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Clinical paper

Intramuscular adrenaline for out-of-hospital cardiac arrest is associated with faster drug delivery: A feasibility study☆

A.E. Pugh[a,*], H.H. Stoecklein[a,b], J.E. Tonna[a,c], G.L. Hoareau[a,d], M.A. Johnson[a], S.T. Youngquist[a,b]

[a] Division of Emergency Medicine, Division of Surgery, University of Utah School of Medicine, 30 North 1900 East, Room 1C26 SOM, Salt Lake City, UT 84132, USA

[b] Salt Lake City Fire Department, Salt Lake City, UT, USA

[c] Division of Cardiothoracic Surgery, University of Utah School of Medicine, UT, USA

[d] Nora Eccles Harrison Cardiovascular Research and Training Institute, USA

Abstract

Background: Early adrenaline administration is associated with return of spontaneous circulation (ROSC) and survival in out-of-hospital cardiac arrest (OHCA). Animal data demonstrate a similar rate of ROSC when early intramuscular (IM) adrenaline is given compared to early intravenous (IV) adrenaline.

Aim: To evaluate the feasibility of protocolized first-dose IM adrenaline in OHCA and it's effect on time from Public Safety Access Point (PSAP) call receipt to adrenaline administration when compared to IO and IV administration.

Methods: This is a before-and-after feasibility study of adult OHCAs in a single EMS service following adoption of a protocol for first-dose IM adrenaline. Time from PSAP call to administration and outcomes were compared to 674 historical controls (from January 1, 2013–February 8, 2021) who received at least one dose of adrenaline by IV or IO routes.

Results: During the study period, first-dose IM adrenaline was administered to 99 patients (December 1, 2019–February 8, 2021). IM adrenaline was given a median of 12.2 min (95% CI 11.4–13.1 min) after the PSAP call receipt compared to 15.3 min for the IV route (95% CI 14.6–16.0 min) and 15.3 min for the IO route (95% CI 14.9–15.7 min) with a time savings of 3 min (95% CI 2–4 min). Rates of survival to hospital discharge appeared similar between groups: 10% for IM, 8% for IV and 7% for IO. However, results related to survival were underpowered for statistical comparison.

Conclusions: Within the limitations of a small sample size and before-and-after design, first-dose IM adrenaline was feasible and reduced the time to adrenaline administration.

Keywords: Out-of-hospital cardiac arrest (OHCA), Intramuscular adrenaline

Abbreviations: AHA, American Heart Association; CPR, cardiopulmonary resuscitation; CQI, Care Quality Improvement; EMS, Emergency Medical Services; IM, intramuscular; IO, intraosseus; IRB, Institutional Review Board; IV, intravenous; OHCA, Out of hospital cardiac arrest; PSAP, Public Safety Access Point; ROSC, return of spontaneous circulation; SLCFD, Salt Lake City Fire Department; TXA, tranexamic acid.

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* Corresponding author.

E-mail address: Andrew.pugh@hsc.utah.edu (A.E. Pugh).

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Background

Guidelines from the American Heart Association (AHA) recommend adrenaline administration as soon as is reasonably possible in out-of-hospital cardiac arrest (OHCA) from non-shockable rhythms.[1] The optimal timing of adrenaline administration to treat shockable rhythms is less clear; observational evidence suggests that early adrenaline administration is positively associated with return of spontaneous circulation (ROSC) and survival in OHCA.[2–8]

In OHCA, intravenous (IV) and intraosseus (IO) access is not always immediately available and attempts at difficult access may distract from quality chest compressions and timely defibrillation.[9] Intramuscular (IM) adrenaline is already widely accepted as a safe and rapid lifesaving treatment in anaphylaxis, even in the hands of nonprofessionals.[10–14] It may therefore represent a promising route of administration since adrenaline could be administered to patients with OHCA early and without difficulty. There are currently limited available data on the use of IM adrenaline in cardiac arrest. In a porcine model, early IM adrenaline demonstrated similar survival compared with early IV adrenaline, and superior survival compared to delayed IV adrenaline.[15]

This study investigates the feasibility of rapid IM adrenaline delivery in OHCA in an urban EMS system. In other words, we sought to answer the question, "Can an intramuscular route of administration feasibly decrease the time from PSAP to adrenaline delivery in out-of-hospital cardiac arrest?". We hypothesized that IM adrenaline would reduce the time from Public Safety Access Point (PSAP) call receipt to adrenaline administration when compared to IO and IV administration.

