460 ± 42 (only 1 subject) and ET Adult CPR+Defib 495 (only 1 subject). None in the CPR-Only groups achieved ROSC.

Conclusion: The ET route should be considered as a first choice for the administration of epinephrine in a pediatric patient who has a cardiac arrest. We do not recommend using the ET route administration of epinephrine in adults.

More Information

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Introduction

The United States military medical commands are tasked to care for all casualties on the battlefield. Over one million adults and children have been killed from trauma in the wars in Iraq, Afghanistan, Pakistan, and Syria [1]. The military’s priority is to care for the US Army, Air Force, Marines, and Navy personnel. However, care is also provided to children who are victims of war. Children have always been victims of war. For example, during the last decade, at least 2 million children have died as a result of war [2,3]. Leidman et al. reported in the Iraq Body Count Project that 174,355 civilian adults and children died from 2003 to 2016 as a consequence of sniper attacks and aerial and roadside bombings [4,5]. Leidman et al. also found between January 2010 and December 2013, there were 7,976 road fatalities in Iraq, with approximately 71.5 % being adults and 28.5 % being children [3]. Also, the current horrific events in Israel and Gaza have led to thousands of adult and child deaths.

The military has a rich history of caring for civilians who are victims of natural disasters such as earthquakes, tornadoes, floods, etc. During the last 30 years, over four million adults and children have died worldwide in natural disasters. Because of climatic changes, the incidence of natural disasters is increasing [5-9]. The worldwide mortality rate was 76,416 deaths per year from natural disasters [10].

The American Heart Association (AHA) and the European Resuscitation Council recommend that if intravenous (IV) is not accessible, intraosseous (IO) and endotracheal (ET) routes be used in order of preference for the administration of epinephrine. For the individual in cardiac arrest, the recommendation for a pediatric patient is 0.1 mg/Kg and 2 mg for the adult patient regardless of weight to be repeated between 3 and 5 minutes [11-14]. These recommendations are based primarily on expert opinion not research. Regardless of the cause of cardiac arrest, vascular access is essential for successful resuscitation: The chance for survival decreases by 9 percent with each minute that passes without resuscitation [15]. However, in a cardiac arrest situation, the person’s veins collapse making IV access extremely difficult, time consuming, or impossible. Further, establishing IV access in children is inherently difficult particularly in cardiac arrest scenarios. Other factors impeding rapid vascular access include limited personnel, limited expertise, poor lighting, and mass casualties. Another factor hindering successful resuscitation is that cardiopulmonary resuscitation (CPR) must be interrupted for the time to acquire IV access.

Few studies have investigated the pharmacokinetics of epinephrine to include the peak concentration or maximum concentration (Cmax), time to maximum concentration (Tmax), mean concentration (MC) over time, and area under the curve (AUC). No study has compared the administration of epinephrine in an ET pediatric (ET Epi Peds) and ET adult model (ET Epi Adult) of cardiac arrest. With this gap, we compared ET Epi Peds and ET Epi Adult administration relative to the pharmacokinetics of epinephrine and return of spontaneous circulation (ROSC) in a normovolemic cardiac arrest model. Specifically, the following research questions guided the study:

1. Are there significant differences in ET Epi Peds and ET Epi Adult of cardiac arrest relative to Cmax, Tmax, AUC, and MC over time when epinephrine is administered?
2. Are there significant differences in the frequency and odds of the occurrence of ROSC in the ET Epi Peds, ET Epi Adult, Cardiopulmonary Resuscitation Defibrillation (CPR+Defib) and CPR Only groups?
3. Are there significant differences in the time to ROSC between ET Epi Peds, ET Epi Adult, CPR+Defib, and CPR Only groups?

Materials and Methods

Study Design and Selection of Subjects

This was a prospective, (within and between) subjects design approved by the Institutional Animal Care and use Committee (IACUC) supporting the Naval Medical Research Unit-San Antonio. Juvenile swine (20-35kg) representing the average weight for a male child between the ages of five and six years, and adult swine (60-80 kg) representing the average weight of an adult military member were used. All swine were classified as sus scrofa and were bred for research purposes only.

