An Evidence-Based Review of Epinephrine Administered via the Intraosseous Route in Animal Models of Cardiac Arrest

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ABSTRACT   Objectives: Intraosseous (IO) access, enabling the rapid administration of epinephrine during cardiac arrest (CA), is crucial in promoting optimal postresuscitation outcomes in patients with poor vascular access. There is a question whether IO-administered epinephrine is equivalent to intravenously administered epinephrine during CA. Methods: The question guiding this evidence-based review was as follows: in adults suffering CA given epinephrine via the IO route, what is the resulting serum concentration of the drug compared to when administered intravenously? A search was conducted and the evidence appraised and leveled. Results: Four animal studies met the inclusion criteria. The sources showed no definitive evidence supporting equivalence between intravenous and IO epinephrine administered during CA. Intravenously administered epinephrine provides increased and faster appearing serum concentrations than IO-administered epinephrine. Evidence indicated epinephrine given via the sternal IO route more closely approaches equivalence with intravenously administered epinephrine than when administered by the tibial IO route. Conclusions: The clinician should consider using proximal IO infusion sites such as the sternum or humerus when administering advanced cardiac life support drugs to rapidly achieve maximal therapeutic concentrations. Further studies are needed to determine the differences seen when epinephrine is administered by these routes during CA.

INTRODUCTION

The yearly incidence of cardiac arrest (CA) in the United States varies between 180,000 and >450,000.[1] When a patient experiences CA, it is critical to establish immediate vascular access to administer lifesaving drugs such as epinephrine. Vascular access procedures may be difficult and time consuming when the patient is in a state of cardiovascular compromise. The difficulty and delay in establishing vascular access may be magnified during scenarios such as a mass casualty situation with multiple instances of traumatic CA.[2,3]

Intraosseous (IO) infusion is the placement of a specialized needle into the bone marrow cavity for the administration of drugs and fluids. The American Heart Association recommends if intravenous (IV) access cannot be attained, drugs (including epinephrine) should be administered by the IO route.[4] IO infusion offers the advantages of ease and speed of placement allowing rapid access to the circulatory system via the rigid, noncollapsible bone marrow matrix. In addition, IO allows the safe administration of fluids and drugs with the potential for similar bioavailability with IV-administered drugs.[5]

HISTORY AND REVIEW OF THE LITERATURE

History

The potential use of the bone marrow as a site for infusion was first discussed in 1922[6] and first used in humans in 1934.[7] The practice of IO infusion has waxed and waned until 1984 when the technique was used in India with children suffering cholera-induced dehydration.[8] This article resulted in the reintroduction of IO infusion for use during pediatric resuscitations in the United States. Use of IO infusion in adults has benefited from the evolution of infusion devices from reusable steel needles to disposable needles.[9] There are currently a number of devices including those that are spring-loaded or use battery power facilitating placement of the catheter into the bone marrow.[9–12]

This new generation of IO devices has the potential to improve patient outcomes, but there are many unanswered questions regarding IO-administered epinephrine including the resulting serum concentration. The purpose of this evidence-based article is to describe the differences seen when epinephrine is administered via the IO route compared to the IV route during CA with ongoing cardiopulmonary resuscitation (CPR).

The PICO Question

The PICO[13] (population, intervention, comparison, outcome) question guiding the search for evidence for this review was as follows: In patients suffering CA given epinephrine (P) via the IO route (I), what are the differences seen (O) compared to when administered via the IV route (C)?

Search Strategy

The search strategy included use of online databases and examination of retrieved articles for additional sources. Databases searched included the Cochrane Database of Systematic Reviews, PubMed, a database from the National Library of Medicine that includes data from MEDLINE (1966–2012) and PREMEDLINE (1996–2012), and SumSearch 2, a database from the University of Kansas School of Medicine that

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includes data from MEDLINE, DARE, and The National Guideline Clearinghouse. Keywords used alone and in combination included "adults," "cardiac arrest," "cardiopulmonary resuscitation," "intraosseous," "epinephrine," and "pharmacokinetics". Evidence sources consisted of randomized controlled trials (RCTs) and non-RCTs examining the pharmacokinetics of epinephrine or the pharmacokinetics of epinephrine correlated with pharmacodynamic measures administered via the IO route or IO compared to IV in animal or human subjects in CA with ongoing CPR, from 1985 to 2012, published in a peer-reviewed English language journal available in full-text form. We included animal studies based on the suspicion there would be few, if any, human studies examining this topic. Systematic reviews with and without meta-analysis were also considered for inclusion. Narrative reviews and other sources not fitting the inclusion criteria were analyzed for additional evidence sources.

