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Clinical paper

Differential outcomes following successful resuscitation in cardiac arrest due to drug overdose

Cora H. Ormseth[a,1], Carolina B. Maciel[a,b,1], Sonya E. Zhou[a], Mary M. Barden[a], Laura C. Miyares[a], Rachel B. Beekman[a], Emily J. Gilmore[a], David M. Greer[c,*]

[a] Division of Neurocritical Care and Emergency Neurology, Department of Neurology, Yale School of Medicine, 15 York Street, New Haven CT, USA

[b] Division of Neurocritical Care and Vascular Neurology, Department of Neurology, University of Florida College of Medicine, 2000 Southwest Archer Road, Gainesville FL, USA

[c] Department of Neurology, Boston University School of Medicine, 75 East Newton Street, Boston MA 02118, USA

Abstract

Background: Data pertaining to clinical characteristics and outcomes of cardiac arrest (CA) due to drug overdose (ODCA) are limited. We hypothesized that patients with ODCA would have binary outcomes (brain death or functional recovery) compared to patients in whom CA was due to another etiology.

Methods: We performed a retrospective analysis of CA cases from a single academic institution from 2012 to 2017. ODCA cases were ascertained by admission notes strongly suggestive of OD or positive toxicology screens not explained by medication administration. Clinical characteristics and outcomes were extracted from medical records, and regression modeling was used to compare ODCA and non-ODCA patients.

Results: Of the 300 CA cases in this analysis, 28 (9%) were attributed to drug overdose, with opioids accounting for 54%. ODCA patients were younger, had fewer comorbidities, were less likely to have witnessed arrests or bystander cardiopulmonary resuscitation, and had longer downtimes. Inpatient mortality did not differ between cohorts (79% ODCA, 73% non-ODCA, $p = 0.66$), but ODCA was associated with higher rates of brain death (43%, 6%, $p < 0.001$). Of patients who survived to discharge, there was no difference in the likelihood of favorable neurological recovery, defined as Cerebral Performance Category score of 1–2 (7%, 7%, $p = 1.00$) or modified Rankin Scale score of 0–3 (7%, 9%, $p = 1.00$).

Conclusions: Despite similar neurological recovery and survival rates to hospital discharge, ODCA patients were more likely than non-ODCA patients to progress to brain death. Larger prospective studies analyzing ODCA are needed to better understand potential treatment options and prognostic tools in this cohort.

Keywords: Drug overdose, Overdose, Opioids, Brain death

Introduction

Deaths from drug overdose have reached epidemic proportions in the U.S. The number of overdose deaths tripled from 1999 to 2015, largely driven by opioid-related overdosing.[1] In 2016, 1 in 65 deaths in the U. S. were opioid-related[2] and the number of individuals lost to overdose increased by 22% from the year prior.[3] Among individuals aged 25 to 34, the population with the greatest increase in opioid fatalities, 1 in 5 deaths are opioid-related.[2] As a result of fatalities in otherwise young and healthy individuals,[4] there has been a 24-fold increase in organ donation from 2000 to 2016.[5]

A common cause of morbidity and mortality in drug overdose is cardiac arrest (CA) from respiratory suppression and progressive hypoxia. Compared to CA from other etiologies, cardiac arrest from drug overdose (ODCA) patients are generally younger and have fewer

* Corresponding author.
E-mail address: dgreer@bu.edu (D.M. Greer).
[1] These authors contributed equally to the manuscript.
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comorbidities.[6] The neuroprotective effects of central nervous system depressants[7] or of hypercarbia[8] may increase their likelihood of favorable neurological recovery. However, in the setting of drug use, their arrests are less likely to be witnessed, less likely to receive bystander cardiopulmonary resuscitation (CPR), have shockable rhythms, or be transported to the hospital.[9–11] Thus, ODCA patients may suffer a greater magnitude of anoxic injury due to prolonged downtimes (low perfusion and no perfusion states), and are more likely to be exposed to prolonged hypercarbia from respiratory depressants.

For these reasons, we hypothesized that ODCA patients are more susceptible to binary outcomes following return of spontaneous circulation (ROSC) — brain death or favorable neurological recovery — compared to CA from other etiologies. While ODCA has been historically understudied, recent data demonstrated similar[6,7,10] or improved[9,11–13] survival between ODCA and non-ODCA groups. We aim to better characterize the successfully resuscitated ODCA population and their outcomes, as this may inform future practice targeting improvement in out-of-hospital CA resuscitation and increase awareness for early recognition of brain death in this setting.

Methods

Study design

The Multimodal Outcome Characterization in Cardiac Arrest (MOCHA) registry is a data repository for the clinical characteristics and prognostic factors that affect neurological outcome following successfully resuscitated CA. Data from consecutive in- and out-of-hospital CA cases treated at Yale-New Haven Hospital from 2012 to 2017 were collected retrospectively. Patients aged ≥18 years who were initially unconscious following ROSC were included in the registry, regardless of CA location, type of non-perfusing rhythm or treatment with targeted temperature management (TTM). The Yale University Institutional Review Board approved the study and waived informed consent.