The number of subjects assigned by group were as follows: ET Epi Pedi (N = 7); ET Epi Adult (N = 7); CPR+Defib Peds (N = 7); CPR+Defib Adult (N = 7); CPR Only Adult (N = 7); and CPR Only Pedi (N = 7). The sequence of using each animal was determined by assignment using a random number generator (https://www.random.org). Castrated male subjects were used to avoid potential hormonal effects. To maintain consistency and health, we used subjects procured from Oak Hill Genetics, Ewing, IL, a supplier of purpose-bred swine for research.

Veterinary Care and Housing

All swine were housed and cared for in accordance with the Animal Welfare Act and Regulations and the Guide for the Care and Use of Laboratory Animals. Swine were allowed to acclimate to the holding areas for 3 days prior to commencement of the study. During that time, veterinarians evaluated them to be in good general health and free of disease. All animals were fed antibiotic-free swine diets and received ad libitum tap water. Animals were allowed social interaction with conspecifics until the procedure day. Twelve hours prior to the anesthesia, animals were not permitted
solid food but were allowed access to water. We assumed that all the subjects were normovolemic because each had moist mucus membranes and appropriate skin turgor determined by the veterinarians. In addition, all the pigs were allowed access to water until the experiment.

**Animal Preparation**

Animals were premedicated with 4.4 mg/kg Telazol (Tiletamine/Zolazepam; Fort Dodge Animal Health, IA) intramuscularly, and Buprenorphine SR (sustained release) at 4 mcg/kg subcutaneously. General anesthesia was induced with inhaled isoflurane at 1-5% in 100% oxygen. After ET placement, isoflurane was maintained between 1-2%.

Subjects were ventilated at 8-10 ml/kg tidal volume at a rate of 10-14 breaths per minute with a Dräger anesthesia machine. Heart rate (HR), mean arterial pressure (MAP), oxygen saturation (O₂), end-tidal capnography, and body temperature (Temp) were monitored continuously using the Dräger monitoring system.

For each pig, vascular access was achieved with an 18-gauge percutaneous catheter placed in the auricular vein. Patency was maintained with Lactated Ringers Solution at a rate of 50 ml/hr. The left carotid and femoral arteries were canulated with 8.5 Fr x 10cm central venous catheters (Arrow International, Reading, PA) using an open surgical approach and secured in place. Carotid lines provided continuous arterial blood pressure monitoring, while femoral lines were used for blood sampling and continuous monitoring of cardiac output (CO) and stroke volume (SV) using a Vigileo hemodynamic monitor (Edwards Lifesciences, Irvine, CA). A forced-air patient warming system (3M™ Bair Hugger™, St Paul, MN) was used to maintain temperature at or above 36°C. For those subjects achieving ROSC, we monitored HR, CO, SV, Mean Arterial Pressure, Temp, Systolic Blood Pressure (SBP), Diastolic Blood Pressure, and oxygen saturation levels every 5 minutes for a total of 30 minutes (6 times). A mean and SD was calculated for each pig for 30 minutes (6 times) and then by group.

