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ORIGINAL RESEARCH ARTICLE

Survival After Intravenous Versus Intraosseous Amiodarone, Lidocaine, or Placebo in Out-of-Hospital Shock-Refractory Cardiac Arrest

BACKGROUND: Antiarrhythmic drugs have not proven to significantly improve overall survival after out-of-hospital cardiac arrest from shock-refractory ventricular fibrillation/pulseless ventricular tachycardia. How this might be influenced by the route of drug administration is not known.

METHODS: In this prespecified analysis of a randomized, placebo-controlled clinical trial, we compared the differences in survival to hospital discharge in adults with shock-refractory ventricular fibrillation/pulseless ventricular tachycardia out-of-hospital cardiac arrest who were randomly assigned by emergency medical services personnel to an antiarrhythmic drug versus placebo in the ALPS trial (Resuscitation Outcomes Consortium Amiodarone, Lidocaine or Placebo Study), when stratified by the intravenous versus intraosseous route of administration.

RESULTS: Of 3019 randomly assigned patients with a known vascular access site, 2358 received ALPS drugs intravenously and 661 patients by the intraosseous route. Intraosseous and intravenous groups differed in sex, time-to-emergency medical services arrival, and some cardiopulmonary resuscitation characteristics, but were similar in others, including time-to-intravenous/intrasosseous drug receipt. Overall hospital discharge survival was 23%. In comparison with placebo, discharge survival was significantly higher in recipients of intravenous amiodarone (adjusted risk ratio, 1.26 [95% CI, 1.06–1.50]; adjusted absolute survival difference, 5.5% [95% CI, 1.5–9.5]) and intravenous lidocaine (adjusted risk ratio, 1.21 [95% CI, 1.02–1.45]; adjusted absolute survival difference, 4.7% [95% CI, 0.7–8.8]); but not in recipients of intraosseous amiodarone (adjusted risk ratio, 0.94 [95% CI, 0.66–1.32]) or intraosseous lidocaine (adjusted risk ratio, 1.03 [95% CI, 0.74–1.44]). Survival to hospital admission also increased significantly when drugs were given intravenously but not intraosseously, and favored improved neurological outcome at discharge. There were no outcome differences between intravenous and intraosseous placebo, indicating that the access route itself did not demarcate patients with poor prognosis. The study was underpowered to assess intravenous/intraosseous drug interactions, which were not statistically significant.

CONCLUSIONS: We found no significant effect modification by drug administration route for amiodarone or lidocaine in comparison with placebo during out-of-hospital cardiac arrest. However, point estimates for the effects of both drugs in comparison with placebo were significantly greater for the intravenous than for the intraosseous route across virtually all outcomes and beneficial only for the intravenous route. Given that the study was underpowered to statistically assess interactions, these findings signal the potential importance of the drug administration route during resuscitation that merits further investigation.

Mohamud R. Daya, MD, MS
Brian G. Leroux, PhD
Paul Dorian, MD, MSc
Thomas D. Rea, MD, MPH
Craig D. Newgard, MD, MPH
Laurie J. Morrison, MD, MSc
Joshua R. Lupton, MD, MPH
James J. Menegazzi, PhD
Joseph P. Ornato, MD
George Sopko, MD
Jim Christenson, MD
Ahamed Idris, MD
Purav Mody, MD
Gary M. Vilke, MD
Caroline Herdeman, BA, CCRC
David Barbic, MD, MSc
Peter J. Kudenchuk MD
For the Resuscitation Outcomes Consortium Investigators

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Clinical Perspective

What Is New?

- Intraosseous is increasingly preferred over intravenous vascular access for drug administration during out-of-hospital cardiac arrest, but its effectiveness is controversial.
- In this prespecified analysis of a randomized, placebo-controlled trial, outcomes were compared between amiodarone, lidocaine, and placebo when administered intravenously or intraosseously during shock-refractory out-of-hospital cardiac arrest.
- Although no significant effect modification by drug administration route was observed, point estimates for the effects of both drugs in comparison with placebo were greater for the intravenous than for the intraosseous route across all outcomes, with significant increases in survival to hospital admission and discharge, and favored improved neurological outcome only with intravenous administration.

What Are the Clinical Implications?

- Amiodarone and lidocaine may be life-saving drugs in patients with shock-refractory out-of-hospital cardiac arrest, when given intravenously but not intraosseously.
- Although provocative, the observed differences in outcome are mitigated by inconclusive evidence of an interaction between the route of vascular access and drug effectiveness.
- Confirming these findings could have important implications for public health and medical practice.

Out-of-hospital cardiac arrest (OHCA) is a leading cause of death and a significant public health problem worldwide. Its treatment consists of a sequence of time-sensitive interventions known as the chain of survival. Antiarrhythmic medications are frequently administered when OHCA is caused by shock-refractory ventricular fibrillation or pulseless ventricular tachycardia (VF/VT). Although showing promise when the OHCA is witnessed, these drugs have not been proven to improve overall survival in patients with witnessed and unwitnessed VF/VT arrest.[1] Whether this apparent inefficacy is influenced by their route of administration, intravenous versus intraosseous, is not known.

American Heart Association resuscitation guidelines preferentially recommend drug administration by a peripheral intravenous route, but endorse the use of an intraosseous route when intravenous access cannot be readily obtained.[2] Technological advances over the past 2 decades have made it easier to access the intraosseous space in adults. Studies suggest this approach is faster and more likely to be successful in achieving vascular access than intravenous cannulation.[3–5] As a result, emergency medical services (EMS) systems have increasingly incorporated intraosseous vascular access into their resuscitation protocols, with some in fact prioritizing this approach over intravenous cannulation. However, little is known about the pharmacokinetics of antiarrhythmic drugs administered intraosseously during the low-flow state of cardiac arrest and ongoing cardiopulmonary resuscitation (CPR). Recent studies have challenged whether resuscitation medications, in particular, epinephrine, are as effective when administered intraosseously rather than intravenously during CPR.[6–8] The effectiveness of intravenous versus intraosseous administration of antiarrhythmic agents during resuscitation, in particular, in the context of a placebo control, has not been previously addressed and could have important implications for patient care.

