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Clinical paper

Early intramuscular adrenaline administration is associated with improved survival from out-of-hospital cardiac arrest *



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Abstract

Background: Early administration of adrenaline is associated with improved survival after out-of-hospital cardiac arrest (OHCA). Delays in vascular access may impact the timely delivery of adrenaline. Novel methods for administering adrenaline before vascular access may enhance survival. The objective of this study was to determine whether an initial intramuscular (IM) adrenaline dose followed by standard IV/IO adrenaline is associated with improved survival after OHCA.

Methods

Study Design: We conducted a before-and-after study of the implementation of an early, first-dose IM adrenaline EMS protocol for adult OHCAs. The pre-intervention period took place between January 2010 and October 2019. The post-intervention period was between November 2019 and May 2024. **Setting**: Single-center urban, two-tiered EMS agency.

Participants: Adult, nontraumatic OHCA meeting criteria for adrenaline use.

Intervention: Single dose (5 mg) IM adrenaline. All other care, including subsequent IV or IO adrenaline, followed international guidelines.

Main Outcomes and Measures: The primary outcome was survival to hospital discharge. Secondary outcomes were time from EMS arrival to the first dose of adrenaline, survival to hospital admission, and favorable neurologic function at discharge.

Results: Among 1405 OHCAs, 420 (29.9%) received IM adrenaline and 985 (70.1%) received usual care. Fifty-two patients received the first dose of adrenaline through the IV or IO route within the post-intervention period and were included in the standard care group analysis. Age was younger and bystander CPR was higher in the IM adrenaline group. All other characteristics were similar between IM and standard care cohorts. Time to adrenaline administration was faster for the IM cohort [(median 4.3 min (IQR 3.0–6.0) vs. 7.8 min (IQR 5.8–10.4)]. Compared with standard care, IM adrenaline was associated with improved survival to hospital admission (37.1% vs. 31.6%; aOR 1.37, 95% CI 1.06–1.77), hospital survival (11.0% vs 7.0%; aOR 1.73, 95% CI 1.10–2.71) and favorable neurologic status at hospital discharge (9.8% vs 6.2%; aOR 1.72, 95% CI 1.07–2.76).

Conclusion: In this single-center before-and-after implementation study, an initial IM dose of adrenaline as an adjunct to standard care was associated with improved survival to hospital admission, survival to hospital discharge, and functional survival. A randomized controlled trial is needed to fully assess the potential benefit of IM adrenaline delivery in OHCA.

Keywords: Adrenaline, Advanced Life Support, Cardiopulmonary Resuscitation, Prehospital, Resuscitation, Vasopressor

Introduction

Despite substantial public health efforts, outcomes following out-of-hospital cardiac arrest (OHCA) remain poor. Adrenaline is a first-

line therapy that may improve successful resuscitation.^{2,3} Multiple epidemiological studies have found an association of early administration of adrenaline with improved outcomes.^{4–8} Guidelines recommend intravenous (IV) or intraosseous (IO) adrenaline as early as feasible in cardiac arrests with a non-shockable rhythm or after initial

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attempts at defibrillation fail in those with shockable rhythms. ^{9,10} Yet delays in establishing vascular access may compromise its prompt administration. ¹¹ It may take 4–7 min to obtain vascular access. ¹² Overall success rates for IV and IO access may be as low as 43% and 51%, respectively. ¹² In a large, randomized trial of adrenaline compared to placebo, the median duration from emergency call to adrenaline delivery was 21.5 min. ² While the IO route of administration is more rapid and successful than the IV route, patients resuscitated with IO adrenaline fare worse in observational studies. ^{11–15}

Given the importance of timely and effective adrenaline administration, alternative delivery routes are essential to consider. The intramuscular (IM) route of adrenaline administration to treat anaphylaxis is well-established, rapid, and has been used by basic life support (BLS) providers for decades. ^{16,17,18} Preclinical studies suggest a potential role for IM adrenaline to treat cardiac arrest. ¹⁹ In a pig model, animals treated with IM adrenaline had similar survival compared to those treated with IV adrenaline. ¹⁹ Further, early IM adrenaline administration was associated with higher survival than delayed IV adrenaline. ¹⁹ However, the translation from preclinical models to humans remains limited. ²⁰

In 2019, the Salt Lake City Fire Department changed its clinical protocol for cardiac arrest care. ²¹ In those for whom adrenaline was indicated, paramedics administered a single dose of IM adrenaline 5 mg concurrent with vascular access attempts. Subsequent doses were delivered via IV or IO. The objective of this study was to determine whether early IM adrenaline in adult, non-traumatic EMS-treated cardiac arrest is associated with improved survival to hospital discharge.

Methods

Study design

We conducted a before-and-after study to assess the impact of introducing early IM adrenaline as an adjunct to existing ACLS care in OHCA. The study was approved by the University of Utah Institutional Review Board IRB_00138043.