**Experimental Procedures**

After a 15-minute stabilization, we passed an electric current to the side of the swine's heart to induce ventricular fibrillation, a procedure developed by the investigators [16]. Anesthesia was discontinued, and 2 minutes of arrest without intervention was implemented to replicate an usual delay in treatment. A Mechanical Compression Device (Model 1008, Michigan Instruments, Grand Rapids, MI) administered mechanical chest compressions at 100 compressions per minute. Manual ventilations were delivered at a rate of 6 to 10 per minute. The quality of chest compressions was confirmed by observing the arterial pressure and capnographic waveforms. After 4 minutes of cardiac arrest, we disconnected the anesthesia circuit from the ET, lifted the subject's head 45 degrees, and administered the AHA Pediatric Advanced Life Support (PALS) recommended dose of epinephrine (0.1 mg/kg; 1 mg/mL) for each subject in the ET Epi Peds group. The epinephrine was diluted in 8 mL 0.9% normal saline. For the ET Epi Adult group, we administered 2 mg of epinephrine regardless of weight according to the AHA guidelines. The CPR+Defib and CPR only groups were control groups and were not administered epinephrine. Serial blood specimens (10 mL) were collected from the left femoral arterial line at 30, 60, 90, 120, 150, 180, 240, and 300 seconds after epinephrine administration. Before each specimen collection, we aspirated and discarded 8 mL of blood to avoid any residual epinephrine in the tubing from the previous time. At the conclusion of each specimen collection, 10 mL of 0.9% normal saline were injected into the arterial line to clear the line and to maintain patency. We defibrillated at AHA recommended energy levels every 2 minutes starting at 3 minutes for the ET and CPR+Defib groups [13,17,18]. For the ET groups, we continued epinephrine administration every 4 minutes and defibrillation every 2 minutes until ROSC [13,17,18]. For the purposes of this study, ROSC was defined as a SBP of at least 60 mmHg and a palpable femoral pulse for 30 minutes. If ROSC occurred, the time was documented, and we continued to document vital signs for 30 minutes. For all subjects, if ROSC were not achieved within 30 minutes, we terminated the study.

Blood specimens were placed in lithium heparin collection tubes and centrifuged immediately (Thermo Fisher Scientific, Waltham, MA) for 15 minutes at 1800g. Separated plasma was pipetted into duplicate 2 mL microcentrifuge vials and frozen to a temperature of −80°C. Blood specimen analysis for epinephrine was performed using high-performance liquid chromatography (HPLC) with tandem mass spectrometry and performed on samples collected only after the first dose of epinephrine.

**Statistical Analyses**

The SPSS Statistics Software package, version 22 (IBM, Armonk, NY, USA) was used for data analyses. Means (M), standard deviations (SD), and standard errors of the mean (SEM) were calculated for the groups. An one-way Multivariate Analysis of Variance (MANOVA) was used to determine if there were significant differences between the groups relative to pretest data and time to ROSC. Fisher’s Exact Test was used to determine if there were differences in the incidence of ROSC between groups. An odds ratio was used to determine the chances for ROSC (https://www.medcalc.org/calc/odds_ratio.php). For all statistical analyses, significance was indicated by a p value < 0.05. When a significant difference was found.
using MANOVA, the Least Significant Difference post hoc test was used to find where the difference was.

**Sample Size Estimation**

The investigators used the means and standard deviations of Cmax, Tmax, and plasma MC over time from similar pharmacokinetic studies and calculated a medium effect size of 0.6 [19,20]. Using an alpha of 0.05, an effect size of 0.6, and a power of 0.80, we determined a sample size of 7 was needed in all the groups. Power analysis was performed using G*Power 3.1 for Windows (Heinrich Heine University). We had one additional pig for model development that was used in the ET Epi Peds group. He met all the requirements for inclusion in the study; therefore, we added him into this group to total 8 subjects.

**Results**

There were no significant differences in pretest data indicating the ET Pedi Groups and the ET Adult Groups were equivalent on these variables (p > 0.05). Only one subject in the ET Epi Adult Group had measurable epinephrine levels (67 ng/mL) at the time of 240 seconds after the first dose of epinephrine administration. For the ET Pedi Group the M ± SEM were as follows: Cmax = 204 ± 35 ng/mL; Tmax = 142 ± 9 seconds; and AUC = 35,245 ± 7,133 ng/mL. Because only one subject had one measurable epinephrine level in the ET Adult group, we did not compare Cmax, Tmax, or AUC between the groups.

The MC of the ET Epi Adult Group was significantly higher than the ET Pedi Group at each time of data collection (p < 0.05) (See Figure 1 for a summary of MC over time).

There was no significant difference in time to ROSC by group (> 0.05). The mean times in seconds ± SD were as follows: ET Pedi Group, 372 ± 163; ET Adult Group, 490 (only 1 subject); ET Pedi CPR+Defib Group, 460 ± 42 (only 1 subject); and ET Adult CPR+Defib 495 (only 1 subject). None in the CPR only groups achieved ROSC.