In this prespecified analysis of a randomized, placebo-controlled trial, we compared survival to hospital discharge in adults with nontraumatic, shock-refractory VF/VT OHCA who were randomly assigned to antiarrhythmic drugs versus placebo in the Resuscitation Outcomes Consortium ALPS trial (Amiodarone, Lidocaine or Placebo Study), stratified by the route of drug administration (intravenous versus intraosseous) during CPR. We hypothesized a beneficial association with survival from amiodarone and lidocaine, in comparison with placebo, when an active drug was administered intravenously during active resuscitation, but an attenuated association when given intraosseously.

METHODS

The ALPS trial has been previously described,[1,9] and anonymized data and materials are publicly available at the National Institutes of Health Biologic Specimen and Data Repository Information Coordinating Center website (https://biolincc.nhlbi.nih.gov/home/). Adults with nontraumatic OHCA presenting as shock-refractory VF/VT were randomly assigned, double-blind by paramedics from 55 EMS agencies across 10 North American sites to receive amiodarone, lidocaine, or placebo. The trial was conducted under exception from informed consent in emergency research in compliance with all applicable regulatory requirements. This included institutional and independent data safety monitoring board oversight, and the US Food and Drug Administration, as well. It was principally supported by the National Heart, Lung, and Blood Institute and the Canadian Institutes of Health Research, with the provision of study drug by Baxter Healthcare (who otherwise played no role in the trial). Eligible patients had established intravenous or intraosseous access and confirmed persistent (nonterminating) or recurrent (only transiently terminated) VF/VT after ≥1 defibrillation shocks at the time of drug administration. Selection of intravenous or intraosseous access was at the discretion of providers and local EMS protocols and was defined as the specified route by which the study drug was administered. This approach varied according to clinical practice across sites. In some cases, intraosseous represented the primary attempt at vascular access, whereas, in other cases, was deployed when intravenous access was unsuccessful or deemed unlikely to be successful. A set of 3 syringes each

containing the same study drug (150 mg amiodarone, 60 mg lidocaine, or matching placebo) for intravenous or intraosseous administration was placed in indistinguishable sealed kits. Kits were randomly assigned to patients in a ratio of 1:1:1. Two syringes were initially administered by bolus injection. This was subsequently followed, if necessary, by the third syringe for persistent or recurring VF/VT, in addition to all other standard advanced life support measures as required. Open-label use of lidocaine or amiodarone was not permitted during prehospital care. All trial interventions were completed before hospital arrival; subsequent hospital care was monitored but not standardized by the trial protocol. The main trial and its prespecified subanalyses were approved by respective institutional review boards in participating communities.

Outcome

The primary study outcome was survival to hospital discharge between active drugs and placebo when administered intravenously and when given intraosseously. Secondary outcomes included survival to hospital admission and survival with favorable neurological function at hospital discharge, defined as a modified Rankin scale ≤3 (range 0 [no symptoms] to 6 [death]), with ≤3 indicating the ability to conduct daily activities independently or with minimal assistance. Primary and secondary outcomes were also assessed comparing intravenous against intraosseous placebo, to distinguish effects associated with active drugs versus placebo at those sites from those that might be associated with the selected route of vascular access itself, as were adverse effects associated with intravenous versus intraosseous treatment.[1,9] Primary and secondary outcome differences between intravenous and intraosseous groups were expressed in terms of relative risk (or risk ratio) with 95% CI and also in absolute differences (95% CI) permitting comparison with how results were expressed in the primary trial.

Data Collection and Analysis

Data from prehospital patient care reports, electronically collected CPR process measures, and hospital records were collected and abstracted without specific knowledge of treatment assignment or route of prehospital vascular access.[1,9] Data collection used a standardized data dictionary and a common web-based electronic data entry platform hosted at the study's Data Coordinating Center. The route of access was a predefined data element and was ascertained by review of the EMS record. If patients received both intravenous and intraosseous access, outcomes were assigned according to the route by which the study drug (amiodarone, lidocaine, or placebo) was administered.

Statistics

Primary and secondary outcomes were evaluated across treatment groups stratified by the route of vascular access. We used multivariable linear regression with robust standard errors to adjust for potential confounding when comparing the association of study drug with outcome according to vascular route. Collected data that served as covariates in the adjusted analyses included age, sex, location of arrest, presumed etiology, witnessed status (bystander and EMS), provision of bystander CPR, emergency call to first EMS arrival, to arrival of advanced life support personnel, and to receipt of study drug (intravenous or intraosseous). In addition, multivariable models were specifically adjusted for clustering of potentially correlated data by study site using the fixed-effects approach[10] on the basis of (dummy) indicator variables for study sites. Unadjusted analyses were performed on all patients with observed outcomes (>99% of cases) and in patients in whom all covariate data were known; adjusted analyses were restricted to the latter population of patients with complete covariate data. The proportion of patients missing complete covariate data was relatively small (5%). We also evaluated a statistical interaction by intravenous versus intraosseous drug treatment on primary and secondary outcomes by adding a multiplicative term (route of access × study drug) to the multivariable model, recognizing that the study was not originally designed or sufficiently powered for determining interactions. Such a design would require 6000 patients to detect an interaction between drug route and outcome with 80% power based on the current study's estimates of survival. Results of analyses were not adjusted for multiple comparisons. Two-sided *P* values ≤0.05 were considered statistically significant.

