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Effects of intraosseous epinephrine in a cardiac arrest swine model

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ABSTRACT

Background: Interruptions in cardiopulmonary resuscitation (CPR) to obtain vascular access reduces blood flow to vital organs. Tibial intraosseous (TIO) access may be a faster alternative to intravenous (IV) access for delivery of vasoactive medications. The purpose of this study was to examine the differences in pharmacokinetics and pharmacodynamics of TIO- and IV-delivered epinephrine.

Materials and methods: A prospective, between subjects, experimental design comparing C_{max}, T_{max}, return of spontaneous circulation (ROSC), and time to ROSC. Adult male swine were divided into three equal groups ($n = 7$) all received CPR and defibrillation: the second group received IV epinephrine and the third group received tibial intraosseous epinephrine. Swine were placed in cardiac arrest for 2 min before CPR was initiated. After 2 min of CPR, epinephrine was delivered by IV or TIO, and serial blood samples were collected over 4 min.

Results: There were no significant differences between IV *versus* TIO epinephrine in achieving ROSC, time to ROSC, and C_{max}. A one-way analysis of variance demonstrated a significant difference between the IV and TIO groups in T_{max} ($P = 0.025$). A Fisher exact test demonstrated a significant difference between IV epinephrine versus CPR/Defib only ($P = 0.035$) and TIO epinephrine *versus* CPR/Defib only ($P = 0.010$) in achieving ROSC. A multivariate analysis of variance showed significant differences in IV *versus* intraosseous epinephrine concentration at specific time intervals: 60 ($P = 0.023$), 90 ($P = 0.001$), and 120 ($P < 0.000$) sec.

Conclusions: In the context of ROSC, epinephrine delivered via TIO route is a clinically relevant alternative to IV administration. When IV access cannot be immediately obtained in cardiac arrest patients, TIO access should be considered.

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1. Introduction

1.1. *Intraosseous and cardiac arrest*

The latest statistics from the American Heart Association (AHA) in 2011 showed that nearly 326,000 people per year suffer from out-of-hospital cardiac arrest in the United States, of which only 10.6% survive to hospital discharge. The AHA defines cardiac arrest "as the cessation of cardiac mechanical activity as confirmed by the absence of signs of circulation." [1]. When this occurs, it is imperative that appropriate interventions begin immediately to achieve a return of

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spontaneous circulation (ROSC). Early cardiopulmonary resuscitation (CPR) provides a temporary means of blood delivery to vital organs, specifically the brain [2]. The addition of early defibrillation is used to restore a normal cardiac rhythm [3]. The pharmacologic intervention that contributes to achieving successful ROSC is the addition of vasoactive medications which enhance myocardial blood flow during CPR [4].

Health care providers trained in advanced cardiac life support (ACLS) can administer vasoactive medications intravascularly to facilitate efforts in achieving ROSC. Intravenous (IV) catheters are currently the standard for obtaining vascular access in medical emergencies [5]. However, attempting to establish IV access in patients with low cardiac output (CO) is more difficult without interrupting CPR [6,7]. Any actions that impede chest compressions during CPR must be minimized as interruptions necessitate a "rebuilding" of coronary reperfusion pressure, decreasing the patient's vital organ perfusion and the ability to circulate medications [8,9]. A decrease in survival has been reported for every 3 min that elapsed after cardiac arrest without epinephrine administration [10]. In severely compromised patients, the time to obtain IV access in relation to the need to rapidly deliver medications means the IV route may not always be the optimal method for delivering the initial rounds of lifesaving medications.

Advances in intraosseous (IO) technology have provided an alternative method for accessing the noncollapsible and highly vascularized intramedullary venous plexus in emergencies. Tibial intraosseous (TIO) access has been shown to have a 91%–97% first time attempt success rate in emergency and routine situations, whereas first time success rates for IV access ranged from 76%–91% [11–13]. Leidel *et al.* found that it took medical providers a mean time of 2 min to insert an IO in patients undergoing resuscitation, whereas Minville *et al.* noted that IV access took an average of 4.4 min [13,14]. Although these previous studies have shown that the modern IO can be quickly inserted into the bone to obtain vascular access with high rates of success, it is not the current standard for establishing initial vascular access in cardiac arrest situations.