**Limitations**

The greatest limitation of our study was the small sample size; however, we had enough power to find differences. Another limitation was that the investigators were not blinded, but the individual who performed the HPLC analyses was. Although the investigators were not blinded, we rigorously adhered to the protocol. Another limitation is that the findings may not be generalizable to humans, but the cardiovascular and pulmonary physiology are very similar to humans and are considered an excellent model for this type of research [21-22]. Another potential limitation was the study continued for only 30 minutes after ROSC. Numerous investigators have found negative effects of epinephrine in long-term neurological survivability [22-26]. Future studies need to expand the time after ROSC to determine the long-term effects.

**Discussion**

This study found that the administration of epinephrine in a pediatric cardiac arrest model was highly effective 8 out of 8 compared to the adult cardiac arrest model of 1 out of 7 achieving ROSC. Our study supports the study by Orlowski, et al. who found that the ET administration of epinephrine in both a hypovolemic and normovolemic adult cardiac arrest model was ineffective [27]. Our study expands their study by comparing adult and pediatric models in a cardiac arrest model and including pharmacokinetics and ROSC variables. Our study also supports the findings of
Burgert who found that the adult ET administration of epinephrine was unreliable in an adult hypovolemic cardiac arrest model [20]. Our study expands their study to include a pediatric model. In addition, our study supports the findings of Yauger, et al. who found that odds of ROSC in a pediatric cardiac rest model was 2.4 times greater than for an IV group [19].

**Conclusion**

Based on the findings of this study, we recommend the use of the ET route administration of epinephrine for normovolemic pediatric patients who are in cardiac arrest. While traditionally considered a contingency plan, these findings indicate that ET administration of Epi is a viable option in the pediatric population in cardiac arrest, especially in situations in which IV catheterization is difficult or delayed.

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 and that the average time for obtain IV access was 2.5 to 16 minutes and in extreme cases as long as 55 minutes in critically ill patients who were not in arrest [28]. Hence, the ET route should be considered as a first choice for a pediatric patient: ET intubation can be placed in less than 30 seconds by an experienced provider [29]. We do not recommend the use of the ET route administration of epinephrine in the adult. Only one out of seven subjects had detectable epinephrine levels and only one achieved ROSC. We speculated that the reason we found the ROSC to be higher in the ET Epi Peds group compared to the ET Epi Adult group was the amount of epinephrine was calculated based on weight rather than the adult recommended dose of 2 mg regardless of weight. Therefore, we recommend future studies to include comparison with IV epinephrine and weight dosing for the adult cardiac arrest model. In the child, the administration of 0.1 mg/Kg compared to 2 mg in the adult translates to 0.02 mg/Kg in an average sized male.

**List of Abbreviations**

- AHA: American Heart Association
- AUC: Area Under the Curve
- Cmax: Concentration Maximum
- CO: Cardiac Output
- CPR: Cardiopulmonary Resuscitation
- CPR+defib: Cardiopulmonary + Defibrillation
- ET EP Adult: Endotracheal Epinephrine Adult
- ET Epi Peds: Endotracheal Epinephrine Pediatrics
- IACUC: Institutional Animal Care and Use Committee
- IO: Intraosseous
- MANOVA: Multivariate Analysis of Variance
- MAP: Mean Arterial Pressure
- MC: Mean Concentration over time
- O2 Saturation: Oxygen Saturation
- ROSC: Return of Spontaneous Circulation
- SD: Standard Deviation
- SEM: Standard Error of Mean
- SV: Stroke Volume
- Temp: Temperature
- Tmax: Time to Maximum Concentration
- SBP: Systolic Blood Pressure
- PALS: Pediatric Advanced Life Support
- HPLC: high-performance liquid chromatography

**Declarations**

DJ, JO, YY, and JH developed the ideas for the study. They were instrumental in the design, approval process, acquiring funding, data analyses, and writing the manuscript. JO and DB were instrumental in collecting the data and assisted in analyzing the results of the study. They, too, were involved in writing the manuscripts. None of the authors have competing interests or conflicts of interest.

All the authors declare permission to publish the manuscript.

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**Approval**

Institutional Animal Care and Use Committee

**Conflict of Interest**

No author has any conflicts of interest.

**References**