Setting

The study comprised cardiac arrest patients treated by the Salt Lake City Fire Department between January 2010 and May 2024. The Salt Lake City Fire Department is a two-tiered fire-based municipal agency delivering prehospital care to a population of 204,657 in Salt Lake City, Utah. ^{22,23} Care teams in cardiac arrests consist of 6 to 10 providers. ²¹ Paramedics have proficiency in ACLS care and the administration of medications through the IV, IO, and IM routes. ¹⁸ The agency provides care for up to 131 OHCAs annually with mean rates of ROSC and survival of 41% and 15%, respectively.

Population

The study cohort consisted of all consecutive EMS-treated cardiac arrests who received adrenaline. We defined cardiac arrest as pulse-lessness requiring EMS-administered chest compressions or bystander shock. Patients were eligible for inclusion in the study if they had continued cardiac arrest despite initial shocks (in those with shockable rhythms) or remained in arrest after the first rhythm analysis (in those with non-shockable rhythms). We excluded individuals under 18 years of age at the time of arrest, those receiving adrenaline before first responder arrival (such as at an outpatient surgical center), traumatic causes of arrest, drowning, strangulation, return

of spontaneous circulation (ROSC) before administration of any adrenaline, evidence of irreversible death, and a known do-not-resuscitate order. Sample size was determined by convenience sampling as there was limited evidence to support a sample size calculation.

Intervention

The study encompassed two phases. The pre-intervention control period consisted of patients treated from January 2010 through October 2019. The intervention period consisted of patients treated from November 2019 through May 2024. Patients received IV or IO adrenaline per standard care during the control period. During the intervention period, paramedics administered an initial IM adrenaline dose of 5 mg to the lateral thigh concurrent with vascular access attempts. Subsequent adrenaline 1 mg IV or IO was provided every 3–5 min once vascular access was established. Our choice of dose was based on the recommendation that no more than 5 mL be injected into the vastus lateralis muscle. Given that the currently available adrenaline concentration in the United States is 1 mg/mL, we had chosen to use a 5 mg dose. Apple 24,25 Based on a linear extrapolation of the anaphylaxis literature, this dose is considered equipotent to a 0.5 mg IV dose.

Paramedics completed 3 h of didactic and clinical training prior to initiation of the protocol with subsequent refreshers at 6-month intervals. A run-in period was not included due to the small sample size.

Outcome measures

We obtained data from the Salt Lake City Fire Department cardiac arrest registry, which follows Utstein guidelines. ²⁷ Salt Lake City Fire Department paramedics manually record interventions in the patient care report. Prehospital care data include patient demographics, clinical characteristics, prehospital interventions, and disposition. Trained abstractors obtained hospital data from medical records. We collected data from the initial incident to reported patient death or hospital discharge.

The primary outcome was survival to hospital discharge. The secondary outcomes included time from EMS arrival to first adrenaline dose, survival to hospital admission, and survival with a favorable neurologic status at hospital discharge. We reported survival to hospital admission rather than ROSC because of variable rates of intra-arrest transport for extracorporeal cardiopulmonary resuscitation (ECPR) consideration. Neurologic outcome was assessed at hospital discharge using the CPC scale. A score of 1 (good cerebral performance) and 2 (moderate cerebral disability) were considered favorable neurologic status.

Statistical analysis

We excluded cases with missing data regarding adrenaline route, model covariates, or outcomes from the primary analysis. Patients who received an initial adrenaline dose through the IV or IO route in deviation from the protocol during the after-phase were crossed over into the before-phase IV/IO cohort. We chose a per protocol analysis as our primary interest was to measure the effectiveness of the intervention. We compared baseline demographic and clinical characteristics between groups with the Chi-square test, Fisher exact test, Fest, or Wilcoxon rank sum tests for categorical and continuous variables, as appropriate.

We used multivariable logistic regression to evaluate the association between IM adrenaline and OHCA outcomes. We developed separate models for each outcome, defining the exposure as the first dose of IM adrenaline compared to the first dose of IV or IO adrenaline. We adjusted the models for age, sex, bystander CPR, witnessed arrest, interval from emergency call to EMS arrival, public location of the arrest, and initial cardiac rhythm. We chose these covariates due to their known associations with cardiac arrest outcomes and per prior reports.²⁷ Before analysis, we assessed the regression model for interactions.

We developed additional models based on intention-to-treat and a model that completely excluded protocol non-compliant cases. All statistical analysis was performed using statistical analysis software (Stata 18 BE, College Station, TX).

Results

Patient population

The study cohort included 1405 patients (Fig. 1). During the study period, there were 1703 EMS-treated non-traumaticout-of-hospital cardiac arrests. Of these, 1414 cases met the inclusion criteria. We excluded nine patients (0.6%) from the primary analysis due to missing data.

