PRELIMINARY REPORTS

CAN NEBULIZED NALOXONE BE USED SAFELY AND EFFECTIVELY BY EMERGENCY MEDICAL SERVICES FOR SUSPECTED OPIOID OVERDOSE?

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ABSTRACT

Background. Emergency medical services (EMS) traditionally administer naloxone using a needle. Needleless naloxone may be easier when intravenous (IV) access is difficult and may decrease occupational blood-borne exposure in this high-risk population. Several studies have examined intranasal naloxone, but nebulized naloxone as an alternative needleless route has not been examined in the prehospital setting. **Objective.** We sought to determine whether nebulized naloxone can be used safely and effectively by prehospital providers for patients with suspected opioid overdose. **Methods.** We performed a retrospective analysis of all consecutive cases administered nebulized naloxone from January 1 to June 30, 2010, by the Chicago Fire Department. All clinical data were entered in real time into a structured EMS database and data abstraction was performed in a systematic manner. Included were cases of suspected opioid overdose, altered mental status, and respiratory depression; excluded were cases where nebulized naloxone was given for opioid-triggered asthma and cases with incomplete outcome data. The primary outcome was patient response to nebulized naloxone. Secondary outcomes included need for rescue naloxone (IV or intramuscular), need for assisted ventilation, and adverse antidote events. Kappa interrater reliability was calculated and study data were analyzed using descriptive statistics. **Results.** Out of 129 cases, 105 met the inclusion criteria. Of these, 23 (22%) had complete response, 62 (59%) had partial response, and 20 (19%) had no response. Eleven cases (10%) received rescue naloxone, no case required assisted ventilation, and no adverse events occurred. The kappa score was 0.993. **Conclusion.** Nebulized naloxone is a safe and effective needleless alternative for prehospital treatment of suspected opioid overdose in patients with spontaneous respirations. **Key words:** prehospital; overdose; nebulized; naloxone; opiate

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INTRODUCTION

Naloxone is an opioid antagonist that is used clinically for the reversal of mental status and respiratory depression. Emergency medical services (EMS) providers commonly administer naloxone to patients with suspected opioid overdose by several different routes, including intravenous (IV), intramuscular (IM), subcutaneous (SQ), sublingual (SL), and intranasal (IN). Intravenous efficacy has been widely documented and remains the most common route of administration.[1] However, IV access is often difficult to obtain in opioid overdose patients because of venous damage from previous IV drug abuse. Additionally, the IV, IM, SQ, and SL routes require the use of a needle, putting the prehospital provider at risk for occupational blood exposure.

Intranasal naloxone is a needleless method of administration that has been used with some success in the prehospital setting.[2–7] Nebulized naloxone is another needleless route favored by some providers for over a decade; however, the published literature on the use of nebulized naloxone for opioid overdose is

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limited. A 1998 meeting abstract demonstrated limited efficacy of nebulized naloxone in volunteers sedated with morphine. In 2003, a case report showed that nebulized naloxone successfully reversed methadone intoxication in a single patient.[8] Finally, in 2009, another meeting abstract concluded that nebulized naloxone effectively improved alertness scores in moderately depressed patients with suspected opiate intoxication in the emergency department. However, nebulized naloxone as an alternative needleless route has not been examined in the prehospital setting.

We sought to determine whether nebulized naloxone can be used safely and effectively by prehospital providers for patients with suspected opioid overdose.

METHODS

We performed a retrospective analysis of all consecutive cases where nebulized naloxone was administered by Chicago EMS from January 1, 2010, to June 30, 2010. The Chicago Fire Department is a multitiered, fire-based municipal EMS provider for a population of 2.8 million with over 220,000 annual transports. Altered mental status calls to our 9-1-1 center receive a standardized, rapid response by Chicago EMS. All dispatchers, first responders, and basic life support (BLS) and advanced life support (ALS) providers operate under uniform medical control with all field-response staff receiving didactic and skill station education for protocol updates before implementing changes. The altered mental status protocol for ALS providers previously included empiric administration of naloxone by IV or IM route for suspected opioid overdose or undifferentiated depressed respirations. In 2009, all ALS providers underwent a four-hour didactic session on biennial regional protocol changes and a subsequent field drill where naloxone by nebulization was introduced as an alternative to the IV or IM route of delivery. The protocol-specified nebulization of 2 mg of naloxone with 3 mL of normal saline as empiric treatment for suspected opioid overdose or undifferentiated depressed respirations as long as the patient had some spontaneous respiratory effort, no apnea, and no severe cardiorespiratory compromise (shock, impending respiratory arrest). Per protocol, patients who did not meet these criteria or who did not respond to nebulized naloxone were to be given naloxone 0.8–2 mg IV or IM. In addition, all ALS providers undergo regular lecture and skills station education by EMS resource hospitals and fire department field training officers.

