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Pharmacokinetic effects of endotracheal, intraosseous, and intravenous epinephrine in a swine model of traumatic cardiac arrest

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ABSTRACT

Introduction: Limited prospective data exist regarding epinephrine's controversial role in managing traumatic cardiac arrest (TCA). This study compared the maximum concentration (Cmax), time to maximum concentration (Tmax), plasma concentration over time, return of spontaneous circulation (ROSC), time to ROSC, and odds of ROSC of epinephrine administered by the endotracheal (ETT), intraosseous (IO), and intravenous (IV) routes in a swine TCA model.

Methods: Forty-nine Yorkshire-cross swine were assigned to seven groups: ETT, tibial IO (TIO), sternal IO (SIO), humeral IO (HIO), IV, CPR with defibrillation (CPRD), and CPR only. Swine were exsanguinated 31% of their blood volume and cardiac arrest induced. Chest compressions began 2 min post-arrest. At 4 min post-arrest, 1 mg epinephrine was administered, and blood specimens collected over 4 min. Resuscitation continued until ROSC or 30 min elapsed.

Results: The Cmax of IV epinephrine was significantly higher than the TIO group ($P = 0.049$). No other differences in Cmax, Tmax, ROSC, and time to ROSC existed between the epinephrine groups ($P > 0.05$). Epinephrine levels were detectable in two of seven ETT swine. No significant difference in ROSC existed between the epinephrine groups and CPRD group ($P > 0.05$). Significant differences in ROSC existed between all groups and the CPR only group ($P < 0.05$). No significant differences in odds of ROSC were noted.

Conclusions: The pharmacokinetics of IV, HIO, and SIO epinephrine were comparable. Endotracheal epinephrine absorption was highly variable and unreliable compared to IV and IO epinephrine. Epinephrine appeared to have a lesser role than volume replacement in resuscitating TCA.

1. Introduction

The rate of return of spontaneous circulation (ROSC) with acceptable neurological outcome at hospital discharge after traumatic cardiac arrest (TCA) is low [1-3]. Rapid response time, hemorrhage control, and volume replacement in damage control resuscitation are well-supported by evidence as effective therapies [1,4,5]. The use of epinephrine during the management of medical cardiac arrest (MCA) and TCA is highly controversial. Some evidence sources suggest epinephrine is a beneficial therapy [6-8]. Other studies suggest the opposite [9-13]. Although some reviews and observational studies exist, there are limited prospective experimental data regarding the pharmacokinetic performance and resuscitative effectiveness of epinephrine in the management of TCA.

Vascular collapse following hypovolemic shock or TCA may delay, or make impossible, placement of intravenous (IV) access. The intraosseous (IO) and endotracheal (ETT) routes, in order of preference, are recommended by the American Heart Association (AHA) and the European Resuscitation Council for administering resuscitative drugs when IV access cannot be obtained [14,15]. Intraosseous injection sites approved by the US Food and Drug Administration (FDA) include the tibial IO (TIO), sternal IO (SIO) and the humeral IO (HIO) [16]. Studies comparing the pharmacokinetic and resuscitative performance of IO and IV administered epinephrine, lidocaine, amiodarone, and vasopressin; during MCA,

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and amiodarone; during TCA, indicated the IO route performed comparably to the IV route [17-23]. However, there are limited data available comparing the pharmacokinetic performance of epinephrine when administered by the ETT, IV, and various IO routes during TCA. A recent literature review reported no randomized, controlled studies comparing IV, IO, and ETT epinephrine administered during cardiac arrest (CA) to children and adults were identified [24].

Based on a review of the literature, we hypothesized the pharmacokinetic performance of epinephrine would not differ between various routes of administration in the presence of TCA. Further, we hypothesized route of epinephrine administration would not affect resuscitative outcome in the presence of TCA. Determining if differences exist in the absorption, distribution, and performance of epinephrine between different administration routes is scientifically and clinically important. Quantification of the pharmacologic performance of epinephrine during TCA would contribute useful data that would increase understanding, address this knowledge deficit and, perhaps, guide translational research that may ultimately determine the utility of epinephrine during TCA.

The primary study goal was to determine if significant differences existed in the maximum plasma concentration (Cmax), time to maximum concentration (Tmax), and mean plasma concentrations over 5 min of epinephrine administered by the IV, ETT, and FDA approved IO routes in a swine model of TCA.

The secondary study goal was to determine if significant differences existed between the different routes of epinephrine infusion relative to the rate, time to, and odds of ROSC in the same model.

