Clinical paper

Trends in overdose-related out-of-hospital cardiac arrest in Arizona

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Abstract

Aim: Opioid overdose mortality has increased in North America; however, recent regional trends in the proportion of treated overdose-related out-of-hospital cardiac arrest (OD-OHCA) compared to out-of-hospital cardiac arrest of presumed cardiac etiology (C-OHCA) are largely unknown. Our aim is to assess trends in the prevalence and outcomes of OD-OHCAs compared to C-OHCAs in Arizona.

Methods: Statewide, observational study utilizing an Utstein-style database with EMS-first care reports linked with hospital records, and vital statistics data from 2010 to 2015.

Results: There were 21,658 OHCAs during the study period. After excluding non-C-OHCAs, non-OD-OHCAs, and cases missing outcome data, 18,562 cases remained. Of these remaining cases, 17,591 (94.8%) were C-OHCAs and 971 (5.2%) were OD-OHCAs. There was a significant increase in the proportion of OD-OHCAs from 2010, 4.7% (95% CI: 3.9–5.5) to 2015, 6.6% (95% CI: 5.8–7.5). Mean age for OD-OHCAs was 38 years compared to 66 years for C-OHCAs, (p < 0.0001). Initial shockable rhythm was present in 7.1% of OD-OHCAs vs. 22.6% of C-OHCAs (p < 0.0001). Overall survival to discharge in the OD-OHCA group was 18.6% vs. 11.9% in C-OHCA (p < 0.0001). After risk adjustment, we found an aOR of 2.1 (95% CI: 1.8-2.6) for survival in OD-OHCA compared to C-OHCA.

Conclusion: There has been a significant increase in the proportion of OD-OHCAs in Arizona between 2010–2015. OD-OHCA patients were younger, were less likely to present with a shockable rhythm, and more likely to survive than patients with C-OHCA. These data should be considered in prevention and treatment efforts.

Keywords: Overdose, OHCA, Out-of-hospital cardiac arrest, Cardiac arrest, OD-OHCA, Naloxone, Resuscitation, CPR, Compression-only CPR, Arizona, Epidemiology, Opioid, Overdose-related, BLS, ACLS

Introduction

Drug overdose is a growing epidemic and public health problem.[1] The increasing use of prescription drugs coupled with the availability of illicit heroin and fentanyl have made drug-related overdoses the leading cause of injury-related deaths in the US.[2] In 2016 there were an estimated 64,000 fatal drug overdoses and an additional 30 non-fatal overdoses for each fatal overdose.[2,3] While there are multiple drugs (e.g., cocaine, methamphetamines, alcohol, benzodiazepines,

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opioids, others) responsible for overdoses, it is estimated that opioids are responsible for 61% of all overdose deaths.[2,4–6] Between 2005 and 2014, the rate of opioid-related emergency department visits increased by 99.4% and heroin overdoses more than tripled from 2010 through 2014.[7] The scope of the problem warrants public health initiatives aimed at better understanding trends in overdose incidence, treatment, and outcomes to help develop more effective interventions for prevention and care.[1]

Despite the significance of this public health problem, there is a paucity of data describing the impact of opioids on out-of-hospital cardiac arrest (OHCA) rates. Previous studies have illustrated wide regional, gender, racial, and socioeconomic differences in the prevalence of overdose out-of-hospital cardiac arrests (OD-OHCAs), ranging between 2.0% and 29.4% of all OHCAs.[8–10] While opioid-related deaths have increased in North America, recent temporal and regional trends in the proportion of OD-OHCAs remain largely unknown. In this study, we used a statewide database to assess the latest trends in epidemiology and outcomes of OD-OHCAs compared to presumed cardiac etiology out-of-hospital cardiac arrests (C-OHCAs).

Methods

Study setting

Data for this study were from the Arizona Department of Health Service's, statewide, Utstein-style, OHCA database that links EMS-first care reports with hospital records and outcomes. Participating EMS agencies contribute to the Save Hearts in Arizona Registry and Education (SHARE) Program, a voluntary, statewide, cardiac resuscitation, quality improvement program that has been described in detail and encompasses more than 80% of the state's population.[11]

Study design and population

This was a retrospective, observational, cohort study of consecutive, adult (aged ≥18-years-old) OHCA patients in Arizona, between January 1, 2010 and December 31, 2015. Cases were excluded if prehospital resuscitation was not initiated, the patient had a do-not-resuscitate order, the cardiac arrest was witnessed by EMS providers, or if the cause of the cardiac arrest was presumed to be non-cardiac or non-overdose related (e.g., respiratory, trauma, or drowning). A detailed review of EMS reports, hospital records, and vital statistics data were used to determine whether subjects qualified for the overdose group. Our inclusion criteria were mention of likely overdose or drug involvement in EMS-first care reports, hospital charts, or vital statistics data. Primary outcomes were OD-OHCA proportion and survival to hospital discharge. Secondary measures included patient age, gender, location of cardiac arrest, bystander cardiopulmonary resuscitation (BCPR), and an initial shockable rhythm. Our analysis compared the prevalence, outcomes, and demographic data between OD-OHCA and C-OHCA cohorts.