RESULTS

Study Population

In all, 3026 patients with OHCA attributable to shock-refractory VF/VT were randomly assigned to receive amiodarone (n=974), lidocaine (n=991), or placebo (n=1054); the route of vascular access for study drug administration was known for 3019 patients and not known in 7 patients who were excluded from the analysis. Of these, 2358 patients (78%) received their study drug intravenously (explicitly specified as an upper extremity vein in 1989 [84%]), and 661 patients (22%) by an intraosseous route (explicitly specified as a tibial intraosseous access in 615 patients [93%]; Figure 1). Follow-up for the primary and secondary study outcomes was complete in >99% of these patients. The use of intravenous versus intraosseous access varied by study site and local practice. Intraosseous drug administration ranged from 1% to 53% across sites; half of sites contributed 89% of patients who received study drugs by intraosseous access (Figure I in the online-only Data Supplement).

A comparable proportion of patients in intravenous and intraosseous groups were randomly assigned to treatment with lidocaine, amiodarone, or placebo, nearly identical to the proportion randomly assigned to each of these study drug arms in the overall ALPS population (Figure 1).[1] A complete set of covariate data for adjusted analyses was available in ≈95% of the study population: in 2876 patients with known survival to hospital admission outcome, in 2861 for survival to discharge, and in 2857 patients with known neurological outcome.

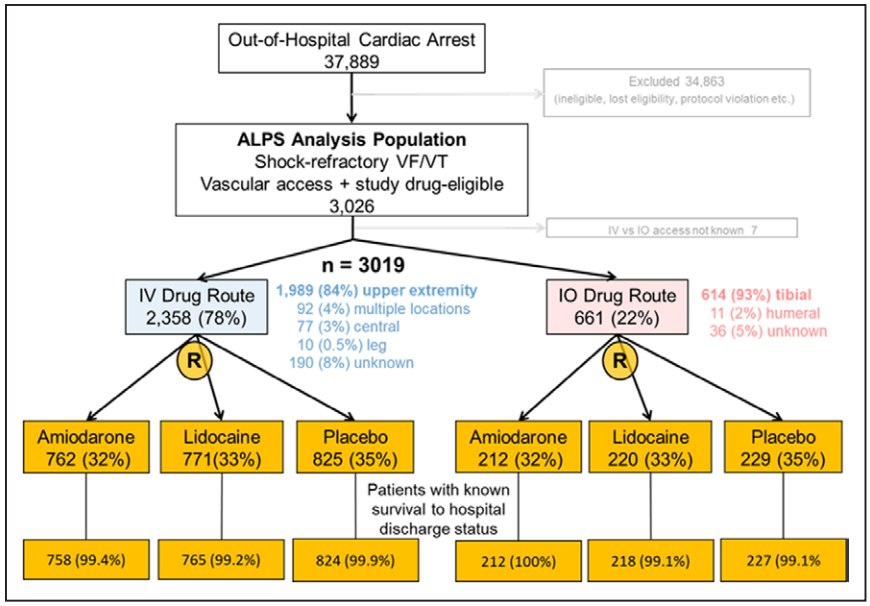

Figure 1. Stratification of patients who were eligible for study drug by the intravenous or the intraosseous route of vascular access, and their randomized treatment assignment to amiodarone, lidocaine, or placebo.
ALPS indicates Amiodarone, Lidocaine, or Placebo Study; IO, intraosseous; IV, intravenous; and VF/VT, ventricular fibrillation/pulseless ventricular tachycardia.

Patients comprising the intravenous and intraosseous groups did not significantly differ in age, the location of their arrest, frequency of bystander- or EMS-witnessed arrest, receipt of bystander shock or CPR, CPR compression rate, duration of perishock pauses, successful advanced airway placement, the time intervals (mean±SD) from the emergency call to intravenous or intraosseous vascular access (14.2±5.6 versus 13.9±5.8 minutes, respectively) and to study drug administration (19.3±7.4 versus 19.4±7.3 minutes), or receipt of other resuscitation drugs (Tables 1 and 2). Differences were observed between intravenous and intraosseous groups in sex, the time interval from emergency call to EMS vehicle arrival and to arrival of paramedics with advanced life support capabilities, chest compression depth and CPR fraction (ie, the proportion of time that chest compressions were administered during pulseless periods). Epinephrine was commonly administered before study drug (Table 2), whose time of administration was similar between intravenous and intraosseous groups and concordant with the same intravenous or intraosseous route as study drug administration (data not shown).

Hospital-initiated treatments, including targeted temperature management, subsequent defibrillator implantation, and the proportion of patients in whom care was limited or withdrawn during their stay, were balanced across intravenous and intraosseous treatment groups. A lower proportion of recipients of intraosseous than intravenous drugs underwent coronary angiography with a percutaneous coronary intervention during the first 24 hours of hospitalization (Table I in the online-only Data Supplement).

Active Drug Versus Placebo Outcome

Among the 3019 randomly assigned patients in the ALPS study with a known intravenous or intraosseous site of vascular access, overall survival to hospital discharge was 23%. Among patients receiving drugs intravenously, unadjusted survival was higher among those randomly assigned to amiodarone than placebo (25.9% versus 20.6% of patients, respectively, *P*=0.014) and approached statistical significance in recipients of intravenous lidocaine in comparison with placebo (24.6% versus 20.6% of patients, *P*=0.06). This corresponded to an unadjusted risk ratio (in the full study population and in the population sample with complete covariate data, respectively) of 1.25 (95% CI, 1.05–1.50) and 1.28 (95% CI, 1.06–1.54) when intravenous amiodarone was compared with placebo, and 1.19 (95% CI, 0.99–1.43) and 1.25 (95% CI, 1.03–1.50) when intravenous lidocaine was compared with placebo (Table 3). Conversely, there was no significant difference in unadjusted survival to hospital discharge between either amiodarone or lidocaine in comparison with placebo when given intraosseously (Table 3).