1.2. Decision to use IO access

The development of semiautomatic IO devices has given the health care provider an alternative route to quickly access the vasculature to administer fluids and medications. However, despite advances in IO technology, many health care providers still underuse or have never used this type of device to obtain vascular access in urgent situations such as cardiac arrests [11,15]. Numerous medical providers are hesitant to use this device because of a lack of equipment and education [16]. James *et al.* found that physicians were more likely to use an IO if assured it would allow for rapid vascular access to facilitate delivery of necessary fluids, prevent the delay of care, and have minimal complications. These physicians were also less likely to use an IO if they felt the nurses lacked understanding of or did not support this technology [15]. Medically trained personnel who use modern IO devices to obtain vascular access have a high success rate and quick access times [12,14]. Zuercher *et al.* demonstrated in a swine model that early vascular access and epinephrine administration via the TIO led to a significant increase in 24-h survivability *versus* the group that received delayed epinephrine via IV [7]. However, there has been limited research addressing both the pharmacokinetics and pharmacodynamics of IO-delivered epinephrine. Although other studies have addressed delivery routes and their effects on the pharmacokinetics of maximum serum concentration (C_{max}) and time to maximum serum concentration (T_{max}), none of these studies have compared the relationship of the pharmacokinetics to the pharmacodynamics of ROSC [17,18].

This study will address the hypothesis that TIO administration of epinephrine is equivalent to IV in a cardiac arrest model, thereby addressing the gap of knowledge regarding C_{max}, T_{max}, and ROSC when epinephrine is administered by TIO *versus* peripheral IV during cardiac arrest.

2. Materials and methods

2.1. Study design and population

The study was a prospective, mixed (within and between subjects) experimental design. The Institutional Animal Care and Use Committee approved the research protocol (Naval Medical Research Unit, JBSA-FSH protocol 12-01), and all subjects received care according to the Animal Welfare Act and the Guide for the Use of Laboratory Animals. Twenty-one male Yorkshire-cross swine, weighing between 60 and 80 kg, were used because they represented the average weight of US military service members [19]. Using Microsoft Office Professional Plus 2010 (Version 14.0.5130.5003), the swine were randomly assigned to one of three equally allocated groups ($n = 7$ per group): CPR and defibrillation only, CPR and defibrillation with epinephrine via TIO, and CPR and defibrillation with epinephrine via IV. To minimize variables, all the swine were adult castrated males purchased from the same vendor (Oak Hill Genetics, Ewing, IL). After arriving at the test facility, the animals were observed for 3 d and allowed to acclimate before testing. They received regular medical screening: daily temperature and weight as well as standard diet consumption were checked during the observation period to ensure a state of good health. Twelve hours before the experiment the animals were transitioned to water only.

2.2. Study preparation

The swine were induced with an intramuscular injection of tiletamine HCl (50 mg/mL) and zolazepam HCL (50 mg/mL) at 4 mg/kg followed by inhalation of isoflurane (4%–5%) with 100% oxygen and then intubated with an 8.0 endotracheal tube (ETT). After confirmation of ETT placement, the subjects were mechanically ventilated with a tidal volume (Vt) of 8–10 mL/kg at a rate of 10–14 breaths per min via a GE Datex-Ohmeda Aestiva anesthesia machine (Datex-Ohmeda, Inc., Madison, WI) with an $ETCO_2$ target of 35–45 mm Hg. Isoflurane inspired concentration was reduced to 1%–2% until a nonperfusing rhythm was induced, at which time inhalation anesthesia was stopped. The subjects' vital signs (pulse oximetry, rectal temperature, 5-lead electrocardiogram, arterial