Within the after-phase, paramedics adhered to the early IM adrenaline protocol in 89% of cases (420 of 472). Fifty-two patients in this period received initial adrenaline in deviation from the new protocol. In the control period, 985 patients (70.1%) received initial IV/IO adrenaline.

The two groups' baseline demographic and clinical characteristics were generally comparable (Table 1). The majority were males. Half of the cases were witnessed arrests. Approximately 26% had an initial shockable rhythm. However, the IM-treated group had a higher proportion of bystander CPR and was younger. The interval from

emergency call to first ambulance arrival was similar between the two cohorts. The median time from the Public Safety Answering Point (PSAP 911) emergency call to the first dose of IM adrenaline was 12.0 min (IQR 9.9–14.3) compared to 15.3 min (IQR 12.5–18.5) in the control group. The interval from EMS arrival to the first adrenaline dose was 4.3 min (IQR 3.0–6.0) in the IM cohort compared to 7.8 min (IQR 5.8–10.4) in the IV/IO cohort.

Outcomes and adjusted analyses

Overall, 115 patients (8.2%) in the study population survived to hospital discharge, a cohort that excludes patients not receiving adrenaline. Survival to hospital admission and discharge were greater in the IM group (Table 2). Survival with favorable neurologic outcome at hospital discharge was 7.3% (102/1405) in the study population. Good neurologic outcome at discharge was higher in the IM group compared to the IV/IO group. Among those who survived to hospital admission, low flow time (defined as the duration of time from the initiation of CPR to the cessation of resuscitation) was shorter in the IM cohort compared to the IV/IO cohort (21.0 min, IQR 13.8–31.1 vs. 23.4 min, IQR 15.7–31).

IM adrenaline was associated with improved survival to hospital admission [37.1% vs 31.6%; aOR 1.37, 95% CI (1.06-1.77)], survival to discharge (11.0% vs 7.0%; aOR 1.73, 95% CI 1.10-2.71) and functional survival (9.8% vs 6.2%; aOR, 1.72, 95% CI 1.07-2.76) (Table 2).

Sensitivity analysis

Fifty-two patients in the post-intervention period received first-dose IV/IO adrenaline in deviation from the protocol. These patients had a greater proportion of witnessed arrest but longer response time and time to first epinephrine (Supplement Table 2). While protocol

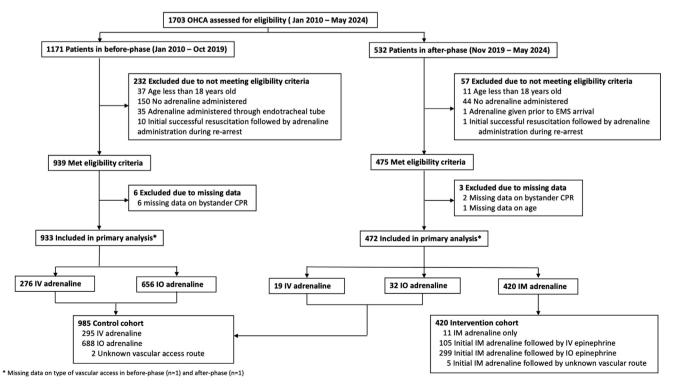


Fig. 1 - Selection of Study Population.

Table 1 - Study Population Baseline Characteristics	Table 1 - Stud	y Population	Baseline	Characteristics
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Characteristic	IV/IO Cohort (n = 985)	IM Cohort (n = 420)
Age, Mean (SD), Years	59.5 (16.6)	56.5 (16.3)
Sex, No. (%)		
Female, No. (%)	305 (31.0)	138 (32.9)
Male, No. (%)	680 (69.0)	282 (67.1)
Race/Ethnicity, No. (%)		
American Indian/Alaskan	17 (1.7)	8 (1.9)
Asian	14 (1.4)	16 (3.8)
Black/African American	38 (3.9)	20 (4.8)
Hispanic/Latino	103 (10.5)	52 (12.4)
Native Hawaiian/Pacific Islander	44 (4.5)	19 (4.5)
White	593(60.2)	268 (63.8)
Unknown	176 (17.9)	37 (8.8)
Witnessed Arrest, No. (%)		
Bystander	509 (51.7)	196 (46.7)
EMS	70 (7.1)	29 (6.9)
Public Location of Arrest, No. (%)	312 (31.7)	139 (33.1)
Bystander CPR	552 (56.0)	293 (69.8)
Initial Cardiac Rhythm, No. (%)		
Ventricular Fibrillation or Tachycardia	267 (27.1)	105 (25.0)
Pulseless Electrical Activity or Asystole	718 (72.9)	315 (75.0)
Number of Adrenaline Dose, Mean (SD)	2.80 (1.2)	3.2 (1.2)
Interval from Emergency Call to EMS Arrival, Min. (IQR)	6.4 (5.2–7.8)	6.3 (5.2–7.6)
Interval from Emergency Call to First Shock, Min. (IQR)	12.4 (9.2–18.6)	12.6 (9.1–18.3)
Interval from Emergency Call to First Adrenaline Dose, Min. (IQR)	15.3 (12.5–18.5)	12.0 (9.9–14.3)
Interval from EMS Arrival to First Adrenaline Dose, Min. (IQR)	7.8 (5.8–10.4)	4.3 (3.0–6.0)

Table 2 – Outcomes of Patients Treated with an Initial Adrenaline Dose Administered through the IV/IO Route Compared to the IM Route.

