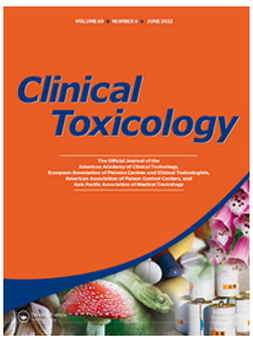

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CLINICAL RESEARCH

Predictors of severe outcome following opioid intoxication in children

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ABSTRACT

Introduction: While the opioid crisis has claimed the lives of nearly 500,000 in the U.S. over the past two decades, and pediatric cases of opioid intoxications are increasing, only sparse data exist regarding risk factors for severe outcome in children following an opioid intoxication. We explore predictors of severe outcome (i.e., intensive care unit [ICU] admission or in-hospital death) in children who presented to the Emergency Department with an opioid intoxication.

Methods: In this prospective cohort study we collected data on all children (0–18 years) who presented with an opioid intoxication to the 50 medical centers in the US and two international centers affiliated with the Toxicology Investigators Consortium (ToxIC) of the American College of Medical Toxicology, from August 2017 through June 2020, and who received a bedside consultation by a medical toxicologist. We collected relevant demographic, clinical, management, disposition, and outcome data, and we conducted a multivariable logistic regression analysis to explore predictors of severe outcome. The primary outcome was a composite severe outcome endpoint, defined as ICU admission or in-hospital death. Covariates included sociodemographic, exposure and clinical characteristics.

Results: Of the 165 (87 females, 52.7%) children with an opioid intoxication, 89 (53.9%) were admitted to ICU or died during hospitalization, and 76 did not meet these criteria. Seventy-four (44.8%) children were exposed to opioids prescribed to family members. Fentanyl exposure (adjusted OR [aOR] = 3.6, 95% CI: 1.0–11.6; $p = 0.03$) and age $\geq$10 years (aOR = 2.5, 95% CI: 1.2–4.8; $p = 0.01$) were independent predictors of severe outcome.

Conclusions: Children with an opioid toxicity that have been exposed to fentanyl and those aged $\geq$10 years had 3.6 and 2.5 higher odds of ICU admission or death, respectively, than those without these characteristics. Prevention efforts should target these risk factors to mitigate poor outcomes in children with an opioid intoxication.

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Supplemental data for this article can be accessed here.

Introduction

In the past two decades, nearly 500,000 people in US died from opioid toxicity, by either prescription overdose or illicit exposure [1]. Increased prescribing has also led to higher rates of opioid addiction [2]. This opioid crisis was declared by the Centers for Disease Control and Prevention (CDC) as the worst drug overdose-related epidemic in history [1,3]. Given the magnitude of the problem, opioid intoxication prevention has been identified as one of the top five public health challenges by the CDC [4]. Fueled by the COVID-19 pandemic, a substantial increase in drug overdose deaths across the US was reported, surpassing 100,000/year, primarily driven by synthetic opioids [5,6]. Subsequently, calls to poison information centers, opioid-related emergency department (ED) visits and hospitalizations across all pediatric age groups are still increasing [7–10]. Despite these alarming data, experts warn that the impact of the opioids epidemic on children received little attention and was infrequently mentioned in national discussions or policy initiatives [11–13].

Children represent a unique population of concern; both toddlers and adolescents are considered high-risk groups for opioid-related morbidity [14–16]. Toddlers are prone to exploratory ingestions of opioids prescribed to family members [17], and are prone to severe toxicity because they are typically opioid naïve [16]; adolescents are at risk of both unintentional and intentional intoxications, which may be difficult to discern due to concomitant substance misuse or mental health conditions [14]. In the US, between 2005 to 2018, more than 200,000 pediatric cases of opioid intoxication were reported to poison control centers, with increasing rates of critical care admissions [18]. In 2017, approximately 769,000 adolescents misused prescription opioids, and 14,000 used heroin [19]. In Canada, the proportion of deaths attributable to prescribed or illicit opioids nearly tripled from 2000 to 2015, with the greatest increase documented in youth, aged 15–24 years [20].

While most of the studies that explored opioid intoxication in the pediatric population have focused on the increasing numbers of children affected by the opioid crisis [7–10], to our knowledge, no prospectively collected data exist with respect to risk factors for severe pediatric outcomes following an opioid intoxication. We sought to identify predictors of severe outcome after an opioid intoxication in children, defined as intensive care unit (ICU) admission or in-hospital death.