Adjusted analyses mirrored these findings. Intravenous drug administration was associated with a significantly higher adjusted survival to hospital discharge in comparison with placebo both for amiodarone recipients (adjusted relative risk, 1.26 [95% CI, 1.06–1.50], or an adjusted absolute survival difference of 5.5% [95% CI, 1.5–9.5]) and lidocaine recipients (adjusted relative risk, 1.21 [95% CI 1.02–1.45]; adjusted absolute survival difference, 4.7% [95% CI, 0.7–8.8]). In contrast, there were no significant differences in adjusted survival outcome between amiodarone and placebo (relative risk, 0.94 [95% CI, 0.66–1.32], or an absolute survival difference of –1.8% [95% CI, –9.2 to 5.6]) or between lidocaine and placebo (relative risk, 1.03 [95% CI, 0.74–1.44], absolute survival difference, 0.3% [95% CI, –7.4 to 7.9]) when administered intraosseous (Table 3 and Figure 2). However, a statistically significant interaction

Table 1. Prehospital Characteristics of the Study Population

Characteristic	Intravenous Route (n=2358)	Intraosseous Route (n=661)
Age, y, mean±SD [n=2351, 660]	62.7±14.3	62.3±14.8
Placebo [n=823, 229]	62.7±14.4	60.5±15.3
Lidocaine [n=770, 220]	62.2±14.6	63.5±15.1
Amiodarone [n=758, 212]	63.2±13.9	63.2±14
Male sex, n (%) [total n=2357, 661]*	1935 (82.1)	481 (72.8)
Placebo [n=825, 229]	682 (82.7)	158 (69)
Lidocaine [n=771, 220]	647 (83.9)	167 (75.9)
Amiodarone [n=761, 212]	606 (79)	156 (73.6)
Public location, n (%) [total n=2355, 661]	739 (31.4)	188 (28.4)
Placebo [n=822, 229]	246 (29.9)	66 (28.8)
Lidocaine [n=771, 220]	245 (31.8)	67 (30.5)
Amiodarone [n=762, 212]	248 (32.5)	55 (25.9)
EMS witnessed, n (%) [total n=2345, 655]	121 (5.2)	34 (5.2)
Placebo [n=820, 228]	44 (5.4)	10 (4.4)
Lidocaine [n=676, 219]	34 (4.4)	10 (4.6)
Amiodarone [n=758, 208]	43 (5.7)	14 (6.7)
Bystander witnessed, n (%) [total n=2345, 655]	1530 (65.2)	409 (62.4)
Placebo [n=820, 228]	547 (66.7)	136 (59.6)
Lidocaine [n=676, 219]	496 (64.7)	139 (63.5)
Amiodarone [n=568, 208]	487 (64.2)	134 (64.4)
Bystander shock, n (%) [total n=2322, 644]	123 (5.3)	47 (7.3)
Placebo [n=812, 225]	42 (5.2)	15 (6.7)
Lidocaine [n=755, 213]	36 (4.8)	15 (7)
Amiodarone [n=755, 206]	45 (6)	17 (8.3)
Bystander CPR, n (%) [total n=2323, 645]	1322 (56.9)	375 (58.1)
Placebo [n=812, 225]	461 (56.8)	131 (58.2)
Lidocaine [n=756, 213]	428 (56.6)	121 (56.8)
Amiodarone [n=755, 207]	433 (57.4)	123 (59.4)
Call to 1st EMS arrival minutes, mean±SD [n=2327, 654]*	5.8±2.6	5.4±2.2
Placebo [n=811, 227]	5.9±2.7	5.5±2.3
Lidocaine [n=762, 218]	5.7±2.5	5.1±2
Amiodarone [n=754, 209]	5.8±2.6	5.7± .3
Call to ALS arrival minutes, mean±SD [n=2345, 658]*	8.3±4.7	6.8±4.1
Placebo [n=822, 229]	8.4±4.8	6.6±3.2
Lidocaine [n=766, 219]	8.2±4.3	6.5±3.9
Amiodarone [n=757, 210]	8.2±5.1	7.4±5.1

The [n=] in the main rows of the table refers to the number of patients in the intravenous and intraosseous groups, respectively, in whom data were available for the indicated measure. ALS indicates advanced life support; Call, emergency call activating the EMS system (911); CPR, cardiopulmonary resuscitation; and EMS, emergency medical services.

*P<0.001 for differences in sex, and call interval to EMS and ALS arrival (respectively) between intravenous and intraosseous treatment groups.

between route of vascular access and survival after study drug was not evident (P=0.32).

Secondary Outcomes

In both unadjusted and adjusted analyses, amiodarone and lidocaine were each associated with a significantly greater likelihood of survival to hospital admission than placebo when administered intravenously, but not when given intraosseously (Table 3, Figure 2). A concordant trend toward a more favorable neurological recovery at hospital discharge with intravenous but not intraosseous administration of these drugs was also observed, but the adjusted difference for this end point between intravenous lidocaine and placebo was less robust than for intravenous amiodarone versus placebo, and was not statistically significant (P=0.13). A significant interaction between the route of vascular access and study drug was also not observed for either secondary outcome (P=0.11, P=0.47, respectively).

Intravenous Versus Intraosseous Placebo

In addition to comparing active drugs (amiodarone or lidocaine) against placebo when given intravenously and intraosseously, placebo was also compared directly against itself by the route of administration to distinguish whether receipt of intravenous or intraosseous access might itself bear an association with outcome. There was no association between receipt of placebo by intravenous versus intraosseous access and primary or secondary study outcomes. This included survival to hospital discharge (20.6% versus 22.5% for intravenous versus intraosseous recipients, respectively; adjusted relative risk, 0.93 [95% CI, 0.71–1.21], P=0.6); admission alive to hospital (39.8% versus 39%; adjusted relative risk, 1.02 [95% CI, 0.85–1.23], P=0.83) and survival with favorable neurological status at discharge (16.6% versus 16.3%; adjusted relative risk, 0.92 [95% CI, 0.66–1.27], P=0.6). Similarly, there were no significant adjusted absolute risk differences for these comparisons between intravenous and intraosseous placebo (data not shown).

Adverse Events

Expected adverse effects, including acute thrombophlebitis, anaphylaxis, seizure activity, or the need for acute cardiac pacing was small overall and did not differ between intravenous versus intraosseous access groups among patients randomly assigned to amiodarone, lidocaine, or placebo (Table II in the online-only Data Supplement).