Outcome	IV/IO Cohort No. (%)	IM Cohort No. (%)	Absolute Difference	Odds Ratio (95% CI) *	
	(n = 985)	(n = 420)	(%)	Unadjusted	Adjusted
Survival to Hospital Admission	311 (31.6)	156 (37.1)	5.6	1.28 (1.01-1.63)	1.37 (1.06–1.77)
Survival to Hospital Discharge	69 (7.0)	46 (11.0)	4.0	1.63 (1.10-2.42)	1.73 (1.10-2.71)
Favorable Neurologic Outcom	e61 (6.2)	41 (9.8)	3.6	1.64 (1.08-2.48)	1.72 (1.07–2.76)

^{*} Multivariate logistic regression model adjusted for age, sex, witnessed arrest, bystander CPR, public location of arrest, initial cardiac rhythm, EMS response time.

Table 3 – Outcomes of Patients Treated with an Initial Adrenaline Dose Administered through the IV/IO Route Compared to the IM Route Based on an Intention to Treat Analysis.

Outcome	Before-Phase Group No. (%)	After-Phase Group No. (%)	Absolute Difference	Odds Ratio (95% CI) *	
	(n = 933)	(n = 472)	(%)	Unadjusted	Adjusted
Survival to Hospital Admission	291 (31.2)	176 (37.3)	6.1	1.31 (1.04–1.65)	1.35 (1.06–1.74)
Survival to Hospital Discharge	60 (6.4)	55 (11.7)	5.2	1.92 (1.31-2.82)	2.06 (1.33-3.20)
Favorable Neurologic Outcome	52 (5.6)	50 (10.6)	5.0	2.01 (1.34-3.01)	2.16 (1.36-3.43)

^{*} Multivariate logistic regression model adjusted for age, sex, witnessed arrest, bystander CPR, public location of arrest, initial cardiac rhythm, EMS response time.

Table 4 – Outcomes of Patients Treated with an Initial Adrenaline Dose Administered through the IV/IO Route Compared to the IM Route with Exclusion of Protocol Non-Compliant Cases.

Outcome	IV/IO Cohort No. (%)	IM Cohort No. (%)	Absolute Difference	Odds Ratio (95% CI) *	
	(n = 933)	(n = 420)	(%)	Unadjusted	Adjusted
Survival to Hospital Admission	n 291 (31.2)	156 (37.1)	6.0	1.31 (1.03–1.66)	1.38 (1.07–1.79)
Survival to Hospital Discharge	60 (6.4)	46 (11.0)	4.5	1.79 (1.20-2.68)	1.91 (1.20-3.03)
Favorable Neurologic Outcom	e52 (5.6)	41 (9.8)	4.2	1.83 (1.20–2.81)	1.95 (1.19–3.17)

Multivariate logistic regression model adjusted for age, sex, witnessed arrest, bystander CPR, public location of arrest, initial cardiac rhythm, EMS response time.

deviation occurred throughout the intervention period, a greater proportion of non-compliance took place during the first year of the intervention (Supplement Table 3). In the primary analysis, we included those cases in the IV/IO cohort. We conducted a sensitivity analysis by incorporating those patients in the after-group using an intention-to-treat analysis (Table 3). We then performed another analysis where we excluded those cases from the study population (Table 4). We continued to identify an association of IM adrenaline with improved outcomes.

Discussion

This is one of the first clinical studies assessing the effectiveness of early IM adrenaline in resuscitation from out-of-hospital cardiac arrest. We found that a strategy of first-dose IM adrenaline delivery as a supplement to standard ACLS care was faster and associated with improved survival to hospital discharge and functional survival compared to traditional routes of adrenaline administration in our cohort of OHCA patients.

Our results align with prior reports that early administration of adrenaline is associated with improved outcomes. 4,5,6,7,8 In a metaanalysis of over 574,392 patients across 24 studies, adrenaline administered within 10 min of EMS arrival was associated with improved rates of ROSC, survival to hospital discharge, and survival with favorable neurologic status at discharge. 4 In two cohort studies, there was a 4-6% decrease in survival for every minute delay from EMS arrival to adrenaline administration.^{6,7} While Ewy et al. also found that survival decreased with increasing time to adrenaline administration (OR 0.94, 95% CI 0.92-0.97) in patients with shockable rhythms, their group found no association of good neurologic outcome with early adrenaline administration (OR 0.96, 95% CI 0.90-1.02).5 In contrast, Tanaka et al. reported that early adrenaline administration was associated with improved neurological outcomes when delivered within 19 min of EMS call (aOR 2.49, 95% CI 1.90-3.27).8 In the present study, the median time from EMS arrival to the first dose of adrenaline delivery was within 10 min in both cohorts. However, there was a significant reduction in time from EMS arrival to drug delivery in the IM group compared to the IV and IO group. This represented an absolute median difference of 3.5 min. While the IO route is faster and has a higher success rate than the IV route. observational studies have shown worse overall outcomes with IO. 14,15.