Methods

This study was approved by the Institutional Review Board at the University of Utah (IRB # IRB_00076654).

Study design and setting

This is an observational analysis of IM administration of adrenaline to treat OHCA. The administration of IM adrenaline was done as part of a change in clinical care for patients with OHCA, as detailed in *Interventions*. The Salt Lake City Fire Department (SLCFD) is a two-tiered, fire-based municipal agency that serves an urban corridor and international airport with a daytime population of approximately 315,000. EMS calls are prioritized and dispatched by a public safety answering point (911) that employs Medical Priority Dispatch System (MPDS, Salt Lake City, UT) protocols to determine acuity and level of response (BLS vs ALS). Calls identified as cardiac arrest are prioritized to the nearest available BLS or ALS unit with a trailing ALS unit if this was not first on scene. Cardiac arrests typically involve 6–10 providers on scene.

Selection of participants

All adult patients with OHCA between December 1, 2019 and February 8, 2021 were eligible for inclusion in the feasibility cohort if they received a shock by a public or first responder automated external defibrillator (AED) or chest compressions by EMS personnel and remained in arrest after the first rhythm analysis. These were compared to historical patients treated for OHCA from January 1, 2013 through November 30, 2019 (and concurrent patients who did not get IM adrenaline according to the new protocol). All controls received a first dose of adrenaline by the IV or IO route at the discretion of the providers on scene. Since 2011, as part of provider training, we have emphasized early IO access in OHCA patients (tibial site only), based on the results of studies showing more rapid vascular access with IO.[16] However, the initial route of delivery was left to the discretion of the providers on scene. During the study period, the route of subsequent doses of adrenaline following IM administration was also left to provider discretion. We excluded children <18 years of age, drownings, strangulation, and traumatic causes of arrest from the treatment protocol and analysis. We also excluded patients who achieved return of spontaneous circulation (ROSC) prior to ALS care, EMS witnessed arrests, arrests in which no adrenaline was administered or in which it was given via endotracheal tube, and when it was given by healthcare providers prior to EMS arrival. We also excluded patients for whom outcome data was missing.

Interventions

The administration of IM adrenaline was protocolized in clinical care guidelines on December 1, 2019 for all patients meeting criteria for standard adrenaline by international guidelines. Paramedics were trained to deliver 5 mg of adrenaline at a concentration 1 mg/mL (5 mL) to the lateral thigh. This approach was familiar to paramedics as they routinely deliver a lower dose of the medication by the IM route for the treatment of anaphylaxis. Subsequent doses of adrenaline at standard ALS dosing (1 mg/dose) were administered by the intravenous or intraosseous route if necessary. The IV route was preferred, if possible, for subsequent medication administration.

Outcome measurements

Since 2009, SLCFD has reported Utstein data along with hospital outcomes on all cardiac arrests to a statewide registry (Cardiac Arrest Registry to Enhance Survival [CARES]). Cardiac arrests were identified by the medical director (SY) through periodic review of electronic patient care reports (ImageTrend, Roseville, MN) for encounters in which the primary or secondary impression of the paramedics is cardiac or respiratory arrest. Discovery of OHCA cases were cross-checked with a standardized query that identifies all encounters in which CPR was performed, a shock was delivered, or adrenaline was administered. We obtained hospital outcomes, including neurologic status at discharge, through hospital record review or correspondence with a hospital liaison. Paramedics were trained to enter the timing of adrenaline administration and all interventions in a flow sheet in the patient care report and it is from these records that timing data has been abstracted since 2013. When timing was missing, the timing was recorded as missing for purposes of analysis.

Outcomes

The primary outcome of this analysis is the time from PSAP (911) call receipt to adrenaline administration comparing the IM to IV and IO routes. The time of PSAP call receipt is routinely imported into the electronic patient care report from computer aided dispatch software from whence we abstracted times. We chose this outcome as the protocol was designed to assess the feasibility of IM administration and any time savings, when compared to alternative routes of

administration. Secondary outcomes include cumulative adrenaline dose, low flow time (defined as time from first ALS compression to ROSC), the proportion of OHCAs achieving ROSC, survival to hospital discharge, and survival to hospital discharge with good neurologic function, defined as a cerebral performance category (CPC) score of 1 or 2. We routinely obtained outcomes in a non-blinded fashion.

