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Clinical paper

National trends and outcomes of cardiac arrest in opioid overdose☆

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ABSTRACT

Aim: To investigate the epidemiology and outcomes of cardiac arrests associated with opioid overdoses. Recent data suggest that drug overdoses are responsible for more deaths than motor vehicle crashes or firearms in the United States each year, with opioids being involved in majority of drug overdose deaths. Despite the potential for opioids to cause cardiac arrest, few studies have examined this association.
Patients and methods: Using data from National (Nationwide) Inpatient Sample database from years 2000–2013, we identified hospitalizations with drug overdoses using ICD-9-CM codes. We further identified those with opioid overdose and those with cardiac arrest. We then assessed the proportion and trends of cardiac arrest and associated mortality in patients with opioid overdose. We also investigated if opioid overdose is an independent risk factor for cardiac arrest and mortality.
Results: Of 3,835,448 United States drug overdose hospitalizations, 16.4% were associated with prescription opioid overdose and 2.3% with heroin overdose. Cardiac arrest was most common with heroin overdose, followed by prescription opioids and least common in non-opioid overdose (3.8% vs 1.4% vs 0.6%; $p < 0.001$). Heroin overdoses have seen the greatest increase in rate of cardiac arrests. Both prescription opioids and heroin overdose were independent risk factors for cardiac arrest and mortality in these patients.
Conclusions: Cardiac arrest is more common in patients with opioid overdoses in comparison to non-opioid overdoses. The rate of cardiac arrest is increasing disproportionately in patients with opioid overdoses. Opioid overdoses are independent risk factors for both cardiac arrest and mortality in patients with overdoses.

Introduction

Recent data from the Centers for Disease Control and Prevention (CDC) shows that drug overdoses are responsible for a higher number of deaths each year in the United States than motor vehicle crashes or firearms [1]. Among those who die of drug overdoses, opioids were involved in 61% of the cases in 2014, making opioids the largest contributor to drug overdose deaths [2]. Opioids have an important role in the management of patients with acute and chronic pain and are a central component of comprehensive cancer pain treatment [3]. However, opioids have a significant potential for great harm and injudicious use of opioids can lead to adverse symptoms ranging from constipation to altered mental status and respiratory depression leading to cardiac arrest. The first decade of the new millennium has seen a rapid increase in opioid prescriptions such that consumption of hydrocodone doubled and that of oxycodone increased by almost 500% between 1999 and 2011 [4]. Alarmingly, the death rate associated with prescription opioid overdose has quadrupled during that time frame [5]. A parallel increase in heroin use has closely mirrored the increasing prescription opioid misuse [2] and up to 80% of heroin users report a history of prescription opioid use [5]. This represents a significant shift in the epidemiology of heroin use compared with the 1960s [6,7]. The highly addictive nature of prescription opioids coupled with relatively higher pricing for diverted prescription agents in comparison to heroin may be responsible for a trend towards increased heroin use [6]. Highly potent synthetic opioids are increasing being

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abused, and heroin contaminated with synthetic fentanyl was associated with 1013 deaths from 2005 to 2007 [8]. In fact, deaths associated with heroin use have nearly quadrupled from 2000 to 2013 [9]. With the ongoing opioid epidemic, the CDC included opioid overdose prevention to its top five public health challenges in 2014 [10] and published exhaustive guidelines for prescribing opioids for chronic pain in 2016 [11].

The epidemiology and treatment of cardiac arrest has likewise evolved over recent years. Multiple studies have shown improvements in survival in patients with cardiac arrest over time, yet cardiac arrest still results in mortality in over three fourths of its victims [12]. Respiratory depression from opioids can lead directly to respiratory arrest and subsequent cardiac arrest, in addition to direct cardiac toxicity from certain opioids [13]. Certain opioids such as methadone have ion channel-blocking properties that can potentially trigger arrhythmias and even cardiac arrest at higher doses [14]. Methadone does this by inhibiting the human Ether-a-go-go gene (hERG) that leads to blockade of the cardiac potassium ion current, leading to delayed cardiac repolarization and thus prolongation of QTc [15]. However, the epidemiology of cardiac arrest in opioid overdose remains unclear. The purpose of this study was to examine the proportion and trend of hospitalized cardiac arrests associated with opioid overdose and to compare the mortality of opioid overdose-associated cardiac arrest to non-opioid overdose-associated cardiac arrest. We further evaluated if opioid overdose is an independent risk factor for cardiac arrest, if opioid overdose is an independent risk factor for mortality among patients hospitalized with drug overdoses and if this association changes in those who suffered a cardiac arrest.