DISCUSSION

In this prespecified analysis of a randomized, placebo-controlled clinical trial of antiarrhythmic drug treatment for

Table 2. Resuscitation Characteristics of the Study Population

Characteristic	Intravenous Route (n=2358)	Intraosseous Route (n=661)
Call to intravenous or intraosseous access, mean minutes±SD [n=2294, 652]	14.2±5.6	13.9±5.8
Placebo [n=805, 228]	14.4±5.8	13.7±4.7
Lidocaine [n=752, 219]	14±5.4	13.6±5.4
Amiodarone [n=737, 205]	14.1±5.6	14.6±7.1
Call to study drug,* mean minutes±SD [n=2213, 617]	19.3±7.4	19.4±7.3
Placebo [n=772, 213]	19.3±7.5	19±6.7
Lidocaine [n=731, 209]	19.3±7.6	19.3±7.6
Amiodarone [n=710, 195]	19.2±7	19.8±7.6
Arrest to study drug,† mean minutes±SD [n=114, 33]	12±6.4	11.7±5.7
Placebo [n=42, 10]	12.7±6.8	9.5±4.8
Lidocaine [n=31, 10]	12.1±7	12.3±5.5
Amiodarone [n=41, 13]	11.2±5.6	13.1±6.5
Chest compression rate, mean cpm±SD [n=2173, 619]	110±10.9	110±11.3
Placebo [n=760, 210]	110±10.9	110±11.9
Lidocaine [n=712, 212]	110±10.8	110±10.6
Amiodarone [n=701, 197]	109±10.9	109±11.3
Chest compression depth, mean mm±SD [n=1118, 326]‡	51.7±10.3	49.7±9.0
Placebo [n=392, 108]	52.3±10.3	50.4±7.6
Lidocaine [n=382, 119]	51.8±11.4	48.7±9.4
Amiodarone [n=344, 99]	51±9	50.2±9.9
Chest compression fraction, mean %±SD [n=2201, 623]‡	0.83±0.10	0.85±0.09
Placebo [n=774, 211]	0.83±0.10	0.84±0.09
Lidocaine [n=718, 212]	0.83±0.09	0.85±0.09
Amiodarone [n=709, 200]	0.83±0.10	0.84±0.10
Preshock pause, mean seconds±SD [n=2112, 594]	10.3±9.6	9.8±9.3
Placebo [n=737, 202]	10.5±9.2	9±8.1
Lidocaine [n=691, 200]	10.3±9	9.7±9.8
Amiodarone [n=684, 192]	10.1±10.7	10.7±10.8
Postshock pause, mean seconds±SD [n=2099, 592]	6.2±32.4	6.7±37.0
Placebo [n=733, 200]	7.6±52.7	5.9±9
Lidocaine [n=688, 200]	5.5±13.6	4.7±5.5
Amiodarone [n=678, 192]	5.3±8.2	9.7±64.2
Prehospital advanced airway success, n (%) [total n=2358, 661]	2007 (85.1)	555 (84.0)
Placebo [n=825, 229]	699 (84.7)	189 (82.50)
Lidocaine [n=771, 220]	668 (86.6)	186 (84.5)
Amiodarone [n=762, 212]	649 (84)	180 (84.9)
Receipt of epinephrine, n (%) [total n=2358, 661]	2329 (98.7)	653 (98.7)
Placebo [n=825, 229]	817 (99)	224 (97.8)
Lidocaine [n=771, 220]	761 (98.7)	218 (99.1)
Amiodarone [n=762, 212]	751 (98.6)	211 (99.5)
Receipt of magnesium, n (%) [total n=2358, 661]	201 (8.5)	64 (9.6)
Placebo [n=825, 229]	88 (10.7)	31 (13.5)
Lidocaine [n=771, 220]	56 (7.3)	12 (5.5)
Amiodarone [n=762, 212]	57 (7.5)	21 (9.9)

The [n=] in the main rows of the table refers to the number of patients in the intravenous and intraosseous access groups, respectively, in whom data were available for the indicated measure. cpm indicates compressions per minute.

*Patients with cardiac arrest before the arrival of emergency medical services.

†Patients with cardiac arrest after the arrival of emergency medical services.

‡$P<0.001$ for differences in chest compression depth and cardiopulmonary resuscitation compression fraction (respectively) between intravenous and intraosseous treatment groups.

Table 3. Unadjusted and Adjusted Primary and Secondary Study Outcomes in the Full Study Population and in Patients Within That Population With Complete Covariate Data (Complete Data Sample)