Critical Appraisal of the Literature

The search of the literature revealed 33 potential sources of evidence of which 4 met inclusion criteria. No human studies were found. These 4 evidence sources[14–17] were RCTs[14,16,17] and a non-RCT[15] using animal models of CA with small sample sizes ranging from 14[16] to 18.[15] Other evidence sources concerning the administration of epinephrine via the IO route were found during the search but did not meet inclusion criteria as they were pharmacokinetic studies conducted in perfusing models,[18,19] pharmacodynamic studies not measuring serum epinephrine concentrations,[20,21] or opinion-based narrative reviews that are not considered strong sources of evidence.[22] Included evidence sources were critically appraised using the method proposed by Melnyk and Fineout-Overholt.[23] Studies were evaluated for validity, reliability, and applicability to appraise the quality of the studies. An evaluation of the included evidence is presented in Table I.

The first evidence source[14] randomized animals into 3 groups including groups receiving epinephrine 0.01 mg/kg followed by a 10 mL saline flush via a tibial IO (TIO) device, epinephrine 0.01 mg/kg followed by a 10 mL saline flush via a central intravenous (CIV) catheter placed into the inferior vena cava, and a control group receiving a 10 mL saline flush though it was not stated by which route it was given. The study correlated the pharmacodynamic outcome measures of mean arterial pressure (MAP) and heart rate (HR) with the pharmacokinetic outcome measures of onset time and serum epinephrine concentration in both perfusing and nonperfusing states. The sample size was not determined by a power analysis although it is possible the sample size may have been based on previous studies in perfusing animal models. The investigators were not blinded and all subjects completed this terminal study within their assigned groups. The data for the nonperfusing phase were described in orders of magnitude above baseline and time with no confidence measure mentioned, though these results were graphically represented. One potential threat to the internal validity of this study is the use of manual chest compressions in which rate and depth are difficult to reproduce from animal to animal and may be subject to experimenter variability.

The second study was a prospective nonrandomized trial[15] using an experimental design correlating the outcome measures of MAP, diastolic blood pressure (DBP), and serum epinephrine concentration. Animals were assigned to experimental groups receiving 0.01 mg/kg IO epinephrine or 0.1 mg/kg IO epinephrine with a 5 mL saline flush at 10 and 20 minutes into the experiment. The control group received saline rather than the study drug. Although 8 animals were assigned to the control group and 5 animals were assigned to each experimental group, this imbalance in group size did not likely affect the results of the study. No power analysis was described nor was blinding of the investigators mentioned. All subjects completed this terminal study in their assigned

TABLE I. Evaluation of Evidence Examining Intraosseous Epinephrine Administration During CA

Evidence Source	Type of Evidence	Subjects	Groups
Andropoulos et al[14]	RCT	5.0–12.6 kg Lambs (N = 15) Pediatric Model	Epi 0.01 mg/kg CIV (n = 5) Epi 0.01 mg/kg TIO (n = 5) CIV Saline Control (n = 5)
Spivey et al[15]	RCT	12–15 kg Swine (N = 18) Pediatric Model	Epi 0.01 mg/kg TIO (n = 5) Epi 0.1 mg/kg TIO (n = 5) CIV Saline Control (n = 8)
Hoskins et al[16]	Nonrandomized Trial	25–35 kg Swine (N = 14) Pediatric Model	SIO vs. TIO (n = 7) SIO vs. CIV (n = 6) Simultaneous Doses of Epi Labeled with 2 Different Dyes Given in Both Groups
Burgert et al[17]	RCT	50–70 kg Swine (N = 15) Adult Model	TIO (n = 5) SIO (n = 5) PIV (n = 5) All Groups Given 1 mg Epi

ANOVA, analysis of variance; CIV, central intravenous; epi, epinephrine; MANOVA, multivariate analysis of variance; PIV, peripheral intravenous; RCT, randomized controlled trial; SD, standard deviation; SEM, standard error of the mean; SIO, sternal intraosseous; TIO, tibial intraosseous.

groups. The data were presented in mean ± standard error of the mean (SEM). The SEMs appeared consistent across all groups.

