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Ronald Klebacher, Matthew I. Harris, Navin Ariyaprakai, Ammundeep Tagore, Vince Robbins, Larissa Sophia Dudley, Robert Bauter, Susmith Koneru, Ryan D. Hill, Eric Wasserman, Andrew Shanes & Mark A. Merlin

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Original Contributions

Incidence of Naloxone Redosing in the Age of the New Opioid Epidemic

Ronald Klebacher, DO, Matthew I. Harris, MD, Navin Ariyaprakai, MD, Ammundeep Tagore, MD, MSHA, MBA, Vince Robbins, FACHE, Larissa Sophia Dudley, MD, Robert Bauter, MAS, NRP, Susmith Koneru, MD, Ryan D. Hill, DO, Eric Wasserman, MD, Andrew Shanes, EMT, Mark A. Merlin, DO, EMT-P

Abstract

Study Objective: Naloxone, an opioid-antagonist deliverable by an intra-nasal route, has become widely available and utilized by law enforcement officers as well as basic life support (BLS) providers in the prehospital setting. This study aimed to determine the frequency of repeat naloxone dosing in suspected narcotic overdose (OD) patients and identify patient characteristics. **Methods**: A retrospective chart review of patients over 17 years of age with suspected opioid overdose, treated with an initial intranasal (IN) dose of naloxone and subsequently managed by paramedics, was performed from April 2014 to June 2016. Demographic data was analyzed using descriptive statistics to identify those aspects of the history, physical exam findings. **Results:** A sample size of 2166 patients with suspected opioid OD received naloxone from first responders. No patients who achieved GCS 15 after treatment required redosing; 195 (9%) received two doses and 53 patients received three doses of naloxone by advanced life support. Patients were primarily male (75.4%), Caucasian (88.2%), with a mean age of 36.4 years. A total of 76.7% of patients were found in the home, 23.1% had a suspected mixed ingestion, and 27.2% had a previous OD. Two percent of all patients required a third dose of naloxone. **Conclusion:** In this prehospital study, we confirmed that intranasal naloxone is effective in reversing suspected opioid toxicity. Nine percent of patients required two or more doses of naloxone to achieve clinical reversal of suspected opioid toxicity. Two percent of patients received a third dose of naloxone.

Key words: heroin; overdose; fentanyl; Naloxone; prehospital; EMS; Emergency Medical Services

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Address correspondence to Mark A. Merlin, DO, Newark Beth Israel Medical Center, Emergency Medicine, 201 Lyons Avenue, Newark, NJ 07112-2027, USA. E-mail: markamerlin@gmail.com

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Introduction

In 2016, the Centers for Disease Control and Prevention (CDC) reported that 91 Americans die every day from opioid and opiate overdoses (OD), with more than thirty-three thousand deaths reported in the United States in 2015.[1] For decades, paramedics, prehospital providers of advanced life support (ALS), have had the ability to reverse suspected opioid OD via intravenous (IV), intramuscular (IM), or subcutaneous (SC) administration of naloxone, an opioid-receptor antagonist. Within recent years, intranasal (IN) delivery of naloxone has not only been considered to be a safer and an equally effective method of administration, but has led to the widespread use by other first responders, community members, and families to reverse potentially fatal opioid overdoses.[2–6]

Further complicating the issue is the predominance of mixed ingestions with other intoxicating agents[7,8] as well as the rising prevalence of stronger illicit opioids including carfentanyl, and the potential need for higher naloxone dosing.[9–14]

Our primary endpoint was to determine the incidence of repeat naloxone dosing for patients with suspected opioid OD. Our secondary endpoint was to describe characteristics of those patients who received additional dosing from paramedics after an initial administration by first responders or community members.

The State of New Jersey is a two-tier EMS system, with first response and basic life support services provided by a mix of volunteer and paid third-party agencies, fire departments, and law enforcement. The dispatch of paramedics providing ALS care is based on standing emergency medical dispatch protocols where certain call-types automatically trigger an ALS response, or where requested by BLS or first responders upon their arrival and evaluation. Currently, dispatch for a drug overdose or altered mental status automatically requires an ALS response, even if first responders provide naloxone and the patient has returned to baseline mental status. At the time of this study, under NJ regulations for naloxone administration, BLS providers could administer a single 2 mg dose. Police can administer more but yield to BLS upon arrival and cannot give less than 2 mg. All second doses of naloxone in our study were given by ALS.

