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Intraosseous compared to intravenous drug resuscitation in out-of-hospital cardiac arrest☆

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ABSTRACT

Aims: Although the intraosseous (IO) route is increasingly used for vascular access in out-of-hospital cardiac arrest (OHCA), little is known about its comparative effectiveness relative to intravenous (IV) access. We evaluated clinical outcomes following OHCA comparing drug administration via IO versus IV routes.

Methods: This retrospective cohort study evaluated Emergency Medical Services (EMS)-treated adults with atraumatic OHCA in a large metropolitan EMS system between 9/1/2012–12/31/2014. Access was classified as IO or IV based on the route of first EMS drug administration. Study endpoints were survival to hospital discharge, return of spontaneous circulation (ROSC) and survival to hospital admission.

Results: Among 2164 adults with OHCA, 1800 met eligibility criteria, 1525 of whom were treated via IV and 275 principally via tibial-IO routes. Compared to IV, IO-treated patients were younger, more often women, had unwitnessed OHCA, a non-cardiac aetiology, and presented with non-shockable rhythms. IO versus IV-treated patients were less likely to survive to hospital discharge (14.9% vs 22.8%, $p = 0.003$), achieve ROSC (43.6% vs 55.5%, $p < 0.001$) or be hospitalized (38.5% vs 50.0% $p < 0.001$). In multivariable adjusted analyses, IO treatment was not associated with survival to discharge (odds ratio (OR) (95% confidence interval) 0.81 (0.55, 1.21), $p = 0.31$), but was associated with a lower likelihood of ROSC (OR = 0.67 (0.50, 0.88), $p = 0.004$) and survival to hospitalization (OR = 0.68 (0.51, 0.91), $p = 0.009$).

Conclusion: Though not independently associated with survival to discharge, principally tibial IO versus IV treatment was associated with a lower likelihood of ROSC and hospitalization. How routes of vascular access influence clinical outcomes after OHCA merits additional study.

Introduction

Out-of-hospital cardiac arrest (OHCA) is a common manifestation of heart disease and is a leading cause of death in western societies (US) [1]. Approximately 347,000 adults experience OHCA in the United States each year, with an estimated survival rate of 10.6% [2]. The treatment of OHCA frequently requires vascular access for administration of drugs, such as adrenaline (epinephrine) and antiarrhythmic medications. Vascular access in the prehospital setting has historically been obtained through peripheral intravenous (IV) catheterization. More recently, the advent of newer intraosseous (IO) vascular access devices enable drug administration through a percutaneous puncture into venous sinusoids within bone. The IO route can provide an alternative route, especially in situations where IV access may be difficult to obtain [3,4].

Resuscitation guidelines consider IV and IO routes of drug administration as equally acceptable during OHCA, though guidelines also highlight the scarcity of comparative evidence. Prior studies have evaluated the success rates of IO versus IV placement, indicating that prehospital personnel can be effectively trained and efficient in both methods [3,4]. Given its ease of use, the IO mode for drug administration is increasingly practised in the prehospital setting [5–7].

There are however no published results investigating the actual comparative effectiveness of the route of drug administration on survival in the context of human OHCA. A limited number of animal studies have evaluated the plasma concentrations and pharmacokinetics of some drugs achieved by the differing routes

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of administration, with mixed findings [8–13]. How such results might apply to OHCA in humans is uncertain. There may be mechanisms that could produce differential pharmacologic and clinical effects. For example, the IO route of access may afford less direct and slower entry of drugs because the drug must first traverse bone before entering the circulation. Absorption of some drugs within bone might also lower the concentration that reaches the circulation.

The purpose of this study was to determine if there are differences in clinical outcome associated with IO compared to IV routes of drug administration during resuscitation of adults with OHCA. We hypothesized that IO access may be a less clinically effective route than IV for drug administration during resuscitation, and thus result in a lower likelihood of survival to hospital discharge, sustained return of spontaneous circulation (ROSC) and survival to hospital admission.

