ejpmr, 2024, 11(10), 33-39

SJIF Impact Factor 7.065

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Research Article

ISSN 2394-3211

EJPMR

STERNAL INTRAOSSEOUS EPINEPHRINE ADMINISTRATION IN A HYPOVOLEMIC PEDIATRIC CARDIAC ARREST MODEL

Dr. Don Johnson[a]*, Julie G. Hensler[b], Dawn Blouin[c], Young John Yauger[d], MAJ Benjamin C. Dixon[e] and Joseph O'Sullivan[f]

[a]PhD, Scientist, The Geneva Foundation USA, 917 Pacific Ave, Suite 600, Tacoma, Washington 98402.
[b]PhD, Professor, US Army Graduate Program in Nursing, Baylor University, San Antonio, Texas.
[c]BS, Research Associate, The Geneva Foundation USA, 917 Pacific Ave, Suite 600, Tacoma, Washington 98402.
[d]CRNA, PhD, Executive Director, TriService Nursing Research Program, 4301 Jones Bridge Road Bethesda MD 20814.
[e]MPH, DVM, DACLAM, DACVPM, Chief, Veterinary Research, Naval Medical Research Unit (NAMRU) – San. Antonio Veterinary Science Directorate (VSD) 4141 Petroleum Road, Bldg. 3260, JBSA - Ft. Sam Houston, TX 78234.
[f]CRNA, PhD, Scientist, The Geneva Foundation USA, 917 Pacific Ave, Suite 600, Tacoma, Washington 98402.

***Corresponding Author: Dr. Don Johnson**

PhD, Scientist, The Geneva Foundation USA, 917 Pacific Ave, Suite 600, Tacoma, Washington 98402.

Article Received on 06/08/2024 **Article Revised on 26/08/2024** **Article Accepted on 16/09/2024**

ABSTRACT

Introduction: The purposes were to compare return of spontaneous circulation (ROSC), the maximum concentration (Cmax), time to maximum concentration (Tmax), mean concentration (MC), and area under the curve (AUC) of epinephrine administered by the sternal intraosseous (SIO) route and the intravenous (IV) route. **Procedures:** Yorkshire (*Sus scrofa*) Swine weighing 20-30 kg representing 9-year-old children were randomly assigned to SIO (n = 9); IV (n = 7); CPR + defibrillation (CPR+defib) (n = 7); CPR-Only (n = 5) groups. Thirty-five percent of their blood volume was exsanguinated. Pigs were then placed in arrest for 2 min; CPR was started for 2 min; epinephrine 0.01 mg/kg was then administered to the SIO and IV groups. Blood samples were collected over 5 minutes. After sample collection, epinephrine was continued every 4 min, and defibrillation was performed every 2 mins. **Results:** The frequency of ROSC was significantly higher in the SIO (9 out of 9) group than the IV (5 out of 7); the CPR+defib (1 out of 7), and CPR-Only groups (0 out of 5) ($p < 0.05$). No significant difference occurred between the time to ROSC between the groups ($p = 0.419$). SIO had an 8.6 times greater chance of ROSC compared to the IV group. Overall, the IV group had higher MC over time, longer Tmax, and higher AUC than the SIO group ($p < 0.05$). **Conclusion:** The SIO group was highly effective and should be considered as a first-line intervention for pediatric hypovolemic patients in cardiac arrest.

KEYWORDS: Pediatric CPR; Hypovolemic shock; Hemorrhage; Cardiac Arrest; Sternal Intraosseous Epinephrine.