2. Materials and methods

This prospective, randomized, between-subjects design laboratory study was approved by the Institutional Animal Care and Use Committee (IACUC) of the Naval Medical Research Unit-San Antonio. Yorkshire-cross, male swine *Sus scrofa* (N = 49) were randomly and equally assigned (n = 7) to one of seven groups using a computerized random number generator: CPR only (CPR); no defibrillation, no epinephrine, CPR and defibrillation (CPRD); defibrillation, no epinephrine, TIO, HIO, SIO, ETT, and IV. Swine weighing between 60 and 80 kg were used as this range approximates the average weight of an adult, male human [25].

2.1. Veterinary care and housing

Housing and care of the swine were in accordance with the Animal Welfare Act and the Guide for the Care and Use of Laboratory Animals [26]. The attending veterinarian examined all swine to ensure good health during the 3-day acclimation period before data collection. The veterinary staff observed the swine daily for signs of illness. Ill swine were removed from the study. Swine were given standard feed and tap water ad libitum. The swine received nothing by mouth after midnight before the experiment except water until 2 h before anesthetic induction.

2.2. Animal preparation

Swine were premedicated with an intramuscular (IM) injection of atropine (0.05 mg/kg) and sedated with an IM injection of Telazol (4.4 mg/kg), (tiletamine/zolazepam, Fort Dodge Animal Health, Fort Dodge, IA, USA). General anesthesia was induced with inhaled isoflurane (2% to 5%) and reduced to a maintenance dose (1% and 2%) after endotracheal intubation using an Aestiva 5 anesthesia machine (Datex-Ohmeda, Madison, WI, USA). Heart rate (HR), electrocardiography (ECG), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), oxygen saturation (SpO_2), end-tidal capnography ($ETCO_2$) and body temperature (°C) were continuously measured using a Datex-Ohmeda Cardiocap 5 monitoring system (GE Healthcare, Helsinki, Finland).

An 18-gauge IV was placed in an auricular vein of each swine and lactated Ringer's solution (100 mL/h) infused to maintain patency. The left carotid and left femoral arteries were surgically exposed and arterial catheters placed in both sites. The 20 ga. left carotid arterial line was used for continuous blood pressure monitoring. The left femoral arterial line was cannulated with an 8.5 French × 10 cm catheter (Arrow International, Reading, PA, USA). The femoral arterial line was used for exsanguination, blood specimen draws, and continuous cardiac output (CO) and stroke volume (SV) monitoring using a Vigileo hemodynamic monitor (Edwards Lifesciences, Irvine, CA, USA). Body temperature was maintained at ≥36 °C using an under-body circulating water blanket (Gaymar Industries, Orchard Park, NY, USA).

Swine had a 15-gauge × 25 mm EZ-IO device (Teleflex Medical, Research Triangle Park, NC, USA) placed per manufacturer's directions in either the proximal, anterior, medial aspect of the tibia, the proximal humerus, or a non-segmented region of the sternum. Surgical exposure of the humerus and sternum was necessary to avoid IO misplacement when using a device designed for humans in swine.

2.3. Experimental procedures

After a 15-minute stabilization period, an American College of Surgeons Class III hemorrhage was simulated by exsanguinating 31% of each swine's estimated blood volume (EBV) using gravity drainage and controlled suction of the femoral artery catheter. The EBV was calculated using a factor of 70 mL/kg of body weight. For example, a 70 kg swine has an EBV of 4900 mL. Thirty-one percent of 4900 mL is 1519 mL. The TIF electronic scale (Thermal Industries of Florida, Owatonna, MN, USA) was used to accurately and precisely measure shed blood volume and was zeroed with a collection canister in place to control for canister weight variation. Suction was applied to exsanguinate approximately 100 mL of blood per minute.

After exsanguination, the swine were placed into CA by passing an electrical current through the heart. Isoflurane anesthesia was discontinued, and midazolam 6 mg IV and buprenorphine 0.6 mg IV were administered. After 2 min in CA without intervention, mechanical chest compressions were administered using a Mechanical Compression Device, Model 1008 (Michigan Instruments, Grand Rapids, MI, USA) at 100 compressions per minute. Manual ventilations were delivered at a rate of 6 to 10 per minute. Quality of chest compressions was confirmed by observing the arterial line and capnographic waveforms.

After 4 min of CA, 1 mg of epinephrine was administered to IV and IO swine through the assigned device followed by a 20 mL NS flush. Endotracheal epinephrine was administered using this procedure; disconnect the anesthesia circuit from the ETT, lift the swine's head 45 degrees, administer 2 mg (1 mg/mL) of epinephrine, diluted in 8 mL 0.9% NS via the ETT, administer four tidal breaths using a bag valve ventilation device, lower the swine's head, reconnect the anesthesia circuit to the ETT. The CPRD and CPR groups were not administered epinephrine. Serial blood specimens (10 mL) were collected at 30, 60, 90, 120, 150, 180, 240, and 300 s from the left femoral arterial line after epinephrine injection. Before each specimen collection, the investigators aspirated and discarded 10 mL of blood to avoid dilution. After each specimen was collected, 10 mL of NS was injected to clear the arterial line. Each swine received 5% albumin (500 mL) following specimen collection. Resuscitation continued until ROSC or 30 min elapsed.