The third study[16] was an RCT using a prospective, experimental, crossover design in which the study animals served as their own control. The investigators analyzed the pharmacokinetic outcome measures of time to maximal concentration (T_{max}), $T_{\frac{1}{2}max}$, and dose delivered (area under the curve or AUC/injected dose). Animals were assigned to 2 experimental groups simultaneously receiving Evans blue- and indocyanine green-labeled epinephrine. Seven animals were assigned to the sternal IO (SIO) compared with TIO group and 6 animals were assigned to the SIO compared with CIV group. The unequal experimental groups did not affect the overall results as the 2 data sets were not compared to each other during statistical analysis. No description of randomization of animals to groups was reported but labeled epinephrine was given in a randomized manner. No power analysis was described nor was blinding of the investigators mentioned. All animals completed this terminal study in their assigned groups. Data were reported in mean ± SEM. The data from the SIO compared with CIV group were presented with and without an extreme outlier, which fell more than 3 SEMs from the mean. The investigators noted when the extreme outlier was removed from the analysis, the resulting SIO dose delivered was 95% of the CIV dose delivered compared to 86% with the outlier included. The SEMs appeared consistent across all groups after the outlying animal was excluded. The investigators acknowledged the use of dye tracers as a surrogate for biologically active drug was a limitation of this study as plasma epinephrine levels were not directly measured. They also stated measurement of plasma epinephrine would have precluded the use of the simultaneous dye injection model. Because the investigator was measuring the pharmacokinetic effects of exogenously administered epinephrine and not pharmacodynamic effects, it was not necessary to measure endogenous epinephrine levels.

The final study[17] was an RCT using a prospective, experimental, mixed design analyzing the pharmacokinetic outcome measures of maximum serum concentration (C_{max}) and T_{max}. Computer-generated numbers were used to randomly and equally assign animals to TIO and SIO experimental groups and to a peripheral IV (PIV) control group. A power analysis was performed for this study based on similar, previous studies. The investigators were not blinded to the subjects or intervention. All animals completed this terminal study in their assigned groups. Data were reported in mean ± SEM. The SEMs appeared very wide across all groups in the both arms of the study with the exception of the TIO group in the T_{max} arm. Potential threats to internal validity to include a small sample size, specimen collection from the CIV system; which may not truly reflect effect site epinephrine concentrations and use of enzyme-linked immunosorbent assay (ELISA) for specimen analysis as high-performance liquid chromatography (HPLC) is considered a more sensitive and specific indicator of plasma epinephrine levels. One strength of this study was the use of 50 to 70 kg swine, which more closely approximates the weight, the anatomic distance between infusion sites, and the volume of distribution of an adult human compared to the other studies using swine ranging in weight from 12 to 35 kg which more closely approximates pediatric subjects. Another is the inclusion of a PIV group, which is a more likely route of administration during CA than a CIV line especially in out-of-hospital CA.

FINDINGS FROM THE EVIDENCE AND DISCUSSION
The evidence suggested that epinephrine administered via the IO route during CA in animal models quickly reaches high serum concentrations though not as fast or in concentrations as great as epinephrine administered via the IV route. The major characteristics of the studies that met inclusion criteria are shown in Table II.

TABLE II. Synthesis of Results in Evidence Sources Pertaining to Intraosseous Epinephrine Administered During CA

Evidence Source	Study Design	Outcome Measures	Plasma Epinephrine Analysis Method	Conclusions of Study
Andropoulos et al[14]	Prospective, Experimental With Crossover Design	MAP, HR, Onset Time, Serum Epi Concentration	HPLC	Epi Given IO in CA Reaches High Serum Conc; No Dosage Change Recommended; Blood Flow to BM Adq for Drug Adm.
Spivey et al[15]	Prospective, Experimental, Within Subjects Design	MAP, DBP, Serum Epi Concentration	HPLC	Epi IO Rapidly Enters Circulation During CA; Larger Doses Needed to ↑ MAP and DBP
Hoskins et al[16]	Prospective, Experimental With Cross-Over Design	T_{max}, $T_{\frac{1}{2}max}$, Dose Delivered (AUC/Injected Dose)	Spectrophotometry	Epi Given Either SIO or TIO Effective; Epi Given SIO Delivers Larger and Faster Dose Than TIO; SIO and CIV Are Equivalent
Burgert et al[17]	Prospective, Experimental, Mixed Design	T_{max}, C_{max}	ELISA	Higher Dose of Epi May be Needed When Given IO; Epi Given SIO Delivers Dose Faster Than TIO; SIO and PIV Rapidly Deliver High Concentrations of Epi

