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Effects of humeral intraosseous versus intravenous epinephrine on pharmacokinetics and return of spontaneous circulation in a porcine cardiac arrest model: A randomized control trial

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HIGHLIGHTS

- No difference in concentration maximum (Cmax) and time to maximum concentration (Tmax) in epinephrine between humeral intraosseous and intravenous routes of administration over time.
- Humeral intraosseous delivers higher concentration than intravenous at 30 s after administration of epinephrine.
- Humeral intraosseous facilitates rapid delivery of epinephrine during cardiac arrest.
- Use of humeral intraosseous had higher number of subjects survived.

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ABSTRACT

Cardiopulmonary Resuscitation (CPR), defibrillation, and epinephrine administration are pillars of advanced cardiac life support (ACLS). Intraosseous (IO) access is an alternative route for epinephrine administration when intravenous (IV) access is unobtainable. Previous studies indicate the pharmacokinetics of epinephrine administration via IO and IV routes differ, but it is not known if the difference influences return of spontaneous circulation (ROSC). The purpose of this prospective, experimental study was to determine the effects of humeral IO (HIO) and IV epinephrine administration during cardiac arrest on pharmacokinetics, ROSC, and odds of survival. Swine (N = 21) were randomized into 3 groups: humeral IO (HIO), peripheral IV (IV) and CPR/defibrillation control. Cardiac arrest was induced under general anesthesia. The swine remained in arrest for 2 min without intervention. Chest compressions were initiated and continued for 2 min. Epinephrine was administered and serial blood samples collected for pharmacokinetic analysis over 4 min. Defibrillation and epinephrine administration proceeded according to ACLS guidelines continuing for 20 min or until ROSC.

Seven HIO swine, 4 IV swine, and no control swine had ROSC. There were no significant differences in ROSC, maximum concentration; except at 30 s, and time-to-concentration-maximum between the HIO and IV groups. Significant differences existed between the experimental groups and the control. The HIO delivers a higher concentration of epinephrine than the IV route at 30 s which may be a survival advantage. Clinicians may consider using the IO route to administer epinephrine during CA when there is no preexisting IV access or when IV access is unobtainable.

1. Introduction

Incidence of death attributable to cardiovascular disease has declined over the past 15 years but still accounts for 1 of every 3

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deaths in the United States. Cardiovascular disease continues to be the leading cause of death in the United States [1,2]. The incidence of sudden cardiac arrest (CA) in 2013 was approximately 326,200 occurrences of out-of-hospital CA and 209,000 occurrences of in-hospital CA [1]. Research has shown that survival depends on a rapid sequence of therapeutic interventions termed the "chain of survival." Vascular access is a vital step in this chain [3,4] [5]. Several studies demonstrate establishing rapid vascular access is essential in enhancing outcomes during cardiac arrest [3,6–10]. However, during CA, environmental conditions and cardiovascular compromise may make intravenous (IV) vascular access difficult or impossible and time consuming. The intraosseous (IO) route has been demonstrated to be a reliable and effective alternative when IV access cannot be obtained [3,11–13]. Several organizations including the American Heart Association (AHA), the European Resuscitation Council (ERC), and several others recommend the use of IO access if IV access is not readily available [3,14–20].

Few studies have investigated the effects of IO epinephrine pharmacokinetics specifically maximal plasma concentration (Cmax) and time to maximum plasma concentration (Tmax) during CA. Investigations conducted by coauthors of this study found that epinephrine administered via tibial IO route achieved a lower Cmax and a demonstrated a prolonged Tmax when compared to either the sternal IO and IV routes [5,11]. Hoskins et al. reported a prolonged Tmax when administering epinephrine during CA using the tibial IO route compared to central venous route [21]. No study to date has examined the effects of IO administration of epinephrine on return of spontaneous circulation (ROSC) and pharmacokinetic measurements of plasma epinephrine during cardiac arrest with ongoing CPR.

The purpose of this study was to determine the effects of the humeral IO administration of epinephrine compared to IV on ROSC and pharmacokinetics in a swine model of cardiac arrest. The research questions that guided this study were:

1. Are there statistically significant differences in the rate ROSC between the humeral IO, IV, and control groups?
2. Are there statistically significant differences in Cmax and Tmax of epinephrine between the humeral IO, IV, and control groups?
3. Are there statistically significant differences in the odds of survival between the humeral IO, IV, and control groups?
4. Are there statistically significant differences in the plasma concentration of epinephrine between the humeral IO and IV groups?