Blood specimens were placed in lithium heparin collection tubes and centrifuged immediately. Separated plasma was pipet-

ted into 2 mL microcentrifuge vials and frozen to minus 40 °C. High-Performance Liquid Chromatography with Tandem Mass Spectrometry was used to quantify plasma epinephrine levels.

2.4. Sample size estimation

The investigators used the means and standard deviations of Cmax, Tmax, and mean plasma concentrations over time from similar pharmacokinetic studies and calculated a large effect size of 0.6 [18,27-31]. Using an α of 0.05, an effect size of 0.6, and a power of 0.80, it was determined a sample size of 49 (n = 7 per group) was needed. Power analysis was performed using G*Power 3.1 for Windows (Heinrich Heine University, Dusseldorf, Germany).

2.5. Statistical analyses

The SPSS Statistics Software package, version 22 (IBM, Armonk, NY, USA) was used for data analysis. Means and standard errors of the mean (SEM) were calculated for the groups receiving epinephrine. Significance was indicated by a P value ≤ 0.05. Fisher's Exact Test was used to determine if there were differences in the rate of ROSC between groups. A one-way Multivariate Analysis of Variance (ANOVA) was used to determine if there were significant differences between the groups relative to pretest data, Cmax, Tmax, and time to ROSC. Repeated measures ANOVA was used to determine if there were statistical differences between the groups relative to the mean plasma concentration of epinephrine at each specimen collection time point. When a significant difference was found, the Least Significant Difference Posthoc test was used to find where the difference was. Odds of ROSC were calculated for each group and compared using MedCalc for Windows, version 17.9 (MedCalc Software, Ostend, Belgium).

3. Results

All swine enrolled in the study completed the experiment. However, detectable plasma epinephrine levels were found in only two of seven ETT group swine. There were no significant differences in pretest data by group (weight, amount of hemorrhage, HR, SBP, DBP, MAP, CO, SV, and temperature) indicating the groups were similar relative to these variables ($P > 0.05$).

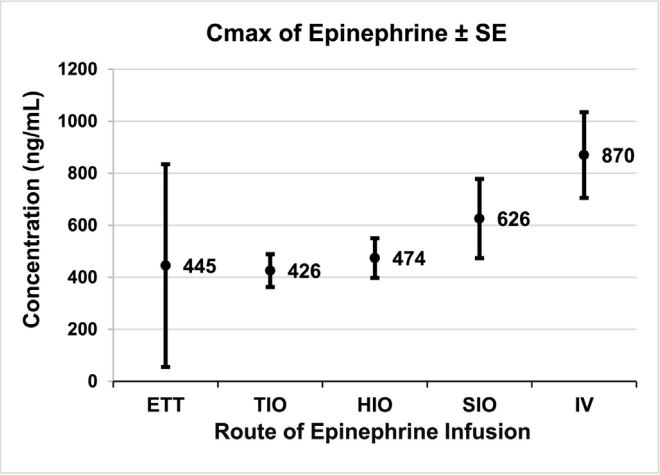

Fig. 1. Comparison of mean maximum plasma concentrations (Cmax) of epinephrine by infusion route. There was a significant difference between the IV and TIO groups ($P = 0.049$). Otherwise, there were no differences between the groups ($P > 0.05$ in all other instances).

3.1. Maximum plasma concentration (Cmax)

One-way Multivariate ANOVA testing indicated the Cmax of the IV group was significantly higher than the TIO group ($P = 0.049$). Otherwise, there were no other significant differences in Cmax among the epinephrine receiving groups ($P > 0.05$ in all pairwise comparisons). The mean Cmax of epinephrine by group are presented in tabular and graphical form (Table 1 and Fig. 1).

3.2. Time to maximum concentration (Tmax)

One-way Multivariate ANOVA indicated the Tmax of the TIO group was significantly longer than the ETT, HIO, SIO and IV groups ($P = 0.008$, 0.024, 0.013 and 0.033, respectively). The mean Tmax of

Table 1
Pharmacokinetics of ETT, IO, and IV Epinephrine during TCA.