Data collection

Data were collected from the SHARE program OHCA database which has been described previously.[11] As an Arizona Department of Health Services (ADHS)-sponsored public health initiative, Arizona's Attorney General determined that the SHARE Program is exempt from the requirements of the Health Insurance Portability and Accountability Act (HIPAA), allowing linkage of EMS and hospital data, tracking of OHCA events, and evaluation of efforts to improve resuscitation care. As a public health initiative, the ADHS Human Subjects Review Board and the University of Arizona Institutional Review Board (IRB) have determined that neither the interventions nor their evaluation constitute Human Subjects Research and have approved the publication of de-identified data. The SHARE Program is registered at clinical Trials.gov#NCT01999036.

Statistical analysis

To maximize the available subjects for analysis, multiple imputation was carried out in SAS (SAS, Version 9.4, SAS Institute, Cary, North Carolina) to impute missing data. Multiple imputation (MI) has been shown to generate less biased estimates with more statistical efficiency when compared with alternative methods of handling incomplete data (e.g., complete-case analysis, single imputation, or missing indicator regression).[12] MI involves three distinct phases: 1) the missing data are filled in m times to generate m complete datasets, 2) the m datasets are analyzed by using standard procedures, and 3) the results from the m complete datasets are combined for the inference. MI replaces each missing value with a set of plausible values that represent the uncertainty about the right value to impute, instead of filling in a single value for each missing value. We used all the variables in Tables 1 and 2 for MI. Twenty imputed datasets were generated and model fit and diagnostics were evaluated. Missing data fit an arbitrary missing pattern and we used the Fully Conditional Specification method to impute data. Linear regression was used to impute all continuous variables, age, and response time. Logistic regression was used to impute categorical variables, i.e., witnessed arrest, BCPR, shockable rhythm, and OCHA locations.

Descriptive statistics were used to describe the study population and are reported as proportion for categorical and binary data and as median and interquartile range for continuous data. All of the tests were two-tailed. A p-value of <0.05 was considered statistically significant. Multivariate logistic regression analysis was carried out using the imputed data, accounting for variance across imputed data sets using Rubin's rules (using Proc MI in SAS).[13]

Results

There were a total of 21,658 confirmed OHCAs during the study period. After excluding 2670 cardiac arrests without overdose or cardiac etiology and 426 cases with missing survival data, 18,562

Table 1 – Cardiac arrest cases, 2010–2015 (N = 18,562).

Incident year	Overdose etiology		Cardiac etiology	
	N	% (95% CI)	N	% (95% CI)
Overall	971	5.2%	17,591	94.8%
2010	121	4.7% (3.9–5.5)	2,435	95.3% (94.4–96.1)
2011	129	4.4% (3.7–5.2)	2,783	95.6% (94.8–96.3)
2012	125	4.2% (3.5–4.9)	2,844	95.8% (95.1–96.5)
2013	152	4.6% (3.9–5.4)	3,124	95.4% (94.6–96.1)
2014	208	6.3% (5.5–7.2)	3,082	93.7% (92.8–94.5)
2015	236	6.6% (5.8–7.5)	3,323	93.4% (92.5–94.2)

Table 2 – Epidemiology and demographics by cardiac arrest etiology.

	Overdose etiology (n = 971)	Cardiac etiology (n = 17,591)	p-value	Missing data	
				Overdose etiology	Cardiac etiology
Age (Median, Q1–Q3)	38 years (26–50)	66 years (54–78)	<0.0001	2 (0.2%)	55 (0.3%)
Gender (male)	63.7% (618)	64.7% (11,374)	0.5101	0	7 (0.04%)
Location (residential)	65.1% (632)	53.8% (9461)	<0.0001	0	0
Bystander-witnessed arrest	24.7% (187/757)	44.1% (6,295/14,267)	<0.0001	214 (22.04%)	3324 (18.9%)
Bystander CPR performed	49.6% (363/732)	48.4% (6,650/13,729)	0.5432	239 (24.6%)	3862 (22.0%)
Response time (Median, Q1–Q3)	5 min (4–7)	5 min (4–7)	0.7791	245 (25.2%)	3747 (21.3%)
Shockable rhythm	7.1% (69)	22.6% (3,971)	<0.0001	0	0
Survived	18.6% (181)	11.9% (2,097)	<0.0001	0	0

cases remained. Overall, 17,591 (94.8%) arrests were presumed C-OHCAs and 971 (5.2%) were OD-OHCAs (Fig. 1).