Analysis

All data were collected and managed using an online database (REDCap electronic data capture tools hosted at the University of Utah).[17] We downloaded data in native Stata format for analysis using Stata/IC 14.2 for Mac (64-bit Intel, StataCorp, College Station, TX). In this report, we provide summary measures of demographic and resuscitation variables, along with secondary outcomes, appropriate to the underlying distribution. We performed linear regression to estimate the average time from PSAP to adrenaline administration in minutes and compare differences in average time between IM, IO, IV. Chi-Square and Fisher's exact tests were performed to compare proportions. Comparison of median low flow times between IM, IV, and IO groups was performed using a Kruskal −Wallis test. We considered a p value <0.05 to be statistically significant for all statistical comparisons.

Results

Characteristics of study subjects

During the period of interest, resuscitation was attempted for 961 OHCAs. After exclusions, 773 subjects administered adrenaline were available for analysis (Fig. 1): 518 cases of initial dose of adrenaline via intraosseous administration, 156 cases of initial dose of adrenaline via intravenous administration, and 99 cases of initial dose of adrenaline via intramuscular administration. Demographic and key resuscitation variables are given in Table 1.

Main results

Box plots for the distribution of time from PSAP call to adrenaline administration are given in Fig. 2. Timing of adrenaline administration

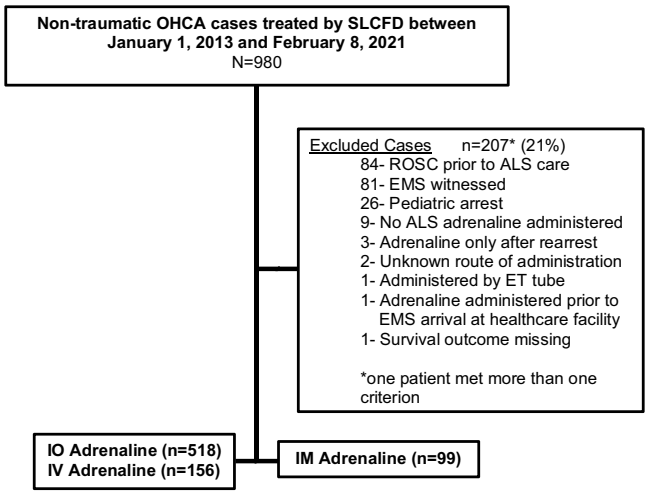

Fig. 1 – Patient workflow and inclusion.

was missing for 3/99 (3%) cases of IM administration, 5/156 (3%) IV cases, and 19/518 (4%) IO cases. When given via the IM route, adrenaline was administered a mean of 12.2 min (95% CI 11.4−13.1 min) from PSAP call receipt, compared to means of 15.3 min (95% CI 14.6−16.0 min) and 15.3 min (95% CI 14.9−15.7 min), respectively via IV and IO routes. The difference between IM and IO and IV was the same when rounded to the minute: 3 min (95% CI 2−4 min, $p < 0.0001$).

The average time from scene arrival to adrenaline administration was 5.9 min (95% CI 5.1−6.6 min) for IM cases, 8.6 min (95% CI 8.0−9.2 min) for IV cases, and 8.6 min (95% CI 8.3−8.9 min) for IO cases. The difference between IM and IV was 2.7 min (95% CI 1.7−3.7 min) and the difference between IM and IO was 2.7 min (95% CI 1.9−3.6 min, $p < 0.0001$).

Secondary outcomes

Secondary outcomes, including low flow time, ROSC and survival are provided in Table 2. None of these comparisons showed statistically significant differences.

Discussion

Early administration of adrenaline in OHCA has been associated with increased rates of ROSC, survival to hospital discharge and favorable neurological outcome.[3,5,8,18−20] The current study demonstrates that adrenaline delivered by paramedics via the IM route is feasible and leads to earlier administration when compared to IV and IO administration. Rates of ROSC and survival were similar to historical rates of such for IO and IV routes of administration, but this feasibility study was underpowered to detect small differences in patient-oriented outcomes and the before-and-after design is vulnerable to temporal trends.

