



Clinical Paper

Recreational drug overdose-related cardiac arrests: Break on through to the other side[☆]

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ABSTRACT

Introduction: The annual rate of recreational overdose (OD)-related death is increasing exponentially, making unintentional overdose the leading cause of injury-related death in America. Unfortunately, little attention in the resuscitation community has focused on the post-arrest care of this rapidly growing population.

Methods: We included patients presenting between January 2009 and February 2014 after out-of-hospital cardiac arrest (OHCA) and abstracted baseline clinical characteristics and neurological outcomes. We considered an arrest to be an OD OHCA if toxicology screens were positive and not explained by therapeutic medication administration or home medications; or if there was a history strongly suggestive of OD. We compared the baseline clinical characteristics and outcomes between the OD and non-OD cohorts.

Results: In total, 591 OHCA patients were admitted, of which 85 (14%) arrests were OD-related. OD OHCA patients were significantly younger, had fewer medical comorbidities, were more likely to present with non-shockable rhythms and had worse baseline neurological function. However, overall survival, neurological outcomes and length of stay did not vary between groups. OD OHCA patients who survived to discharge had a significantly higher rate of favorable discharge dispositions (83% of OD OHCA survivors discharged to home or acute rehabilitation vs 62% of non-OD OHCA ($P = 0.03$)).

Conclusion: Patients who have suffered an OD OHCA make up a significant proportion of the overall OHCA population. Despite poor baseline prognostic factors, survival after OD OHCA was no worse than after non-OD OHCA, and among survivors a majority had a good neurological outcome.

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1. Introduction

Recently, considerable media and public health attention has focused on what has been termed an “epidemic” of unintentional recreational drug overdose-related deaths in the United States.^{1–3} The annualized rate of overdose-related death is increasing exponentially, making unintentional overdose the leading cause of

injury-related death in America.³ Respiratory depression leading to asphyxial cardiac arrest is the final common pathway of a majority of these deaths, especially after overdoses of opioids and/or sedative-hypnotic agents such as benzodiazepines. Indeed, drug overdoses make up between 2 and 29.4% of out-of-hospital cardiac arrests (OHCA), and are particularly common in young adults.^{4–7}

Despite its public health significance, little attention in the resuscitation community has focused on the post-arrest management of this rapidly growing population. In the pre-hospital setting, physicians and emergency medical service (EMS) providers perceive and manage overdose-related OHCA due to common drugs of abuse (OD OHCA) differently than other arrest etiologies, despite the absence of evidence or consensus recommendations.^{5,8} However, to our knowledge, no studies have specifically examined the cohort of OD OHCA patients that are resuscitated and survive to hospital admission.

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We describe the clinical characteristics and outcomes of patients successfully resuscitated from OD OHCA who survived to hospital admission. We hypothesized that this population would be demographically distinct from patients admitted after non-OD OHCA, and that patient outcomes would differ between these groups.

2. Methods

UPMC Presbyterian Hospital is a 795-bed tertiary care referral center. Since 2007, a unique Post-Cardiac Arrest Service (PCAS) has standardized care for the more than 200 patients annually who are successfully resuscitated and admitted after cardiac arrest, and maintains a prospective database including all patients.⁹ The present study is a retrospective, observational cohort study including patients who presented between January 1, 2009 and February 12, 2014 after OHCA. We excluded patients for age under 18 years, in-hospital cardiac arrest, or uncertain location of arrest. We further excluded patients OHCA secondary to blunt or penetrating trauma, stroke or subarachnoid hemorrhage. The University of Pittsburgh Institutional Review Board deemed review of the database to be exempt from need for informed consent.

Our primary exposure of interest was OD OHCA in which the overdose was related to commonly abused drugs. We performed a structured chart review of all emergency department (ED) and inpatient admission notes, electronic medication administration record, and EMS trip sheets. We recorded the results of all serum and urine toxicology screens, ED or EMS administration of opiates and benzodiazepines, and historical details indicative of OD OHCA (i.e. found with drug paraphernalia or witnessed overdose). We considered an arrest to be overdose-related if toxicology screens were positive and not explained by therapeutic medication administration prior to sampling or home medication history; or if there was a documented history strongly suggestive of overdose. We did not consider arrests to be overdose-related when the only positive toxicology results were cannabis and/or ethanol, or if there was a clearly defined alternative etiology (e.g. strangulation or witnessed arrest during outpatient hemodialysis).