Adm, administration; adq, adequate; AUC, area under the curve; BM, bone marrow; CA, cardiac arrest; CIV, central intravenous; C_{max}, maximum serum concentration; conc, concentration; DBP, diastolic blood pressure; ELISA, enzyme-linked immunosorbent assay; epi, epinephrine; HR, heart rate; HPLC, high performance liquid chromatography; IO, intraosseous; MAP, mean arterial pressure; PIV, peripheral intravenous; SIO, sternal intraosseous; TIO, tibial intraosseous; T_{max}, Time to maximum serum concentration; $T_{\frac{1}{2}max}$, time taken to reach half of maximal serum concentration.

The first evidence source[14] determined epinephrine concentrations were highest in the CIV group (377× baseline) followed by the TIO group (196× baseline) and the CIV saline control group (75× baseline). The increased concentration in the CIV saline group was likely triggered by endogenous release. Onset times, determined by increased MAP and HR, were found to be significantly faster in the CIV group compared to the TIO epinephrine group. The investigators concluded IO epinephrine given during CA quickly reaches high concentrations and did not recommend a dosage change. They also inferred bone marrow blood flow during CA is sufficient enough to mobilize injected epinephrine from the marrow cavity into the circulation, a finding confirmed in a later study.[21]

The second study[15] reported 0.01 mg/kg epinephrine given TIO increases serum epinephrine concentrations but not the MAP or DBP. Epinephrine given TIO at 0.1 mg/kg increased serum epinephrine concentration, MAP, and DBP. The investigators concluded epinephrine given IO rapidly enters the circulation during CA though it may partially depend on a saline bolus administered behind it to mobilize epinephrine from the marrow cavity into the circulation. In addition, supratherapeutic doses of epinephrine administered IO may be needed to produce significant changes in MAP and DBP. Specifically, the authors stated only the animals receiving 0.1 mg/kg epinephrine TIO achieved a DBP of between 30 and 40 mmHg, considered the minimum DBP necessary to ensure myocardial perfusion and improve resuscitation outcome.

The third study,[16] an RCT, concluded the SIO route delivers higher concentrations of epinephrine faster than the TIO route and the SIO route delivers a similar dose of epinephrine in nearly the same time as the CIV route during CA. Further, the SIO and TIO routes are effective in administering epinephrine during CA. Dye tracers in all groups reached maximal levels in less than 2 minutes. They recommend clinicians consider using SIO in preference to TIO during resuscitation. Lastly, the SIO and CIV routes are equivalent in rapidly delivering high levels of labeled epinephrine.

The final evidence source,[17] also an RCT, reported the PIV administration of 1mg of epinephrine resulted 5.87 and 2.86 times greater serum concentration compared to TIO and SIO routes, respectively. The investigators concluded the SIO route delivers epinephrine faster than TIO and PIV delivers epinephrine faster and in higher concentrations than SIO and TIO. Further, the SIO and PIV routes are similar in their ability to rapidly deliver high concentrations of epinephrine. The investigators recommended no change in dosage as there were study limitations but indicated a higher dose of epinephrine may be needed when given TIO. Further, the study should be repeated using a larger sample size, sampling from the arterial circulation, preferably at the aortic outlet, use of a large-volume saline flush following epinephrine administration, and use of HPLC for analysis.

Notable Characteristics

Analysis across the studies reviewed revealed several characteristics of note. Two of 4 evidence sources correlated pharmacokinetic and pharmacodynamic outcome measures.[14,15] Only 1 study was performed in an adult model.[17] With 1 exception,[14] all studies used mechanical chest compression devices helping to ensure uniform compressions. There was only 1 study that included a PIV group.[17] Two[14,15] of 4[14–17] studies used HPLC for specimen analysis. The others used spectrophotometry[16] or ELISA.[17] Two studies state there is no clinical significance between IV- and IO-administered epinephrine, and no increase in IO dosage is indicated.[14,16] However, 2 studies suggest an increase in dosage may be necessary to achieve maximal therapeutic effect,[15] especially when given via the TIO route.[17]