The study population included all patients transported by ALS providers where nebulized naloxone was administered for any reason. Included in our study analysis were cases where naloxone was administered for suspected opioid overdose, altered mental status, or depressed respirations. Excluded from analysis were cases where nebulized naloxone was given for opioid-triggered asthma and cases with incomplete outcome data. This study was approved by the Stroger Cook County Hospital Institutional Review Board and the Region 11 EMS System Data/Research Committee.

The primary outcome was patient response to nebulized naloxone documented by paramedics as complete, partial, or no improvement. Secondary outcomes included need for rescue naloxone (IV or IM), need for assisted ventilation by bag–valve–mask (BVM) assistance or intubation, and adverse antidote events (respiratory arrest, cardiac arrest, death in the field). Study data were abstracted from the Chicago Fire Department EMS electronic patient care reporting system. In this system, patient data are entered manually by EMS staff during and immediately at the conclusion of the patient encounter. The patient care data registry includes closed-format response categories for relevant patient demographic data (age, gender), past medical history, social history, medications, vital signs, physical examination, EMS-delivered interventions, clinical response to interventions, time stamps, and a free-text comment section. This EMS patient care data registry undergoes monthly quality evaluation by paramedic field chiefs and a multidisciplinary committee including physician members. Data for our study were abstracted from this registry by two independent physicians and entered into a structured Microsoft Excel database (Microsoft Corp., Redmond, WA). Variables and outcomes were determined a priori and a standardized data-abstraction instrument was created and piloted. Data abstractors underwent training before the start of the study and periodic meetings were held to monitor the progress of the data abstractors and review the coding rules. Ambiguous data were resolved by physician committee. Ten percent of the study cases were randomly selected and underwent data abstraction by a second reviewer to assess interrater reliability. To meet the objectives of our study, data abstracted from this registry included age, gender, time of scene arrival, indication for nebulized naloxone administration, time and dose of nebulized naloxone administration, clinical response to nebulized naloxone (complete, partial, none), administration and timing of a rescue dose, rescue dose route (IV or IM), response to rescue dose (complete, partial, none), time to hospital arrival, initial and final vital signs, and initial and final Glasgow Coma Scale score (GCS).

Primary study data were analyzed using descriptive statistics. Kappa coefficient interrater reliability for data abstractors was calculated. StatsDirect (version 2.7.8, 2010, Cheshire, UK) was used for all data management.

RESULTS

Out of 129 consecutive cases in which nebulized naloxone was administered during the six-month study period, 105 cases met the study inclusion criteria.

Twenty-one cases were excluded because naloxone was given for opioid-triggered asthma and three cases were excluded because of incomplete outcome data. For the 105 cases included in our analysis, 74% of the patients were male and the mean age was 45.4 years (range 16 to 77). The documented indication for nebulized naloxone administration was suspected opioid overdose in 70 patients (66.7%), altered mental status in 34 patients (32.3%), and respiratory depression in one patient (0.9%). Twenty-three (22%) had complete response, 62 (59%) had partial response, and 20 (19%) had no response to nebulized naloxone. Table 1 lists the clinical characteristics associated with the outcome groups, and the mean time to hospital (total scene and transport time). Eleven cases (10%) received rescue naloxone: IV six times and IM five times. Of these, five had a complete response, four had a partial response, and two had no response. Patients with a complete response to nebulized naloxone received naloxone earlier than the nonresponders (mean 5.1 to 8.9 minutes). No case needed intubation or BVM ventilation, and no adverse events occurred. The kappa score was 0.993 between the two data abstractors.

DISCUSSION

We found that nebulized naloxone is a safe and effective needleless antidote for prehospital treatment of suspected opioid overdose in patients with spontaneous respirations. Eighty percent of the patients treated had some response to treatment, and only 10% of the patients were given a second dose of naloxone. No patient required intubation or BVM-assisted ventilation.