We abstracted baseline clinical characteristics from our registry, including age, sex, initial arrest rhythm (ventricular tachycardia/fibrillation (VT/VF), pulseless electrical activity (PEA), asystole, or unknown), bystander-administered cardiopulmonary resuscitation (CPR), Charlson Comorbidity Index, initial Glasgow Coma Scale score (GCS), use of mild therapeutic hypothermia, cardiac catheterization, and Pittsburgh Cardiac Arrest Category (PCAC). The PCAC is a validated clinical prediction tool that stratifies CA survivors by their risk of subsequent death or neurological deterioration based on clinical characteristics during the first 6 h after ROSC.¹⁰ The tool stratifies survivors of CA into four categories that are strongly predictive of survival and functional outcome. In the subgroup of patients for whom the results of continuous electroencephalography (EEG) monitoring were available from previous work, we abstracted the presence (yes/no) of a suppression-burst pattern, generalized periodic epileptiform discharges, myoclonic status epilepticus, nonconvulsive status epilepticus, and reactivity in the first 72 h of monitoring.¹¹

We also abstracted patient outcomes from our registry, including survival to hospital discharge, hospital length of stay, Cerebral Performance Category at hospital discharge, favorable discharge disposition (home or acute rehabilitation), and mode of death (brain death; withdrawal for poor anticipated neurological prognosis; re-arrest or refractory hemodynamic instability; or withdrawal based on surrogate representation of the patient's goals of care). We included multiple measures of outcome as they measure different components of recovery.¹²

We used descriptive statistics to summarize baseline characteristics and outcomes, and report means with standard deviations

for continuous variables and numbers with corresponding percentages for categorical variables. We used *t*-tests or Chi-Square tests as appropriate to compare the cohort of OD OHCA patients to the cohort of non-OD OHCA. Finally, we constructed an adjusted logistic regression model to test for an independent association of OD OHCA with survival after controlling for potential confounders. We forced OD OHCA into the model, and included other predictors with an unadjusted association with overdose status. We excluded GCS from this model because it is collinear with PCAC. We used Stata Version 13.1 (StataCorp, College Station, TX) for all analyses.

3. Results

A total of 591 OHCA patients were admitted during the study period. There were 183 subjects with positive toxicology screens. Of these, 50 had received opioids or benzodiazepines by emergency providers prior to the toxicology screen, 15 had insufficient pre-hospital documentation to determine if opioids or benzodiazepines had been administered, 17 toxicology screens were positive only for ethanol or cannabis, and 16 had a clearly defined non-toxicologic etiology of arrest. Thus, 85 (14%) arrests were deemed to be recreational drug overdose-related. OD OHCA patients were significantly younger, had fewer medical comorbidities, were more likely to present with non-shockable rhythms, had worse baseline GCS and PCAC scores, and were less likely to undergo cardiac catheterization (Table 1). The most common agents identified on toxicology screens were opiates and benzodiazepines (Table 2), and the median number of positive results in the OD OHCA subgroup was 2 (interquartile range 1–3). Coingestion of opiates and benzodiazepines was common (35 patients (41%) of all overdoses). Only two patients (2%) in the OD OHCA cohort had isolated stimulant (cocaine and/or amphetamine) intoxication, while the remainder had toxicology screens that were also positive for benzodiazepines and/or opioids. Among OD OHCA patients, 40 (47%) received naloxone and naloxone use was not associated with survival ($P=0.54$).

Continuous electroencephalographic data were available for 241 patients (33 overdose-related (39%) and 208 non-overdose (41%)). There was no difference in the incidence of various patterns between groups (Table 3). Overall survival, neurological outcome and length of stay did not vary between groups (Table 4), and OD OHCA was not independently associated with mortality in adjusted analysis (Table 5). However, OD OHCA patients who survived to discharge had a significantly higher rate of favorable discharge dispositions (83% of OD OHCA survivors discharged to home or acute rehabilitation vs 62% of non-OD OHCA ($P=0.03$)). Among those who did not survive to discharge, brain death accounted for 34% of deaths in the OD OHCA cohort compared to 12% in the non-OD OHCA cohort ($P=0.002$).