Case ascertainment

ODCA was ascertained as drug overdose when the history documented in admission notes was strongly suggestive of overdose. A positive urine toxicology screen not explained by therapeutic medication administration supported findings from the history and physical examination, but was not itself indicative of acute overdose. CA cases from all other etiologies were considered non-ODCA.

Variables

Baseline variables abstracted from the medical record included age, sex, race/ethnicity, insurance, Charlson Comorbidity Index (CCI), CA etiology, location of CA, whether the CA was witnessed and bystander CPR was performed, time to ROSC, non-perfusing rhythm (ventricular tachycardia, ventricular fibrillation, pulseless electrical activity or asystole), defibrillation/cardioversion, use and degree of TTM, mean arterial pressure (MAP) within 24 h of CA, cumulative vasopressor index (CVI) within 24 h of CA, highest $PaCO_2$ within 24 h of head computed tomography (CT), initial pH, lactate and bicarbonate, and Full Outline of Unresponsiveness (FOUR) score on presentation and at 72 h post-CA. Details of the neurological exam were abstracted: pupillary reaction to light, corneal reaction and Glasgow Coma Scale (GCS) motor scores on days 3, 4 and 5 post-CA. Variables were extracted from electroencephalography (EEG) reports: seizures, status epilepticus, burst-suppression pattern and reactivity. Two blinded board-certified neurointensivists (DMG and CBM) independently adjudicated neuroimaging for evidence of hypoxic-ischemic brain injury (HIBI) on head CT and magnetic resonance imaging (MRI); diffusion-weighted imaging (DWI) and fluid attenuation inversion recovery (FLAIR) sequences. Discrepancies were adjudicated by a third blinded board-certified neurointensivist (EJG).

Outcome measures

Outcome measures collected were inpatient death by circulatory or neurological criteria, withdrawal of life-sustaining therapy (WLST), Cerebral Performance Category (CPC) and modified Rankin Scale (mRS) scores at discharge based on review of rehabilitation services assessments. Brain death was defined as irreversible cessation of all functions of the entire brain, determined in accordance with institutional and national guidelines, and required documentation of brain death determination by two attending physicians. Two blinded board-certified neurointensivists adjudicated CPC and mRS scores at discharge (EJG and CBM). Favorable outcome was defined as a CPC score of 1–2 and mRS score of 0–3, both reflecting independent functional states.

Statistical analysis

We performed two-tailed comparison of ODCA and non-ODCA cohort characteristics using the chi-squared test for categorical variables and t-test or Mann–Whitney U test as appropriate for continuous variables. Categorical variables are reported as N (%) and continuous variables as mean (standard deviation) or median (interquartile range). An alpha level of 0.05 was used as the threshold for statistical significance. All statistical analyses were conducted using RStudio software, version 1.1.419 (RStudio®, Boston MA, USA).

Results

A total of 304 cases met inclusion criteria for the study period. Four cases were excluded due to uncertain etiology (unable to rule out overdose), leaving 300 patients for analysis.

Etiology of arrest

Of 300 cases, 28 (9%) were ODCA and 272 (91%) were non-ODCA [103 (34%) respiratory, 48 (16%) cardiac ischemia, 35 (12%) other, 35 (12%) unknown medical cause, 23 (8%) arrhythmia, 12 (4%) hypovolemia, 9 (3%) septic shock, 7 (2%) metabolic]. Of ODCA cases, 15 (54%) were due to opioids, 10 (36%) to polysubstances and 3 (11%) to cocaine. Opioids were implicated in 9 of the 10 polysubstance cases.

Clinical characteristics

The clinical characteristics of ODCA and non-ODCA cohorts are displayed in Table 1. Compared to non-ODCA patients, ODCA patients were younger [mean age 40 (SD 13) ODCA, 59 (16) non-

ODCA; $p < 0.001$] had lower CCI scores [1 (2), 4 (3); $p < 0.001$] and had a higher proportion of Medicaid as insurance [17 (68%), 68 (26%); $p < 0.001$]. ODCA patients were more likely to have an out-of-hospital CA [27 (96%), 159 (59%); $p < 0.001$], less likely to have their CA witnessed [10 (36%), 218 (80%); $p < 0.001$], less likely to receive bystander CPR [6 (22%), 166 (62%); $p < 0.001$], and had longer times from pulselessness to ROSC [mean minutes 45 (40), 20 (18); $p < 0.001$]. The presenting non-perfusing rhythm was not significantly different between groups. ODCA patients were more likely to receive TTM than non-ODCA patients [21 (75%), 139 (51%); $p = 0.027$]. Median MAP within 24 h of CA was higher for the ODCA group [89 (13), 80 (13); $p = 0.002$], and there was no significant difference in CVI [4 (4), 5 (5); $p = 0.424$], highest $PaCO_2$ within 24 h of initial CT scan [59 (30), 51 (19); $p = 0.065$], or initial pH [7.18 (0.22), 7.22 (0.20); $p = 0.366$], lactate [8 (5), 7 (5); $p = 0.265$] or bicarbonate [17 (5), 18 (6); $p = 0.614$] values. On presentation, FOUR scores were lower for the ODCA group than the non-ODCA group [1 (2), 3 (3); $p = 0.002$].