Outcome (full study population)				Relative Risk, % (95% CI)				Overall *P* for IV/IO Interaction§
				Unadjusted Outcome (full study population) Unadjusted Outcome (complete data sample)		Adjusted Outcome‡ (complete data sample)		
Vascular Access* [n in each treatment arm]†	Placebo n (%)	Lidocaine n (%)	Amiodarone n (%)	Amiodarone Versus Placebo	Lidocaine Versus Placebo	Amiodarone Versus Placebo	Lidocaine Versus Placebo	
Survival to hospital admission (full study population n=3019; complete data sample n=2876)								
IV 1070/2353 (45.5%) [n=825, 768, 760]	328 (39.8)	372 (48.4)	370 (48.7)	1.22 (1.09–1.37) 1.25 (1.11–1.40)	1.21 (1.09–1.36) 1.24 (1.11–1.39)	1.23 (1.11–1.37)	1.24 (1.11–1.38)	
IV/IO interaction (*P*)						0.15	0.85	0.11
IO 259/660 (39.2%) [n= 228, 220, 212]	89 (39)	95 (43.2)	75 (35.4)	0.91 (0.71–1.16) 0.92 (0.71–1.18)	1.11 (0.89–1.39) 1.15 (0.92–1.45)	0.95 (0.75–1.21)	1.20 (0.97–1.49)	
Survival to hospital discharge (full study population n=3004; complete data sample n=2861)								
IV 554/2347 (23.6%) [n= 824, 765, 758]	170 (20.6)	188 (24.6)	196 (25.9)	1.25 (1.05–1.50) 1.28 (1.06–1.54)	1.19 (0.99–1.43) 1.25 (1.03–1.50)	1.26 (1.06–1.50)	1.21 (1.02–1.45)	
IV/IO interaction (*P*)						0.22	0.48	0.32
IO 137/657 (20.9%) [n= 227, 218, 212]	51 (22.5)	45 (20.6)	41 (19.3)	0.86 (0.60–1.24) 0.88 (0.61–1.27)	0.92 (0.64–1.31) 0.94 (0.66–1.35)	0.94 (0.66–1.32)	1.03 (0.74–1.44)	
Survival with mRS≤3 at hospital discharge (full study population n=2999; complete data sample n=2857)								
IV 431/2342 (18.4%) [n= 823, 764, 755]	137 (16.6)	142 (18.6)	152 (20.1)	1.21 (0.98–1.49) 1.25 (1.01–1.55)	1.12 (0.90–1.38) 1.17 (0.94–1.45)	1.24 (1.02–1.52)	1.17 (0.95–1.44)	
IV/IO interaction (*P*)						0.31	0.48	0.47
IO 97/657 (14.8%) [n= 227, 218, 212]	37 (16.3)	30 (13.8)	30 (14.2)	0.87 (0.56–1.36) 0.87 (0.55–1.36)	0.84 (0.54–1.32) 0.86 (0.55–1.34)	0.94 (0.61–1.43)	0.96 (0.63–1.46)	

Full study population refers to all patients with a known survival outcome (>99% of cases); complete data sample refers to patients in whom all covariate data were known (≈95% of cases). CPR indicates cardiopulmonary resuscitation; EMS, emergency medical services; IO, intraosseous vascular access; IV, intravenous vascular access; and mRS, modified Rankin scale.

*The numerator of the fractions shown in the first column corresponds to the combined number of patients in the placebo, lidocaine, and amiodarone groups who achieved the described end point, and the denominator to the total number of patients who received that (intravenous or intraosseous) route of treatment.

†The [n =] refers to the number of patients in the placebo, lidocaine, and amiodarone groups, respectively, in whom data were available for the indicated end point.

‡Adjusted for age, sex, cardiac cause, public location, EMS witnessed, bystander witnessed, bystander CPR, EMS arrival time, ALS arrival time, time to study drug, and study site.

§Comparing the overall interaction between intravenous and intraosseous access treatment for amiodarone versus placebo and lidocaine versus placebo in the adjusted outcome analysis. The corresponding *P* values for the overall interaction for unadjusted outcomes in the full study population and in the sample with complete data were 0.08 and 0.09, respectively, for survival to hospital admission; 0.18 and 0.18 for survival to hospital discharge; and 0.29 and 0.36 for survival with mRS≤3 at hospital discharge.

refractory VF/VT OHCA, we found that amiodarone and lidocaine were each associated with significantly increased survival to hospital admission and discharge in comparison with placebo, and favored an improved neurological outcome at hospital discharge when the drugs were administered intravenously. Conversely, we did not observe significant differences in these end points between amiodarone or lidocaine in comparison with placebo when administered intraosseously. Although underpowered for and mitigated by inconclusive evidence for an interaction between the mode of drug delivery and outcome, the consistency of these findings across multiple outcome measures and drugs signals the potential importance of the route of vascular access for drug treatment in OHCA and how this might influence treatment effectiveness.

Previous Studies

The pharmacokinetic profiles and acute effects of parenteral antiarrhythmic drugs used for the treatment of OHCA have mainly been described after intravenous administration.[11–14] However, successful intravenous cannulation can be challenging when the quality of patients' peripheral vasculature is poor or access is compromised by poor perfusion. In such instances, intraosseous access provides an alternate means of vascular access via noncollapsible venous plexi within the bone marrow space; the proximal tibia ultimately draining to the popliteal vein, and the proximal humerus to the axillary vein.[15,16] Comparable concentrations and physiological responses to a number of drugs given by an intraosseous or intravenous route can be achieved under normal circulatory conditions,[17] but with less certainty in animal models under conditions of hypovolemic and electrically induced VF/VT cardiac arrest that required CPR.[18–26] The critical question is whether intravenous and intraosseous approaches to vascular access are equally effective in patients with clinical OHCA.

Thus far, clinical studies have not resolved this issue, having reported both similar and concerning disparities in