Measurement	Group	Mean	±SE	P values
Cmax (ng/mL)	ETT	445	390	ETT vs. HIO = 0.91
				ETT vs. IV = 0.10
	TIO	426	63	ETT vs. SIO = 0.48
				ETT vs. TIO = 0.94
	HIO	474	76	HIO vs. IV = 0.08
				HIO vs. SIO = 0.49
	SIO	626	152	HIO vs. TIO = 0.82
				SIO vs. TIO = 0.36
	IV	870	165	IV vs. SIO = 0.27
				IV vs. TIO = 0.049*
Tmax (s)	ETT	120	53.3	ETT vs. HIO = 0.41
				ETT vs. IV = 0.35
	TIO	223	17	ETT vs. SIO = 0.56
				ETT vs. TIO = 0.01*
	HIO	150	18.5	HIO vs. IV = 0.89
				HIO vs. SIO = 0.78
	SIO	141	17	HIO vs. TIO = 0.03*
				SIO vs. TIO = 0.01*
	IV	154	17.8	IV vs. SIO = 0.68
				IV vs. TIO = 0.03*

Cmax, maximum plasma concentration; ETT, endotracheal; HIO, humeral intraosseous; IV, intravenous; SE, standard error of the mean; SIO, sternal intraosseous; TIO, tibial intraosseous; Tmax, time to maximum plasma concentration; TCA, traumatic cardiac arrest. *Significance indicated by P value ≤ 0.05.

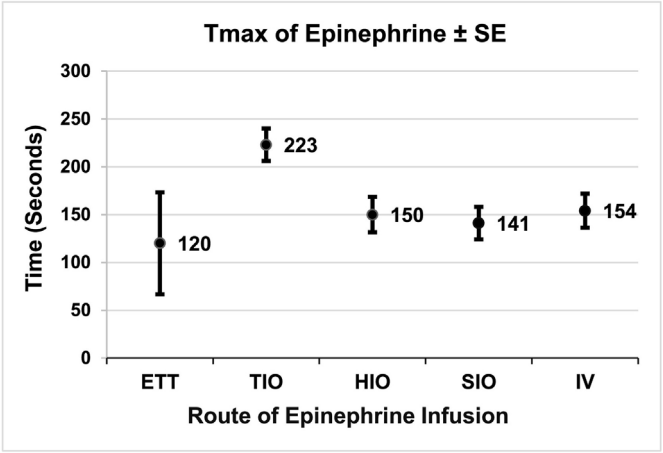

Fig. 2. Comparison of mean time to maximum plasma concentration (Tmax) of epinephrine by infusion route. Significant differences in Tmax were found between the TIO and the ETT ($P = 0.01$), HIO ($P = 0.03$), SIO ($P = 0.01$), and IV ($P = 0.03$) groups, respectively.

epinephrine by group are compared in tabular and graphical form (Table 1 and Fig. 2).

3.3. Mean plasma concentration of epinephrine over 5 min

Repeated ANOVA revealed no statistically significant differences in mean plasma epinephrine concentration between the groups at the 30 or 60 s time points ($P > 0.05$). Significant differences in mean plasma epinephrine concentration over time existed between the ETT and IV groups at 90, 120, 150, 180, & 240 s and the IV and TIO groups at 90, 120, 150, & 180 s ($P < 0.05$). There were further significant differences in mean plasma epinephrine concentration over time between the ETT and SIO groups at 120, 150, 180, & 240 s and the IV and HIO groups at 120 & 180 s ($P < 0.05$). The mean plasma concentrations of epinephrine vs. time by group are presented in tabular and graphical form (Table 2 and Fig. 3).

3.4. Rate of ROSC

Fisher's Exact Test indicated no significant differences in the rate of ROSC among the ETT, TIO, HIO, SIO, IV, and CPRD groups ($P > 0.05$). There were significant differences in the rate of ROSC between the HIO, IV, and TIO groups compared to the CPR group ($P < 0.05$). The rate of ROSC results is presented in tabular form (Table 3).

3.5. Mean time to ROSC and odds of ROSC

One-way multivariate ANOVA revealed no significant differences in mean time to ROSC by group ($P > 0.05$ in all pairwise comparisons). The mean times to ROSC by group are compared graphically (Fig. 4). There was no significant difference between the groups relative to odds of ROSC ($P > 0.05$ in all pairwise comparisons).

4. Discussion

4.1. Discussion of pharmacokinetic effects results

The primary goal of this study was determining if there were differences in the pharmacokinetic measures of Cmax, Tmax, and mean plasma concentrations over 5 min when epinephrine was administered by the ETT, IV, and IO routes during TCA. There were no differences in the Cmax of epinephrine except the IV group was significantly higher than the TIO group. The Tmax of the TIO group was significantly longer than all other epinephrine groups. More interesting was the mean concentration over time curves.