Neurological examination

We compared the neurological exams of the ODCA and non-ODCA cohorts on days 3–5 post-CA, and day 3 post-rewarming for patients who underwent TTM (Table 2). On day 3 post-CA, the cohorts had no difference in the proportion of patients with bilaterally reactive pupillary reflexes [13 (65%), 126 (69%); $p = 0.921$] or corneal reflexes [6 (35%), 55 (49%); $p = 0.441$], but the ODCA cohort had lower GCS motor scores [2 (1), 3 (2); $p = 0.026$] and lower FOUR scores [3 (4), 6 (5); $p = 0.012$]. On days 4 and 5 post-CA and day 3 post-rewarming, there were no differences in pupillary or corneal reflexes or GCS motor scores.

Seizures and EEG

There were no differences in the occurrence of clinical seizures [7 (25%), 89 (33%); $p = 0.535$] or post-anoxic status epilepticus [6 (21%), 63 (23%); $p = 0.744$]. Of the 240 patients who underwent EEG [25 (89%) ODCA, 215 (79%) non-ODCA], electrophysiological findings of reactivity [7 (41%), 42 (31%); $p = 0.575$] or unreactive burst-suppression pattern [14 (58%), 100 (52%), $p = 0.699$] within 72 h post-CA were similar.

Table 1 – Descriptive statistics stratified by ODCA and non-ODCA.

Covariate	Total N = 300	ODCA N = 28	Non-ODCA N = 272	*p*
Demographics				
Female, N (%)	136 (45)	10 (36)	126 (46)	0.382
Age, mean (SD)	58 (17)	40 (13)	59 (16)	<0.001
Race, N (%)				0.354
White	184 (61)	21 (75)	163 (60)	
Black	68 (23)	3 (11)	65 (24)	
Hispanic	35 (12)	4 (14)	31 (11)	
Asian	4 (1)	0 (0)	4 (2)	
Unknown	9 (3)	0 (0)	9 (3)	
CCI, mean (SD)	4 (3)	1 (2)	4 (3)	<0.001
Insurance, N (%)				<0.001
Medicaid	85 (29)	17 (68)	68 (26)	
Medicare	112 (39)	0 (0)	112 (42)	
Private	93 (32)	8 (32)	85 (32)	
Resuscitation characteristics				
Out of hospital, N (%)	186 (62)	27 (96)	159 (59)	<0.001
Witnessed, N (%)	228 (76)	10 (36)	218 (80)	<0.001
Bystander CPR, N (%)	172 (58)	6 (22)	166 (62)	<0.001
Minutes to ROSC, mean (SD)	22 (21)	45 (40)	20 (18)	<0.001
Initial rhythm, N (%)				0.500
Ventricular fibrillation	59 (22)	4 (17)	55 (23)	
Ventricular tachycardia	21 (8)	1 (4)	20 (8)	
Pulseless electrical activity	131 (49)	11 (46)	120 (50)	
Asystole	53 (20)	8 (33)	45 (19)	
Defibrillation, N (%)	106 (36)	9 (32)	97 (37)	0.806
TTM, N (%)	160 (53)	21 (75)	139 (51)	0.027
Median MAP within 24 h of CA, mean (SD)	81 (14)	89 (13)	80 (13)	0.002
CVI within 24 h of CA, mean (SD)	5 (5)	4 (4)	5 (5)	0.424
Highest $PaCO_2$ within 24 h of CT, mean (SD)	52 (20)	59 (30)	51 (19)	0.065
Initial pH, mean (SD)	7.21 (0.20)	7.18 (0.22)	7.22 (0.20)	0.366
Initial lactate, mean (SD)	7 (5)	8 (5)	7 (5)	0.265
Initial bicarbonate, mean (SD)	18 (6)	17 (5)	18 (6)	0.614
Initial FOUR score, mean (SD)	3 (3)	1 (2)	3 (3)	0.002

*CCI = Charlson Comorbidity Index, CPR = cardiopulmonary resuscitation, TTM = targeted temperature management, MAP = mean arterial pressure, CA = cardiac arrest, CVI = cumulative vasopressor index, FOUR = Full Outline of Unresponsiveness.

Table 2 – Neurological exam.