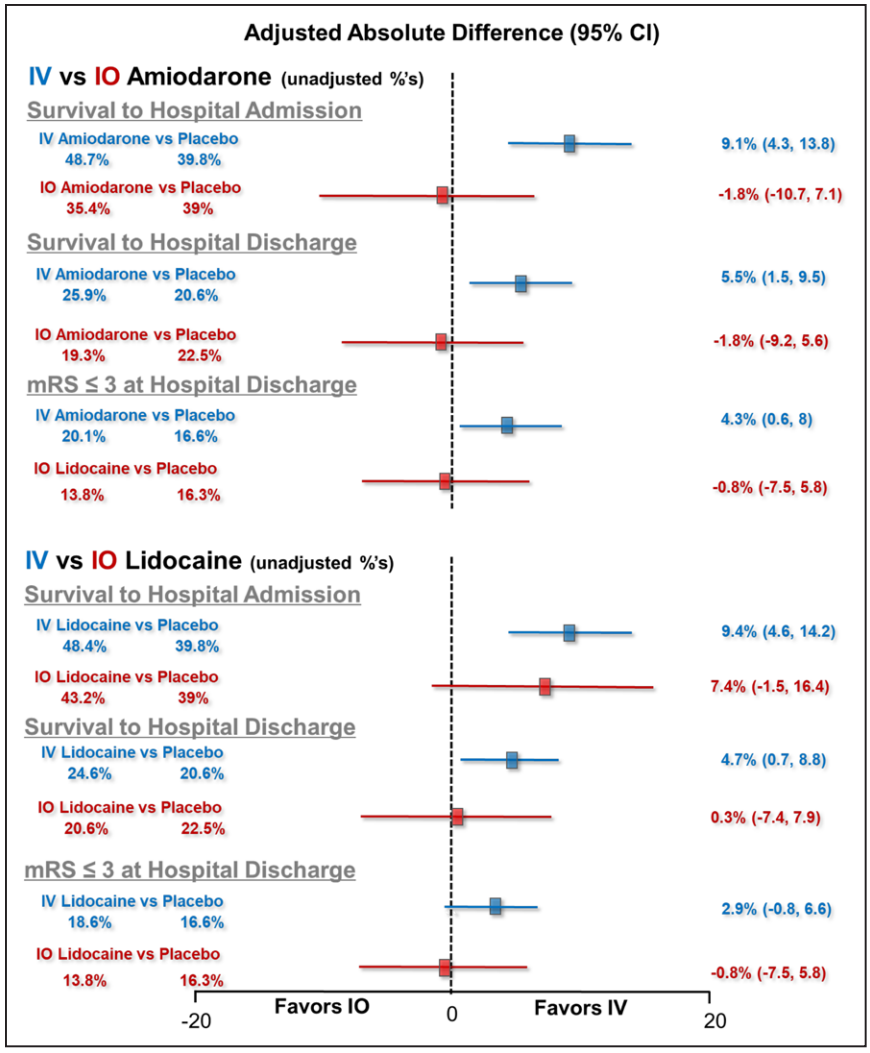

Figure 2. Unadjusted and adjusted absolute differences in survival to hospital admission, survival to hospital discharge, and functional status (modified Rankin Scale ≤3) at hospital discharge.
The left side of the figure describes the unadjusted percentages of patients who achieved the described end points. The forest plot and numerical values on the right side of the figure depict the adjusted absolute differences (with 95% CIs) in the described end points. The upper forest plot depicts outcomes comparing intravenous amiodarone versus placebo and intraosseous amiodarone versus placebo. The lower plot depicts outcomes comparing intravenous lidocaine versus placebo and intraosseous lidocaine vs placebo. Significant differences in survival to hospital admission, to hospital discharge, and favoring improved functional status at hospital discharge were observed in association with intravenous administration of amiodarone and lidocaine in comparison with placebo, but not when these drugs were administered intraosseously. A statistically significant interaction between the route of drug administration and outcome was not found. IO indicates intraosseous; IV, intravenous; and mRS, modified Rankin Scale.

outcomes between intravenous and intraosseous drugs such as epinephrine when administered to patients during OHCA.[6–8,27] None to date has specifically addressed the clinical use of intraosseous antiarrhythmic drugs during cardiac arrest, or in the context of a placebo control. As such, the observations that emerge from the present study have importance in adding new knowledge and potential concerns about the equivalence of intraosseous in comparison with intravenous access in patients with OHCA and whether drug effectiveness could be also affected by the choice of vascular access.[7]

The parent trial (ALPS) from which this predesignated analysis was drawn found no significant improvement in survival between amiodarone or lidocaine and placebo in its overall population of randomly assigned patients (composed of intravenous and intraosseous drug recipients).[1] As a result, there is waning enthusiasm in the resuscitation community for the use of these drugs altogether in cardiac arrest on the basis of this negative trial. Findings from the current study differentiated the potential effects of these drugs depending on how they were given during the parent trial. Such stratification demonstrated a significant improvement in survival over placebo associated with intravenous administration of amiodarone or lidocaine (resulting in an absolute improvement in survival of 5.5% and 4.7%, corresponding to risk ratios of 1.26 and 1.21, respectively). This survival benefit might have been offset by the null association when these medications were given intraosseously, producing a smaller and statistically insignificant net survival difference in the combined population of treated patients.[1] From this perspective, the actual life-saving potential of amiodarone and lidocaine may have been concealed by the manner in which they were administered in the parent trial and potentially correctable in clinical practice.

Mechanisms

The relationship between the effectiveness of a drug and its route of administration is complex. If the differences in outcome observed in the present study are actual, it is possible that intraosseous drug administration may be attenuated by local absorption related to the physical and chemical characteristics of the agent. For example, lidocaine is well recognized as an effective

local anesthetic and is commonly used to minimize pain during intraosseous drug administration,[28] suggesting some degree of local absorption of the drug in the periosteum, whereas amiodarone, being more lipophilic,[29] would be expected to be even more highly absorbed in fatty marrow. A reduction in drug dose resulting from such absorption when given intraosseously might be manifested in an attenuated antiarrhythmic drug effect in comparison with intravenous administration. Even if attenuated differentially by periosteum or marrow absorption, the net effect was nonetheless sufficient to mitigate the apparent effectiveness of both drugs by comparison with placebo when given intraosseously.

Alternatively, the anatomic site of administration (upper versus lower body) could itself play a role in a drug's effective delivery to the heart during active CPR, independent of whether it is given intravenously or intraosseously. Experimental work has shown drugs that achieve a delayed time-to-peak, and lower peak concentrations in the heart, as well, when given via an intravenous route that reaches the heart via the inferior vena cava rather than the superior vena cava during active CPR.[30] These pharmacokinetic differences were also seen in an animal model of cardiac arrest when epinephrine was given by tibial intraosseous access in comparison with a peripheral intravenous route, but not when comparing humeral intraosseous administration with peripheral intravenous administration.[31] This phenomenon, which is not observed during spontaneous circulation, may be attributable to the presence of venous valves in the region of the superior vena cava as contrasted with their absence in the inferior vena cava. Closure of these valves in response to the high intrathoracic pressures achieved during the compression phase of CPR can minimize regurgitant blood flow that might otherwise oppose venous blood return and drug delivery from upper extremity veins draining to the heart via the superior vena cava during CPR.[32] Such is not the case for lower extremity vessels draining to the heart via the inferior vena cava, where, lacking such valves, venous blood return and drug delivery to the heart can be impeded during CPR.[33] This phenomenon could explain the apparent effectiveness of intraosseous-administered drugs observed under normal circulatory conditions, in contrast to cardiac arrest with ongoing CPR. If true, the preferential selection of an upper extremity for drug administration (such as the proximal humerus or sternum when other intravenous access is not feasible) might address the possible limitations associated with a lower extremity site (such as the tibial intraosseous site) observed in this study during active CPR.[34,35] Other considerations might also apply. For example, blood flow to bone marrow (and other peripheral body compartments) may be diminished during circulatory shock or in response to vasopressors, requiring a fluid bolus and continuously pressurized infusion to facilitate egress of an intraosseous-administered drug into the central circulation during CPR.[36] Unrecognized misplacement of the intraosseous access device could have also contributed to poor drug delivery by this route. Such factors, whether alone or taken in combination, could potentially account for the attenuated clinical effects associated with receipt of an active antiarrhythmic drug intraosseously that were observed in this study.