Methods

Study design and population

We conducted a retrospective cohort study of EMS-treated, non-traumatic OHCA among persons ≥18 years of age in King County, WA (excluding Seattle) between September 1, 2012 and December 31, 2014. This period was chosen based on the availability of study variables, specifically the full implementation and recording of IO access. The study excluded 1) patients who did not receive vascular access, 2) patients for whom there was missing information about the route of access or missing key Utstein measures of initial arrest rhythm or arrest aetiology, and 3) patients who did not receive full resuscitation measures due to physician orders for life-sustaining treatment (POLST), a Washington State advanced directive that provides direction regarding do not resuscitate wishes. This study was approved by the University of Washington Human Subjects Committee (HSD #49514) and Public Health – Seattle and King County Research Administrative Review Committee.

Setting

King County (excluding Seattle) has an area of approximately 2000 square miles and includes urban, suburban, and rural areas. The estimated population of King County (excluding Seattle) from the 2014 census date is 1,411,625 [14]. King County is served by a two-tiered Emergency Medical Services (EMS) system that is activated by calling a central dispatch via 9-1-1. The first tier consists of fire fighter- emergency medical technicians (EMT) who are trained in basic life support (BLS) and defibrillation. The second tier consists of paramedics who are trained in advanced life support (ALS). Both tiers are dispatched simultaneously in the case of a suspected OHCA. First tier EMS providers arrive on scene an average of 5 min after dispatch. The second tier arrives on average 5 min after the first tier. The EMS system follows the AHA guidelines for management of OHCA. The primary approach to vascular access in OHCA in this system is by peripheral venous catheterization whereas providers are trained in obtaining tibial IO access when initial peripheral IV access attempts are unsuccessful.

Data collection

The EMS Division has maintained an ongoing registry of all EMS-treated OHCA since 1976. Information is ascertained from prehospital patient care records, dispatch tape recordings, time-stamped cardiac defibrillator continuous electronic rhythms and resuscitation audio recordings, and hospital records. The registry contains information pertaining to patient demographics, event circumstances, presenting rhythm, on-scene care including response intervals, time of interventions, type of vascular access, immediate outcome (ROSC), hospital admission or death, and survival to hospital discharge. The anatomic location of vascular access, the interval to vascular access, and the interval from access to drug administration were not previously abstracted, and were separately ascertained by the investigators from the prehospital patient care records, inclusive of the resuscitation continuous rhythm and audio recordings in which field providers narrated their care. In determining the interval from access placement to first drug administration, the investigators reviewed a selected sample of recordings. The latter sample was derived by a-priori matching of the two cohorts (160 patients from the IO group and 100 from the IV group) by age (±10 years), initial rhythm, witnessed status, location, arrest aetiology, bystander CPR status and vascular access interval (±2 min).

Cardiac monitor defibrillators were synchronized with EMS dispatch time and the official National Institutes of Standards and Technology time. When the defibrillator time was not synchronized, events heard on the audio recording were synchronized with events noted on the computer-aided dispatch report or heard on-scene, to establish a more precise timeline of events.

Definitions

The primary route of vascular access (IV or IO) was defined as the first patent access site used for drug administration. Vascular access interval was defined as the interval from the receipt of the incident call to EMS IV or IO access placement, derived from information from the dispatch report, the EMS written report, and the defibrillator's time-stamped audio recording.

The aetiology of arrest was classified as either cardiac or non-cardiac related based on all available information including medical report forms, hospital records and death certificates [15]. The current study excluded traumatic aetiology arrest. The initial presenting rhythm was classified as shockable (ventricular fibrillation or ventricular tachycardia) versus non-shockable (asystole or pulseless electrical activity). The witnessed status was classified as either unwitnessed, witnessed by EMS, or witnessed by bystanders. The location was classified as private residence, public, assisted living facility/nursing home or outpatient medical facility (clinic/medical office). EMS response interval was the time elapsed from call receipt to EMS arrival at the incident address.