The scope of practice for ALS providers is guided by State protocols, but ultimately established by the institutional protocols set forth in cooperation with the medical director. ALS providers are paramedics; no intermediate level providers exist in the state. Paramedics can initiate treatment with standing orders but are required to consult an online medical control physician during each patient interaction, optimizing the provision of high quality prehospital care. They can obtain intravenous and intraosseous access, perform advanced airway protective maneuvers, and administer medications through a number of delivery routes. By law, in New Jersey two paramedics must staff each ALS unit.

Data were obtained from the largest provider of EMS services in the State of New Jersey, responding to more than 80000 patients per year with 420 paramedics, EMTs, nurses, and EMS physicians. This agency, a hospital-based regional system with paid paramedics and basic EMTs, utilized 25 ALS and 12 BLS units to deliver patients to 43 receiving hospitals in a diverse environment that includes rural, suburban, and urban settings. The majority of towns have individual volunteer basic life support ambulances and the system provides ALS. Most of the towns are capable of providing intranasal naloxone.

METHODS

The study was approved by the Institutional Review Board at an academic teaching hospital. We performed a retrospective chart review of the electronic medical record (EMR) (RescueNet Zoll ePCR_Broomfield, CO, USA) from the largest provider of EMS services in the State of New Jersey. Five of the authors (RK, MH, RB, RH, AS) underwent training to identify target cases. Charts were selected first by the presence of documentation of naloxone administration, and secondly by the appearance of keywords including: drug overdose, substance abuse, poisoning, unconscious, and unresponsive. We targeted our search to identify patients for whom ALS providers responded for suspected opioid OD and for whom naloxone was administered.

We included all patients over the age of 17 years treated from April 2014 to June 2016. All patients received a dose of naloxone from BLS or ALS providers. Patients were initially given a minimum of 2-mg IN naloxone via law enforcement or BLS first responders under state regulations. We excluded patients less than 18 years or patients who received naloxone in cardiac arrest in conjunction with other lifesaving efforts when the cause of the arrest was not obviously related to narcotics. We defined the resolution of symptoms as the return of a normal mental status, specifically a GCS 15, as evidence for successful naloxone reversal in an opioid overdose. GCS 15 was utilized as objective criteria for reversal of agent since RR was felt to be too subjective. GCS 15 was confirmed for each patient by a narrative description in the EMR and a drop down menu. For charts with missing, conflicting or ambiguous data points, the abstractors reviewed the written narrative in the EMR for clarification. Inter-rater agreement was confirmed by one of the authors (RK), who independently reviewed each abstraction.

We extracted demographic data, assessments, interventions, and prehospital outcomes for the purpose of both descriptive and statistical analysis. Data that was examined included the following demographics: age, gender, ethnicity, prior OD, the presence of drug paraphernalia, weight, past medical history, current use of chronic pain medications, concomitant use of benzodiazepines, alcohol use, and known mixed ingestion. Additional data included times of ALS dispatch, arrival and transport times, and physical exam findings.

We described the data using descriptive statistics; continuous variables were presented with mean, standard deviation, and median. Categorical variables were presented with counts and percentages. The data was assessed for normality and Student's T test was used to assess the mean difference between the variables. A sub-group analysis of a subset of patients receiving a third dose of naloxone was conducted. All statistical analyses were performed with SPSS (version 24.0; IBM Corporation, Armonk, NY) with level of significance defined as $p < 0.05$.

RESULTS

From April 2014 through June 2016, 2,166 patients received naloxone for suspected opioid OD. One thousand nine hundred-seventy one (91%) experienced complete resolution and reversal of symptoms after a single dose of IN naloxone and required no further management by ALS providers. The remaining 195 patients (9%) received a second dose of naloxone by ALS providers after failing to improve with the initial IN dose. 53 (2.4%) required a third dose of naloxone. Patient demographics, physical exam findings, and scene characteristics are listed in Table 1A and B.

TABLE 1. Demographics, scene description, and biometric data.