Methods

Study design and database

The Healthcare Cost and Utilization Project – National (Nationwide) Inpatient Sample (NIS) from years 2000–2013 was utilized for this study. NIS is the largest all-payer inpatient care database publicly available in the United States. It includes data from a 20% stratified sample of the United States community hospitals [16]. Information regarding patient age, race and sex along with primary payer, and hospital characteristics – teaching status, location (rural vs. urban), the size of hospital and hospital region – is provided in the database. In addition, each hospitalization entry provides information about principal, secondary, and procedural diagnoses. As the current study was a retrospective analysis of a hospital-based discharge data set that is available publicly from the Agency for Healthcare Research and Quality, it did not require institutional review board approval.

Study population

All hospitalizations of patients aged 20 years or older with drug overdoses were included in this analysis. In congruence with previous literature, drug overdoses were identified by ICD-9-CM codes 960–979, E850-858, E950.0-950.5, E962.0 and/or E980.0-980.5 [17]. As per previous literature, prescription opioid overdose was defined by ICD-9-CM codes 965.00, 965.02 and 965.09 whereas heroin overdose was defined as the presence of ICD-9-CM code 965.01 [17].

Study variables

We used NIS variables to determine demographic characteristics (age, sex and race), hospital characteristics (teaching status & location, bed-size, and region) and primary payer. We divided hospitals into tertiles based on the annual volume of overdose discharges (<66, 66–157, >157 per year). The burden of co-morbid diseases was identified using Deyo's modification of Charlson Comorbidity Index (CCI) [18]. We identified individuals on mechanical ventilation using ICD-9-CM procedure codes 96.70, 96.71, and 96.72. Cardiac arrest was defined using the ICD-9-CM code 427.5 and respiratory arrest using ICD-9-CM code 799.1.

Outcomes

Our primary outcomes of interest were the proportion and trends of cardiac arrest and associated mortality in patients with opioid overdose. We also evaluated if opioid overdose is an independent risk factor for mortality among patients hospitalized with drug overdoses and if the magnitude of this association changes in those with cardiac arrest.

Statistical analysis

STATA 14.0 (StataCorp, College Station, TX) was used for all statistical analyses. We used discharge weights with survey commands as recommended by HCUP-NIS to generate national estimates [19]. We used chi square and *t*-tests to compare categorical and linear variables respectively. We used linear regression to compare trends over time. We used Chow test to compare slopes of trend lines [20–22].

We generated a multivariable regression model to assess if prescription opioid and/or heroin overdose are independent predictors of cardiac arrest. The model was adjusted for patient age, sex, race, primary payer, Charlson's score, hospital bed size, volume, region, location & teaching status, use of mechanical ventilation, respiratory arrest, classification of intent of poisoning as suicidal, homicidal, accidental or unknown and year of admission. The c-statistic of the model was 0.87 suggesting excellent predictive value of the model used.

Similarly, a multivariable regression model was generated to assess if prescription opioid and/or heroin overdose are independent predictors of mortality. The model was adjusted for patient age, sex, race, primary payer, Charlson's score, hospital bed size, volume, region, location & teaching status, use of mechanical ventilation, respiratory arrest, cardiac arrest, classification of poisoning as suicidal, homicidal, accidental or unknown and year of admission. The c-statistic of the model was 0.92 suggesting excellent predictive value of the model used. We then performed an exploratory analysis by including the interaction term between variables for cardiac arrest and opioid overdose in the final model to assess for the differential effect of opioid overdose on odds of mortality based on presence of cardiac arrest.

Missing values were less than <1% for all variables except race that was missing in 19.1% observations. We used casewise deletion to handle missing data. To make sure that this method of handling missing data did not affect our results we performed logistic regressions by using missing values of race as a "missing" category in the models.

Results

There were 3,835,448 (95% CI: 3,712,849–3,958,048) hospitalizations associated with drug overdoses in the 14-year study period. Of these, 16.4% were associated with prescription opioid overdose and 2.3% with heroin overdose. The total number of hospitalizations for drug overdose per year increased by 48.9% during the study period, from 207,155 in 2000–308,625 in 2013. Admissions with heroin overdose more than doubled during the same time (from 5251 in 2000–12,025 in 2013), and the annual number