INTRODUCTION

Hemorrhage from trauma is the leading cause of death in children.[1] Approximately 6,000 hospitalized and 9,500 out-of-hospital children receive cardiopulmonary resuscitation (CPR) per year just in the United States.[2,5] The American Heart Association (AHA) recommends that epinephrine be administered by the intravenous (IV) route. However, if not attainable, the intraosseous (IO) route can be used for individuals in cardiac arrest (CA). Several sites, including the tibia, humerus, and sternum, can be used. The AHA recommendations are based primarily on expert opinions and normovolemic models. IV access may be difficult for a child, particularly one who is in shock. Rapid access to vascular space is critical: Every minute without epinephrine increases the chance of mortality by 9%.[6,8] Consequently, it is paramount to find the most efficacious route of epinephrine for resuscitation, such as the SIO route. Our experience was that it took only 5 seconds to insert. However, Voelckel et al. found that blood flow to the bone is diminished to 20 to 30% after a hemorrhage of 35% and may not be appropriate in administering epinephrine in a patient in shock. Blood loss results in less circulating volume, and endogenous and exogenous catecholamines cause vasoconstriction.[9] The subsequent decreased blood flow may slow drug uptake from the marrow. Further, hypovolemia may alter resuscitation drugs' pharmacokinetics, the distribution volume, and,

ultimately, the probability of return of spontaneous circulation (ROSC). No studies have examined the effects of hypovolemia on SIO administration of epinephrine in a hypovolemic pediatric model. The sternal IO (SIO) has some advantages. The site is more vascular (red marrow) than other sites with more fat (yellow marrow). Also, the SIO has a much shorter route to the heart. This study addresses an important gap in knowledge and was guided by the following objectives

1. Compare the frequency and odds of ROSC occurrence in the SIO, IV, CPR + defibrillation (CPR + defib), and CPR-Only groups.

2. Compare the maximum plasma concentration (Cmax), time to maximum concentration (Tmax), mean concentration (MC) of plasma epinephrine over time, and area under the curve (AUC) when epinephrine is administered by IV or SIO routes.

3. Compare the time to ROSC between SIO, IV, CPR+defib, and CPR-Only groups.

For this study, MC was defined as the average concentration at each time a sample was collected (at 0.5, 1, 1.5, 2, 2.5, 3, 4, and 5 minutes), The Cmax was defined as the peak concentration, the Tmax was defined as the time it takes to reach Cmax, and AUC was defined as the amount of a particular drug over time, specifically 5 minutes for this study.

MATERIAL AND METHODS

This was a prospective, randomized, within and between, blinded-experimental study using a hypovolemic pediatric Yorkshire (*Sus scrofa*) swine model. The within-subjects design compared the MC over time and time to ROSC by group. The between-subjects design compared the number of ROSC achieved, Cmax, Tmax, MC, AUC, and time to ROSC between all the groups. The Pigs weighing between 20 and 30 kg represented nine-year-old human subjects.[10,11] According to several authorities, the pig has the same average blood volume and similar cardiovascular, pulmonary, and bone physiology to humans.[10,12,13] We selected male pigs to control for any potential hormonal effects. Young castrated male swine were purchased from a single vendor to reduce variability. The local Institutional Animal Care and Use Committee (IACUC) required restricting the number of animals in the IV and CPR+defib to seven and the CPR-Only group to five to prevent unnecessary sacrificing of swine.

The IACUC approved the study, and the swine were cared for according to the Animal Welfare Act and the Guide for the Use of Laboratory Animals.[14,16] The pigs were randomized into four groups using a computerized random number generator: SIO (N=9), IV (n=7), CPR+defib (n=7), and CPR-Only (n=5).

Animal Preparation

Animals were premedicated with an intramuscular (IM) injection of 0.05 mg/kg atropine and sedated with an IM injection of 4.4 mg/kg Telazol (tiletamine/zolazepam, Fort Dodge Animal Health, Fort Dodge, IA, USA). General anesthesia was induced by nose cone with 2%-5% inhaled isoflurane before endotracheal intubation. Isoflurane was then reduced to a maintenance dose (1% and 2%) using a Dräger Apollo anesthesia machine (Drägerwerk AG & Co., Lübeck, Germany). 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 monitored using an Infinity Delta XL monitoring system (Draeger Medical Systems Inc., Telford, PA, USA). An 18-gauge, 1.25inch IV catheter (Terumo Medical Products, Somerset, NJ, USA) was placed percutaneously in an auricular vein of each swine, and 100mL/hour lactated Ringer's solution was infused to maintain patency. The left carotid and left femoral arteries were surgically exposed, and 9 French, 60cm with 12cm insertable length, silicone arterial catheters (SAI-Infusion technologies, Lake Villa, IL, USA) were placed in both sites. The left carotid arterial line was used for continuous blood pressure monitoring. The femoral arterial line was used for blood withdrawal, blood sampling, 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 by placing the animal on a circulating water blanket (HotDog, Augustine Biomedical + Design, Eden Prairie, MN, USA). A 15-gauge, 25 mm EZ-IO device (Teleflex Medical, Research Triangle Park, NC, USA) was surgically placed per the manufacturer's directions in each subject's non-segmented region of the sternum.