Covariate	Total N = 300	ODCA N = 28	Non-ODCA N = 272	p
Day 3 post-CA				
Bilaterally reactive pupils, N (%)	139 (69)	13 (65)	126 (69)	0.921
Bilaterally reactive corneals, N (%)	61 (47)	6 (35)	55 (49)	0.441
GCS motor score, mean (SD)	3 (2)	2 (1)	3 (2)	0.026
FOUR score, mean (SD)	6 (5)	3 (4)	6 (5)	0.012
Day 4 post-CA				
Reactive pupils, N (%)	130 (73)	13 (72)	117 (74)	1.00
Reactive corneals, N (%)	53 (51)	5 (39)	48 (52)	0.529
Day 5 post-CA				
Reactive pupils, N (%)	123 (75)	12 (71)	111 (75)	0.919
Reactive corneals, N (%)	44 (52)	6 (46)	38 (54)	0.852
Day 3 post-rewarming				
Reactive pupils, N (%)	69 (69)	11 (73)	58 (68)	0.928
Reactive corneals, N (%)	37 (55)	6 (55)	31 (55)	1.00
GCS motor score, mean (SD)	3 (2)	2 (2)	3 (2)	0.315

*CA = cardiac arrest, GCS = Glasgow Coma Scale, FOUR = Full Outline of Unresponsiveness.

Neuroimaging

The results of head CT and brain MRI are displayed in Table 3. Head CT was obtained within 6 h of CA for 25 (93%) ODCA and 153 (69%) non-ODCA patients. Definite signs of HIBI were observed more commonly in ODCA [10 (37%), 19 (10%); $p < 0.001$]. MRI scans were available for 122 (41%) patients and were obtained on median day 4 (IQR 3–5). There were no differences between cohorts in DWI [11 (69%), 68 (64%); $p = 0.938$] or FLAIR [9 (56%), 53 (51%); $p = 0.900$] sequences. The ODCA cohort was less likely to show a predominantly cortical pattern of ischemia [0 (0%), 12 (24%); $p = 0.038$] and more likely to show a global pattern of ischemia [6 (67%), 13 (26%); $p = 0.038$] on FLAIR; no other regional differences were found.

Mortality

Overall, 220 (73%) patients died by hospital discharge (Table 4). In-hospital mortality did not differ between cohorts [22 (79%), 198 (73%); $p = 0.664$)]. ODCA patients were less likely to undergo WLST than non-ODCA patients [9 (32%), 167 (61%); $p = 0.004$] and were more likely to be declared brain dead [12 (43%), 16 (6%); $p < 0.001$]. Median days from CA to WLST was 6 (IQR 5–10) for the ODCA cohort and 4 (1–8) for the non-ODCA cohort ($p = 0.247$). Median days from CA to brain death was 3 (2–5) for the ODCA and 4 (2–6) for the non-ODCA cohort ($p = 0.573$). Of the 12 ODCA patients who progressed to brain death, 9 (75%) were treated with TTM, 10 (83%) had definite or probable signs of HIBI on CT within 12 h of CA, and 11 (92%) underwent nuclear medicine studies to confirm no cerebral perfusion (Table 5).

Functional outcomes

Favorable neurological outcome at hospital discharge did not differ between ODCA and non-ODCA cohorts. Among the 6 (21%) ODCA and 74 (27%) non-ODCA patients who survived, 2 (7%) ODCA and 19 (7%) non-ODCA patients achieved CPC 1–2 ($p = 1.00$); 2 (7%) ODCA and 23 (9%) non-ODCA patients achieved mRS 0–3 ($p = 1.00$).

Table 3 – Radiological findings.

Covariate	Total N = 300	ODCA N = 28	Non-ODCA N = 272	p
HIBI on initial CT, N (%)				<0.001
Definite	29 (13)	10 (37)	19 (10)	
Probable	6 (3)	2 (7)	4 (2)	
Possible	10 (5)	0 (0)	10 (5)	
None	178 (80)	15 (56)	163 (83)	
Abnormal MRI - DWI, N (%)	79 (65)	11 (69)	68 (64)	0.938
Ischemic regions on DWI, N (%)				
Frontal lobe	57 (47)	7 (44)	50 (47)	1.00
Parietal lobe	62 (51)	10 (63)	52 (49)	0.463
Occipital lobe	69 (57)	11 (69)	58 (55)	0.432
Temporal lobe	43 (35)	8 (50)	35 (33)	0.296
Basal ganglia	41 (34)	6 (38)	35 (33)	0.944
Thalamus	24 (20)	5 (31)	19 (18)	0.362
Cerebellum	33 (27)	4 (25)	29 (27)	1.00
Motor strip	21 (17)	4 (25)	17 (16)	0.596
Hippocampus	23 (19)	0 (0)	23 (22)	0.084
Predominant area of ischemia				0.109
Cortical	40 (53)	3 (27)	37 (58)	
Deep gray matter	13 (17)	2 (18)	11 (17)	
Global	22 (29)	6 (55)	16 (25)	
Abnormal MRI - FLAIR, N (%)	62 (52)	9 (56)	53 (51)	0.900
Ischemic regions on FLAIR, N (%)				
Frontal lobe	47 (39)	6 (38)	41 (39)	1.00
Parietal lobe	49 (41)	7 (44)	42 (40)	1.00
Occipital lobe	53 (44)	7 (44)	46 (44)	1.00
Temporal lobe	35 (29)	6 (38)	29 (28)	0.623
Basal ganglia	46 (38)	8 (50)	38 (37)	0.450
Thalamus	24 (20)	6 (38)	18 (17)	0.123
Cerebellum	32 (27)	5 (31)	27 (26)	0.887
Motor strip	4 (3)	0 (0)	4 (4)	0.960
Hippocampus	8 (7)	0 (0)	8 (8)	0.542
Predominant area of ischemia				0.038
Cortical	12 (20)	0 (0)	12 (24)	
Deep gray matter	28 (48)	3 (33)	25 (50)	
Global	19 (32)	6 (67)	13 (26)	