The IV, SIO, and HIO concentration over time curves had similar gradual absorption phases with peak mean plasma epinephrine concentrations reached at 120 s for the IV (802 ± 188 ng/mL) and SIO (572 ± 155 ng/mL) groups and 150 s for the HIO group (408 ± 66 ng/mL) followed by gradual, declining distribution phases in all groups. The absorption phase of the TIO group was unexpectedly prolonged peaking at 240 s (381 ± 72 ng/mL). Considering 240 s was the last measured data point, it is conceivable the TIO absorption phase could have continued its upward trend. It is equally likely the distribution phase began its downward trend after peaking at 240 s. Most surprising was the immediate, but low and highly variable, plasma epinephrine concentration peak of the ETT group at 30 s (238 ± 230 ng/mL) with no apparent absorption phase and immediate progression into a steadily declining distribution phase. Although anecdotal, it is intriguing that the two swine in which epinephrine was detected had ROSC while the five swine with undetectable epinephrine levels did not have ROSC.

The weight of these findings led us to reject the null hypothesis that the pharmacokinetic performance of epinephrine would not differ between the various routes of administration in the presence of TCA. The kinetic findings of this study are consistent with studies that found quantitative differences in the pharmacokinetic performance of epinephrine between the IV and various route of IO administration [17,19,22,31,32]. Particularly, that the TIO route has a longer Tmax than the IV route. However, when the pharmacokinetic findings of this study are considered against the findings relative to the ROSC, time to ROSC, and odds of ROSC, there is greater support for the concept that neither epinephrine nor the route of epinephrine administration influence resuscitative outcome in this swine model of TCA.

Lastly, the finding that two of seven ETT swine had detectable, but low and immediately declining plasma concentrations of epinephrine, are consistent with the studies reporting absorption of ETT administered epinephrine is unreliable and highly variable [33-37]. The Cmax obtained in a study of an adult TCA model

Table 2
Mean plasma concentration of epinephrine over 5 min by group.

Mean plasma epinephrine concentration ± SE over time					
Time in seconds	ETT	TIO	HIO	SIO	IV
30	238 ± 230	0 ± 0	69 ± 69	0 ± 0	0 ± 0
60	217 ± 212	0 ± 0	143 ± 114	138 ± 82	268 ± 153
90	206 ± 200	42 ± 42	292 ± 106	433 ± 128	666 ± 186
120	171 ± 157	94 ± 66	380 ± 82	572 ± 155	802 ± 188
150	153 ± 136	176 ± 58	408 ± 66	538 ± 150	733 ± 171
180	104 ± 86	267 ± 49	333 ± 52	479 ± 140	652 ± 123
240	102 ± 79	381 ± 72	302 ± 42	306 ± 93	436 ± 87

ETT, endotracheal; HIO, humeral intraosseous; IV, intravenous; SE, standard error of the mean; SIO, sternal intraosseous; TIO, tibial intraosseous.

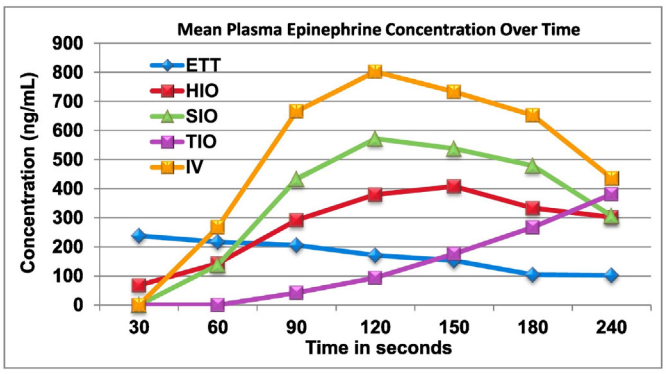

Fig. 3. Comparison of mean concentrations of epinephrine over 5 min by infusion route. High plasma concentrations were achieved by the IV, HIO and SIO groups within 120 s. TIO epinephrine had a prolonged absorption phase peaking at 240 s. ETT epinephrine had a low immediate peak within 30 s followed by a progressively declining distribution phase. Significant differences existed between the ETT and IV groups at 90, 120, 150, 180, & 240 s and the IV and TIO groups at 90, 120, 150, & 180 s ($P < 0.05$).

Table 3
Rate of ROSC by group.

Group	ROSC	No ROSC	*P* values
ETT	2 (28.6%)	5 (71.4%)	HIO vs. CPR = 0.018*
TIO	4 (57.1%)	3 (42.9%)	TIO vs. CPR = 0.018*
HIO	4 (57.1%)	3 (42.9%)	IV vs. CPR = 0.018*
SIO	3 (42.9%)	4 (57.1%)	
IV	4 (57.1%)	3 (42.9%)	All other pairwise
CPRD	2 (28.6%)	5 (71.4%)	comparisons: ($P > 0.05$)
CPR	0 (0%)	7 (100%)	

CPR, cardiopulmonary resuscitation only; CPRD, CPR with defibrillation; ETT, endotracheal; HIO, humeral intraosseous; IV, intravenous; ROSC, return of spontaneous circulation; SIO, sternal intraosseous; TIO, tibial intraosseous. *Significance indicated by *P* value ≤ 0.05.

