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Clinical paper

Prehospital Tibial Intraosseous Drug Administration is Associated with Reduced Survival Following Out of Hospital Cardiac Arrest: A study for the CARES Surveillance Group

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Abstract

Background: Recent reports have questioned the efficacy of intraosseous (IO) drug administration for out-of-hospital cardiac arrest (OHCA) resuscitation. Our aim was to determine whether prehospital administration of resuscitative medications via the IO route was associated with lower rates of return of spontaneous circulation (ROSC) and survival to hospital discharge than peripheral intravenous (IV) infusion in the setting of OHCA.

Methods: We obtained data on all OHCA patients receiving prehospital IV or IO drug administration from the three most populous counties in Michigan over three years. Data was from the Michigan Cardiac Arrest Registry to Enhance Survival (CARES) database. The association between route of drug administration and outcomes was tested using a matched propensity score analysis.

Results: From a total of 10,626 OHCA patients, 6869 received parenteral drugs during their prehospital resuscitation (37.8% by IO) and were included in analysis. Unadjusted outcomes were lower in patients with IO vs. IV access: 18.3% vs. 23.8% for ROSC ($p < 0.001$), 3.2% vs. 7.6% for survival to hospital discharge ($p < 0.001$), and 2.0% vs. 5.8% for favorable neurological function ($p < 0.001$). After adjustment, IO route remained associated with lower odds of sustained ROSC (OR 0.72, 95% CI 0.63–0.81, $p < 0.001$), hospital survival (OR 0.48, 95% CI 0.37–0.62, $p < 0.001$), and favorable neurological outcomes (OR 0.42, 95% CI 0.30–0.57, $p < 0.001$).

Conclusion: In this cohort of OHCA patients, the use of prehospital IO drug administration was associated with unfavorable clinical outcomes.

Keywords: Out-of-hospital cardiac arrest, Intraosseous drug administration, Cardiopulmonary resuscitation

Introduction

Outcomes following out-of-hospital cardiac arrest (OHCA) remain poor, with only 7.6%–12% of patients surviving to hospital discharge nationally.[1,2] While high-quality cardiopulmonary resuscitation (CPR) is the mainstay of initial treatment, guideline-based care also includes the delivery of medications such as epinephrine and amiodarone. Despite conflicting data in the literature to support some pharmacological therapy in OHCA to

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improve patient outcomes,[3,4] the standard of care established by the American Heart Association (AHA) Advanced Cardiac Life Support (ACLS) guidelines recommend establishing either intravenous (IV) or intraosseous (IO) access for pharmacological therapy during cardiac arrest.[5] Traditionally there has not been a distinction between IV and IO access with respect to efficacy of drug delivery. Emergency medical services (EMS) guidelines vary between regions, resulting in varied practice patterns. Some providers may commonly utilize IO cannulation as the initial access; others may only use it as a last resort. Given its ease of use and high rate of placement success, however, IO access has become increasingly common in the pre-hospital setting.[6–9]

Although IO infusion is well-established as an effective route for the prehospital resuscitation of trauma, pediatric and shock patients,[10,11] its efficacy in cardiac arrest resuscitation has recently been called into question.[12–15] The purpose of this study was to compare OHCA clinical outcomes according to IO or IV route of drug administration using data obtained from the Michigan Cardiac Arrest Registry to Enhance Survival (CARES) database.

Methods

Study hypothesis

The study hypothesis was that the rates of return of spontaneous circulation (ROSC), survival to hospital discharge, and favorable neurological survival (defined as a cerebral performance category score of 1 or 2 at hospital discharge) were worse in patients receiving prehospital drug delivery through IO access than IV access.

Study design, setting, and population

The CARES database is a prospective, multicenter registry of patients with OHCA in the United States. The Centers for Disease Control and Emory University established CARES for cardiac arrest surveillance and quality improvement activities. Prior publications describe the design for the registry.[16,17] In brief, CARES captures OHCA patients for whom an emergency medical services (EMS) provider attempts resuscitation. Throughout the United States, more than 1400 EMS

Table 1 – Baseline demographics of out-of-hospital cardiac arrest patients.