Demographics, Scene Description, and Biometric Data				
	Count (n)	Percentage		
A.				
Patients receiving 2nd dose	195	100.0		
Age (yrs.) [mean (SD)]	36 (13.2)			
Male	147	75.4		
Ethnicity				
Caucasians	172	88.2		
African American	11	5.6		
Hispanic	12	6.2		
Location				
Home	151	77.4		
Street	19	9.7		
Other	3	1.5		
Drug paraphernalia present	103	52.8		
Presumed Mixed Ingestion	44	22.6		
Daily Alcohol use	25	12.8		
Chronic Pain Med Use	25	12.8		
Prior Overdose				
Yes	53	27.2		
Unknown	142	72.8		
Physical Exam Findings ($n = 195$)	Count (%)	Mean (SD)	Median	Range (min-max)
B.				
Weight (kgs.)	195 (100)	84.9 (22.5)	81.7	147 (34–181)
Altered Mental Status	195 (100)	—	—	—
Mental Status		—	—	—
Alert	70 (35.9)	—	—	—
Voice	13 (6.7)	—	—	—
Pain	21 (10.7)	—	—	—
Unresponsive	91 (46.7)	—	—	—
Glasgow Coma Scale	195 (100)	5.2 (3.7)	3.0	12 (3–15)
Heart Rate (bpm)	195 (100)	110.3 (25.7)	111.0	220 (0–220)
Respiratory Rate (bpm)	195 (100)	10.4 (6.9)	10.0	36 (0–36)
Systolic Blood Pressure (mm Hg)	188 (96.4)	136.5 (33.3)	137.0	238 (0–238)
Diastolic Blood Pressure (mm Hg)	183 (93.4)	82.0 (27.2)	83.0	217 (0–217)
Oxygen Saturation (%)	148 (75.8)	86.8 (24.7)	95.5	100 (0–100)
Pupil Size (mm)		—	—	—
Apneic	48 (24.6)	—	—	—
Cardiac arrest	14 (7.2)	—	—	—

TABLE 2. Advanced life support interventions and patient outcomes.

Time to ALS Arrival (mean, range)	11	1–27
ALS Scene Time	19	2–65
Transport Time	11	1–26
Route of Administration		
Intravenous	162	83%
Intranasal	30	15%
Intramuscular	2	1%
Intraosseous	2	1%
Naloxone Dosage		
0.4 mg	50	26%
1 mg	21	21%
2 mg	100	51%
Other	5	2%
Received 3rd Dose of Naloxone	53	27%
ET intubation	13	7%
Transported by ALS	193	98%
Refusal of Medical	2	2%
Mortality	1	0.05%

Patients were predominantly male (75.4%), Caucasian (88%), with a mean age 36.4 years, and were most often found at home (77%). Drug paraphernalia was present at 52.8% of scenes, and 27.2% of patients had experienced a previous OD. The response time from dispatch of ALS to scene arrival averaged eleven minutes, and on-scene time averaged 19 minutes.

All patients who received a second dose of naloxone had a depressed mental status on arrival of ALS providers with a mean GCS score of 5.3 ± 3.7 and a median GCS score of 3. The mean respiratory rate was 10.4 breaths per minute (bpm) with a mean oxygen saturation of 86.8% (median of 95.5%). A total of 48 of the 198 (24.6%) patients were found to be apneic. Fourteen (7.2%) patients were reported to have been in cardiac arrest upon arrival of law enforcement or BLS, received compressions and 13 had return of spontaneous circulation prior to ALS arrival. Of note, data

TABLE 3. Physical exam findings for patients who received a third dose.

Physical Exam findings of patients who received 3rd dose.	Count (%)	Mean (SD)	Median	Range (Min–Max)
Altered Mental Status	53 (100)	—	—	—
Mental Status	53 (100)	—	—	—
Alert	20 (37.7)	—	—	—
Voice	3 (5.7)	—	—	—
Pain	7 (13.2)	—	—	—
Unresponsive	23 (43.4)	—	—	—
GCS	53 (100)	4.91 (3.5)	3	12 (3–15)
Heart Rate	53 (100)	108.5 (22.1)	109	110 (66–176)
Respiratory Rate	53 (100)	12.3 (9.1)	10	36 (0–36)
Systolic Blood Pressure	51 (96.2)	142.5 (28.7)	138	148 (90–238)
Diastolic Blood Pressure	50 (94.3)	87.1 (28.9)	87	217 (0–217)
Oxygen Saturation	41 (77.4)	86.4 (25.4)	96	100 (0–100)
Pupil < 2 mm	28 (52.8)	—	—	—
Apneic	13 (24.5)	—	—	—
Cardiac Arrest	2 (3.7)	—	—	—
Endotracheal Intubation	12 (22.6)	—	—	—
No Clinical Improvement	16 (30.2)	—	—	—

was incompletely recorded in pre-naloxone oxygen saturation in 49 patients (24.6%) and blood pressure measurements in 7 patients (3.6%).