There was a significant increase in the proportion of OD-OHCAs between 2010, 4.7% (95% CI: 3.9–5.5) and 2015, 6.6% (95% CI: 5.8–7.5) (Table 1). The only statistically significant proportional increase of OD-OHCAs between two consecutive years was from 2013 (4.6%; 95% CI: 3.9–5.4) to 2014 (6.3%; 95% CI: 5.5–7.2) (Table 1).

Mean age for patients with OD-OHCA was 38 years compared to 66 years for C-OHCA (p < 0.0001) (Table 2). A residential location was more likely for OD-OHCA (65.1%) than C-OHCA (53.8%) (p < 0.0001) (Table 2). A bystander-witnessed cardiac arrest was less likely for OD-OHCA (24.7%) than C-OHCA (44.1%) (p < 0.0001) (Table 2). A shockable rhythm was present in 7.1% of OD-OHCAs vs. 22.6% for C-OHCAs (p < 0.0001) (Table 2). There were no statistically significant differences for patient gender, for whether bystanders performed CPR, or for EMS response times for patients with OD-OHCA vs. C-OHCA (Table 2). Overall survival to discharge in the OD-OHCA group was 18.6% vs. 11.9% in the C-OHCA group (p < 0.0001) (Table 2). After risk adjustment for age, gender, bystander-witnessed arrest, BCPR, EMS response time, and shockable rhythm, we found an aOR of 2.1 (1.8–2.6) for survival in the OD-OHCA group compared to the C-OHCA group.

Discussion

This is the first statewide study that we are aware of analyzing OD-OHCA in the United States. In addition, this is the first retrospective study to demonstrate a significant increase in the proportion of OD-OHCAs over the recent study period. In Arizona, as demonstrated in Table 1, there was a significant increase in the proportion of OD-OHCAs between 2013 (4.6%; 95% CI: 3.9–5.4%) and 2014 (6.3%; 95% CI: 5.5–7.2). North American overdose data, in contrast, have shown gradual growth during the years of this study.[2] There have
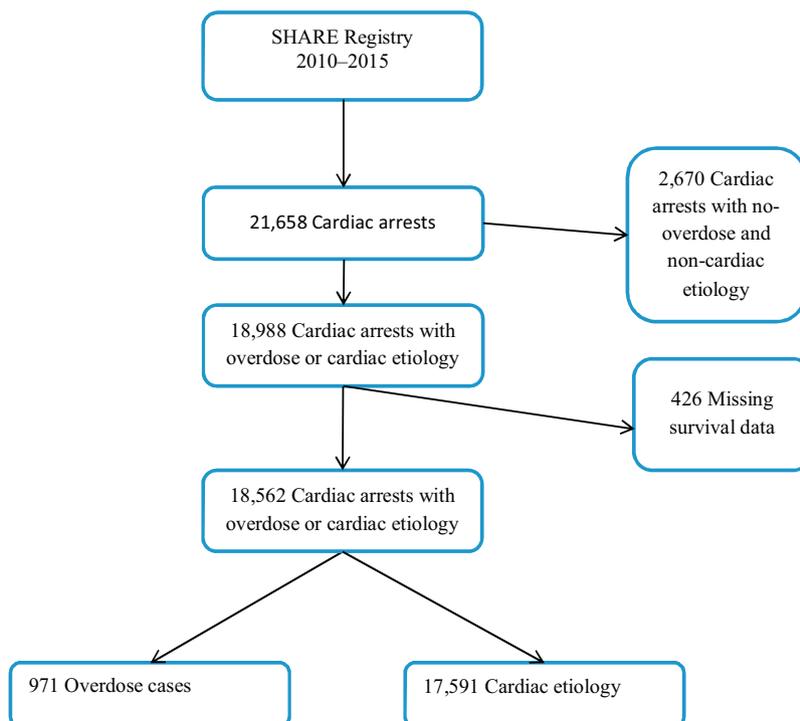
Fig. 1 – Subject Inclusion Flow Diagram.

been large-scale opioid mitigation efforts in Arizona which started after the data collection period for this study.[14] The cause(s) of the significant statewide increase in OD-OHCAs between 2013 and 2014 is unclear and underscores the importance of monitoring OD-OHCA trends locally, regionally, and statewide as there is wide variability.