Outcomes

The primary outcome of interest was survival to hospital discharge. Secondary outcomes were sustained ROSC and survival to hospital admission.

Statistical analysis

We compared patient characteristics, event circumstances and patient care procedures according to the primary route of access using the Student's *t*-test for continuous variables and the Pearson's chi-square test for categorical variables. We used multivariable logistic regression to evaluate the independent association of the route of initial access and outcome including ROSC, survival to hospital admission, and survival to hospital discharge. We a-priori chose Utstein data elements because they have previously been related to outcome. Hence, the model adjusted for arrest aetiology, age, gender, initial rhythm, witnessed status, receipt of bystander CPR, arrest location, and EMS response interval. We conducted an a-priori sensitivity analysis, restricted to those patients for whom there was a vascular access interval, and adjusted for this interval from call receipt to IV or IO placement along with other known confounders. All statistical analyses were performed using IBM SPSS, version 22 (Armonk, NY), and statistical significance indicated by a two-tailed alpha level of 0.05.

Results

From September 1, 2012 to December 31, 2014, 2164 persons experienced atraumatic OHCA and received attempted resuscitation by EMS. A total of 364 were excluded because age <18 years, POLST status, or missing covariate information. The remaining 1800 comprise the primary study cohort, 1525 in the IV group and 275 in the IO group (Fig. 1). Compared to IV, those treated via IO were on average younger, more often women, had a non-cardiac aetiology, an unwitnessed OHCA, and initially presented with a non-shockable rhythm (Table 1). Vascular access interval was determined in 1241 patients, 220 in the IO group and 1021 in the IV group. The mean call-to-vascular access interval was longer in the IO group compared to the IV group (18.4 (SD 6.8) minutes versus 16.3 (SD 6.0) minutes, p < 0.001). Conversely, the mean time from vascular access to drug administration, determined in a matched subgroup of 160 IO and 100 IV patients, was shorter in the IO than IV group (47.9 (SD 33.6) seconds compared to 62.8 (SD 46.0) seconds, respectively, p < 0.001). Though differing by access route, it is notable that in this matched subgroup the interval to vascular access and to first drug administration were generally only about a minute apart, suggesting the one interval could potentially be taken to approximate the other. Among those for whom the IO site could be verified with certainty in this subgroup, it was uniformly in the tibial location. Epinephrine was the first drug administered in 255 of these cases (98%) regardless of the route of access

Outcome

In an unadjusted analysis, patients in the IO group compared to IV group were less likely to survive to hospital discharge (14.9% vs 22.8%, respectively, p = 0.003), or achieve sustained ROSC (43.6% vs 55.5%, p < 0.001) and survive to hospital admission (38.5% vs 50.0%, p < 0.001) (Table 2). In multivariable adjusted analyses, treatment via IO was not associated with survival to discharge (odds ratio (95% confidence interval) OR = 0.81 (0.55, 1.21), p = 0.31), but was associated with a lower likelihood of ROSC (OR = 0.67 (0.50, 0.88), p = 0.004) and survival to hospital admission (OR = 0.68 (0.51, 0.91), p = 0.009).

Sensitivity analysis

In the subset of patients with a recorded interval from call to vascular access (n = 1241), unadjusted outcomes between IO and IV access were similar to the results from the overall cohort (survived to hospital discharge 13.6% vs 19.1%, p = 0.07; ROSC 42.3% vs 52.9%, p = 0.004; and survived to hospital admission 37.7% vs 47.2%, p = 0.01, respectively) (Table 2). Outcomes were also directionally similar among the 559 patients in whom times to vascular access were not specified (data not shown). Multivariable adjusted ORs between IO access and outcome were similar to the results from the overall cohort when the vascular access interval was included in the model (survival to discharge OR = 0.87 (0.54, 1.40), p = 0.56; ROSC OR = 0.69 (0.50, 0.95), p = 0.02), although survival to hospital admission was no longer statistically significant (OR = 0.72 (0.51, 1.01), p = 0.06).