Experimental Procedures

After a 15-minute stabilization period, a Class III hemorrhage was created by withdrawing 35% of each swine's estimated blood volume (EBV) using gravity drainage and controlled suction of the femoral artery catheter. As with previous studies, the EBV was calculated at 70 mL/kg of body weight.[17,27] The data collection mixer (DCM 3000, GenesisBPS, Ramsey, NJ, USA) was used to measure withdrawn blood volume accurately and precisely. It was zeroed with a collection canister in place to control for canister weight variation. Suction was applied to withdraw approximately 100 mL of blood per minute. After blood withdrawal, the subjects were placed into CA by passing an electrical current through the heart as previously described.[17,27] Isoflurane anesthesia was discontinued, and midazolam 6 mg IV and buprenorphine 0.6 mg IV were administered.

After 2 minutes without intervention, mechanical chest compressions were administered using a Pneumatic 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. The quality of chest compressions was confirmed by observing arterial blood pressure and capnography. After 4 minutes of CA, 0.01 mg/kg of epinephrine was administered to IV and IO swine through the assigned device, followed by a 20 mL NS flush. The CPR+defig and CPR groups were not administered epinephrine. After the epinephrine injection, serum blood specimens (10 mL) were collected at 30, 60, 90, 120, 150, 180, 240, and 300 s from the left femoral arterial line. 10 mL of blood was aspirated and discarded before blood sample collection to avoid residual epinephrine from the previous sample. To maintain patency, 10 mL of NS was injected to clear the arterial line after collecting each specimen. To maintain patency, 10 mL of NS was injected to clear the arterial line after collecting each specimen. Defibrillation was started at 3 minutes after epinephrine administration and continued every 2 minutes until ROSC or 30 minutes had elapsed. The CPR Only Group did not receive defibrillations. Resuscitation continued until ROSC or 30 minutes had elapsed. Blood specimens were placed in lithium heparin collection tubes and centrifuged immediately. Separated plasma was placed 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.

Power Analysis

We used means and standard deviations from previous studies and calculated a large effect size of .06.[22,28,30] Using an effect size of 0.6, an alpha of 0.05, and a power of .80, we calculated that we needed 7-8 subjects per group.

RESULTS

Baseline and Post-Hemorrhage Data

A Multivariate Analysis of Variance (MANOVA) indicated there were no significant differences in the baseline data, including weights, amount of hemorrhage, SBP, DBP, MAP, core body temperature, pulse oxygenation level, CO, or SV ($p > 0.05$) indicating the groups were equivalent on these variables. There were also no significant differences in the groups on these variables after hemorrhage ($p > 0.05$) (**See Table 1 for a summary baseline and after hemorrhage data**). The end-tidal CO_2 before the arrest was expected for each subject in all groups and ranged from 11-15 for all subjects immediately after arrest and went down from 5-9 after 5 minutes of arrest.

Group	Weight in Kg	Amt of Hemorrhage in mL	SBP mm/Hg	DBP mm/Hg	HR	MAP mm/Hg	CO L/min	SV ml	CO_2 mm/Hg	O_2 %	Temp C°
SIO Baseline	30	760	92	60	76	76	7.9	88	44	98	36.3
SIO After Hemorrhage			66	37	94	46	6.0	58	40	98	36.8
IV Baseline	29	710	93	59	84	65	7.6	82	40	97	36.2
IV After Hemorrhage			59	42	96	47	6.9	67	41	98	36.0
CPR+defib Baseline	30	733	96	64	80	76	6.2	85	42	99	36.9
CPR+defib after hemorrhage	29	710	58	38	92	45	7.7	70	40	99	36.7
CPR-Only Baseline	31	720	98	61	82	77	7.8	92	45	100	37.8
CPR-Only after hemorrhage	30	733	66	36	95	47	6.0	70	41	99	37.5