	All patients	IO Access	IV Access	IO vs IV
Characteristics	N = 6896	N = 2603	N = 4293	P-value
Age in years (Mean ± SD)	64.8 ± 18.1	65.2 ± 17.9	64.5 ± 18.2	0.13
Sex n (%)				
Female	2754 (39.9)	1155 (44.4)	1599 (37.2)	<0.0001
Male	4142 (60.1)	1448 (55.6)	2694 (62.8)	
Race n (%)				
African American	1525 (22.1)	580 (22.3)	945 (22.0)	0.59
White	3350 (48.6)	1279 (49.1)	2071 (48.2)	
Other/unknown	2021 (29.3)	744 (28.6)	1277 (29.7)	
Medical problems n (%)				
Cancer	362 (5.2)	114 (4.4)	248 (5.8)	0.038
Diabetes	996 (14.4)	347 (13.3)	649 (15.1)	0.097
Heart disease	1293 (18.8)	483 (18.6)	810 (18.9)	0.95
Hypertension	1290 (18.7)	459 (17.6)	831 (19.4)	0.16
Hyperlipidemia	153 (2.2)	50 (1.9)	103 (2.4)	0.42
Pulmonary disease	656 (9.5)	251 (9.6)	405 (9.4)	0.95
Renal disease	410 (5.9)	137 (5.3)	273 (6.4)	0.17
History of stroke	215 (3.1)	68 (2.6)	147 (3.4)	0.17
First rhythm type n (%)				
Non-shockable	5739 (83.2)	2278 (87.5)	3461 (80.6)	<0.0001
VF/pVT	1157 (16.8)	325 (12.5)	832 (19.4)	
Bystander CPR n (%)	2483 (36.0)	1033 (39.7)	1450 (33.8)	<0.0001
Arrest location n (%)				
Home	4728 (68.6)	1696 (65.2)	3032 (70.6)	<0.0001
Assisted living	1231 (17.9)	587 (22.6)	644 (15.0)	
Public	937 (13.6)	320 (12.3)	617 (14.4)	
Incident county n (%)				
Macomb	1640 (23.8)	605 (23.2)	1035 (24.1)	0.18
Oakland	1988 (28.8)	784 (30.1)	1204 (28.0)	
Wayne	3268 (47.4)	1214 (46.6)	2054 (47.8)	
Targeted temperature management n (%)	683 (9.9)	199 (7.6)	484 (11.3)	<0.0001
Witnessed arrest n (%)	3102 (45.0)	1102 (42.3)	2000 (46.6)	0.0006
Naloxone given n (%)	1337 (19.4)	505 (19.4)	832 (19.4)	0.98
Epinephrine given n (%)	6780 (98.3)	2597 (99.8)	4183 (97.4)	0.45
First responder present n (%)	1394 (20.2)	522 (20.1)	872 (20.3)	0.80
Endotracheal tube placed n (%)	2857 (41.4)	1013 (38.9)	1844 (43.0)	0.0010

IO = intraosseous, IV = intravenous, VF = ventricular fibrillation, pVT = pulseless ventricular tachycardia, CPR = cardiopulmonary resuscitation.

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systems provide data to CARES. CARES also incorporates data from 911 dispatch centers and receiving hospitals and uses standardized international Utstein definitions for clinical variables and outcomes.[18]

After securing Institutional Review Board (IRB) approval, de-identified data were obtained in collaboration with SaveMIheart (Michigan) from the CARES database on all nontraumatic OHCA patients age ≥18 years from the three most populous counties in Michigan (Wayne, Oakland, and Macomb). The dates of patient inclusion were January 1, 2015 through December 31, 2017. Patients who did not receive drug delivery through either IO or IV access were excluded from the study. Although CARES data collection did not include the site of IO placement, review of EMS agency protocols in the included counties confirmed that proximal tibial placement was designated in all protocols. Additionally, these EMS agency protocols provide medics with the option to use either IO or IV access as first line access rather than protocolizing IO as being first or second line for access.[19,20] Data on number of attempts for access or time-to-access was not available.

The CARES registry collects patient-level EMS data on patient demographics and clinical characteristics, geographic location of cardiac arrest, presenting cardiac rhythm, presence of a witness, bystander CPR, route of vascular access, timing of arrest to EMS arrival, time to death or return of spontaneous circulation (ROSC), transportation time, medication administration, and interventions. Data collected from destination hospitals includes survival to hospital admission, survival to hospital discharge, and neurological survival. Favorable neurological survival is defined as survival to hospital discharge with a cerebral performance category (CPC) score of 1 (mild to no neurological disability) or 2 (moderate neurological disability).[18]

Outcomes

The primary outcome was survival to hospital discharge. Secondary outcomes included sustained ROSC and survival to hospital discharge with favorable neurological recovery.