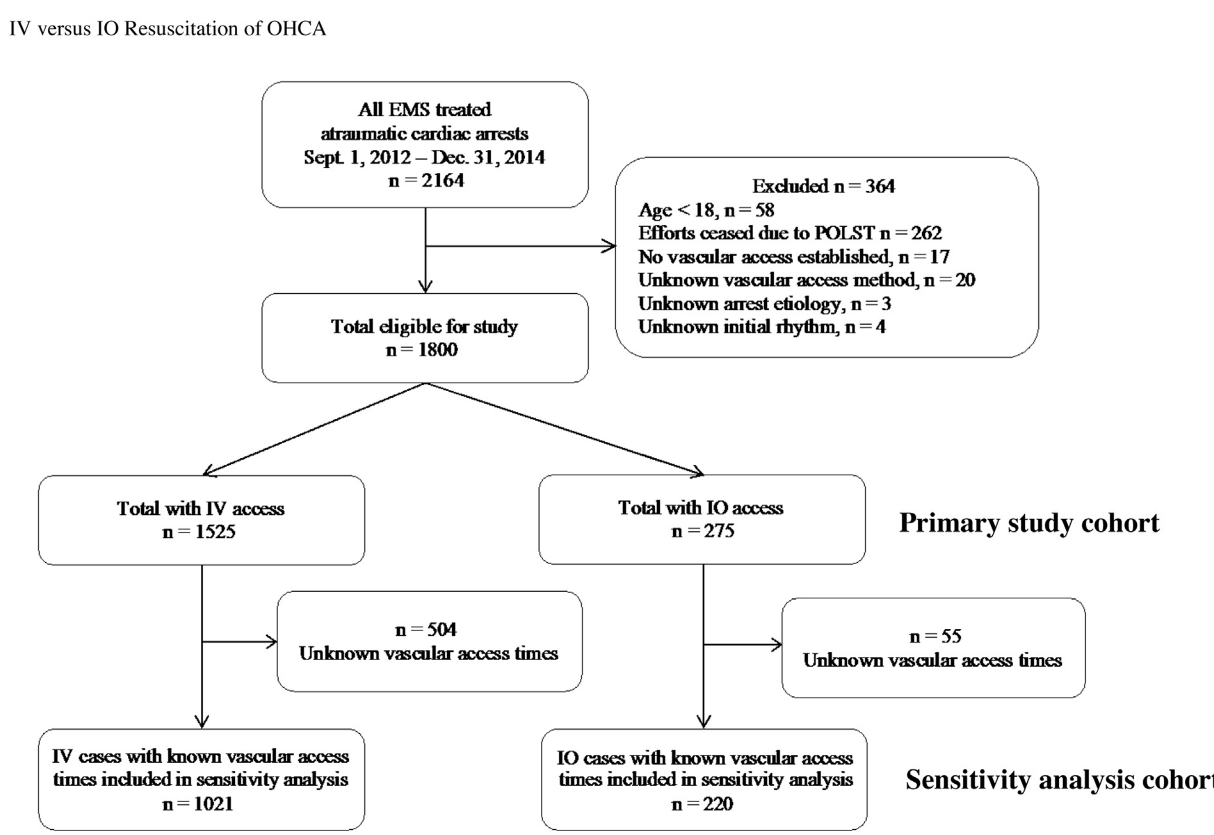

Fig. 1. Flowchart of patient inclusion. EMS- emergency medical services. POLST – physician orders for life sustaining treatment IV intravenous IO- intraosseous.

Table 1
Distribution of baseline study demographics.