Faster time to drug administration with intramuscular delivery makes intuitive sense. Intravenous access can be challenging, especially in a patient in cardiac arrest, and establishing intraosseous access is more time consuming than the delivery of a single intramuscular injection. Furthermore, prehospital providers are already familiar with IM administration as a treatment for anaphylaxis, making its administration in OHCA an easily transferrable skill with only a difference in dosing and indication. Intramuscular compared with IV drug administration has the advantage of a reduced plasma peak concentration and a prolonged duration of action in the patient in anaphylactic shock.[15,21] This could potentially decrease the need for redosing, subsequently mitigating task fatigue and distraction from quality CPR in OHCA. However, the pharmacokinetics of IM administration during cardiac arrest are currently unclear.

Whether the slower onset, lower peak concentration, and longer duration of action of IM administration confer physiologic and neuroprotective benefit is not known. Studies of cerebral perfusion during cardiac arrest have shown incrementally decreased effectiveness of successive adrenaline boluses over time.[22,23] In comparing bolus dosing versus continuous infusion of adrenaline during cardiac arrest, studies have shown conflicting results. Nosrati et al. showed transient increases in cerebral perfusion with bolus but not continuous adrenaline dosing whereas Johansson et al. showed significantly higher cerebral perfusion with continuous compared to bolus dosing.[22,24] While IM pharmacokinetics may be more similar to continuous IV dosing than bolus IV dosing, no studies exist with

Table 1 – Demographic and key resuscitation variables for 773 OHCAs in which adrenaline was administered, according to route of first dose.

	IM (n = 99)		IO (n = 518)		IV (n = 156)	
Age (SD)	61	(17)	60	(16)	61	(18)
Female gender	33	(33%)	161	(31%)	39	(25%)
Race/ethnicity						
Caucasian	57	(58%)	315	(61%)	101	(65%)
Hispanic/Latino	13	(13%)	55	(11%)	15	10%)
Black/African American	3	(3%)	26	(5%)	3	(2%)
Asian	3	(3%)	6	(1%)	4	(3%)
Hawaiian/Pacific Islander	3	(3%)	28	(5%)	7	(4%)
Native American	2	(2%)	14	(3%)	1	(1%)
Unknown	18	(18%)	74	(14%)	25	(16%)
Public location of arrest	36	(36%)	171	(33%)	46	(29%)
Arrest witnessed	49	(49%)	242	(47%)	84	(54%)
Bystander CPR	71	(72%)	317	(61%)	98	(63%)
Bystander shock	1	(1%)	15	(3%)	6	(4%)
Initial rhythm						
VF/VT	27	(27%)	136	(26%)	39	(25%)
PEA	17	(17%)	92	(18%)	26	(17%)
Asystole	40	(40%)	224	(43%)	65	(42%)
Unknown non-shockable	15	(15%)	66	(13%)	26	(17%)
EMS response interval (min, SD)	6.3	(1.8)	6.5	(2.1)	6.4	(2.3)
CPR metrics						
Rate (cpm, SD)	112	(7)	110	(8)	111	(8)
Depth (cm, SD)	6	(1)	6	(1)	6	(1)
Chest compression fraction (SD)	83	(11)	92	(7)	91	(8)
Advanced airway placed	90	(92%)	456	(88%)	127	(81%)
Cumulative adrenaline doses (SD)	3	(1)	3	(1)	3	(1)
Duration of resuscitation before field termination (min, IQR)	23	(20–29)	26	(19–33)	28	(20–33)

comparisons of IM and either continuous or bolus dosed IV adrenaline. Furthermore, all of this data is derived from animal studies and studies evaluating these questions in humans are not available to our knowledge.

In a porcine model comparing early IV adrenaline, early IM adrenaline and delayed IM adrenaline administration, early IM adrenaline resulted in similar survival compared with early IV adrenaline and was superior to delayed IV adrenaline.[15] In this porcine model, time to ROSC was, on average, 2 min faster in the IV compared to IM group (2 versus 4 min). Our study showed even greater mean differences in time to ROSC (low flow time) between IM and IV (4 min) and between IM and IO (6 min) groups, although these differences did not reach statistical significance. Even a 1-min delay in time to adrenaline administration may be enough to significantly reduce survival in OHCA, according to models.[8,18] Thus the time saved in medication administration and the decrease in low flow times observed here suggest a potentially significant possible benefit to IM administration.[8,18]