The IM adrenaline-treated patients were more likely to survive with a favorable neurologic status. While the effects of adrenaline on the brain are controversial, multiple investigators have reported improvements in cerebral perfusion pressure, cerebral blood flow,

and cerebral oxygenation following adrenaline administration in preclinical models. $^{29,30}\,$

Limitations

This study had several limitations. The before-and-after design could not account for temporal trends or unmeasured and uncontrolled confounders. Although we noted an association with improved outcomes, a randomized, controlled trial would provide further insight. Immortal time bias is a confounder. We lacked the sample size to perform adjustments based on time to drug administration. Although the population-based approach limited selection bias, protocol compliance was 89% which may bias results toward the null. We did not have a monitor to ascertain intervention delivery times. As recall bias and misclassification would likely affect both groups similarly, we do not expect this to alter findings substantially. While post-cardiac arrest care was not protocolized, hospitals followed standard care guidelines. We could not assess the influence of variations in postcardiac arrest management on outcomes. An extracorporeal cardiopulmonary resuscitation (ECPR) program was initiated at one of the EMS agency's major receiving hospitals in April 2015. However, there was no difference in rates of ECPR or targeted temperature management between the before-and-after cohorts.

We noted increased rates of bystander CPR and younger age of arrest over time. This trend has also been noted in other registries.31,32 One possibility arises from the implementation of collection of dispatch files and feedback to dispatchers starting in 2016. Prior to that time, bystander CPR documentation was based solely on the paramedic's documentation. The dispatch files and feedback to dispatchers may have influenced the rates of bystander CPR in two manners: 1) dispatch files allow for a more accurate assessment of whether bystander CPR was performed and 2) dispatcher performance improved. We also considered the impact of COVID-19 factors, such as social distancing and isolation on the provision of bystander CPR. We did not identify interactions between bystander CPR and other variables of interest. While we recognize that bystander CPR can have a significant influence on survival, increasing the odds of survival by two-fold, the treatment effects persisted after adjustment for these variables. 33,34.

Concurrent with improved resuscitation characteristics were competing risks, which may have diminished the effects of IM adrenaline. The SARS-CoV-2 pandemic took place during most of the intervention period. In 2021, COVID-19 was the third leading cause of death in the state of Utah. During the study period, the state experienced 5605 cumulative deaths due to the pandemic with an ageadjusted mortality rate of 201 per 100,000. Utah had an 11.1% increase in all-cause mortality between 2019 and 2020. Prehospital personnel donned personal protective equipment before interacting

with patients, which may have contributed to delays in care. ^{39,40} Several reports found significant decreases in the rate of ROSC, survival to hospital discharge, functional survival, and 30-day survival during the COVID-19 pandemic. ⁴¹ We did not have sufficient COVID-19 related data to adjust for the pandemic.

Given the small sample size, the study pooled subgroups and did not stratify based on initial cardiac rhythm, type of vascular access, or provision of bystander CPR, limiting our ability to perform subgroup analyses.

The optimal IM dose of adrenaline is unknown. The 5 mg administered was equipotent to a 0.5 mg IV dose, which represents half the current standard ACLS dose. 9,10,24 In a clinical trial, high dose epinephrine resulted in greater rates of return of spontaneous circulation but did not improve survival or neurologic outcome. 42 A different dose may have impacted findings. Studies of the pharmacokinetics and pharmacodynamics of IM adrenaline in cardiac arrest are also lacking.

The study occurred in a single-center, urban EMS agency, which may limit its external validity. These limitations notwithstanding, this is the first clinical study demonstrating an association of IM adrenaline and improved outcomes in patients suffering from OHCA.

Implications

IM adrenaline is a novel method to deliver adrenaline that does not require vascular access. The PARAMEDIC2 trial demonstrated increased 30-day survival (aOR 1.47, 95% CI 1.09–1.97) in patients treated with adrenaline compared to placebo.² In the trial, paramedics followed guideline recommendations to attempt IV access first, with IO reserved for cases where they could not establish IV access.² In this trial, the median time from emergency calls to drug administration was 21.5 min.² In the US, BLS providers are trained to administer medications through the IM route.¹8 In the Resuscitation Outcomes Consortium (ROC) Cardiac Epistry, 3% of cardiac arrests were attended only by BLS crews.⁴³In tiered EMS systems, BLS providers are the first prehospital providers on the scene 53% of the time.⁴³ Expanding IM adrenaline use to BLS providers would increase patient access to this drug at the earliest point of contact with prehospital providers.