Statistical analysis

We present demographic data with mean (standard deviation) or median (interquartile range) for continuous variables, or frequency (percentage) for categorical variables. Demographic data for patients with IO and IV access were compared using chi-square tests for categorical variables and a t-test or Wilcoxon–Mann–Whitney test for continuous variables.

To account for the non-random selection of access route, we performed a matched propensity-score analysis, which accounted for age, sex, initial cardiac rhythm, witnessed status, bystander CPR, location and history of cancer.[14] Logistic regression models were used to examine the relationship between attempted access (IO or IV) and survival to discharge, return of spontaneous circulation (ROSC), and good neurological recovery after adjusting for age, sex, race, initial cardiac rhythm, bystander CPR, location, incident county, witnessed status, use of targeted temperature management, nalox-one administration, first responder presence, endotracheal intubation and comorbidities. Patients were matched 1-to-1 on their propensity score with a caliper width of no more than 0.2 times the standard deviation of the logit of the propensity score. Conditional logistic regression adjusting for these variables above was performed. All analyses were performed using Statistical Analysis System (SAS Institute Inc., Cary, NC). A p-value < 0.05 was considered statistically significant.

Results

We identified 10,887 patients in the CARES database in the included counties over the study period, with the final study population consisting of 6896 patients who received either IO or IV access for drug delivery. Intraosseous access was placed in 2603 (37.7%) patients and IV access in 4293 (62.3%) patients. Comparative demographic and clinical characteristics of OHCA patients based on IO versus IV access are shown in Table 1. There were higher proportions of females and higher rates of non-shockable rhythms in patients receiving IO access. Patients receiving IV access had a higher rate of witnessed arrest. Reported comorbid conditions were similar between the IO and the IV groups, except for cancer. The proportion of patients receiving epinephrine was similar in each group. There were less than 20 patients total in each group receiving other medications including amiodarone, dextrose, bicarbonate, or calcium. Table 2 compares baseline demographics after propensity matching.

Table 3 shows the unadjusted association between IO and survival outcomes of sustained ROSC, survival to hospital discharge, and favorable neurological outcome. The unadjusted rate of survival to hospital discharge was lower in patients receiving IO access compared with IV access (3.2% versus 7.6%, p = 0.001). After multivariable adjustment and propensity score matching, IO access continued to be significantly associated with decreased survival (adjusted OR 0.51, 95% CI 0.40–0.67), as well as ROSC (adjusted OR 0.75, 95% CI 0.66–0.85) and good neurological function (adjusted OR 0.44, 95% CI 0.32–0.61). As seen in Table 3, the odds ratios were nearly identical with propensity score matching.

Time from EMS dispatch to arrival on scene was available in 2639 patients. Repeating the multivariable analysis using only patients with time from EMS dispatch to scene arrival data, there remained a significant association with reduced odds of survival to hospital discharge (OR 0.43, 95% CI 0.27–0.68) and good neurological function (OR 0.53, 95% CI 0.32–0.88) with IO compared to IV access.

Table 2 – Baseline demographics of out-of-hospital cardiac arrest patients after propensity score matching.

	IO Access	IV Access	IO vs IV
Characteristics	N = 2597	N = 2597	P-value
Age in years (Mean ± SD)	65.3 ± 17.8	65.3 ± 18.0	0.97
Sex n (%)			
Female	1149 (44.2)	1160(44.7)	0.76
Male	1448 (55.8)	1437 (55.3)	
First rhythm type n (%)			
Non-shockable	2272 (87.5)	2266 (87.3)	0.80
VF/pVT	325 (12.5)	331 (12.7)	
Witnessed arrest n (%)	1102 (42.4)	1127 (43.4)	0.48
Bystander CPR n (%)	1027 (39.5)	1012 (39.0)	0.67
Public location n (%)	320 (12.3)	306 (11.8)	0.55
Cancer* n (%)	114 (4.4)	102 (3.9)	0.70

IO = intraosseous, IV = intravenous, VF = ventricular fibrillation, pVT = pulseless ventricular tachycardia, CPR = cardiopulmonary resuscitation.
* Past history of cancer was included in propensity score matching due to significant difference in incidence of cancer among the IO and IV groups.

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Table 3 – Outcomes of patients with out-of-hospital cardiac arrest receiving either IO or IV access, after multivariable adjustment (3A) and propensity score matching (3B).