Fifty-three (2.4%) of the 2,166 patients received a third dose of naloxone. Compared to those patients who recovered after a second dose, patients who received a third dose of naloxone had similar GCS scores (4.9 vs. 5.3, P = 0.305), oxygen saturations (86.4 vs. 86.9, P = 0.734 and systolic blood pressures (142.5 vs. 133.6, P = 0.42). Thirty-seven of the 53 patients who received this third dose demonstrated clinical improvement. Twelve patients underwent endotracheal intubation. One patient, who was found in cardiac arrest, did not survive.

DISCUSSION

The United States is in the midst an epidemic of opioid drug abuse. Between 1999 and 2011, the rate of overdose deaths from prescription opioids has gone up 400%, and heroin related deaths have increased 45%.[15] Moreover, in the past three years the rate of death from heroin overdose has nearly tripled from 1.0 per 100000 to 2.7 per 100000.[16] Between 1997 and 2007, the rate of opioid prescribing increased by 600%. Recent estimates suggest that 25 million Americans are now using opioids for recreational purposes.[15]

The past decade has seen the emergence of two important changes in the use of naloxone. First, the widespread use of mucosal atomizer devices (MAD) has allowed for the safe and effective administration of naloxone through an intranasal route. This advancement has led to the distribution of naloxone to other first responders including firefighters, police officers, and BLS emergency medical technicians. Also prevalent over the past few years has been the emergence of naloxone community programs, where family members have become the true first responders, often administering the first dose of naloxone prior to the arrival of medical aid.

The implications of this data are far-reaching. Medical directors and public safety officials are tasked with providing high quality prehospital care. An understanding of the need for advanced life support providers at these call-types affects the availability of valuable resources to respond to other emergencies. Public health officials could use this data to target both law enforcement and public health programs in areas where heroin use is most prevalent or a where scarcity of health resources exist.

To our knowledge, this retrospective chart review is the largest cohort study of patients with a suspected opioid OD who required repeat dosing of naloxone in the prehospital setting. In this study, 91% of patients improved after a single dose of naloxone, achieving the necessary GCS score of fifteen to meet our definition of clinical reversal. This finding is consistent with prior research.[2,17] The remaining 9% of patients had diminished mental status on arrival of our paramedics. This 9% did not respond to an initial dose of IN naloxone administered by first responders, and as such, would warrant continued ALS response for further evaluation. However, for patients with suspected opioid OD who achieve a GCS of 15 after a single administration of IN naloxone additional resources may not be required. To be clear, none of the patients who achieved a GCS score of 15 had a relapse in symptoms or required additional resources.

Patients were most commonly non-Hispanic Caucasian, young, and found in their home with drug paraphernalia present. Of the 195 patients who required further intervention, paramedics most often opted to administer naloxone intravenously, instead of a second IN administration (83% vs. 15%). Local and institutional protocols allow state paramedics to choose from IV, IO, IM, or IN routes. It is likely that paramedics are obtaining IV access in the anticipation of additional resuscitation in patients who did not respond to an initial dose of naloxone. The preference toward the IV administration of naloxone after a failure to improve after IN administration may have biased our providers towards the IV route. This is despite numerous studies that have demonstrated the non-inferiority of IN naloxone when compared to IV dosing to reverse opioid overdoses.[2–6]

As noted previously, relapse was defined as a GCS < 15. Patients were observed for an average of 30 minutes from arrival to BLS leaving the scene or transport to the hospital. This 30-minute period is excessive in some systems; however, in our two-tiered system, BLS or ALS can wait prolonged periods for the other to arrive in order to determine disposition or the decision to transport.

There was variability in the repeat dose of naloxone. In this study, 9% needed a second dose and 2% needed a third dose to achieve a GCS 15. Standing orders in New Jersey generally recommend a range of 0.4–2.0 mg/dose intravenously. Paramedics administered a 2 mg dose to 51% of patients in this cohort. A total of 26% of patients received 0.4 mg and 21% received 1 mg. All intranasal naloxone was given at 2-mg per dose. Different providers may offer different dosing recommendations based on their experience and expertise. While some healthcare providers suggest that naloxone should be given in small doses or that adequate ventilation using a bag-valve-mask is sufficient to prevent hypercapnia from hypoventilation.[17] The ability to adequately ventilate with good Bag-Valve-Mask seal while transporting a patient in a moving ambulance is limited. Additionally, ongoing monitoring of respiratory rate, pulse oximetry, end-tidal CO2, and airway maintenance is limited by the numbers of providers in an ambulance and by the unpredictable movements experienced in the back of a moving vehicle.

We found it interesting that our cohort of 195 patients who received additional naloxone dosing had higher respiratory rates than we would have expected. This may be in part due to the fact that all of these patients received prior intranasal dosing by first responders, and as such, may have been partially resuscitated.