Return of Spontaneous Circulation

One subject in the SIO group had no detectable plasma epinephrine levels in the samples collected but did achieve ROSC. This subject was included in the analyses of ROSC data. The pharmacokinetic calculations did not include these data because the pharmacokinetic calculations were zero and more than two standard deviations from the mean. A Fisher’s Exact Test indicated that the SIO group (9 out of 9 subjects) had a significantly higher rate of ROSC than the IV group (5 out of 7) ($p = 0.001$). Also, the SIO group had a significantly higher rate of ROSC compared to the CPR+defib group and CPR-Only group ($p = 0.001$). One out of 7 subjects in the CPR+defib group and none in the CPR Only group achieved ROSC. The SIO group had an 8.6 times greater chance of achieving ROSC than the IV group, 82 times greater than the CPR+defib group, and 285 times greater than the CPR Only group. (**See Figure 1 for a summary**).

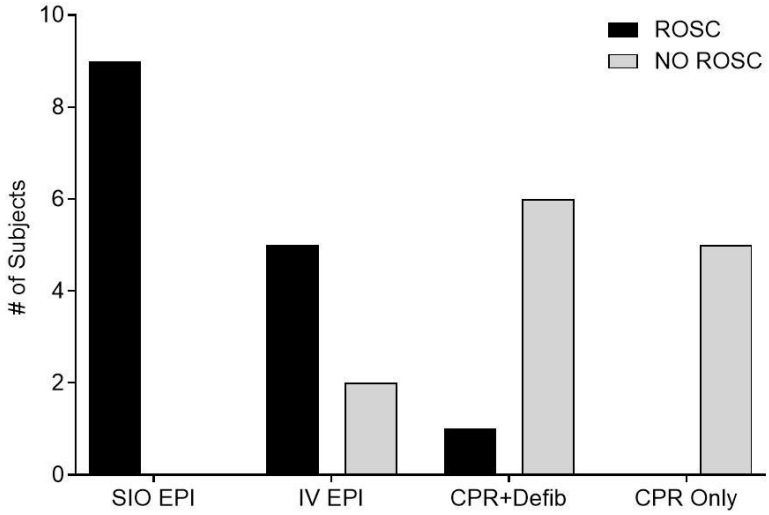

Figure 1: Comparison of ROSC by Group.

Time to ROSC was not significantly different between the IV and SIO groups (p= 0.419). The means and standard deviations (SD) for time to ROSC for the IV, SIO, and CPR+defib groups were 493 ± 57 seconds, 548 ± 51 seconds, and 525 seconds, respectively. The number of times for defibrillation before ROSC was as follows: SIO (3 had 1, 6 had 2); IV (2 had 1, 3 had 2); CPR+defib (1 had 2). The remaining subjects did not achieve ROSC in each group and had 10 defibrillations. The number of doses of epinephrine for each group before ROSC was as follows: SIO (3 with 1, 6 with 2) and IV (2 with 1, 3 with 2 doses, and 2 with 5). The remaining subjects that did not achieve ROSC each had 5 doses.

None of the subjects in the SIO or IV groups had blood started before achieving ROSC. The range of blood administered after ROSC for each group was as follows: SIO 150-350 ml; IV 190-379 ml; and CPR+defib 230 (only one). The range of amount blood for the IV group (N=2) that did not achieve ROSC was 300-410, for the CPR+def (N=7) was 320-436, and for the CPR-Only (N=5) 340-430 group.

Epinephrine Pharmacokinetics

The MC of plasma epinephrine for the SIO group was significantly higher only at the 30-second time point (p = 0.001). By contrast, the IV group had a significantly higher MC of epinephrine at 90 seconds (p = 0.005), 120 seconds (p = 0.001), 150 seconds (p = 0.004), 180 seconds (p = 0.008), and 240 seconds (p = 0.023). The MC was not significantly different between the SIO and IV groups at the 60-second (p = 0.486) and 300-second (p = 0.106) (**See Figure 2 for a Summary**).