Previous studies have shown wide-ranging proportions of OHCA attributed to overdose.[8,9,10] In a Resuscitation Outcomes Consortium (ROC) study, Salcido et al. published data from multiple geographic regions across North America and demonstrated 2.4% of OHCAs from 2006 to 2010 were caused by overdoses with a geographical range in incidence from 0.5 to 2.7 per 100,000 person years.[10] They noted the incidence of OD-OHCA varied significantly across North America, similar to the variability exhibited by cardiac-etiology OHCA. Additionally, differences in OD-OHCA prevalence in single-population studies, such as Koller et al., in the Pittsburgh area and Orkin, et al., in Ontario, suggest large geographic variability [8,9].

In addition to geographic variation, the differing OD-OHCA estimates may, in part, be related to differing methods of case ascertainment. For example, documented naloxone administration has been used in several studies as an inclusion criterion for OD-OHCA.[8,9,10,15] It has been estimated that this may not be a sensitive method of calculating the number of OD-OHCA victims because many who are given naloxone by EMS have not overdosed and administration was not recommended for OHCA during some study periods.[8,16,17] To avoid this possible inclusion bias, we chose not to use naloxone administration, but instead to search EMS reports, hospital records, and vital statistics data for any mention of likely overdose or drug involvement. With the exception of Orkin, et al., the majority of other studies used only EMS data.[8,9,10,15] We believe using both hospital and EMS databases increase the accuracy of etiology designation.

Previous epidemiological studies of OD-OHCA have similarly shown younger median ages and increased survival rates of patients with OD-OHCA vs. C-OHCA.[18,19] A study by Elmer, et al. reported patients in the OD-OHCA subgroup were significantly younger, had fewer comorbidities, and were more likely to present with a non-shockable rhythm.[15] Our patient outcomes were consistent with literature showing that OD-OHCA victims are significantly more likely to survive than C-OHCA victims despite presenting with decreased rates of shockable rhythms.[9,10] This suggests there may be an increased survivability of OD-OHCA vs. C-OHCA based on available treatments, younger age, fewer comorbidities, or other factors that were not measured. Studies have hypothesized the pathophysiology of OD-OHCA to be primarily due to respiratory depression which can potentially be mitigated with appropriate and timely airway management, oxygenation, and naloxone administration.

When there is suspicion that a cardiac arrest is due to an opioid overdose, patients are often empirically treated with intravenous naloxone, a complete opioid antagonist with a rapid onset of action.[20-22] Nasal naloxone is becoming more readily available to bystanders and its use is especially common among first responders.[23,24] In addition to naloxone's therapeutic effect on hypoventilation, some studies have demonstrated naloxone has antiarrhythmic activity similar to both class I and III antiarrhythmic medications in guinea pig, canine, rabbit, and sheep in-vitro myocardia.[25,26] A study by Saybolt, et al. could not firmly determine causality between naloxone and successfully treating human arrhythmias; however, they supported its use in suspected OD-OHCA, citing its low risk and potential benefit.[21] Additionally, the 2015 American Heart Association (AHA) CPR guidelines recommend use of naloxone in any case of suspected opioid toxicity.[27] While naloxone may play a role in the positive outcomes from OD-OHCA, high quality CPR remains the foundation of treating OD-OHCA.[27]

Limitations

This is a retrospective, observational, resuscitation study with its inherent limitations. It is possible our results using Arizona data may not be generalizable to other regions. Additionally, we had a significant amount of missing data due to the challenges of matching prehospital with hospital data (Table 2). We elected to include hospital data because it allowed for more accurate determination of cardiac arrest etiology. We used multiple imputation to minimize any bias that might have arisen from missing data. Despite our efforts to be as accurate as possible, it is possible that some arrests were inaccurately categorized. We were not able to determine whether an overdose was intentional and this may be the subject of further investigations. Additionally, there may be novel therapies which could impact OD-OHCA outcomes (e.g., ECMO, IV intralipid emulsification) and this data was not collected. Finally, the structure of the AZ-SHARE project limits patient-specific data available for analysis. Therefore, our analyses lack some details regarding medical history and we did not have access to toxicological data confirming the class of drug implicated in the OD. However, the published literature points to opioids as the most common cause of fatal overdose in the United States.[7] Linking specific drugs to OD-OHCA victims warrants further study.

Conclusions

This statewide study found a significant increase in the proportion of OD-OHCAs from 2010–2015. Patients with OD-OHCAs were younger, more likely to arrest in residential locations, less likely to present with shockable rhythms, and more likely to survive. Tracking trends in local OD-OHCA prevalence and outcomes may provide opportunities for prevention strategies, such as dispensing naloxone to opioid users and their families and friends to administer in their homes, and guiding future resuscitation efforts, such as pursuing aggressive resuscitation in spite of initial non-shockable rhythms in patients with likely OD-OHCA.

Conflicts of interest statement

None.

Acknowledgments

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