	IO Access	IV Access	Adjusted OR	p-Value
3A. Primary study cohort (N = 6896)				
ROSC n (%)	475 (18.3)	1023 (23.8)	0.75 (0.66–0.85)	<0.001
Survival to hospital discharge n (%)	84 (3.2)	328 (7.6)	0.51 (0.40–0.67)	<0.001
Good neurological function n (%)	51 (2.0)	247 (5.8)	0.44 (0.32–0.61)	<0.001
3B. Propensity score matched cohort	IO Access (N = 2597)	IV Access (N = 2597)		
ROSC n (%)	475 (18.3)	599 (23.1)	0.78 (0.67–0.90)	<0.001
Survival to hospital discharge n (%)	84 (3.2)	168 (6.5)	0.50 (0.37–0.66)	<0.001
Good neurological function n (%)	51 (2.0)	119 (4.6)	0.42 (0.30–0.60)	<0.001

IO = intraosseous, IV = intravenous, OR = odds ratio, ROSC = return of spontaneous circulation.

The association with IO access and ROSC was not statistically significant (OR 0.85, 95% CI 0.69–1.05), when taking into consideration time from EMS dispatch to arrival.

Discussion

Our study includes a large cohort of OHCA patients, in which a significant proportion (37.7%) received medications via the tibial IO route. After propensity matching and adjustment for many confounding variables, intraosseous access was negatively associated with return of spontaneous circulation, survival to hospital discharge, and favorable neurological outcome.

Given increasing popularity of IO access, our study, along with a growing body of literature, highlights the urgent need for prospective studies to evaluate the efficacy of IO drug delivery in OHCA resuscitation. Feinstein et al. demonstrated decreased rates of ROSC associated with IO drug delivery but no difference in survival to hospital discharge.[11] Kawano et al. showed decreased rates of ROSC, survival to hospital discharge, and favorable neurological outcome in patients receiving IO access.[13] In this study, only 5% of the cohort received IO access, and receiving IO access could have been secondary to characteristics predictive of difficult IV access, thus altering outcomes.

Mody et al. also recently demonstrated a reduction in sustained ROSC associated with IO access but no change in survival to hospital discharge or neurological outcomes.[14] Their analysis included a large data set of patients across multiple sites in North America, which increases the generalizability of these findings. Clemency et al showed no significant difference in ROSC between patients receiving IO or IV access. In this study, 39.9% of patients received IO access as the first route for parental drug administration.[15] Finally, Daya et al. evaluated the efficacy of amiodarone and lidocaine stratified by route of drug delivery in the Resuscitation Outcomes Consortium Amiodarone, Lidocaine or Placebo Study. In this population of 3019 patients with ventricular fibrillation or pulseless ventricular tachycardia, increased survival to hospital discharge was associated with the intravenous route of drug administration.[21]

More recently, a prospective cluster-randomized study evaluated outcomes in OHCA patients receiving IV versus IO prehospital medications.[22] In this study, OHCA patients were randomly assigned to an IV access group or an IV + IO group in which IO access was attempted after two failed IV attempts or after 2 min (whichever came first). In this study, patients in the IV + IO group had a shorter time to vascular access and to epinephrine administration than the IV group. However, there was no difference in the rate of ROSC, survival to hospital discharge or good neurological outcome between the two groups despite prior studies demonstrating a potential for improved outcomes with early epinephrine administration.[23–25] Despite a lack of subgroup analysis of outcomes in patients receiving IO medications compared to IV medications, this study did not show any benefit of IO access as a rescue vascular access method when attempts at IV access failed.

Animal models have attempted to address the efficacy of drugs administered through the IO route. Normotensive and shock animal models have shown that the intraosseous route of medication administration was comparable in effect with central and peripheral intravenous routes for multiple medications including epinephrine, sodium bicarbonate, and calcium chloride.[26] Human studies have shown no significant differences in pharmacokinetics observed between IO and IV administration of morphine in normotensive patients.[11] However, bone marrow flow rates are greatly reduced during cardiopulmonary resuscitation to about 20%–30% normal.[27] Further animal studies have shown that during resuscitation after hypovolemic cardiac arrest, bone marrow blood flow is nearly absent after high-dose epinephrine injection, but was maintained after high-dose vasopressin, which is no longer included in the ACLS protocols for cardiac arrest resuscitation.[28] Given that epinephrine is the initial drug administered in cardiac arrest resuscitation, the low bone marrow flow that ensues may prevent further resuscitative medications from reaching the central circulation. This flow reduction could account for the reduced rates of ROSC found in our study and in the literature.