Fifty-three or 2.4% of the 2166 patients received a third dose of naloxone for suspected opioid OD, despite a lack of clinical response to two prior doses. We expected perhaps that these patients would have certain defining characteristics, namely that their clinical presentation may have been more severe. We were surprised to find that these 53 patients had no statistically significant differences from the larger cohort. There may be some clinical significance that patients receiving greater than two doses had a more depressed GCS score (3 vs. 5), but neither GCS nor any other physiologic parameter met statistical significance. However, approximately one third of the 53 patients who received a third dose of naloxone did not improve, suggesting other etiologies for altered mental status that should be considered by the ALS provider.

We found that repeat doses of naloxone were given for altered mental status yet patients had mean oxygen saturations of 95 percent with mean respiratory rates of 10.4. We are surprised more hypoventilation did not exist at the same time patients were altered. It is possible that the respiratory rate was erroneously recorded as faster than it actually was or a mixed opioid overdose affects mental status more than respiratory status.

Fourteen patients were documented to be in cardiac arrest with evidence of opioid overdoses. This was determined either by drug paraphernalia at the scene or bystander statements at the scene. CPR was initiated by law enforcement or bystanders. Upon arrival of BLS, no one had shockable rhythm and CPR was continued. Intranasal naloxone was given by either law enforcement or BLS. All of the cardiac arrest patients had CPR done by police or bystanders and had return of spontaneous circulation before the arrival of ALS subsequently making initial cardiac arrest difficult to verify. It is possible these patients had extreme hypoventilation and hypotension or bradycardia which resulted in the interpretation of cardiac arrest. In general, protocols continue to support naloxone administration in cardiac arrest with evidence of opioid overdoses.[18] Subsequently, we included this population in the study group.

Two-thirds of the 53 patients who received a third dose of naloxone demonstrated marked clinical improvement to a GCS 15, suggesting in fact that opioid intoxication was the primary reason for their clinical presentation. Recent studies have shown that an emerging class of potent street narcotics, such as carfentanyl, have required higher doses of naloxone to achieve clinical reversal of symptoms.[12,14] The presence of other intoxicating substances may also have been a confounder. Mixed ingestions were common in this cohort of patients. With the emergence of carfentanyl and other extremely potent opioids in the recreational drug use arena, and without the benefit of extensive toxicological testing, it is difficult to draw conclusions regarding the possibility of a dose-dependent relationship between these potent opioids and the need for escalating dosing of naloxone for reversal of symptoms. The possibility of co-ingestions, particularly with substances that can lead to respiratory depression and altered mental status, may explain why some patients required repeat dosing or failed to improve at all after multiple administrations of naloxone by ALS providers.

It is difficult to draw conclusions regarding the best dose or route of delivery of naloxone by ALS providers after the administration of an initial IN dose by primary responders, as there is great variability in training, experience, and comfort level for EMTs, firefighters, and police offers in the management of suspected opioid OD. The authors are unable to comment on the dosing or efficiency of delivery by the primary responders, as their training and protocols do not fall under the same medical supervision. However, the growing presence of community programs providing IN naloxone delivery systems to the public suggests that administration via the nasal route is relatively easy, with minimal differences in delivery, and relatively harm-free.[2–4]

LIMITATIONS

There are a number of limitations to this study, including those inherent to a retrospective chart review: limitations in selecting a cohort population and the accuracy and completeness of recorded data points in the EMR. Even though this agency utilizes a common electronic medical record, requiring certain data points for chart completion, data points are manually entered and therefore subject to human error.

The presumptive diagnosis of suspected opioid OD is a clinical one, based on the initial physical assessment of the paramedics as well as other information including the presence of drug paraphernalia. Our paramedics often, in attempt to offer early and effective interventions for patients with suspected OD, will administer naloxone prior to or concomitant with the completion of the physical exam and vital signs. As such, we cannot be certain that all the reported initial vital signs were in fact obtained prior to the administration of naloxone by our providers.

CONCLUSION

This study supports evolving literature that patients with an opioid OD can be successfully reversed with IN naloxone provided by first responders. Patients who fail to achieve a GCS of 15 warrant further evaluation by advanced providers. Our study aimed to provide an evidence-based recommendation to identify patient characteristics that might cue prehospital providers to the need for repeat doses of naloxone. In the austere prehospital environment, with limited resources to confirm a diagnosis, delivering naloxone—a medication with few side effects—may be life-saving.

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