Characteristics	Eligible Patients N = 1800	IO Recipients N = 275	IV Recipients N = 1525	IO vs IV (p)
Gender				<0.001
Female n (%)	674 (37.4)	133 (48.4)	541 (35.5)	
Age (years)				0.010
Mean (standard deviation)	63.9 (16.6)	61.5 (16.1)	64.3 (16.7)	
Witnessed status n (%)				0.006
EMS	200 (11.1)	21 (7.6)	179 (11.8)	
Bystander	824 (45.8)	113 (41.1)	711 (46.6)	
Unwitnessed	776 (43.1)	141 (51.3)	635 (41.6)	
Bystander CPR n (%)	1244 (69.1)	197 (71.6)	1047 (68.7)	0.32
Aetiology of cardiac arrest n (%)				<0.001
Cardiac	1085 (60.3)	137 (49.8)	948 (62.2)	
Non-cardiac	715 (39.7)	138 (50.2)	577 (37.8)	
Location of cardiac arrest n (%)				0.087
Public	331 (18.4)	41 (14.9)	290 (19.0)	
Private	1211 (67.3)	185 (67.3)	1026 (67.3)	
Assisted Living/Clinic	230 (12.8)	46 (16.7)	184 (12.1)	
MD office	281 (1.5)	3 (1.1)	25 (1.6)	
Initial cardiac arrest rhythm n (%)				<0.001
VF/VT	501 (27.8)	47 (17.1)	454 (30.0)	
Non-shockable	1299 (72.2)	228 (82.9)	1071 (70.0)	
EMS response interval (min)				0.76
Mean (standard deviation)	5.86 (2.51)	5.82 (2.44)	5.87 (2.53)	

CPR – cardiopulmonary resuscitation; IV – intravenous; IO – intraosseous; EMS – emergency medical services; MD – medical doctor; VF – ventricular fibrillation; VT – ventricular tachycardia.

Table 2
Likelihood of outcome for IO compare to IV access following OHCA.

Outcome	IO	IV	P value	Multivariable OR[a] (95% CI)	P value
All patients, n (%)	275	1525			
Sustained ROSC	120 (43.6%)	846 (55.5%)	<0.001	0.67 (0.50, 0.88)[b]	0.004
Admission alive to hospital	106 (38.5%)	762 (50%)	<0.001	0.68 (0.51, 0.91)[b]	0.009
Survival to discharge	41 (14.9%)	348 (22.8%)	0.003	0.81 (0.55, 1.21)[b]	0.31
Patients with interval from call to vascular access	220	1021			
Sustained ROSC	93 (42.3%)	540 (52.9%)	0.004	0.69 (0.50, 0.95)[c]	0.02
Admission alive to hospital	83 (37.7%)	482 (47.2%)	0.01	0.72 (0.52, 1.01)[c]	0.06
Survival to discharge	30 (13.6%)	195 (19.1%)	0.07	0.87 (0.54, 1.40)[c]	0.56

[a] OR odds ratio, IO in relation to IV. ROSC – return of spontaneous circulation.
[b] The multivariable model was adjusted for cardiac arrest aetiology, age, gender, initial rhythm, witnessed status, bystander CPR, cardiac arrest location, vascular access type, and EMS response interval.
[c] The multivariable model was adjusted for cardiac arrest aetiology, age, gender, initial rhythm, witnessed status, bystander CPR, cardiac arrest location, vascular access type, and vascular access interval.

Discussion

In this retrospective cohort study of OHCA, the route of access comparing IO to IV was not associated with survival to hospital discharge after adjustment for potential confounders. However, IO access was associated with a lower likelihood of intermediate outcomes of ROSC and survival to hospital admission.