Our findings merit validation with a prospective clinical trial. There are many important considerations in the design of a clinical trial. Blinding and randomization are ideal in an RCT; this could be facilitated by comparing IM adrenaline vs. IM saline placebo. Given that BLS units are trained in IM drug administration, a potential trial design would be to deploy the study intervention to both BLS and ALS units. While BLS units in a tiered system would have a time advantage compared with ALS, we note that in this study, we observed outcome differences even with ALS deployment alone. Sample size is also an important consideration. Our study offers preliminary estimates of potential effect sizes to drive the sample size estimate. Another consideration is whether varying dosages of IM epi should be explored in an adaptive dose-finding design. Lastly, the use of IM adrenaline has similar utility in pediatric OHCA. Incorporation of children into the trial is a consideration, although the optimal dosages for different age and weight ranges need to be defined.

Conclusion

In this single-center before-and-after implementation study, an initial IM dose of adrenaline as an adjunct to standard ACLS was associ-

ated with improved survival to admission, survival to hospital discharge and functional survival. Given the limitations of the before-and-after study design, these results should be interpreted with caution. Randomized, controlled trials are needed to fully assess the potential benefit of IM adrenaline delivery in OHCA.

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None.

Disclosures

Austin Johnson is a co-founder and advisor to Certus Critical Care, Inc.

Guillaume L. Hoareau is an advisor and share-holder of Certus Critical Care, Inc.

Scott T. Youngquist reports acting as a consultant to CoLabs, Inc.

Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this work the author(s) used ChatGPT 3.5 to improve readability and language. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the publication.

CRediT authorship contribution statement

Helen N. Palatinus: Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Conceptualization. M. Austin Johnson: Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Conceptualization. Henry E. Wang: Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis. Guillaume L. Hoareau: Writing – review & editing, Writing – original draft, Methodology, Investigation. Scott T. Youngquist: Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.resuscitation.2024.110266.

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REFERENCES

- Tsao CW, Aday AW, Almarzooq ZI, et al. Heart disease and stroke statistics-2022 update: a report from the american heart association [published correction appears in circulation. 2022 Sep 6;146(10): e141]. Circulation 2022;145:e153–639. https://doi.org/10.1161/CIR.0000000000001052.
- Perkins GD, Ji C, Deakin CD, et al. A randomized trial of adrenaline in out-of-hospital cardiac arrest. N Engl J Med 2018;379:711–21. https://doi.org/10.1056/NEJMoa1806842.
- Jacobs IG, Finn JC, Jelinek GA, Oxer HF, Thompson PL. Effect of adrenaline on survival in out-of-hospital cardiac arrest: A randomised double-blind placebo-controlled trial. Resuscitation 2011;82:1138–43. https://doi.org/10.1016/j.resuscitation.2011.06.029.
- Ran L, Liu J, Tanaka H, Hubble MW, Hiroshi T, Huang W. Early administration of adrenaline for out-of-hospital cardiac arrest: a systematic review and meta-analysis. J Am Heart Assoc 2020;9: e014330. https://doi.org/10.1161/JAHA.119.014330.
- Ewy GA, Bobrow BJ, Chikani V, et al. The time-dependent association of adrenaline administration and survival from out-ofhospital cardiac arrest. Resuscitation 2015;96:180–5. https://doi.org/10.1016/j.resuscitation.2015.08.011.
- Okubo M, Komukai S, Callaway CW, Izawa J. Association of Timing of Adrenaline Administration With Outcomes in Adults With Out-of-Hospital Cardiac Arrest. JAMA Netw Open. 2021;4(8): e2120176. Published 2021 Aug 2. doi:10.1001/jamanetworkopen.2021.20176.
- Hansen M, Schmicker RH, Newgard CD, et al. Time to adrenaline administration and survival from nonshockable out-of-hospital cardiac arrest among children and adults. Circulation 2018;137:2032–40. https://doi.org/10.1161/ CIRCULATIONAHA.117.033067.
- Tanaka H, Takyu H, Sagisaka R, et al. Favorable neurological outcomes by early adrenaline administration within 19 minutes after EMS call for out-of-hospital cardiac arrest patients. Am J Emerg Med 2016;34:2284–90. https://doi.org/10.1016/j.ajem.2016.08.026.
- Panchal AR, Bartos JA, Cabañas JG, et al. Part 3: Adult basic and advanced life support: 2020 American heart association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. Circulation. 2020;142:S366–468. https://doi.org/10.1161/ CIR.00000000000000016.
- Perkins GD, Graesner JT, Semeraro F, et al. European Resuscitation Council Guidelines 2021: Executive summary [published correction appears in Resuscitation. 2021 May 4;163:97-98]. Resuscitation 2021;161:1–60. https://doi.org/10.1016/i.resuscitation.2021.02.003.
- Hooper A, Nolan JP, Rees N, Walker A, Perkins GD, Couper K. Drug routes in out-of-hospital cardiac arrest: A summary of current evidence. Resuscitation 2022;181:70–8. https://doi.org/10.1016/j.resuscitation.2022.10.015.
- Reades R, Studnek JR, Vandeventer S, Garrett J. Intraosseous versus intravenous vascular access during out-of-hospital cardiac arrest: a randomized controlled trial. Ann Emerg Med 2011;58:509–16. https://doi.org/10.1016/j.annemergmed.2011.07.020.
- Tan BKK, Chin YX, Koh ZX, et al. Clinical evaluation of intravenous alone versus intravenous or intraosseous access for treatment of out-of-hospital cardiac arrest. Resuscitation 2021;159:129–36. https://doi.org/10.1016/j.resuscitation.2020.11.019.