4. Discussion

We report the demographics and outcomes of patients admitted after OD OHCA. Consistent with previous reports, OD OHCA was common, comprising 14% of our total OHCA population.^{4–7} Importantly, despite a higher incidence of non-shockable arrest rhythm and deeper coma on presentation, survival after OD OHCA was no worse than after non-OD OHCA. Moreover, among survivors, 83% were discharged to home or acute rehabilitation. This suggests that despite the high incidence of poor baseline prognostic features after return of spontaneous circulation (ROSC), OD OHCA patients may have excellent neurological recoveries and warrant aggressive neurocritical care. Some patients required initial specialized toxicologic interventions such as antidotal therapy, treatment of sodium channel blockade and recurrent ventricular dysrhythmia, or seizures/agitation. However, the mainstay of

Table 1

Comparison of baseline characteristics between overdose and non-overdose out-of-hospital cardiac arrests.

Characteristic	Non-overdose (<i>n</i> = 506)	Overdose (<i>n</i> = 85)	<i>P</i> value
Age, years	50 ± 16	39 ± 13	<0.001
Male sex	291 (58)	41 (48)	0.11
Presenting rhythm			
VT/VF	214 (43)	18 (21)	<0.001
PEA	131 (26)	18 (21)	
Asystole	116 (23)	32 (38)	
Unknown	45 (9)	17 (20)	
Bystander CPR	115 (50)	21 (60)	0.28
CCI	1.5 ± 1.8	0.35 ± 0.72	<0.001
Age-adjusted CCI	2.6 ± 2.2	0.54 ± 1.0	<0.001
Pittsburgh Cardiac Arrest Category			
I	94 (20)	6 (8)	0.003
II	117 (25)	11 (14)	
III	37 (8)	9 (12)	
IV	227 (48)	51 (66)	
Glasgow Coma Scale score			
3–4	232 (51)	53 (68)	0.04
5–8	146 (32)	20 (26)	
9–13	146 (29)	20 (24)	
14–15	28 (6)	2 (2)	
Missing	48 (9)	7 (8)	
Therapeutic hypothermia	353 (70)	58 (68)	0.89
Cardiac catheterization	176 (35)	16 (19)	0.007

Data are presented as number with corresponding percentage or mean ± standard deviation.

Abbreviations: VT/VF – Ventricular tachycardia/fibrillation; CPR – Cardiopulmonary resuscitation; CCI – Charlson Comorbidity Index.

treatment of the poisoned patient following ROSC is provision of aggressive, protocolized supportive care with specific focus on systemic and cerebral perfusion, adequate oxygenation and ventilation, and prevention and management of secondary injury such as rhabdomyolysis and aspiration. As many of these patients were previously young and healthy, once the initial toxicity is adequately managed and the subsequent hypoperfusion injury resolved, meaningful recovery is common.

Beyond the clinical significance of our findings, these results have important research implications. Many recent and ongoing multicenter clinical trials of OHCA have excluded patients with suspected overdose.^{13–15} In part, this may be due to the perception

among researchers that there is a low probability of survival or functional outcome after OHCA from etiologies that are not “presumed cardiac.” Given the rapidly growing incidence of OD related deaths, exclusion of these patients from clinical trials may adversely impact patient enrollment and will limit our ability to translate knowledge from these trials to this large patient population.

Several factors may help explain the discrepancy between the prevalence of poor baseline prognostic factors and comparable survival after OD OHCA. Although it lacks sufficient sensitivity and specificity to allow definitive neurological prognostication, depth of coma after ROSC is strongly associated with patient outcomes.¹⁰ In the case of OD OHCA, the initial neurologic examination may be confounded by the presence of central nervous system (CNS)

Table 2

The rate of positive toxicology screen results among overdose cardiac arrests, stratified by agent.

Substance	Positive results(<i>n</i> = 83)
Serum – <i>n</i> (%)	
Ethanol	12 (15)
Acetaminophen	8 (10)
Salicylate	6 (7)
Tricyclic antidepressants	5 (6)
Urine – <i>n</i> (%)	
Opiates	48 (58)
Benzodiazepines	46 (55)
Both opiates and benzodiazepines	41 (49)
Cocaine	17 (20)
Methadone	11 (20)
Marijuana	9 (10)
Amphetamines	5 (6)
Barbiturates	2 (2)

Data are presented as number with corresponding percentage.