Methods

Study design

Employing the Toxicology Investigators Consortium (ToxIC) pediatric opioids-dedicated sub registry, we conducted a prospective cohort study of all patients 0–18 years of age, who presented with opioid toxicity to participating hospitals in the US, Canada and Thailand from August 1, 2017 to June 30, 2020. All study participants had exposure to opioids, confirmed either clinically by the consulted medical toxicology service and/or by laboratory testing.

Data sources

The pediatric opioid sub registry was established as a dedicated part of the ToxIC case registry in 2017. The ToxIC case registry was established in 2010 by the American College of Medical Toxicology [21]. ToxIC prospectively compiles data from 35 participating sites, comprised of 50 medical centers across the US, which represent approximately 60% of all medical toxicology training programs in the country, as well as international sites in Canada, Israel, and Thailand [22]. All prospectively identified patients consulted on and managed by participating medical toxicologists are entered in real-time into the ToxIC registry. If the case involved a pediatric opioid exposure, additional detailed data were collected, and the patient was entered into the dedicated pediatric opioid exposure sub-registry. Thus, our patient cohort was derived from the opioid exposure sub-registry with complimentary data from the ToxIC registry. The latter collects patient-level clinical and demographic data, including circumstances of exposure, substances involved, signs and symptoms on presentation, management, disposition, and outcome.

ToxIC functions under the approval of the Western Institutional Review Board (IRB), and all participating sites obtain study approval and a waiver of informed consent from their respective IRB. The study adheres to the STROBE guideline for observational studies (eAppendix).

Study patients

The cohort includes all children, 0–18 years of age, who presented to the ED of a participating ToxIC hospital with an opioid toxicity after establishment of the dedicated prospective pediatric opioids registry, within the study timeframe. The following demographic and clinical data were extracted from the patients' medical records into the pre-defined data collection form: age, sex, ethnicity, medical history, including psychiatric history (unipolar and bipolar depression, anxiety, post traumatic syndrome disorder), social history (previous child protective services involvement, history of substance abuse, prior non-pharmacologic ingestion, high risk sexual behavior, school failure). Relevant extracted historical data included a reason for opioid exposure (intentional or unintentional), opioid type, route of administration, location of exposure, source of drug procurement, indication for opioid prescription, and the type of formulation. Clinical data identified in the ED included vital signs [heart rate (HR), blood pressure (BP), oxygen saturation, temperature, Glasgow Coma Scale (GCS)], toxidrome type, signs of respiratory depression or central nervous system (CNS) involvement, electrocardiogram (ECG),and chest x-ray (CXR) findings, and laboratory results such as blood and urine drug screens. Interventions including cardiopulmonary resuscitation (CPR), intubation, bag valve mask (BVM) ventilation, decontamination, antidote treatment, additional pharmacologic support, ED disposition (home, ward, ICU), length of hospital stay

(LOS), in-hospital death, and child protective services involvement after discharge were also collected.

Outcomes

The primary outcome was a composite "severe outcome" endpoint indicating high illness severity, defined as ICU admission or death in the ED or during hospitalization. While various clinical and non-clinical factors affect admission decisions, we focused our comparisons on the presence or absence of this composite outcome.

Candidate predictors of severe outcome

Based on literature review [23] and the group's clinical experience, we investigated potential risk factors for severe outcome following opioid intoxication comparing the two study groups. The following potential demographic and clinical risk factors were examined: age, opioid type, exposure intent (intentional vs. unintentional), self-harm intent [18], co-exposure to central nervous system depressants (i.e., sedative hypnotic agents, anticholinergic/antihistamine agents, alcohol) [24], co-exposure to stimulants [24], chronic disease, and psychosocial risk factors [14]. We defined a positive psychosocial history as any documented mental health condition (e.g., major depression), previous drug intoxication, known polysubstance abuse, prior self-harm attempt, school failure, homelessness, reported high-risk sexual behavior, or child protective services involvement prior to the index hospital presentation.