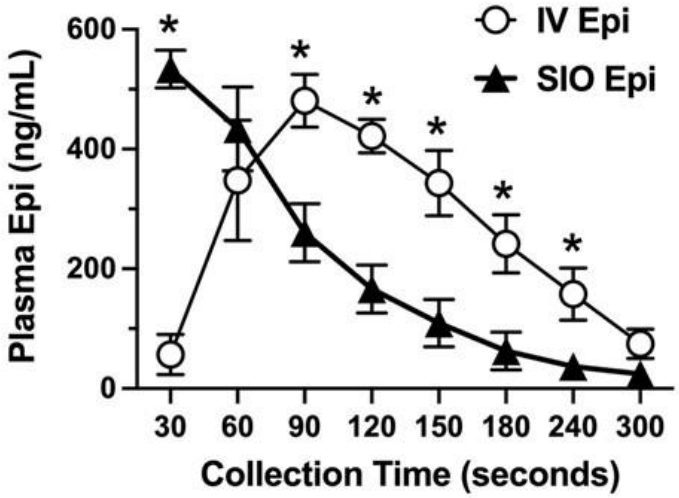

Figure 2: Comparison of MC over 5 Minutes.

The Cmax of plasma epinephrine was not statistically different for the IV group (547 ± 33 ng/ mL) and SIO (572 ± 46 ng/mL) groups (p = 0.93) (**See Figure 3A for a summary**). The Tmax, however, was significantly longer for the IV Group (103 ± 13 seconds) than for the SIO group (53 ± 11 seconds) (p = 0.050) (**See Figure 3B for a summary**). The AUC for the SIO group (42035 ± 6060 ng/mL) was significantly less than for the IV group

(71216 ± 4064 ng/mL) (p = 0.011) (**See Figure 3C for a summary**).

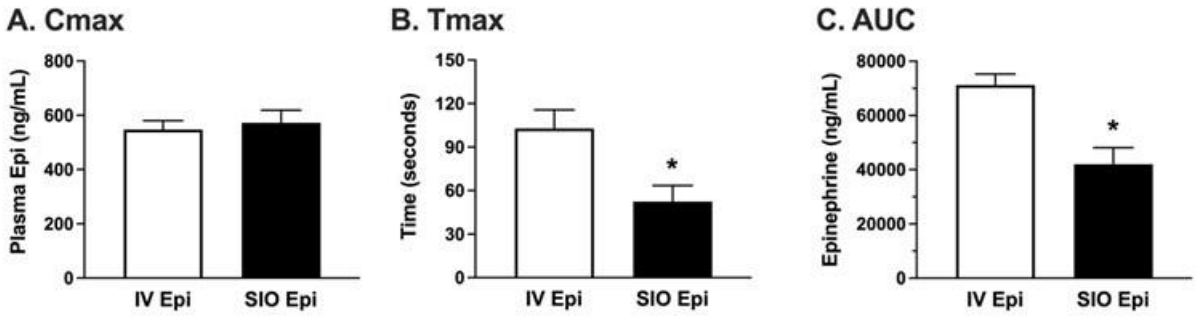

Figure 3: A Comparison of Cmax by Group Figure 3 B Comparison of Tmax by Group Figure 3 C Comparison of AUC by Group.