Table 3

Continuous electroencephalography results from the first 72 h of monitoring for overdose and non-overdose out-of-hospital cardiac arrest patients.

Electroencephalogram pattern	Non-overdose (<i>n</i> = 208)	Overdose (<i>n</i> = 33)	<i>P</i> value
Suppression-burst	109 (52)	15 (45)	0.29
Myoclonic status epilepticus	44 (21)	5 (15)	0.30
Non-convulsive status epilepticus	19 (9)	2 (6)	0.43
Generalized periodic epileptiform discharges	48 (23)	6 (18)	0.35
Epileptiform discharges	55 (26)	6 (18)	0.22
Reactivity	48 (23)	8 (24)	0.52

Data are presented as number with corresponding percentage.

Table 4

Comparison of outcomes between overdose and non-overdose out-of-hospital cardiac arrests.

Outcome	Non-overdose (n = 506)	Overdose (n = 85)	P value
Survival	195 (40)	31 (38)	0.65
Length of stay, days	11 ± 13	10 ± 12	0.90
Survivors	17 ± 14	20 ± 15	
Nonsurvivors	5 ± 9	4 ± 3	
Cerebral performance category			0.51
1–2	79 (17)	11 (13)	
3–5	383 (83)	67 (87)	
Discharge disposition (% of survivors)			0.03
Home/Acute rehabilitation	115 (62)	24 (83)	
Subacute rehabilitation /LTAC/Hospice	72 (39)	5 (17)	
Mode of death (% of nonsurvivors)			0.002
Brain death	23 (12)	15 (34)	
Poor neurologic prognosis	129 (66)	20 (46)	
Unstable/re-arrest	37 (19)	9 (20)	
Surrogate representation of wishes	6 (3)	0 (0)	

Data are presented as number with corresponding percentage or mean ± standard deviation.

Abbreviations: LTAC – Long-term acute care facility.

Table 5

Adjusted odds of survival after out-of-hospital cardiac arrest.

Predictor	Odds ratio (95% CI)	P value
Overdose arrest	1.21 (0.53–2.79)	0.66
Age (per year)	0.98 (0.96–1.01)	0.13
Presenting rhythm		
VT/VF	Ref	
PEA/Asystole	0.58 (0.31–1.07)	0.08
Unknown	1.05 (0.40–2.76)	0.91
Age-adjusted CCI	1.07 (0.89–1.28)	0.49
Pittsburgh Cardiac Arrest Category	0.30 (0.24–0.38)	<0.001
Cardiac catheterization	3.15 (1.73–5.74)	<0.001

Abbreviations: VT/VF – ventricular tachycardia/fibrillation; CPR – cardiopulmonary resuscitation; CCI – Charlson Comorbidity Index.

depressants. Our cohort of OD OHCA patients was enriched for those with a GCS of 3–4 and PCAC of IV (corresponding to a Full Outline of UnResponsiveness (FOUR) brainstem + motor subscores <4, i.e. deep coma).¹⁶ In the original cohort, OD-OHCA were excluded from PCAC determination.¹⁰ We did not observe any increase in the incidence of suppression-burst pattern on EEG in the OD OHCA cohort, which would have supported the idea of drug-induced CNS depression. However, this does not exclude the possibility of a confounded neurological examination, particularly in the context of concomitant anoxic brain injury. Pre-hospital EMS practices may also bias our OD OHCA cohort for favorable outcomes. In a large, retrospective review of OHCA in Melbourne, Australia, Deasy et al. reported that compared to presumed-cardiac etiology OHCA, EMS is less likely to initiate resuscitation of OD OHCA; however, OD OHCA victims were more likely to be resuscitated than other non-cardiac etiologies (trauma, hanging and other).⁵ Selection bias at the time of initiation of resuscitation may enrich the population that survives to hospital admission for potentially salvageable patients.

Another important factor that may have improved outcomes in the OD OHCA cohort compared to what otherwise might have been expected is a decrease in the rate of withdrawal of life-sustaining therapy based on anticipated neurological prognosis. Despite the well-recognized challenges of accurate neurological prognostication after cardiac arrest,^{17–20} withdrawal based on perceived neurological injury is the most common mode of death after OHCA.²¹ Despite the apparently more severe initial brain

injury judged by neurological examination, the length of stay did not differ between OD OHCA and non-OD OHCA cohorts, perhaps demonstrating reluctance by providers to withdraw life-sustaining therapy in the OD OHCA cohort. This may be due to their younger age or concern for an inaccurate neurological assessment in the presence of CNS depressants which may protect these patients from excess mortality related to early limitations in care.