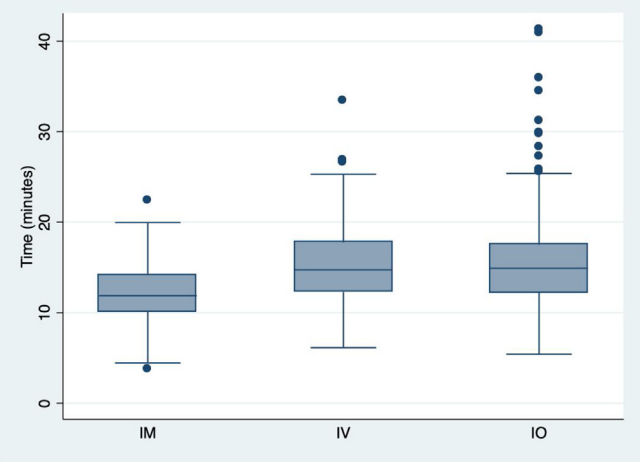

Fig. 2 – Box plot distributions for time from PSAP call to adrenaline administration in 773 OHCA cases in Salt Lake City, Utah categorized by route of first dose. Timing of administration was missing for 3/99 cases of IM administration, 5/156 IV cases, and 19/518 IO cases.

The PARAMEDIC2 trial, published in 2018, demonstrated higher 30-day survival in the cohort randomized to adrenaline (3.2%) when compared to placebo (2.4%), albeit with a greater proportion of survivors discharged with severe neurologic deficits in the adrenaline group (31% vs 18%).[25] In PARAMEDIC2, the median interval between emergency call and administration of trial drug was just over 21 min (IQR 16–27), with an EMS response interval of 6.6–6.7 min. It is possible that this prolonged interval between arrest and adrenaline administration mitigated the potential benefit of adrenaline in that study population. It is also possible that adrenaline administration during a later physiologic phase of cardiac arrest is more neurologically harmful than during earlier phases of cardiac arrest physiology. Despite a similar EMS response interval (6.2–6.5 min), our cohorts received adrenaline earlier than those in the PARAMEDIC2 trial, with a median (IQR) time from emergency call to first dose of 12 min (10–14 min) for IM adrenaline, 15 min (12–18 min)

Table 2 – Outcomes for 773 OHCAs in which adrenaline was administered, according to route of first-dose administration. Differences were not statistically significant.

	IM (n = 99)		IO (n = 518)		IV (n = 156)	
Any return of spontaneous circulation (ROSC)	39	(39%)	214	(41%)	65	(42%)
Shockable	15/27	(55%)	74/136	(54%)	21/39	(54%)
Non-shockable	24/72	(33%)	140/382	(37%)	44/117	(38%)
Rearrest	66	(67%)	354	(68%)	102	(65%)
Survival to hospital discharge	10	(10%)	37	(7%)	13	(8%)
Shockable	9/27	(33%)	31/136	(23%)	12/39	(31%)
Non-shockable	1/72	(1%)	6/382	(2%)	1/117	(1%)
Survival to hospital discharge with CPC 1–2	7	(7%)	32	(6%)	12	(8%)
Shockable	7/27	(26%)	27/136	(20%)	11/39	(28%)
Non-shockable	0/72	(0%)	5/382	(1%)	1/117	(1%)
Low flow time[a] (min, IQR)	13	(8–22)	17	(10–30)	15	(11–28)

[a] Defined as time from first ALS compression to ROSC as abstracted retrospectively from defibrillator/monitor data.

for IV and IO adrenaline. We observed higher survival to hospital discharge in our cohort (as high as 9% in the IM adrenaline group) compared to that in the PARAMEDIC2 trial. The reason for earlier administration of adrenaline (via IV and IO routes) compared to Paramedic 2 after arrival on scene is unclear, although we speculate that this reflects differences in team configuration; SLCFD employs a pit crew approach to resuscitation, typically with 6–10 providers on scene, with immediate actionable items, such as establishing IV or IO access, assigned to individual team members upon arrival.

In a post-hoc analysis of trial data, the PARAMEDIC2 investigators found a time-dependent decrease in the probabilities of ROSC and survival in both arms.[26] The probability of ROSC was higher in a statistically significant and time-dependent fashion in the adrenaline arm throughout the resuscitation interval. Likelihoods of 30-day survival and survival with good neurologic function were, on average, higher for the adrenaline group up until approximately the 25 and 20 min points in the resuscitation attempt, respectively, after which rates of both were similar between groups. These early benefits for survival with adrenaline were not, in contrast to ROSC, statistically significant.