*HIBI = hypoxic-ischemic brain injury, MRI = magnetic resonance imaging, DWI = diffusion-weighted imaging, FLAIR = fluid attenuation inversion recovery.

Table 4 – Discharge outcomes.

Covariate	Total N = 300	ODCA N = 28	Non-ODCA N = 272	*p*
Inpatient mortality, N (%)	220 (73)	22 (79)	198 (73)	0.664
WLST, N (%)	176 (59)	9 (32)	167 (61)	0.004
Days to WLST, median (IQR)	4 (1-8)	6 (5-10)	4 (1-8)	0.247
Brain death, N (%)	28 (9)	12 (43)	16 (6)	<0.001
Days to brain death, median (IQR)	4 (2-5)	3 (2-5)	4 (2-6)	0.573
CPC score at discharge, N (%)				0.616
1	15 (5)	2 (7)	13 (5)	
2	6 (2)	0 (0)	6 (2)	
3	43 (14)	4 (14)	39 (14)	
4	16 (5)	0 (0)	16 (6)	
5	220 (73)	22 (79)	198 (73)	
mRS score at discharge, N (%)				0.063
0	1 (0)	1 (4)	0 (0)	
1	13 (4)	1 (4)	12 (4)	
2	3 (1)	0 (0)	3 (1)	
3	8 (3)	0 (0)	8 (3)	
4	29 (10)	3 (11)	26 (10)	
5	26 (9)	1 (4)	25 (9)	
6	220 (73)	22 (79)	198 (73)	
Disposition, N (%)				0.494
Acute rehabilitation	12 (15)	2 (33)	10 (13)	
Home	16 (20)	2 (33)	14 (18)	
Skilled nursing facility	26 (32)	2 (33)	24 (32)	
Short term rehabilitation	15 (18)	0 (0)	15 (20)	
Hospice	10 (12)	0 (0)	10 (13)	
Long-term acute care hospital	3 (0)	0 (0)	3 (4)	

*WLST = withdrawal of life-sustaining therapy, CPC = Cerebral Performance Category, mRS = modified Rankin Scale.

Discussion

As hypothesized, successfully resuscitated ODCA patients were more likely than non-ODCA patients to be declared brain dead. However, favorable neurological outcomes among survivors did not differ between groups. Upon hospital arrival, ODCA patients represented a distinct cohort driven by younger age and lower comorbidity burden, but with less favorable resuscitation characteristics (longer total downtimes and lower bystander CPR rates). Within 24 h of arrest, 37% of the ODCA cohort showed signs of HIBI on CT imaging, compared to 10% of the non-ODCA cohorta finding associated with poor outcome[14,15] and progression to brain death.[16] By discharge, 73% of patients had died, with no significant difference between ODCA and non-ODCA patients. The high overall mortality rate was likely driven by the higher proportion of patients with pulseless electrical activity or asystole as non-perfusing rhythm.

ODCA patients were less likely to have witnessed arrests, subsequently suffering a greater magnitude of anoxic injury. Prolonged hypoventilation, resulting in hypoxemia and hypercarbia, leads to catastrophic respiratory acidosis and cerebral edema. It is possible that the extent of cerebral edema and subsequent herniation resulted in 43% of ODCA patients progressing to brain death in our cohort, compared to only 6% in non-ODCA. Similar findings were seen in out-of-hospital CA, with 34% in ODCA versus 12% in non-ODCA.[7] This is in contrast with the 13% (10–15%) overall rate of brain death following CA from a recent meta-analysis.[17] The high rate of brain death in the ODCA population helps explain the 24-fold increase in organ donation from 2000 to 2016.[4,5] The development of severe HIBI readily seen on neuroimaging coupled with higher rates of brain death in ODCA may suggest a potential utility for early head CT in identifying those at higher risk for brain death, in whom TTM might be futile and only delay death determination. It is important to interpret findings of cerebral edema with preservation of gray-white differentiation with caution, as this patient population tends to be younger with less atrophy and more likely to have hypercarbia, which has been shown to be associated with reversible cerebral edema on neuroimaging.[18]