An intriguing possibility is that arrest in the context of antecedent use of opioids or benzodiazepines may actually protect the brain from anoxic injury, either by decreasing the cerebral metabolic oxygen demand or through direct neuroprotective mechanisms. Animal models of cardiac arrest or anoxic brain injury have supported the concept of neuroprotection by benzodiazepines²² and opioid agonists.^{23,24} In humans, observational data have associated opioid use immediately before or during CPR with improved survival from in-hospital cardiac arrest.²⁵ In vivo rat data further suggest that benzodiazepines may be protective in a brain injury model through: (1) inhibition of excitotoxicity resulting from N-methyl-D-aspartate (NMDA)-mediated intracellular calcium influx, (2) hyperpolarization through enhanced chloride influx, and (3) prevention of mitochondrial apoptotic mediator release.²¹ In that model, intracellular calcium was felt to alter GABA receptor subunit expression and conformation thereby diminishing sensitivity to endogenous GABA agonists and potentiating progressive cellular injury. De facto “pretreatment” with benzodiazepines may therefore be neuroprotective in this subset of patients, particularly as it relates to neurologic outcomes in survivors without affecting cardiovascular survival. This proposed mechanism also suggests potential protective benefit of NMDA receptor antagonist properties present in many drugs of abuse. Traditional concern has been for elevation in intracranial pressure, however use of the NMDA antagonist ketamine has been associated with similar ICP effects as opioids when used for sedation in patients with intracranial pathology.²² Finally, opioid agonists, while contributing to sedation and potentially diminished cerebral oxygen demand, may also contribute to cerebral cellular preservation via δ -opioid receptor associated reduction in the kinases ERK1 and ERK2 and TNF- α inflammatory mediator activity and production.²³ Opioid agonist effects at receptors other than the well-studied μ -receptor may have neuroprotective applications as further evidence is elucidated.

We acknowledge several important limitations of our work. Like all observation studies, we are able to report associations but cannot comment on causality. While we performed a comprehensive chart review of both EMS and hospital records, we may have inappropriately coded patients as OD OHCA or non-OD OHCA. Our heavy reliance on the decision by medical providers to obtain a toxicology screen, potential unreliability of these screens and limitation of these screens to common drugs of abuse may well have contributed to misallocation of subjects. Furthermore, our cohort of OD OHCA patients was not large enough to allow meaningful subgroup analyses, for example by type of ingestion, or to report secular trends. Moreover, grouping into a single exposure variable ODs from stimulants, sedative/hypnotics, and agents such as salicylates or tricyclic antidepressants that are not used recreationally, may oversimplify a heterogeneous exposure and patient population. The pharmacologic profiles of these agents differ considerably, as do the patients that were exposed (e.g. recreational drug users compared to patients who have intentionally overdosed). We grouped these patients together to avoid multiple hypothesis testing and to preserve our sample size, and because “OD” has been treated as a single exposure variable in previous research studies or as an exclusion criterion for OHCA research. Another potential limitation is the fact that we chose to omit several traditional Utstein-style covariates such as resuscitation intervals or witnessed arrest since we have previously found these parameters to be inconsistently and inaccurately reported in our system.²⁶ By contrast, we were able to control for a range of patient and treatment factors not traditionally captured by prehospital databases. These differences in available covariates may help explain why our results differ from those reported in our prior work, where OD OHCA was independently associated with improved survival.⁴

5. Conclusion

Patients who have suffered an OD OHCA make up a significant proportion of the overall OHCA population. Despite an increased incidence of poor baseline prognostic factors, survival after OD OHCA was no worse than after non-OD OHCA, and among survivors a large majority had a good neurological outcome. Patients admitted after OD OHCA warrant aggressive care. Furthermore, unnecessary exclusion of OD OHCA patients from clinical trials may both adversely impact patient enrollment and limit our understanding of this important population.

Conflict of interest statement

None.

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Appendix A. The Pittsburgh Post-Cardiac Arrest Service investigators

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