DISCUSSION

The objective of this study was to determine the effectiveness of the SIO compared to the IV route of administration of epinephrine in a pediatric hypovolemic cardiac arrest model. Specifically, frequency and time to ROSC and pharmacokinetics of epinephrine were compared. All subjects (9 out of 9) in the SIO group, compared to 5 out of 7 in the IV group, achieved ROSC. The MC was higher in the SIO group at 30 seconds and was higher in the IV compared to the SIO group at 90, 120, 50, 180, and 240 seconds. The Cmax and time to ROSC were insignificant in the 2 groups; the AUC was significantly less for the IV group. This study expands the study by Burgert et al., who found that IV administration of 1 mg of epinephrine resulted in an IV serum concentration 5.87 and 2.86 times greater than for the tibial and SIO routes, respectively, in an adult, normovolemic model. They did not evaluate ROSC nor use a pediatric hypovolemic model.[17] In a systematic review, Burgert et al. concluded that there was evidence that epinephrine given via the SIO route more closely approaches equivalence with IV-administered epinephrine compared to the tibial IO route; however, this applied only to the adult model.[31] In an adult hypovolemic model, researchers found that the pharmacokinetics of IV, HIO, and SIO epinephrine were comparable; however, in the SIO group, only 3 out of 7 achieved ROSC.[23] Perhaps the reason for the differences in our study was that 1 mg was given regardless of weight in the adult, and in the current study, 0.01/kg was administered. In an investigation using the same model as the current study, Neill et al. found that the Cmax was significantly higher, and Tmax was shorter in the IV group compared to the HIO group. Also, they found that only 1 out of 7 in the humerus intraosseous group, compared to 5 of 7 IV groups, achieved ROSC.[32] Perhaps this is because the SIO is closer to the heart than the humerus. Conversely, Vallier et al. found that all in the SIO (7 out of 7) compared (5 out of 7) in the IV group achieved ROSC; however, this was in an adult cardiac arrest model and using vasopressin.[21]

LIMITATIONS

The major limitation of this study is the small sample size, although we had enough power to find statistically significant differences. Another limitation is the use of swine. Generalizations may not translate to humans; however, cardiovascular, pulmonary, and bone physiology are very similar to humans. Researchers conclude that the swine model is appropriate for this type of study. Another potential limitation was we used an 18-gauge needle for vascular access. In the real-world scenario, a large bore needle may not be accessible, particularly for a 9-year-old child. This study used an 18 ga needle for the IV group to administer epinephrine, providing easy blood and epinephrine administration.

FUTURE STUDIES

Future replicated studies should use a larger sample size. Studies should also be implemented to determine whether fewer doses of epinephrine can be administered using the SIO site than other sites. Studies must be implemented to determine and compare the long-term effects of using the SIO and IV routes.

CONCLUSION

The results of this study demonstrated that the SIO was very effective and should be considered a first-line intervention. Our previous and current studies found it took less than 5 seconds to insert the IO device compared to several minutes for the IV route. Leidel et al. found that IV failure rates were from 10 to 40% for adult patients not in arrest and that the time for obtaining IV access was 2.5 to 16 minutes and as long as 55 minutes in critically ill patients who were not in arrest.[33,34] The valuable time saved using the SIO route probably translates into a greater chance of achieving ROSC.

Authorship Contribution Statement

Don Johnson: Conceptualization, Methodology, Funding acquisition, Supervision, Data Analysis, Writing – original draft. **Julie G. Hensler:** Conceptualization, Methodology, Funding acquisition, Writing of original, Final Editing. **MAJ Benjamin C. Dixon** assisted in the data collection and writing of the manuscript. **Dawn**

Blouin: Coordinated research scheduling, data collection, writing parts of the manuscript, final editing, and proofing. **Young John Yauger:** Conceptualization, Funding acquisition, Writing - review & editing. **Joseph O'Sullivan:** Conceptualization, Funding acquisition, Writing sections, and final submission, editing, and editing. All authors have reviewed and approved the final submission.

Funding Source: Tri-Service Nursing Research Program, Uniform Services University, Bethesda, MD.

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Declaration of Competing Interest

None of the authors declare personal or financial conflicts of interest.

Declaration of Generative AI in Scientific Writing

All the authors declare that they did not use any AI software to prepare and write the manuscript.