We hypothesized that ODCA patients might have favorable outcomes despite less immediate resuscitation because of their lower comorbidity burden and exposure to hypercarbia. There are several reasons why this did not bear out. There is controversy surrounding the effect of comorbidity burden on outcome: CCI was not associated with neurological outcomes[19] or mortality[20] in out-of-hospital CA patients or in patients treated with TTM.[21] Hypercarbia also had differential effects: poor neurological outcome in an observational study[22] and beneficial effect in a randomized controlled trial.[8]

The ODCA population, historically excluded from CA clinical trials,[23–25] warrants continued study. In our cohort including out-of-hospital and in-hospital CA with ROSC, 9% were due to OD (of which 96% were out-of-hospital). This is similar to the overall 7–9% ODCA rates among CA patients treated with TTM reported in other large cohorts that included non-cardiac etiologies.[26,27] Among out-of-hospital CA in our cohort, 15% were ODCA. A prior cohort study reported 14% ODCA in the out-of-hospital setting.[7]

The question of differential treatment courses and neuroprognostication for ODCA and non-ODCA remains open. While the American Heart Association guidelines promote aggressive reversal of the underlying cause of CA, specific treatment protocols are not differentiated by etiology.[35] A survey of emergency medical providers found that a majority perceive ODCA patients as different than non-

Table 5 – Summary of ODCA cohort.

Drug	Witnessed	Bystander CPR	Minutes to ROSC	HIBI on CT	TTM	Outcome
Heroin	No	Yes	20	Probable	Yes	Brain death confirmed on NM scan day 8
Benzodiazepines, opiates, cannabinoids	No	No	120	Definite	Yes	Brain death confirmed on NM scan day 1
Methadone	No	No	15	Probable	Yes	Brain death confirmed on NM scan day 5
Heroin	No	No	NA	None	No	Brain death confirmed on NM scan day 5
Benzodiazepines, opiates	No	No	NA	Definite	Yes	Brain death confirmed on NM scan day 2
Heroin	Yes	No	33	Definite	No	Brain death confirmed on NM scan day 3
Cocaine, opiates	No	No	NA	Definite	No	Brain death confirmed on NM scan day 2
Cocaine, methadone	No	No	39	Definite	Yes	Brain death confirmed on NM scan day 4
Heroin	Yes	Yes	10	Probable	Yes	Brain death confirmed on NM scan day 5
Opiates	No	No	120	Definite	Yes	Brain death confirmed on NM scan day 2
Cocaine	Yes	No	25	None	Yes	Brain death confirmed on NM scan day 2
Benzodiazepines, cannabinoids, cocaine, opiates	No	Yes	90	Definite	Yes	Declared brain dead day 3 based on clinical exam and apnea test
Cocaine, opiates, cannabinoids	No	No	80	None	No	WLST day 17
Heroin	Yes	No	25	None	Yes	WLST day 6
Opioids	Yes	No	15	None	Yes	WLST day 11
Cocaine	No	No	45	None	Yes	Made DNR, became pulseless day 23
Heroin laced with other toxin	No	No	NA	None	Yes	WLST day 6
Cocaine, heroin	No	No	NA	Definite	No	WLST day 1
Heroin	Yes	No	25	Definite	No	WLST day 1
Ethanol, opiates, benzodiazepines, oxycodone	No	No	NA	None	Yes	WLST day 8
K2, cocaine	No	No	NA	None	Yes	WLST day 6
Benzodiazepine, opiate	Yes	No	NA	None	Yes	WLST day 11
Cocaine	Yes	Yes	15	None	Yes	Discharged to acute rehabilitation with CPC 3, mRS 5
Oxycodone, benzodiazepines, heroin, cocaine	No	No	10	None	No	Discharged to skilled nursing facility with CPC 3, mRS 4
Heroin	Yes	Yes	11	None	Yes	Discharged home with CPC 1, mRS 1
Methadone	No	No	NA	None	Yes	Discharged home with CPC 1, mRS 0
Opioids	Yes	No	32	None	Yes	Discharged to acute rehabilitation with CPC 3, mRS 4
Cocaine, opioids, PCP	No	No	120	None	Yes	Discharged to skilled nursing facility with CPC 3, mRS 4

*CPR = cardiopulmonary resuscitation, ROSC = return of spontaneous circulation, HIBI = hypoxic ischemic brain injury, CT = computed tomography, TTM = targeted temperature management, NM = nuclear medicine, WLST = withdrawal of life-sustaining therapy, DNR = do not resuscitate, CPC = Cerebral Performance Category, mRS = modified Rankin Scale.