Statistical analysis

Baseline characteristics were compared between patients who experienced a severe outcome versus those who did not. Chi square or Fisher exact test were used for comparison of categorical variables and two-tailed *t* test was employed for continuous variables. Categorical variables were described by percent proportions, and continuous variables were described as a mean a standard deviation (SD), or median and interquartile range (IQR).

A univariate analysis was performed to compare patients with severe outcomes vs. those without, as the binary dependent variable, and the plausible predictors of severe outcome listed below as independent variables. A 2-tailed $p < 0.05$ value was considered statistically significant. All parameters with a significance level of $p < 0.2$ and those considered clinically relevant in the univariate analysis were inserted into the multivariable models, to assess whether which unique potential risk factor predicted severe outcome. In the multivariable logistic regression analysis, we included the parameters which were significant in the univariate analysis or were considered clinically important. All analyses were performed using SPSS Statistics, version 26 (SPSS Inc, Chicago, Illinois).

Results

During the study period, 166 children were enrolled in the ToxIC prospective opioid registry following an opioid intoxication. Of them, one (0.6%) patient had incomplete data and was excluded. The study cohort comprised 165 patients (87 females, 52.7%).

Exposure characteristics and outcomes

The study cohort included 89 (54%) children 10–18 years of age and 76 children (46%) were younger than 10 years. The demographics, intoxication, and clinical details of patients with and without severe outcome are summarized in Table 1. Eighty-nine children (54%) were intoxicated by opioids intentionally and 76 (46%) unintentionally (Figure 1); self-harm intent was documented in almost one third of the patients. Overall, 117/165 (71%) children were intoxicated by opioids at home; 74 (45%) accessed an opioid prescribed to a family member for trauma, cancer, arthritis-related or post-procedural pain, or for treatment of an opioid use disorder. Only 12/165 (7%) children were intoxicated by exposure to their own prescribed opioids. Ninety (55%) children had a positive confirmatory laboratory testing for opioids, conducted as part of their assessment.

While half of the patients exhibited a typical opioid toxidrome, 66 patients (40%) manifested a mixed clinical picture, reflecting a multi-drug intoxication. Overall, two thirds of the patients had CNS involvement, half had opioid-related respiratory depression, and 10 percent manifested abnormal cardiovascular system (CVS) signs. Twenty-five children (15%) were intubated and mechanically ventilated. Naloxone was administered to more than half of the children, 20 of these received naloxone by a continuous infusion. Of the 165 intoxicated children, 150 (91%) were admitted to the hospital, with a median LOS of 2 days (IQR 1 to 3 days). One hundred and three patients (62%) had a positive psychosocial history, while 62 did not; Table 2.

Predictors of severe outcomes

Eighty-nine (54%) patients had severe outcome (ICU admission or in-hospital death), and 76 (46%) children were either discharged home from the ED or admitted to the inpatient ward; Table 1.

In the univariate analysis, age $\geq$10 years (62% vs. 45%, $p = 0.04$) and presence of psychosocial risk factors (71% vs. 53%, $p = 0.01$) were more common in children with severe outcome. In the univariate analysis, fentanyl intoxications were two-and-a-half times more likely to result in severe outcome than non-severe outcome. In contrast, buprenorphine intoxications were two-and-a-half times more likely to result in non-severe outcome than severe outcome (Table 1). Notably, children $\geq$10 years old were more likely to engage in intentional intoxication (95% vs. 4%; $p < 0.001$), and in polypharmacy ingestion than their younger counterparts (76% vs. 35%; $p < 0.001$).

Table 1. Clinical characteristics of 165 children with opioid intoxication.