REFERENCES

1. Kuisma M, Alaspää A. Out-of-hospital cardiac arrests of non-cardiac origin. Epidemiology and outcome. European heart journal., 1997; 18(7): 1122.
2. Bhanji F, Topjian AA, Nadkarni VM, Praestgaard AH, Hunt EA, Cheng A, et al. Survival Rates Following Pediatric In-Hospital Cardiac Arrests During Nights and Weekends. JAMA Pediatr., 2016.
3. Nishiuchi T, Hayashino Y, Iwami T, Kitamura T, Nishiyama C, Kajino K, et al. Epidemiological characteristics of sudden cardiac arrest in schools. Resuscitation, 2014; 85(8): 1001-6.
4. SCAFoundation. AHA Releases Latest Statistics on Out-of-Hospital Cardiac Arrest, 2014.
5. Takei Y, Nishi T, Kamikura T, Tanaka Y, Wato Y, Kubo M, et al. Do early emergency calls before patient collapse improve survival after out-of-hospital cardiac arrests? Resuscitation, 2015; 88: 20-7.
6. Andersen LW, Berg KM, Saindon BZ, Massaro JM, Raymond TT, Berg RA, et al. Time to Epinephrine and Survival After Pediatric In-Hospital Cardiac Arrest. JAMA, 2015; 314(8): 802-10.
7. Andersen LW, Kurth T, Chase M, Berg KM, Cocchi MN, Callaway C, et al. Early administration of epinephrine (adrenaline) in patients with cardiac arrest with initial shockable rhythm in hospital: propensity score matched analysis. BMJ., 2016; 353: i1577.
8. Larsen P, Eldridge D, Brinkley J, Newton D, Goff D, Hartzog T, et al. Pediatric peripheral intravenous access: does nursing experience and competence really make a difference? J Infus Nurs., 2010; 33(4): 226-35.
9. Voelckel WG, Lurie KG, McKnite S, Zielinski T, Lindstrom P, Peterson C, et al. Comparison of epinephrine with vasopressin on bone marrow blood flow in an animal model of hypovolemic shock and subsequent cardiac arrest. Crit Care Med., 2001; 29(8): 1587-92.
10. Hannon JP, Bossone CA, Wade CE. Normal physiological values for conscious pigs used in biomedical research. Lab Anim Sci., 1990; 40(3): 293-8.
11. Valenza J, Calvet H, Orue J. [Intensive fattening of Senegalian Peulh zebus (Gobra). II. 7 to 10-year-old castrated males, average weight 330 Kg]. Rev Elev Med Vet Pays Trop., 1971; 24(1): 111-24.
12. Swindle MM. The development of swine models in drug discovery and development. Future Med Chem., 2012; 4(14): 1771-2.
13. Swindle MM, Makin A, Herron AJ, Clubb FJ, Jr., Frazier KS. Swine as models in biomedical research and toxicology testing. Vet Pathol., 2012; 49(2): 344-56.
14. Jones EM. The laboratory animal welfare act: regulations, standards, enforcement, and progress. J Am Vet Med Assoc., 1968; 153(12): 1874-7.
15. Keeling L, Tunon H, Olmos Antillon G, Berg C, Jones M, Stuardo L, et al. Animal Welfare and the United Nations Sustainable Development Goals. Front Vet Sci., 2019; 6: 336.
16. Mellor DJ, Beausoleil NJ, Littlewood KE, McLean AN, McGreevy PD, Jones B, Wilkins C. The 2020 Five Domains Model: Including Human-Animal Interactions in Assessments of Animal Welfare. Animals (Basel), 2020; 10(10).
17. Burgert J, Gegel B, Loughren M, Ceremuga T, Desai M, Schlicher M, et al. Comparison of tibial intraosseous, sternal intraosseous, and intravenous routes of administration on pharmacokinetics of epinephrine during cardiac arrest: a pilot study. AANA J., 2012; 80(4 Suppl): S6-10.
18. Burgert JM. Intraosseous infusion of blood products and epinephrine in an adult patient in hemorrhagic shock. AANA J., 2009; 77(5): 359-63.
19. Beaumont LD, Baragchizadeh A, Johnson C, Johnson D. Effects of tibial and humerus intraosseous administration of epinephrine in a cardiac arrest swine model. Am J Disaster Med., 2016; 11(4): 243-51.
20. Long LRP, Gardner LSM, Burgert J, Koeller LCA, O'Sullivan LJ, Blouin D, Johnson CD. Humerus intraosseous administration of epinephrine in normovolemic and hypovolemic porcine model. Am J Disaster Med., 2018; 13(2): 97-106.
21. Vallier DJ, Torrence AD, Stevens R, 3rd, Arcinue PN, Johnson D. The effects of sternal and intravenous vasopressin administration on pharmacokinetics. Am J Disaster Med., 2016; 11(3): 203-9.
22. Burgert JM, Johnson AD, Garcia-Blanco J, Froehle J, Morris T, Althuisius B, et al. The effects of proximal and distal routes of intraosseous