ODCA patients and report making different decisions when treating ODCA patients.[36] In our cohort, ODCA patients were more likely than non-ODCA patients to undergo TTM, perhaps driven by their young age and hope for recovery. This is despite sparse data supporting the use of TTM in the overdose setting: ODCA were excluded from TTM landmark trials, while a recent retrospective review of 121 presumed ODCA cases found TTM was associated with survival.[37] Drug clearance and delayed awakening are particularly important in determination of brain death in this population. According to the American College of Medical Toxicology's position statement on determining brain death after overdose, waiting five drug half-lives is necessary but may not be sufficient to ensure drug clearance.[38] TTM slows metabolism, which may prolong drug toxicity.

Our study has limitations. This was a single-center retrospective study, limiting generalizability of findings. While our cohort may be representative of the U.S. CA population in relation to CCI, there are significant differences in ODCA incidence[13] and overall survival across regions.[39] Our cohort consisted of successfully resuscitated CA cases for whom neuroprognostication is most difficult: those who attained ROSC but did not immediately regain consciousness. This created a selection bias towards more severe ODCA with HIBI, as we evaluated only those who remained unconscious post-ROSC, and does not serve as a comprehensive outcome evaluation of all ODCA patients. There was a large difference in the number of patients comprising the ODCA and non-ODCA cohorts, and our small ODCA sample size precluded a subgroup analysis by drug class or analysis of interactions between drugs in polysubstance cases.

Our findings have important implications for future clinical care and guideline development. Early resuscitation efforts are paramount: we underscore the crucial role that activation of emergency medical services plays in lowering mortality after ODCA.[40] For opioid cases in particular, expansion of naloxone access laws and Good Samaritan laws encouraging individuals to call for assistance in 30 U.S. states reduced OD deaths by 14% and 15%, respectively.[41] Further harm-reduction efforts such as legislation to develop medically supervised injection facilities may reduce the proportion of unwitnessed arrests.[1]

Conclusion

Following ROSC, ODCA is associated with higher rates of brain death and lower rates of death due to WLST than non-ODCA. These differential outcomes are likely driven by patient characteristics and the circumstances of arrest, where ODCA patients are less likely to receive immediate resuscitation efforts. Larger prospective studies are needed to analyze specific treatment courses and prognostic tools in this population. ODCA patients more frequently underwent TTM in this cohort, which has implications for brain death determination. Harm-reduction efforts are needed to mitigate the high proportion of ODCA who progress to brain death.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Disclosures

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Author contributions

Conception and design of the study: CHO, CBM, DMG. Acquisition and analysis of data: CHO, CBM, SEZ, MMB, LCM, RBB, EJG. Drafting a significant portion of the manuscript or figures: CHO, CBM, SEZ, MMB, LCM, RBB, EJG, DMG.