These potential mechanisms, while speculative, lend biological support and plausibility to the findings from this and previous cited studies as to whether and why differences in outcome might be expected between intravenous and intraosseous drug administration during ongoing CPR.

Limitations

The study results are consistent across primary and secondary outcomes with the study's a priori hypothesis, but should be interpreted cautiously. Although prespecified and derived from a blinded, placebo-controlled trial of antiarrhythmic drug treatment, the route of drug administration was not randomized, and a small proportion of patients had incomplete data. Thus, unmeasured confounders could also explain the results. The study was not designed or sufficiently powered to detect interactions and none were found, rendering an effect modification attributable to the intravenous versus intraosseous route of drug administration inconclusive. There are nonetheless valid reasons to consider an association between access route and clinical outcome, apart from risk of a type II (false negative) error attributable to an underpowered study that might have obscured a true interaction. Among these, the analysis itself was prespecified, its findings are biologically plausible, supported by other work challenging the efficacy of intraosseous drug administration, and were consistent across multiple predesignated outcomes for 2 different drugs in both unadjusted and adjusted analyses. The evaluation was also conducted in the context of a placebo control. The resulting null association across all study end points when comparing the receipt of placebo by an intravenous versus intraosseous route also suggests that neither the underlying morbidity of the patient nor other factors that might have been involved in the site's selection rendered the access route itself a surrogate marker of outcome. Furthermore, although strengthening study findings, the presence of a significant statistical interaction would not obviate the need for their prospective confirmation.

The study also did not evaluate other aspects of drug delivery such as administration techniques (rapidity of study drug injection, whether accompanied by fluid boluses or a pressurized infusion), which may have differentially affected route-specific drug effects. Nor were there sufficient patients in tibial intraosseous versus humeral intraosseous treatment arms to test the mechanistic

hypothesis related to the location of vascular access proposed in this analysis. In addition, the commercially available formulation of amiodarone (branded Nexterone) used in ALPS is electrophysiologically identical to amiodarone, but differs from the more widely used generic product with regard to its solvent properties (Captisol versus polysorbate 80), which may have resulted in differing intravenous/intraosseous performance. These limitations should be balanced against the study's strengths, including its prespecified design, prospective data collection, multicenter performance, relatively large size, and unique inclusion of a placebo control in its assessment of intravenous versus intraosseous outcomes.

Implications

The findings from this study are observational and not clinically definitive, but they are nonetheless provocative. They suggest that amiodarone and lidocaine might each be life-saving drugs in patients with shock-refractory OHCA, although only when they are given intravenously. Confirmation of this hypothesis could have an important public health impact, if, as in the present study, it might be found to spare 1 additional life for every 20 patients treated for shock-refractory OHCA.

Conclusions

In this subgroup analysis of the ALPS trial, we found no significant effect modification by drug administration route for amiodarone or lidocaine in comparison with placebo. However, point estimates for the effects of both drugs in comparison with placebo were greater for the intravenous than intraosseous route for all outcomes in both unadjusted and adjusted analyses. This included a significant improvement in adjusted survival to hospital admission and survival to hospital discharge, and it favored an improved neurological outcome at hospital discharge, but only when these drugs were given intravenously. Given that the study was underpowered to statistically assess interactions, these findings signal the potential importance of the drug administration route during resuscitation and an opportunity to improve outcome from OHCA that merits further investigation.

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Correspondence

Peter J. Kudenchuk, MD, Division of Cardiology, Box 356422, University of Washington, 1959 NE Pacific St, Seattle, WA 98195-6422. Email kudenchu@u.washington.edu

Affiliations

Department of Emergency Medicine (M.R.D., J.R.L.) and Center for Policy and Research in Emergency Medicine, Department of Emergency Medicine (C.D.N.), Oregon Health & Science University, Portland. Department of Biostatistics, University of Washington Clinical Trial Center, Seattle (B.G.L.). Division of Cardiology (P.D.) and Rescu, Li Ka Shing Knowledge Institute (L.J.M.), St Michael's Hospital, University of Toronto, Canada. Department of Medicine (T.D.R.) and Department of Medicine, Division of Cardiology (P.J.K.), University of Washington, Seattle. Department of Emergency Medicine, University of Pittsburgh School of Medicine, PA (J.J.M.). Virginia Commonwealth University Health System, Richmond (J.P.O.). National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, MD (G.S.). Department of Emergency Medicine (J.C.), University of British Columbia, Vancouver, Canada (D.B.). Departments of Emergency Medicine and Internal Medicine (A.I.) and Division of Cardiology, Department of Internal Medicine (P.M.), UT Southwestern Medical Center, Dallas, TX. Department of Emergency Medicine, University of California San Diego (G.M.V.). Department of Emergency Medicine, Medical College of Wisconsin, Milwaukee (C.H.). Centre for Health Evaluation Outcome Sciences, St Paul's Hospital, Vancouver, Canada (D.B.).

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None.

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