	All patients ($N = 165$)	Non severe outcome ($N = 76$) (%)	Severe outcome ($N = 89$) (%)	p Value
Age 10–18 years	89 (54)	34 (45)	55 (62)	0.04
Age (mean, SD)	9.1 ± 6.8	8.4 ± 6.9	9.9 ± 6.8	0.12
Sex (male)	78 (47)	32 (42)	46 (52)	0.27
Chronic disease	8 (5)	3 (4)	5 (6)	0.72
Developmental delay	4 (2)	3 (4)	1 (1)	0.33
Psychosocial history	103 (62)	40 (53)	63 (71)	0.01
Reason:				
Intentional	89 (54)	35 (46)	53 (60)	0.08
Self-harm intent	47 (28)	19 (25)	28 (31)	0.38
Opioid type:[a]				
Buprenorphine	31 (19)	21 (27)	10 (11)	0.01
Fentanyl	28 (16.9)	7 (9.2)	21 (24)	0.01
Oxycodone	31(19)	16 (21)	15 (17)	0.55
Methadone	12 (7)	4 (5)	8 (9.0)	0.38
Unknown	66 (40.0)	27 (35.5)	39 (44)	1.00
Multi-drug exposure	76 (46)	37 (49)	39 (44)	0.63
Co-exposure to CNS depressants	26 (16)	15 (20)	11(12)	0.14
Co-exposure to CNS stimulants	14 (8)	6 (8)	8 (9)	>0.99
Location of exposure: home	116 (70)	54 (71)	62 (70)	0.86
Method of intoxication:				
Oral	133 (81)	60 (79)	73 (82)	0.69
Intravenous	2 (1)	2 (3)	0 (0.0)	0.21
Intranasal/inhalation	5 (3)	2 (3)	3 (3)	0.62
Sublingual	4 (2)	3 (4)	1 (1)	0.33
Other/unknown	21 (13)	9 (13)	12 (13)	0.81
Clinical presentation:				
Hypotension	12 (7)	2 (3)	10 (11)	0.03
Bradypnea	27 (16)	4 (5)	23 (26)	<0.001
Respiratory depression	65 (39)	11(14)	50 (56)	<0.001
CNS depression	115 (70)	39 (51)	76 (85)	<0.001
Opioid toxidrome	66 (40)	24 (32)	42 (47)	0.03
Naloxone treatment	87 (52)	25 (33)	50 (56)	<0.001
Intubation	25 (15)	0 (0.0)	25 (28)	<0.001
Bag mask ventilation	37 (2222.4)	4 (5)	33 (37)	<0.001

[a]Calculated from patients with opioid as primary agent ($N = 122$); ICU: intensive care unit; CNS: central nervous system.

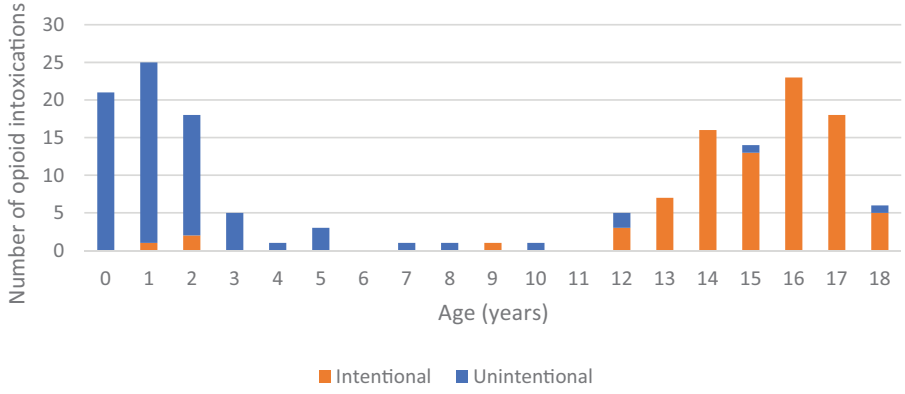

Figure 1. Intentional and unintentional opioid intoxications by age.

All parameters with a significance level of $p < 0.2$ in the univariate analysis and those considered clinically plausible, i.e., co-intoxication with CNS depressants, co-intoxication with stimulants, fentanyl intoxication, age ≥10 years and psychosocial risk factors (Table 2), were inserted into the multivariable model, to explore independent predictors of severe outcome following opioid intoxication. However, intentional intoxication was not, because it is co-linear with adolescence compared to younger children. Fentanyl intoxication (adjusted OR [aOR] = 3.6, 95% CI: 1.0–11.6; $p = 0.03$) and age ≥10 years (aOR = 2.5, 95% CI: 1.2–4.8; $p = 0.01$) were independent predictors of severe outcome. Documented psychosocial history (aOR = 1.5, 95% CI 0.7–3.1; $p = 0.29$), co-ingestion of sedatives (aOR = 0.5, 95% CI 0.2–1.1; $p = 0.09$) and co-ingestion to stimulants (aOR = 1.3, 95% CI 0.4–4.1, $p = 0.65$) were not independent risk factors for severe outcome.