We believe ours is the first study to evaluate the use of protocolized intramuscular adrenaline in OHCA. However, the use of IM drug administration versus IV administration has been studied previously in other time sensitive conditions such as status epilepticus, anaphylaxis and trauma.[27,28] Silbergleit et al. demonstrated faster median time to drug delivery for IM Midazolam versus IV Lorazepam in prehospital status epilepticus while demonstrating non-inferiority for their primary outcome of time to seizure cessation.[27] Furthermore, Grassin-Delyle et al. demonstrated safety and a comparable pharmacokinetic profile for IM compared to IV Tranexamic Acid (TXA) in adult trauma patients.[28] These prior studies confirm the notion of superior time to delivery with IM drug delivery without deleterious effects on patient outcomes. Our current study is not powered to compare meaningful patient orientated outcomes at this stage, thus signifying the need for a large, randomized trial.

Implications

OHCA is a leading cause of mortality worldwide.[29,30] In the US, the estimated incidence is 55 per 100 000 person years, with a reported percentage survival to hospital discharge of 6.8%.[31] Regional variations in reporting and survival mean the exact burden of OHCA to public health is unknown, however even within the United States, substantial regional variations in the management of OHCA and survival are known to exist.[31] In tiered systems where BLS providers arrive on scene long before ALS providers or in systems that are BLS only, adrenaline administration may be quite delayed or impossible. If safety and efficacy of early paramedic administration of IM adrenaline for OHCA can be established, then expanding scope of practice to allow BLS providers to administer IM adrenaline for OHCA may have significant impacts on survival in these systems. Furthermore, in countries with rudimentary prehospital systems, or with no prehospital infrastructure at all, where rapid IV adrenaline delivery may be even more challenging, survival is likely to be even less than the estimates above.[29,32] It is possible that IM adrenaline could be given by trained first responders and even untrained bystanders, with important reductions in time to treatment.[33,34] Ideally, prompt treatment would be further facilitated by the development of an easy-to-use auto- injector or pre-filled syringes. Finally, the optimal IM dose is an area needing further research.

Limitations

This study has several limitations, including a small sample size and a before-and-after comparison with controls. The study is observational by design, evaluating response times before and after a protocol change. The data and results are therefore subject to potential bias from unmeasured and uncontrolled confounders and temporal trends, and the reader should be cautioned from over interpretation. However, given that dispatch protocols and team configuration have remained stable over the study period, we feel that the results likely represent a true benefit in time to delivery of adrenaline in OHCA. The cardiac arrests of a majority of patients treated with IM adrenaline occurred during periods of widespread local infection from the worldwide COVID-19 pandemic. Multiple other communities have reported lower survival from OHCA during the pandemic, including a 17% reduction in survival in U.S. communities reporting to the CARES registry and even a 50% reduction in survival to discharge in one Australian study.[35] It is unclear how IM adrenaline interacted with competing risks such as COVID-19 in our cohort, although we have not observed a decrease in survival in OHCA patients during the pandemic (most of whom received IM adrenaline) compared to pre-pandemic survival rates in

our system. The impact of the pandemic on time to adrenaline administration is unclear. During the study period, which included a large period of pandemic effects, providers would don PPE prior to patient contact, which may have increased the time to adrenaline administration during the study period. Additionally, the dose chosen for this investigation is lower than an equipotent intravenous dose, equivalent to approximately 0.5 mg IV. The only other study to directly compare IV and IM dosing of adrenaline to our knowledge used a ten-fold dose difference between IM and IV doses.[15] It is possible that a higher dose would be more effective and should be considered for further study.

Conclusion

The current study demonstrates that adrenaline delivered by paramedics via the IM route leads to earlier administration when compared to IV and IO administration in OHCA. This study provides evidence that the intervention is feasible and was easily integrated into an urban EMS OHCA care model. A larger randomized trial is needed to assess it's effect on patient orientated outcomes.

Credit author

All authors have made substantial contributions to all of the following: the conception and design of the study, interpretation of data, drafting the article and revising it critically for important intellectual content. All authors have approved the manuscript for submission. The contents of this manuscript (including tables and figures) have not been published elsewhere.

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Approval

University of Utah IRB # IRB_00076654.

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Conflicts of interest

JET received speaker fees and travel compensation from LivaNova and Philips Healthcare, unrelated to this work. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.

We have no other conflicts of interest to declare.

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