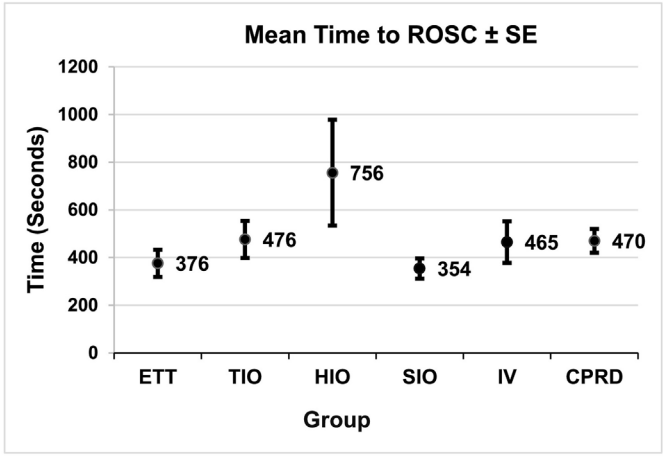

Fig. 4. Comparison of the mean time to ROSC between all groups. There was no significant difference between the groups ($P > 0.05$ in all instances).

(445 ng/mL ± 390) is consistent with the Cmax reported by the Vali et al. study in a neonatal model of asphyxial arrest (130 ng/mL ± 240) [37]. The unreliable and variable absorption and distribution found in many studies are likely because of severely decreased pulmonary blood flow during CA [38] and decreased circulating volume secondary to hemorrhage.

The AHA, ACLS guidelines advise doubling the recommended IV dose from 1 mg to 2 mg diluted in a total volume of 5 to 10 mL of NS when administering epinephrine using the ETT route [14]. The AHA states the pharmacokinetics of ETT epinephrine is variable and optimal dosing is unknown. Limited experimental and observational studies in animals [34,35,37,39] and humans [36] in MCA support this statement.

4.2. Discussion of resuscitative effects results

The secondary goal of this study was determining if there were differences in the occurrence of ROSC, time to ROSC, and odds of ROSC when epinephrine was administered by the ETT, IV and IO routes of administration in an adult swine model of TCA. There were no significant differences in the rate of ROSC, time to ROSC and odds of ROSC among the ETT, TIO, HIO, SIO, IV and CPRD groups indicating epinephrine had no effect on these measures of short-term resuscitative outcome. Rather, the results indicated that volume repletion, and possibly defibrillation of shockable rhythms, had more influence on successful short-term resuscitative outcome since these variables were common factors among these groups.

Unsurprisingly, there were significant differences in the rate of ROSC between the HIO, IV, and TIO groups compared to the CPR group since no CPR swine had ROSC. However, there was no difference in time to ROSC and odds of ROSC between these groups. Interestingly, there was no difference in the occurrence of ROSC among the SIO and CPRD groups and the CPR group. This inconsistency created some doubt that defibrillation was as important as volume resuscitation for successful resuscitative outcome among the groups during this experiment. Anecdotally, both ETT swine with detectable plasma epinephrine levels had ROSC.

These findings compelled us to accept the null hypothesis that the route of epinephrine administration did not affect resuscitative outcome. The findings of this study were consistent with most of the literature in that epinephrine has no beneficial effect on resuscitative outcome in the setting of TCA [11,12,40]. Further, these results support the recommendations of Harris et al. and Smith et al. that ACLS guidelines should not be used for the management of TCA unless MCA preceded traumatic injury [4,41]. Lastly, these findings support prioritizing hemorrhage control and volume repletion during TCA management over rate and rhythm control.

4.3. Epinephrine in the management of traumatic cardiac arrest

Epinephrine is a direct, nonspecific, α and β adrenergic agonist used for decades as a component of MCA management [14,42]. By extension, epinephrine has been used, in some instances, as a component of TCA management. Considerable controversy exists regarding the therapeutic benefit of epinephrine in both circumstances [43]. Some observational [7] and retrospective [44] studies support epinephrine use in MCA. Conversely, there is evidence indicating epinephrine used for the management of MCA has no beneficial effect [45] or increased the rate of ROSC but decreased the rate of 30-day survival to hospital discharge with acceptable neurologic outcome [9,46,47]. The recently published PARAMEDIC2 trial results indicated epinephrine used to treat adult out-of-hospital MCA resulted in a significantly higher rate of 30-day survival than placebo ($P = 0.02$), but no between-group difference ($P > 0.05$) in the rate of favorable neurologic outcome between the groups. However, more epinephrine group survivors (31%) had severe neurologic impairment compared to placebo (17.8%) at hospital discharge [48]. These results are consistent with a randomized, double-blind trial of 8014 out-of-hospital CA patients receiving epinephrine or placebo that found 130 patients (3.2%) receiving epinephrine survived to 30 days post-CA compared to 94 receiving placebo (2.4%) (95% CI, 1.06 to 1.82; P = 0.02) [13].