Discussion

In this prospective multicentre cohort study of children who presented to the ED with opioid toxicity we identified both host and exposure-related predictors of ICU admission or in-hospital mortality. Intoxication with the opioid fentanyl and age ≥10 years were associated with severe outcome. Strengths of this study include prospective data collection by medical toxicologists directly caring for all included patients [22].

Table 2. Characteristics of 103 children with opioid intoxication and a positive psychosocial history.

	$N = 103$ (%)
Age:	
0-9 years	33 (32.1)
10-18 years	70 (67.9)
Documented high-risk behavior[a]	75 (72.8)
Polysubstance use	33 (32.0)
High risk sexual practice	5 (4.8)
Delinquency	8 (7.7)
School failure	8 (7.7)
Unhoused	3 (2.9)
Prior self harm	21 (20.3)
Past CPS[b] involvement	36 (34.9)
Past substance misuse – total[a]	84 (81.5)
Alcohol	19 (18.4)
Stimulants	11 (10.6)
Heroin	4 (3.8)
Cannabis	33 (32.0)
Prescription opioids	28 (27.1)
Prescription sedative-hypnotics	9 (8.7)
Prescription muscle relaxants	3 (2.9)
Mental health history – total[a]	43 (41.7)
Major depression	31 (30.0)
Bipolar disease	4 (2.4)
Other psychiatric disorders[c]	14 (13.5)

[a]There is overlap between groups. [b]CPS = Child Protective Services. [c]Anxiety, post traumatic stress disorder.

Fentanyl intoxication was associated with an almost four-fold higher odds of severe outcome compared to children exposed to other opioids. Fentanyl and its analogues have 50–100 times the potency of morphine [25]. US deaths from fentanyl and its analogs have surged in recent years [26]. New York City alone saw nearly 30 times as many fentanyl related deaths in 2017 than in 2014 [27]. We also found that adolescence is an independent predictor of severe outcome, compared to younger children. Opioid-related mortality among adolescents and young adults increased 3-fold from 1999 to 2016 [28]. Adolescents are prone to intentional misuse of prescription medications, attributed to either self-harm intent, recreational use or high-risk behaviors [14]. Indeed, in our cohort, patients older than 10 years had higher rates of intentional intoxication and self-harm intent. A previous study found that suicidal intent among youth with opioids intoxication was associated with higher odds of receiving ICU level care [18]. In our study, one in four adolescents were further vulnerable to intoxication with opioids combined with other substances. This mirrors a recent MMWR report finding that most opioid related deaths included other drugs – most commonly benzodiazepines, cocaine, or methamphetamine [28]. Polypharmacy presents both diagnostic and management challenges, compared to opioid intoxication alone [24,29].

Almost half of the children in our study were exposed to a family member's prescription opioid. This finding corroborates prior research highlighting the risk of opioid intoxication in young children ($\leq$10 y) and youth (11–26 y) whose family members had recent opioid prescriptions [17,30]. These findings suggest that enhanced safeguards and education efforts are required when prescribing opioids to patients with children in the household. For example, physicians should routinely inquire about presence of children in the home, educate about safe storage, restrict the number of opioid tablets prescribed, and prescribing naloxone to patients who take opioids, as naloxone may be beneficial in case of opioid intoxication in household members [31].

Several limitations merit mention. First, most hospitals that are involved in the ToxIC network are large referral hospitals. These characteristics may result in a population of patients with more severe toxicity compared to patients presenting to community institutions, which can somewhat affect generalizability. Second, the number of deaths compared to ICU admissions did not permit a stable statistical stratified sub-analysis. ICU admission decisions may be somewhat influenced by local practices. Thirdly, confirmatory blood/urine testing was not done in all patients, however, all cases were clinically confirmed by a medical toxicologist at the bedside. Finally, almost half of the intoxications involved polypharmacy, which may affect the disposition decision and management. However, in all mixed intoxications, opioids played a central role, by study design. Further, our data represent 'real-life' scenarios and related complex exposure clinical realities [28].

In summary, prescriptions for other family members were the most common source of opioid access in children who presented to the ED with an opioid toxicity. Fentanyl intoxication and adolescence were independently associated with ICU admission or in-hospital death. To mitigate these severe pediatric outcomes, preventative efforts should focus on the identified risk factors when prescribing opioids to patients with children in the household.

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