2. Methods

This study was a prospective, between groups, experimental design approved by the TriService Research Laboratory Institutional Animal Care and Use Committee. The animals received care in compliance with the Animal Welfare Act and the Guide to the Care and Use of Laboratory Animals. The investigators used a swine model because of ease of care, relatively inexpensive, and, more importantly, because the cardiovascular system and bone marrow of swine are comparable to humans and accepted as analogs in research [22,23].

We used a computer generated random number to assign twenty-one Yorkshire-cross swine (*Sus scrofa*) to three groups: humeral IO ($n = 7$), peripheral IV ($n = 7$), and CPR/defibrillation control ($n = 7$). Food was withheld after midnight before the experiment. Water was allowed *ad libitum* up to the time of the experiment.

Thirty minutes prior to instrumentation, the swine were sedated, anesthetized, and placed on mechanical ventilation. Anesthesia was induced with an intramuscular injection of Telazol (4–8 mg/kg) and inhaled isoflurane (4%–5%). An 18-gauge peripheral IV was started in an auricular (ear) vein in all subjects. The auricular peripheral IV was used as the site of epinephrine administration for the IV experimental group. The auricular IV was maintained at a keep-vein-open (KVO) rate to ensure patency. After placement of an endotracheal tube, the isoflurane concentration was decreased to a maintenance dose (1%–2%) until CA was induced.

The animals were ventilated at 8–10 mL/kg tidal volume with a Narkomed 3A anesthesia machine (Dräger, Telford, PA). Respiratory rate was set at 10–14 breaths per minute. In all groups a 20 gauge catheter was placed in the left carotid artery using a cut-down technique. The arterial catheter was connected to a Phillips MP 50 system (Phillips Healthcare, Andover, MA) for continuous monitoring of systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean arterial pressure (MAP). The arterial line was also connected to a Vigileo Hemodynamic Monitor (Edwards Lifesciences, Irvine, CA) for continuous monitoring of cardiac output (CO) and stroke volume (SV). The Phillips MP 50 system was also used to monitor heart rate and rhythm, pulse oximetry (SpO_2), end-tidal carbon dioxide ($ETCO_2$), and rectal temperature. Normothermia was maintained using a forced air-warming blanket to maintain body temperature $\geq$37.0 °C.

Swine in the HIO group had a 15 gauge $\times$ 45 mm EZ-IO device (Teleflex Medical, San Antonio, TX) inserted in the humerus following surgical exposure. Surgical exposure was necessary to ensure correct placement of the HIO device because of the thick overlying soft tissue present in swine not found in humans. Placement of the HIO needle was verified by aspiration of bone marrow and ease of irrigation with 10 mL of normal saline.

Swine were stabilized for 5 min prior to beginning the experiment. Cardiac arrest was induced in all swine using the transcutaneous electrical induction technique. Specifically, a needle was inserted at the left sternal border between the second and third intercostal space at a depth of 3.25 cm. A second needle was inserted immediately caudal to the xiphoid process at a depth of 6 cm. Lead wires were attached to both needles. One lead wire was connected to the negative pole of three 9-V batteries connected in series. The other lead wire was rapidly tapped on the positive pole placing the swine into ventricular fibrillation. Cardiac arrest was operationally defined as any nonperfusing arrhythmia resulting in a SBP $\leq$60 mm/Hg. The subjects remained in arrest for 2 min without intervention. Most of the swine had ventricular fibrillation within 10 s, and all achieved arrest within 30 s. CPR was initiated at 2 min post-arrest using the "Thumper" Mechanical Compression Device, Model 1008 (Michigan Instruments, Grand Rapids, MI). The device was used to reproducibly compress the sternum to a predetermined depth of two inches and a rate of hundred compressions per minute. Ventilations were administered at 12 breaths per minute [24].

At 4 min post-arrest, the investigators administered epinephrine 1 mg to the IV and humeral IO groups according to group assignment followed by 10 mL of NS flush. The control group did not receive epinephrine. CPR continued for an additional 4 min. During this 4 min, the researchers collected aerial arterial blood samples pharmacokinetic analysis from the carotid arterial line. Seven samples were collected at 30, 60, 90, 120, 150,180 and 240 s. At 8 min post-arrest, the swine were defibrillated with 360 J (J). Defibrillation was repeated at 2 min intervals and epinephrine administration repeated every 4 min for 20 min (24 min post-arrest) or until ROSC was achieved. Animals achieving ROSC received standard AHA post-cardiac arrest care and were monitored for 30 min. Anesthesia, as tolerated by the animal, was immediately resumed.