Pharmacokinetic Equivalence

Two evidence sources reviewed reported equivalence or near equivalence between IV- and SIO-administered epinephrine.[16,17] Bioavailability is defined as the fractional extent to which a dose of drug reaches its effect site and is measured by calculation of AUC. Bioequivalence is defined as the rate and extent to which the bioavailability of the active ingredient in 2 products is not significantly different under similar test conditions and is calculated by measuring AUC, C_{max}, and T_{max}.[24] The equivalence between many IV- and IO-administered drugs in perfusing subjects has been well established. Evidence supporting the equivalence between IV- and IO-administered drugs in CA remains unclear. The third study[16] is the only evidence source that considered AUC as an outcome measure. The external validity of future studies could be improved if the pharmacokinetic properties of AUC, C_{max}, and T_{max} were used as outcome measurements. Potential explanations for the lack of pharmacokinetic equivalence between IV and IO and even between different IO infusion sites exist. Among the explanations for the lack of pharmacokinetic equivalence between IV and IO include the potential for wide variability in bone marrow blood flow during CPR, particularly in more distal IO infusion sites such as the tibia. Another is a reservoir or depot effect in bones with higher ratios of less well-perfused yellow marrow to richly perfused red marrow. Red marrow is most abundant in flat bones such as the sternum and pelvis and in the epiphyseal ends of the humerus and femur. The adult tibia does not possess substantial amounts of red marrow. Moreover, although all marrow is red at birth, the ratio of red to yellow marrow declines with age.[25]

Applicability of Animal Studies

The translation of results from animal studies to human interventions may be limited by several threats to external validity. The third evidence source[16] summarizes several of them. Most importantly, conclusive extrapolations to humans from porcine models cannot be made because of anatomic

differences to include the apical shape of the pig thorax and the lack of a direct heart pump mechanism as the right ventricle does not underlie the sternum as it does in humans. Further, pig ventricles are surrounded by lung tissue on all sides. All these factors complicate the delivery of effective chest compressions in the pig resulting in significant variability in cardiac output during CPR causing animal to animal variability in pharmacokinetic outcome measures. Last, the shorter pig tibia may not be comparable to the longer tibia of humans that lies further away from the heart indicating marrow blood flow could be less in humans than pigs during CPR.[16]

SUMMARY

Intravenously administered epinephrine provides increased and faster appearing serum concentrations than IO-administered epinephrine. There is evidence indicating epinephrine given via the SIO route during CA more closely approaches equivalence with IV-administered epinephrine than the TIO route. Based on the data analyzed for this evidence-based review, when IV access is not possible, the clinician should use proximal IO infusion sites such as the sternum or humerus whenever possible when administering advanced cardiac life support drugs to rapidly achieve maximal therapeutic plasma concentrations.

There is no definitive evidence supporting equivalence between IV and IO epinephrine administered during CA with ongoing CPR. Further studies are needed to determine if epinephrine administered via the IO and IV routes during CA is bioequivalent. Pharmacokinetic studies of IO epinephrine in adult models of CA with the outcome measures of C_{max}, T_{max}, and AUC should be conducted. Specimens should be collected from the arterial circulation as close as possible to the aortic outlet. HPLC should be used for specimen analysis as it is the "gold standard" for measurement of serum epinephrine. The administration of epinephrine IO via the humeral head should be investigated because it is more proximal to the heart than the tibia, the surface anatomy is readily recognizable, easy to access with existing IO technology, and is located in an anatomical site that lowers the risk of accidental dislodgement of the IO device secondary to chest compressions. Further, accessing the humeral head minimizes interference with chest compressions and other resuscitation interventions. Cardiocerebral resuscitation is emerging as a method that may provide the highest level of post-arrest survivability with favorable neurologic outcome.[26] In light of this evolution in resuscitative therapy, future studies should consider correlating pharmacokinetic measurements of C_{max}, T_{max}, and AUC with pharmacodynamic measurements including DBP, MAP, central venous pressure, and cerebral perfusion pressure. Experimental models should be developed that as closely as possible replicate out-of-hospital CA, in which survival studies would be conducted that correlate pharmacokinetic and pharmacodynamic measurements with return of spontaneous circulation, immediate survival, and 24-hour survival with acceptable neurologic outcome.

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