The Cochrane Collaboration recently published a systematic review and meta-analysis of 26 studies, with 21,704 participants, regarding the survival benefits of epinephrine during MCA [49]. The investigators reported moderate-quality evidence indicated standard-dose epinephrine compared to placebo improved ROSC (RR 2.86, 95% CI 2.21 to 3.71), survival to hospital admission (RR 2.51, 95% CI 1.67 to 3.76), and survival to hospital discharge (RR 1.44, 95% CI 1.11 to 1.86). Further, they reported there was no evidence that epinephrine, at any dose, improved neurologic outcomes [49].

One retrospective study favoring epinephrine use for TCA found the epinephrine group had a higher sustained rate of ROSC than the non-epinephrine group (41.9% vs. 17.6%, respectively, $P < 0.01$) and a higher survival to discharge rate (14.0% vs. 3.0%, respectively, $P < 0.01$) [6]. However, only 43 of the 514 (8.4%) cases included in this study received epinephrine.

Evidence against epinephrine use for TCA includes retrospective studies [11,12,40], and narrative reviews [4,41] but limited prospective data. Irfan et al. reported in a retrospective study of 410 out-of-hospital TCA patients, epinephrine decreased the odds of survival to hospital discharge compared to shockable rhythm, hemorrhage control, blood transfusion and surgery which were associated with higher odds of survival [11]. A subgroup analysis of another retrospective study found 84 of 133 children (63%), aged 14 years or less who had TCA, did not survive resuscitation including catecholamines compared with 49 resuscitation survivors (36%) who did not receive catecholamines ($P < 0.001$) [12]. The authors of this study were not specific as to which catecholamines were used or the percentage of each type of catecholamine used within the 133-patient subgroup. Lin et al. retrospectively studied 388 children treated with epinephrine for TCA and found 38 (9.8%) survived to discharge and 12 (3.1%) survived to discharge with good neurologic outcome. The investigators stated there were no significant differences in survival to hospital discharge ($P = 0.234$) or survival to hospital discharge with acceptable neurologic outcome ($P = 0.874$) regardless of whether the first epinephrine dose was administered <15 min, between 15 and 30 min, or >30 min post-arrest [40].

The narrative reviews by Harris et al. and Smith et al. agreed little robust evidence supporting the use of epinephrine in TCA exists, and exogenous use of epinephrine could be harmful [4,41]. Theoretically, the normal physiologic response to a critical reduction of central blood volume by 30% [50] is an endogenous catecholamine release from the adrenal medulla [41]. This high plasma level of endogenous epinephrine could combine with the approximately 200 pg/mL of exogenous epinephrine measured after IV injection of 1 mg of epinephrine [41]. The addition of additional exogenous epinephrine may be counterproductive causing profound vasoconstriction and a resultant decrease of tissue perfusion [4].

4.4. Alternative routes of epinephrine administration

Clinicians may consider alternative routes for administering epinephrine when IV access is not rapidly available. In the AHA order of preference, they are the IO and ETT routes [14]. In the modern era, the IO route has been used for pediatric resuscitation since the latter 1980s [51] and in adult resuscitation since the latter 1990s [52]. Before the resurgence of the IO route, the ETT route was used as the alternative for IV epinephrine administration. The IO route is particularly useful as it also facilitates circulatory access for the infusion of resuscitative fluids [53], an advantage the ETT route does not possess. The IO and ETT routes access the circulation indirectly since a permeable tissue barrier must be crossed to gain access to the circulation. This is in contrast with the direct access provided by the IV route.

Intuitively, one may rationalize the IV, TIO, HIO, and SIO routes are pharmacokinetically equivalent. This concept is true in perfusing subjects [54]. However, this concept is untrue in studies of non-perfusing subjects that found quantitative differences in the pharmacokinetics of epinephrine between these routes [17,19,22,31,32]. Circulatory changes occurring during hemorrhage, such as decreased circulating volume, peripheral vasoconstriction, reduction of pulmonary blood flow to <20% of normal, or pulmonary vasoconstriction may significantly alter the absorption, distribution, or performance of drugs administered by the ETT or the various IO routes [38].