An alternate needleless route of naloxone administration for EMS is important for many reasons. First, deaths from unintentional drug overdoses have been on the rise since 1990 and are now the second leading cause of accidental death in the United States.[9] The increase is in large part due to the rising number of opioid (synthetic narcotic) overdoses, which resulted in 11,499 deaths in 2007. Heroin alone resulted in an additional 2,000 accidental deaths in 2007. Despite other drug choices for substance users, visits to emergency departments for opioid abuse doubled between 2004 and 2008. Preventing occupational blood exposure is a second important reason for needleless routes of administration of naloxone. EMS providers function on the frontline, treating a problem that is growing at astounding rates in a high-risk patient population with an increasing prevalence of blood-borne infections, including hepatitis B and C and human immunodeficiency virus (HIV). A 2006 study estimated 49,000 occupational blood exposures per year for U.S. paramedics, including over 10,000 needlesticks.[10] Additionally, anecdotal evidence and a published case report suggest that nebulized naloxone administration can more gently awaken a patient than IV bolus administration, thus averting sudden patient agitation.[8] In our study, no patient signed out against medical advice and all patients were transported to the hospital.[11] Nebulization may represent a potentially safer way for the prehospital provider to reverse opioid overdose. Finally, the resource investment needed by EMS systems to implement nebulized naloxone is minimal. Most ALS and some BLS systems already use nebulization equipment for the treatment of asthma, and naloxone is almost universally used by ALS systems.

Previous studies of nebulized naloxone were lacking in the medical literature. Our study used a rigorous retrospective methodology.[12] Data were abstracted in a systematic manner with predefined variables and outcomes, data abstractors were trained, and we had excellent interrater reliability. All data were collected in real time by paramedics who were not aware of this study, therefore limiting potential bias. Finally, our study was conducted in a large urban EMS system that provides care to a population with broad racial and socioeconomic representation.

LIMITATIONS AND FUTURE RESEARCH

Some limitations to our study need to be acknowledged. First, the retrospective nature of the study is not ideal. However, we took steps to maintain the highest possible standard of data management by using data from a rigorously maintained clinical registry, defining strict inclusion and exclusion criteria, defining all study variables and definitions a priori, and assessing

TABLE 1. Characteristics of the Patients by Their Response to Nebulized Naloxone

Clinical Characteristics	Complete Response $N = 23$	Partial Response $N = 62$	No Response $N = 20$
Gender—% male	60%	75%	86%
Age—mean (SD), years	46 (11.6)	45 (12.4)	47 (12.0)
Dose—mean (range), mg	1.8 (0.4–3.0)	1.7 (0.4–4.0)	1.4 (0.4–2.0)
Time to medication—mean (SD), min	5.1 (5.2)	7.2 (5.2)	8.9 (6.5)
Initial RR—mean (SD), breaths/min	13.7 (4.3)	14.6 (3.8)	18.2 (5.9)
Initial GCS—mean (SD)	11.9 (3.8)	11.8 (3.8)	10.9 (4.8)
Time to hospital—mean (SD), min	18.5 (9.9)	20 (7.5)	22.7 (6.3)

GCS = Glasgow Coma Scale score; RR = respiratory rate; SD = standard deviation.

interrater reliability. Second, patient response to treatment was subjective and based on paramedic impression; however, this is how real treatment decisions are made in the field. No objective measurement scale currently exists to quantify opioid-induced sedation and response to treatment in the prehospital or emergency department setting. The literature on intranasal naloxone exemplifies this problem, thus the GCS, respiratory rate (RR), and paramedic impression have been used as outcome measures by others as well.[4–7] Future studies should include unbiased observers in the field to grade patient response to treatment using a universally accepted measurement tool. Despite an electronic record and real-time data collection, in some cases data were incomplete, which occurs in many busy EMS systems where the need for urgent patient care takes precedence over documentation. We sought to minimize this limitation by using only cases with complete outcome data recorded. Finally, we did not compare nebulized naloxone with IV naloxone, the recognized "gold standard," nor were we able to confirm opioid overdose through hospital records. It is important to note that this was a pilot study to assess the safety and efficacy of nebulized naloxone by prehospital providers, and a future study will attempt comparison between these two routes of administration.

CONCLUSION

Nebulized naloxone is a safe and effective needleless alternative for prehospital treatment of suspected opioid overdose in patients with spontaneous respirations.

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