epinephrine administration on short-term resuscitative outcome measures in an adult swine model of ventricular fibrillation: a randomized controlled study. Am J Emerg Med., 2016; 34(1): 49-53.
23. Burgert JM, Johnson AD, O'Sullivan JC, Blalock WJ, Duffield BC, Albright BP, et al. Pharmacokinetic effects of endotracheal, intraosseous, and intravenous epinephrine in a swine model of traumatic cardiac arrest. Am J Emerg Med., 2019; 37(11): 2043-50.
24. Johnson D, Garcia-Blanco J, Burgert J, Fulton L, Kadilak P, Perry K, Burke J. Effects of humeral intraosseous versus intravenous epinephrine on pharmacokinetics and return of spontaneous circulation in a porcine cardiac arrest model: A randomized control trial. Ann Med Surg (Lond)., 2015; 4(3): 306-10.
25. Beaumont D, Johnson M, Hensler JG, Blouin D, O'Sullivan J, Johnson D. Humerus Intraosseous and Intravenous Administration of Epinephrine in Normovolemic and Hypovolemic Cardiac Arrest Porcine Models. Med J (Ft Sam Houst Tex), 2022; (Per 22-01/02/03): 11-6.
26. Johnson D, Hensler JG, O'Sullivan J, Blouin D, de la Garza MA, Yauger Y. Effects of Endotracheal Epinephrine on Pharmacokinetics and Survival in a Swine Pediatric Cardiac Arrest Model. Pediatr Emerg Care., 2024; 40(3): 197-202.
27. Yauger YJ, Beaumont DM, Brady K, Schauer SG, O'Sullivan J, Hensler JG, Johnson D. Endotracheal Administered Epinephrine Is Effective in Return of Spontaneous Circulation Within a Pediatric Swine Hypovolemic Cardiac Arrest Model. Pediatr Emerg Care, 2022; 38(1): e187-e92.
28. Wong MR, Reggio MJ, Morocho FR, Holloway MM, Garcia-Blanco JC, Jenkins C, Johnson AD. Effects of intraosseous epinephrine in a cardiac arrest swine model. J Surg Res., 2016; 201(2): 327-33.
29. Fulkerson J, Lowe R, Anderson T, Moore H, Craig W, Johnson D. Effects of Intraosseous Tibial vs. Intravenous Vasopressin in a Hypovolemic Cardiac Arrest Model. West J Emerg Med., 2016; 17(2): 222-8.
30. Yost J, Baldwin P, Bellenger S, Bradshaw F, Causapin E, Demotica R, et al. The pharmacokinetics of intraosseous atropine in hypovolemic swine. Am J Disaster Med., 2015; 10(3): 217-22.
31. Burgert JM, Austin PN, Johnson A. An evidence-based review of epinephrine administered via the intraosseous route in animal models of cardiac arrest. Mil Med., 2014; 179(1): 99-104.
32. Neill MJ, Burgert JM, Blouin D, Tigges B, Rodden K, Roberts R, et al. Effects of humeral intraosseous epinephrine in a pediatric hypovolemic cardiac arrest porcine model. Trauma Surg Acute Care Open, 2020; 5(1): e000372.
33. Leidel BA, Kirchhoff C, Bogner V, Braunstein V, Biberthaler P, Kanz KG. Comparison of intraosseous versus central venous vascular access in adults under resuscitation in the emergency department with inaccessible peripheral veins. Resuscitation, 2012; 83(1): 40-5.
34. Leidel BA, Kirchhoff C, Bogner V, Stegmaier J, Mutschler W, Kanz KG, Braunstein V. Is the intraosseous access route fast and efficacious compared to conventional central venous catheterization in adult patients under resuscitation in the emergency department? A prospective observational pilot study. Patient Saf Surg., 2009; 3(1): 24.