REFERENCES

1. Wood E. Strategies for reducing opioid-overdose deaths - lessons from Canada. New Engl J Med 2018;378:1565–7.
2. Gomes T, Tadrous M, Mamdani MM, Paterson J, Juurlink DN. The burden of opioid-related mortality in the united states. JAMA Network Open 2018;1:e180217.
3. Seth P, Scholl L, Rudd RA, Bacon S. Overdose deaths involving opioids, cocaine, and psychostimulants - United States, 2015-2016. MMWR Morb Mortal Wkly Rep 2018;67:349–58.
4. Cholankeril G, Li AA, Cholankeril R, Toll AE, Glenn JS, Ahmed A. Impact of drug overdose deaths on solid organ transplantation in the United States. J Gen Intern Med 2018;33:1423–5.
5. Durand CM, Bowring MG, Thomas AG, et al. The drug overdose epidemic and deceased-donor transplantation in the United States: a national registry study. Ann Intern Med 2018;168:702–11.
6. Katz AZ, Grossestreuer AV, Gaieski DF, Abella BS, Kumar V, Perrone J. Outcomes of patients resuscitated from cardiac arrest in the setting of drug overdose. Resuscitation 2015;94:23–7.
7. Elmer J, Lynch MJ, Kristan J, et al. Recreational drug overdose-related cardiac arrests: break on through to the other side. Resuscitation 2015;89:177–81.
Eastwood GM, Schneider AG, Suzuki S, et al. Targeted therapeutic mild hypercapnia after cardiac arrest: a phase II multi-centre randomised controlled trial (the CCC trial). Resuscitation 2016;104:83–90.
9. Koller AC, Salcido DD, Callaway CW, Menegazzi JJ. Resuscitation characteristics and outcomes in suspected drug overdose-related out-of-hospital cardiac arrest. Resuscitation 2014;85:1375–9.
10. Orkin AM, Zhan C, Buick JE, et al. Out-of-hospital cardiac arrest survival in drug-related versus cardiac causes in Ontario: a retrospective cohort study. PLoS One 2017;12:e0176441.
11. Salcido DD, Torres C, Koller AC, et al. Regional incidence and outcome of out-of-hospital cardiac arrest associated with overdose. Resuscitation 2016;99:13–9.
12. Smith G, Beger S, Vadeboncoeur T, Chikani V, Walter F, Bobrow B. Trends in overdose-related out-of-hospital cardiac arrests in Arizona. Resuscitation 2018;134:122–6.
13. Alqahtani S, Nehme Z, Williams B, Smith K. The incidence and outcomes of out-of-hospital cardiac arrest precipitated by drug overdose: a systematic review and meta-analysis. Resuscitation 2018;134:10–8.
14. Metter RB, Rittenberger JC, Guyette FX, Callaway CW. Association between a quantitative CT scan measure of brain edema and outcome after cardiac arrest. Resuscitation 2011;82:1180–5.
15. Torbey MT, Selim M, Knorr J, Bigelow C, Recht L. Quantitative analysis of the loss of distinction between gray and white matter in comatose patients after cardiac arrest. Stroke 2000;31:2163–7.
16. Vigneron C, Labeye V, Cour M, et al. Gray matter-white matter de-differentiation on brain computed tomography predicts brain death occurrence. Transplant Proc 2016;48:1893–7.
17. Sandroni C, D'Arrigo S, Callaway CW, et al. The rate of brain death and organ donation in patients resuscitated from cardiac arrest: a systematic review and meta-analysis. Intensive Care Med 2016;42:1661–71.
18. Roh D, Merkler AE, Al-Mufti F, et al. Global cerebral edema from hypercapnic respiratory acidosis and response to hyperosmolar therapy. Neurology 2016;86:1556–8.
19. Terman SW, Shields TA, Hume B, Silbergleit R. The influence of age and chronic medical conditions on neurological outcomes in out of hospital cardiac arrest. Resuscitation 2015;89:169–76.
20. Winther-Jensen M, Kjaergaard J, Nielsen N, et al. Comorbidity burden is not associated with higher mortality after out-of-hospital cardiac arrest. Scand Cardiovasc J 2016;50:305–10.
21. Nayeri A, Bhatia N, Holmes B, et al. Pre-existing medical comorbidity is not associated with neurological outcomes in patients undergoing targeted temperature management following cardiac arrest. Heart Vessels 2017;32:1358–63.
22. Roberts BW, Kilgannon JH, Chansky ME, Mittal N, Wooden J, Trzeciak S. Association between postresuscitation partial pressure of arterial carbon dioxide and neurological outcome in patients with post-cardiac arrest syndrome. Circulation 2013;127:2107–13.
23. Arrich J, Holzer M, Havel C, Warenits AM, Herkner H. Pre-hospital versus in-hospital initiation of cooling for survival and neuroprotection after out-of-hospital cardiac arrest. Cochrane Database Syst Rev 2016;3:Cd010570.
24. Bernard SA, Gray TW, Buist MD, et al. Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. New Engl J Med 2002;346:557–63.
25. Donnino MW, Andersen LW, Berg KM, et al. Temperature management after cardiac arrest: an advisory statement by the advanced life support task force of the international liaison committee on resuscitation and the American heart association emergency cardiovascular care committee and the council on cardiopulmonary, critical care, perioperative and resuscitation. Circulation 2015;132:2448–56.
26. Lee BK, Jeung KW, Lee HY, Jung YH, Lee DH. Combining brain computed tomography and serum neuron specific enolase improves the prognostic performance compared to either alone in comatose cardiac arrest survivors treated with therapeutic hypothermia. Resuscitation 2013;84:1387–92.
Jung YH, Lee BK, Lee DH, Lee SM, Cho YS, Jeung KW. The association of body mass index with outcomes and targeted

27. temperature management practice in cardiac arrest survivors. Am J Emerg Med 2017;35:268–73.
35. Travers AH, Rea TD, Bobrow BJ, et al. Part 4: CPR overview: 2010 American heart association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. Circulation 2010;122:S676–84.
36. Koller AC, Salcido DD, Menegazzi JJ. Physician and nonphysician health-care provider perspectives on resuscitation of suspected drug-related out-of-hospital cardiac arrest. Prehosp Emerg Care 2014;18:483–8.
37. Khan S, Meyers CM, Bentley S, Manini AF. Impact of targeted temperature management on ED patients with drug overdose-related cardiac arrest. J Med Toxicol 2018;15:22–9.
38. Neavyn MJ, Stolbach A, Greer DM, et al. ACMT position statement: determining brain death in adults after drug overdose. J Med Toxicol 2017;13:271–3.
39. Albaeni A, Beydoun MA, Beydoun HA, et al. Regional variation in outcomes of hospitalized patients having out-of-hospital cardiac arrest. Am J Cardiol 2017;120:421–7.
40. Paredes VL, Rea TD, Eisenberg MS, et al. Out-of-hospital care of critical drug overdoses involving cardiac arrest. Acad Emerg Med 2004;11:71–4.
41. McClellan C, Lambdin BH, Ali MM, et al. Opioid-overdose laws association with opioid use and overdose mortality. Addict Behav 2018;86:90–5.