IO access can be established quickly and reliably to administer therapeutic interventions like fluids, some drugs and blood into the central circulation [16–20]. Though its feasibility has been validated, the clinical effectiveness of IO treatment remains uncertain. Some comparisons of IV and IO vasoactive drug administration have shown comparable hemodynamic effects in animals, while other studies suggest that drug delivery to the central circulation may be slower or less effective by the IO route as compared to IV [9]. For example, animal models of cardiac arrest have indicated that the IO compared to IV route result in lower serum concentrations of adrenaline and that higher doses are required via the IO route to achieve comparable coronary perfusion pressures [8,21]. The paucity of clinical studies in human resuscitation has been highlighted as an important knowledge gap in guidelines [22]. The current study attempts to help address this gap; the results suggest that route of treatment may indeed have distinct effects such that the tibial IO route compared to IV route could adversely influence clinical outcomes.

What might explain the observed associations? One could contend that patient, circumstance, or time-to-treatment differences between the IO and IV groups account for the differences in ROSC and survival to admission. We attempted to address these potential confounders by using multivariable adjustment though unmeasured confounding may still influence the association. To this end, IO placement is typically an alternate approach, so a second line strategy to IV placement, and could be associated with patients who are more difficult to resuscitate. These more challenging characteristics may not be fully captured by the Utstein data elements included in the current investigation's multivariable models.

The lower likelihood of ROSC and survival to hospital admission among the IO group may also be due to anatomic considerations. IO placement in this cohort was principally in the tibial location. A cadaveric study observed that maximum flow rates from tibial cannulation were only one-third to one-half of sternal or humeral IO locations [25–27]. In an animal model of arrest, chest compressions increase venous pressures in the subdiaphragmatic inferior vena cava but not the internal jugular system, which would potentially impede venous return to the heart from the lower but not upper body during CPR [28]. Cineangiographic and radioisotope imaging studies also suggest that use of the lower limb compared to upper limb access may produce slower or lower medication levels [29].

We did not observe an independent association between the route of access and outcome of survival to discharge. This lack of association may represent a true null effect of the route of access whereby the route of treatment truly has no physiologic or clinical effects. This seems unlikely, given the more immediate outcome differences (ROSC and survival to hospital admission) observed between the IO and IV treatment groups. The findings may also represent a true difference in the physiologic effects from treatment itself, irrespective of its route of administration, potentially similar to the results of randomized trials of adrenaline where IV administration of adrenaline compared to placebo achieved higher rates of ROSC and hospital admission, but without an accompanying improvement in survival [23,24]. Or the IO route of access may in fact have an adverse effect on survival that was not detected given the modest power afforded by the cohort comparison. The magnitude of the odds ratio (0.81–0.87) between IO route and survival to hospital discharge would be clinically important if such a difference were true. The power of the current study to detect such a difference was less than 50%, supporting the need for additional investigations evaluating the relationship between the route and location of access and clinical outcomes following OHCA.

Limitations

As noted, this investigation was a retrospective cohort study. The observed relationships could be due to confounding despite efforts in analysis to limit this bias. Some characteristics such as patient body habitus or reasons why the initial IV access attempt was unsuccessful are not routinely documented by EMS personnel so cannot be accounted for in the current comparison. Although providers were trained to perform IO access at the tibial location during the study period, we were not able to verify this site with certainty in all cases. Nonetheless, our results should not necessarily be generalized to the humeral or sternal upper torso IO access sites. The study occurred in the context of a mature EMS system with paramedics who generally have substantial experience with conventional IV access. Whether the results would be similar in other systems with distinct characteristics and competencies is uncertain. These results should be balanced with the strengths of the study: the results included a relatively large cohort for which the route of access was systematically assessed and involved analyses that accounted for important confounders.

Conclusions

Drug treatment for OHCA principally via the tibial IO as compared to IV route showed no association between route of access and survival to hospital discharge, but was independently associated with a lower likelihood of achieving sustained ROSC and survival to hospital admission. These findings suggest that the route of vascular access may have differential physiological or clinical effects, and support the need for additional research to investigate if and how this might influence outcomes following OHCA.

Conflict of interest

The authors have no conflicts of interest to declare. This study received funding from the University of Washington Medical Student Research Training Program (MSRTP). This study received no outside agency or company support or loan equipment.

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