Most often, epinephrine given by the TIO route has been found to have a lower Cmax and longer Tmax than the IV, SIO, and HIO routes which behave comparably to each other. Animal studies of the resuscitative effects of IV and IO epinephrine usually find no difference in ROSC between different infusion routes in the MCA model. While no studies have compared the IV and IO routes of epinephrine administration in a TCA model, studies have compared the resuscitative or kinetic effects of IV and IO vasopressin [28,55] and amiodarone [21,56,57] in a TCA model.

4.5. Limitations

The investigators acknowledge limitations exist that limit generalization of the results of this study to human populations. Swine were chosen as the animal model as their cardiovascular systems are anatomically and physiologically similar to humans making this species an appropriate choice for resuscitative research [58,59]. The method of inducing CA in this study did not precisely replicate the mechanism of human TCA as the swine were not exsanguinated to the point of CA. There are clear differences between MCA and TCA. Medical CA occurs typically in older patients with occlusive coronary artery disease resulting in sudden CA and VF [41]. Traumatic CA may occur at any age, irrespective of preexisting disease, and results from hypovolemia resulting in a low cardiac output state progressively leading to bradycardia, pulseless electrical activity and asystole [4]. During model development, we were unable to consistently and reliably induce PEA. Because of this, we chose to induce VF electrically to create a consistent and reproducible point of CA in each swine to minimize variability and facilitate blood specimen collection. Determination of the origin of CA may be challenging for clinicians when MCA precedes traumatic injury such as a fall from height or motor vehicle accident [60]. Future researchers are well-advised to differentiate between MCA and TCA during experimental design.

Blood specimens were not collected from swine not receiving epinephrine nor was there a placebo group. This decision was based on our observations from model development during previous experiments that plasma epinephrine levels were not detected at baseline nor after inducing CA in swine before exogenous epinephrine administration. Additionally, by not including a placebo group, the number of swine sacrificed during the experiment was reduced, consistent with the Three R's of Research, as recommended by the local IACUC. The investigators acknowledge that this decision may have affected the results as the contribution of endogenous epinephrine to the total plasma epinephrine level cannot be quantified or excluded.

Further, defibrillation of a shockable rhythm was delayed until after blood specimen collection so as not to confound the primary study objective. This variation from normal resuscitative therapy may have affected resuscitative outcome measurements.

The inclusion of the ETT route in this study could be viewed as superfluous since this route cannot be used for volume replacement. However, we believed there was scientific value in collecting quantitative kinetic data as the ETT route is still used for resuscitative drug administration in the absence of vascular access. Further,

little recent quantitative data exists regarding ETT epinephrine administration during TCA. The inability to obtain plasma epinephrine levels from five ETT group swine created heterogeneous experimental groups which may have affected the results. This result may reflect the inconsistent absorption properties of ETT administered epinephrine.

Ideally, volume repletion should be accomplished using blood products during the experiment [5,8,61]. However, we were limited in our ability to collect and autotransfuse shed blood back into the swine and elected to use 5% albumin instead. Future investigators could consider autotransfusion of shed whole blood in their experimental protocol for studies of this nature [62]. Lastly, short-term outcome measures of ROSC, time to ROSC, and odds of ROSC were considered in this study. Further, the small number of subjects in the interventional groups limits generalization of the resuscitation effects results. Future investigators should consider long-term outcome measurements including 30-day post-ROSC survival with acceptable neurologic outcome.

The investigators advise the results of this animal study be considered only within the broader context of the existing literature concerning the use of epinephrine during the resuscitation of TCA. The investigators make no recommendations for changes to existing treatment guidelines.

5. Conclusions

The pharmacokinetic performance of the IV, SIO, and HIO routes was comparable. The TIO route took twice as long to reach peak mean concentration over time compared to the IV, SIO and HIO groups. Epinephrine administered by the ETT route had highly variable absorption and was the most unreliable route for epinephrine administration compared to the reliable absorption and distribution patterns seen in the IV and IO routes. Epinephrine appeared to play a lesser role than volume replacement in the resuscitation of TCA since no significant differences in occurrence, time and odds of ROSC existed between the epinephrine groups and the CPRD group. Defibrillation of shockable rhythms increased the occurrence of ROSC but did not affect the time to or odds of ROSC. Overall, neither epinephrine nor the route of epinephrine administration appeared to affect resuscitative outcome in a swine model of TCA. However, generalization of the resuscitative effects results of this study is limited because of the small number of subjects in the interventional groups.

Presentations

The manuscript, including related data, figures, and tables has not been published previously and is not under consideration for publication elsewhere. The data from this study were presented as a poster at the World Congress of Nurse Anesthetists, Budapest, Hungary on 18 June 2018.

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Disclosure

The authors have no commercial associations that may pose a conflict of interest in connection with this work. The views expressed in this work are those of the authors and do not represent the US Army, US Department of Defense, or the US Government.

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