Although there is paucity of recent literature, some studies have identified slower drug transport rates to the inferior vena cava versus superior vena cava in cardiac arrest.[29–31] This may be related to the lack of a pressure gradient between the inferior vena cava and right atrium. The suggestion without studies comparing upper and lower extremity IVs, that lower extremity vascular access, rather than IV vs IO access may play a role in resuscitation rates.[32]

Animal models have also shown that proximal IO drug administration sites (humeral or sternal) more rapidly achieve maximal therapeutic plasma concentrations than more distal IO sites (tibial).[33] Additionally, in a cardiac arrest swine model, O'Sullivan et al. showed that there was a significant delay in time to ROSC and a significant difference in odds of ROSC when drugs were administered via the tibial IO route compared to the sternal IO or IV routes. There was no difference in odds of ROSC between the sternal IO route and IV route of drug administration.[34] Burgert et al. however showed no significant

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differences in ROSC between epinephrine administration via the humeral IO, tibial IO, or IV route in an adult swine model of ventricular fibrillation.[35]

It is possible that use of the proximal tibia IO insertion site is suboptimal for the treatment of OHCA. The proximal tibia is far removed from the central circulation, and has been observed to have significantly lower flow rates and higher resistance to flow than the humeral or sternal IO insertion sites.[36,37] It is unknown whether use of the sternal or humeral IO sites would have been associated with different outcomes, although the prospect of improved flow rates would appear to offer benefit. Given the conflicting data in animal models with regards to equivalency of distal and proximal IO, it is unclear if patients with humeral or sternal IO would have similar outcomes to those with IV access. Future human studies are needed to determine if the location of IO access is associated with different outcomes in OHCA.

Limitations

Several limitations of our study are notable. First, our study included only data on OHCA in the metropolitan Detroit area, which may limit generalizability to patient populations in other geographic areas. Second, our data set did not specify timing to first drug administration, information on number of attempts for IV compared to IO access, and whether drug administration was followed by fluid bolus or pressure bags, which can affect drug distribution.[13] Third, the route of vascular access chosen for a given patient may not have been randomly selected and was not standardized across EMS agencies. EMS agencies in the three counties studied did not specify IO or IV access as first or second line. Medics were provided the option to use either IO or IV. Again, data on timing of access or number of attempts at access were not available. Patients perceived to have difficult-to-obtain IVs may have been selectively given IO access. Inability to obtain an IV could be a surrogate marker of unaccounted comorbidities and possibly unrecognized long downtime. While propensity score matching may reduce the effect of potential selection bias in choice of access on the main results of this study, residual confounding is possible as data was incomplete on certain comorbidities such as end stage renal disease and obesity. Fourth, outcomes could also be affected by hospital interventions and post-ROSC care including cardiac catheterization. Cardiac catheterization data was sparse within our database and was therefore not included. Finally, our data only includes patients who have received proximal tibial IO. Therefore, our results cannot be generalized to patients receiving humeral or sternal IO access in OHCA.

Conclusions

In this large sample of OHCA patients with a high proportion of IO use for drug delivery, we found that reduced ROSC, worse neurological function, and reduced rates of survival to hospital discharge were associated with the use of IO compared to IV drug administration. We observed that OHCA patients that receive prehospital IO drug infusions also have characteristics that are unfavorable to survival and may confound investigations into this question. These results, along with those from other recent studies, underscore the need for randomized controlled trials to properly evaluate the relative efficacy of the IO routes of drug delivery for OHCA resuscitation.

Conflicts of interest

The authors have no conflicts of interest to report.

CRediT authorship contribution statement

Mohamed Serhan Hamam: Data curation, Writing - original draft, Visualization. **Howard A. Klausner:** Conceptualization. **John France:** Investigation, Writing - review & editing. **Amy Tang:** Methodology, Formal analysis. **Robert A. Swor:** Writing - review & editing. **James H. Paxton:** Writing - review & editing. **Brian J. O'Neil:** Writing - review & editing. **Christine Brent:** Writing - review & editing. **Robert W. Neumar:** Writing - review & editing. **Robert B. Dunne:** Writing - review & editing. **Swetha Reddi:** Writing - review & editing. **Joseph B. Miller:** Conceptualization, Methodology, Writing - review & editing, Supervision.

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