- Zhang Y, Zhu J, Liu Z, et al. Intravenous versus intraosseous adrenaline administration in out-of-hospital cardiac arrest: A retrospective cohort study. Resuscitation 2020;149:209–16. https://doi.org/10.1016/j.resuscitation.2020.01.009.
- Mody P, Brown SP, Kudenchuk PJ, et al. Intraosseous versus intravenous access in patients with out-of-hospital cardiac arrest: Insights from the resuscitation outcomes consortium continuous chest compression trial. Resuscitation 2019;134:69–75. https://doi.org/10.1016/j.resuscitation.2018.10.031.
- Use of Adrenaline for Out-of-Hospital Treatment of Anaphylaxis. Prehosp Emerg Care. 2019;23: 592. doi:10.1080/ 10903127.2018.1551453.
- Lyng JW, White 4th CC, Peterson TQ, et al. Non-auto-injector adrenaline administration by basic life support providers: a literature review and consensus process. Prehosp Emerg Care 2019;23:855–61. https://doi.org/10.1080/10903127.2019.1595235.
- National Association of State EMS Officials. (2021, August). National EMS scope of practice model 2019: Including change notices 1.0 and 2.0 (Report No. DOT HS 813 151). National Highway Traffic Safety Administration.
- Mauch J, Ringer SK, Spielmann N, Weiss M. Intravenous versus intramuscular adrenaline administration during cardiopulmonary resuscitation - a pilot study in piglets. Paediatr Anaesth 2013;23:906–12. https://doi.org/10.1111/pan.12149.
- Lind PC, Johannsen CM, Vammen L, Magnussen A, Andersen LW, Granfeldt A. Translation from animal studies of novel pharmacological therapies to clinical trials in cardiac arrest: A systematic review. Resuscitation 2021;158:258–69. https://doi.org/ 10.1016/j.resuscitation.2020.10.028.
- Pugh AE, Stoecklein HH, Tonna JE, Hoareau GL, Johnson MA, Youngquist ST. Intramuscular adrenaline for out-of-hospital cardiac arrest is associated with faster drug delivery: A feasibility study. Resusc Plus. 2021;7:100142. Published 2021 May 31. Doi:10.1016/j. resplu.2021.100142.
- 22. Salt Lake City Fire Department. (2023, October). About SLC Fire. Salt Lake City Fire Department, Utah. https://www.slc.gov/fire/about/
- United States Census Bureau. (2023, October). Quick Facts Salt Lake City, Utah. https://www.census.gov/quickfacts/fact/table/ saltlakecitycityutah/PST045222.
- Highlights of Prescribing Information. (2021). [Prescribing information. In Epinephrine Injection (Vols. 1–1, pp.1). https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/205029s006lbl.pdf.
- Ogston-Tuck S. Intramuscular injection technique: an evidence-based approach. Nursing standard (Royal College of Nursing (Great Britain): 1987), 2014; 29(4), 52–59. https://doi-org.ezproxy.lib.utah.edu/10.7748/ns.29.4.52.e9183.
- Sheikh A, Shehata YA, Brown SG, Simons FE. Adrenaline for the treatment of anaphylaxis: Cochrane systematic review. Allergy 2009;64:204–12. https://doi.org/10.1111/ji.1398-9995.2008.01926.x.
- 27. Perkins GD, Jacobs IG, Nadkarni VM, et al. Cardiac arrest and cardiopulmonary resuscitation outcome reports: update of the utstein resuscitation registry templates for out-of-hospital cardiac arrest: a statement for healthcare professionals from a task force of the International liaison committee on resuscitation (American Heart Association, European Resuscitation Council, Australian and New Zealand Council on Resuscitation, Heart and Stroke Foundation of Canada, InterAmerican Heart Foundation, Resuscitation Council of Southern Africa, Resuscitation Council of Asia); and the American Heart Association Emergency Cardiovascular Care Committee and the Council on Cardiopulmonary, Critical Care, Perioperative and Resuscitation [published correction appears in Circulation. 2015 Sep 29;132(13):e168-9]. Circulation 2015;132:1286–300. https://doi.org/10.1161/CIR.00000000000000144.
- Jennett B, Bond M. Assessment of outcome after severe brain damage. Lancet 1975;1:480–4. https://doi.org/10.1016/s0140-6736 (75)92830-5.

- Choi DH, Hong KJ, Kim KH, et al. Effect of first adrenaline administration time on cerebral perfusion pressure and cortical cerebral blood flow in a porcine cardiac arrest model. Resuscitation. Published online September 15, 2023. doi:10.1016/j. resuscitation.2023.109969.
- Mavroudis CD, Ko TS, Morgan RW, et al. Adrenaline's effects on cerebrovascular and systemic hemodynamics during cardiopulmonary resuscitation. *Crit Care*. 2020;24:583. Published 2020 Sep 29.doi:10.1186/s13054-020-03297-4.
- Nishiyama C, Kiguchi T, Okubo M, et al. Three-year trends in out-of-hospital cardiac arrest across the world: Second report from the International Liaison Committee on Resuscitation (ILCOR).
 Resuscitation 2023;186:109757. Available from: https://doi-org.ezproxy.lib.utah.edu/10.1016/i.resuscitation.2023.109757.
- Khosla S, Del Rios M, Kotini-Shah Weber J, Vanden HT. Yeas of potential life lost and mean age of adults experiencing nontraumatic, out-of-hospital cardiac arrests – Chicago, 2014–2021. MMWR Morb Mort Wkly Rep 2024;73:199–203.
- Song J, Guo W, Lu X, Kang X, Song Y, Gong D. The effect of bystander cardiopulmonary resuscitation on the survival of out-ofhospital cardiac arrests: a systematic review and meta-analysis. Scand JJ Trauma Resusc EmergMed 2018;26:86. https://doi.org/10.1186/s13049-018-0552-8.
- 34. Naim MY, Burke RV, McNally BF, Song L, Griffis HM, Berg RA, et al. Association of bystander cardiopulmonary resuscitation with overall and neurologically favorable survival after pediatric out-of-hospital cardiac arrest in the United States: a report from the Cardiac Arrest Registry to Enhance Survival Surveillance Registry. JAMA Pediatr 2017;171:133–41. https://doi.org/
 10.1001/jamapediatrics.2016.3643.
- Centers for Disease Control and Prevention (n.d.). COVID-19
 Timeline. David J. Sencer CDC Museum: In Association With the Smithsonian Institution. https://www.cdc.gov/museum/timeline/covid19.html.

- Curtin, S. C., Tejada-Vera, B., Bastian, B. A., U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Health Statistics, & National Vital Statistics System. (2024). Deaths: leading causes for 2021. In National Vital Statistics Reports (No. 4; Vol. 73). https://www. cdc.gov/nchs/data/nvsr/nvsr73/nvsr73-04.pdf.
- CDC. (2020, March 28). COVID Data Tracker. Centers for Disease Control and Prevention. https://covid.cdc.gov/covid-data-tracker/ #trends totaldeaths totaldeathratecrude 49.
- HDPulse An Ecosystem of Minority Health and Health Disparities Resources National Institute of Minority Health and Health Disparities, Created on 05/2/2024.
- Riera-López N, Gaetano-Gil A, Martínez-Gómez J, et al. The COVID-19 pandemic effect on the prehospital Madrid stroke code metrics and diagnostic accuracy. PLoS One. 2022;17:e0275831. Published 2022 Oct 10. doi:10.1371/journal.pone.0275831.
- Drozd A, Smereka J, Filipiak KJ, et al. Intraosseous versus intravenous access while wearing personal protective equipment: a meta-analysis in the era of COVID-19. Kardiol Pol 2021;79:277–86. https://doi.org/10.33963/KP.15741.
- Bielski K, Szarpak A, Jaguszewski MJ, et al. The Influence of COVID-19 on Out-Hospital Cardiac Arrest Survival Outcomes: An Updated Systematic Review and Meta-Analysis. J Clin Med. 2021;10:5573. Published 2021 Nov 27. doi:10.3390/jcm10235573.
- Callaham M, Madsen CD, Barton CW, Saunders CE, Pointer J. A randomized clinical trial of high-dose epinephrine and norepinephrine vs standard-dose epinephrine in prehospital cardiac arrest. JAMA 1992 Nov 18;268:2667–72. PMID: 1433686.
- Kurz MC, Schmicker RH, Leroux B, et al. Advanced vs. basic life support in the treatment of out-of-hospital cardiopulmonary arrest in the resuscitation outcomes consortium. Resuscitation 2018;128:132–7. https://doi.org/10.1016/j.resuscitation.2018.04.031.