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Selected Topics: Prehospital Care

PREHOSPITAL NALOXONE AND EMERGENCY DEPARTMENT ADVERSE EVENTS: A DOSE-DEPENDENT RELATIONSHIP

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☐ **Abstract—Background: The purpose of this study was to evaluate prehospital and emergency department (ED) interventions and outcomes of patients who received prehospital naloxone for a suspected opioid overdose. Objectives: The primary objective was to evaluate if the individual dose, individual route, total dose, number of prehospital naloxone administrations, or occurrence of a prehospital adverse event (AE) were associated with the occurrence of AEs in the ED. Secondary objectives included a subset analysis of patients who received additional naloxone while in the ED, or were admitted to an intensive care or step-down unit (ICU). Methods: This was a retrospective, observational chart review of adult patients who received prehospital naloxone and were transported by ambulance to a suburban academic tertiary care center between 2014 and 2017. Descriptive, univariate, and multivariate statistics were used, with $p < 0.05$ indicating significance. Results: There were 513 patients included in the analysis, with a median age of 29 years, and median total prehospital naloxone dose of 2 mg. An increasing number of prehospital naloxone doses, an occurrence of a prehospital AE, and a route of administration other than intranasally for the first dose of prehospital naloxone were significantly associated with an increased likelihood of an ED AE. Patients who received < 2 mg of prehospital naloxone had the least likelihood of being admitted to an ICU, whereas patients who received at least 6 mg had a dramatically increased likelihood of ICU admission. Conclusions: Our results suggest that an increasing number of prehospital naloxone doses was significantly associated with an increased likelihood of an ED adverse event.**

☐ **Keywords—prehospital; emergency medical services; paramedic; naloxone; opioid; overdose**

INTRODUCTION

According to a recently released Centers for Disease Control and Prevention National Drug Overdose Deaths Report, from 2007 to 2017, the United States experienced a 2.6-fold increase in opioid-related overdose deaths (1). Specifically, there has been a 6.5- and 12.9-fold increase in overdose deaths involving heroin and synthetic narcotics such as fentanyl and its analogs, respectively (1). Heroin-related overdose deaths began to rise around 2007, and in 2014 there was a marked

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rise in overdose deaths involving synthetic narcotics (1). Mirroring this was a 75% increase in the rate of naloxone administration by emergency medical services (EMS) providers from 2012 to 2016, according to the National Emergency Medical Services Information System database (2).

This dramatic rise in overdose deaths related to synthetic narcotics has raised questions about the ideal dose, concentration, route, and number of administrations needed to achieve clinical efficacy of prehospital-administered naloxone (3–11). This is further complicated by greater community availability of naloxone, as well as the occurrence of polysubstance use (3).

Related literature with cohorts inclusive of patients since 2014 have examined the increased rate of multiple naloxone administrations by EMS, the impact of provider level on successful naloxone usage, the association between dose of prehospital naloxone and the occurrence of pulmonary complications, and the duration of observation after prehospital naloxone administration (4–8,12). However, papers that highlight the route, dose, or sequence of individual prehospital naloxone administrations lack evaluation of emergency department (ED) outcomes, whereas papers that focus on ED outcomes do not offer specific details of the prehospital administrations, or are not inclusive of all patients receiving prehospital naloxone for a suspected opioid overdose (4–8,12).

The purpose of this study was to retrospectively evaluate prehospital and ED interventions and outcomes of patients who received prehospital naloxone for a suspected opioid overdose between January 1, 2014 and December 31, 2017 and were transported by ambulance to the Stony Brook University Hospital Emergency Department. The primary objective was to evaluate if the individual dose, individual route, total dose, number of prehospital naloxone administrations, or occurrence of a prehospital adverse event (defined as patient agitation requiring medication or restraints, seizure, dysrhythmias excluding sinus rhythms, or concern for pulmonary edema, after prehospital administration of naloxone) were associated with the occurrence of adverse events (AE) in the ED (defined as naloxone administration in the ED; pulmonary edema confirmed by thoracic ultrasound, chest x-ray study, or chest computed tomography scan; seizure; dysrhythmias excluding sinus rhythms; agitation requiring medication or restraints; documented hypoxemia (SpO_2 < 92%); or supplemental oxygen administration). Secondary objectives included a subset analysis of patients who received additional naloxone while in the ED (ED naloxone), or were admitted to an intensive care or step-down unit from the ED.

MATERIALS AND METHODS

Study Design

This study was a retrospective, observational chart review of adult patients who received prehospital naloxone for a suspected opioid overdose and were transported by ambulance to the Stony Brook University Hospital (SBUH) Emergency Department between January 1, 2014 and December 31, 2017.

The Suffolk County Emergency Medical Services Medical Control Database was queried for patient encounters in the given date range that included naloxone administration and transport to SBUH. The corresponding patient names and dates were used to locate the hospital electronic medical record (EMR) for the patient. The EMRs, including the scanned prehospital care reports (PCR) were abstracted by investigators using a standardized data collection form into a database maintained on REDCap (Research Electronic Data Capture). Investigators were trained on the standardized data collection form by the first author (LMM), who audited every database record for consistency (7). This study was reviewed and approved by the Stony Brook University institutional review board.

Population and Setting

SBUH is a suburban, academic, Level I trauma and tertiary care center with an annual ED census of approximately 110,000 patients. Emergency medical response to the surrounding county is provided by 69 volunteer fire departments, 27 volunteer community ambulance corps, four career-based commercial ambulance services, two hospital-based ambulance services, and one career-based air medical service.

During the study period, county-wide standing orders for advanced life support (ALS) providers (paramedics and emergency medical technician-critical care) included "[for] suspected opiate overdoses who are unconscious, unresponsive with hypoventilation: Administer naloxone 0.4 mg IV [intravenous] titrated to adequate ventilations to a total of 2 mg. If an IV is unable to be established, administer naloxone 2 mg IN/IM [intranasal/intramuscular]," with additional doses, routes such as i.o. (intraosseous), or use in cardiac arrest available after consultation with on-line medical control. State-wide standing orders for basic life support (BLS) providers included "if [a] patient has a suspected narcotic overdose: respirations less than 10/minute and signs of respiratory failure or respiratory arrest … administer 2 mg/2 mL of naloxone via a mucosal atomizer device … after 5 minutes if patient's respiratory rate is not greater than 10 breaths/minute, administer a second dose of naloxone

2 mg/2 mL." Additionally, local law enforcement officers were able to administer naloxone 2 mg/2 mL intranasally (i.n.) for a suspected opioid overdose. All levels of providers administered i.n. naloxone using a widely available injectable naloxone solution (1 mg/mL) with an attached i.n. mucosal atomization device (MAD Nasal; Wolfe-Tory Medical, Inc., Salt Lake City, UT), delivering 1 mL of volume per nostril.

Inclusion criteria for the study were: age ≥ 18 years, prehospital administration of naloxone for a suspected opioid overdose, and transport by ambulance to the SBUH ED. Exclusion criteria included death in the ED, and incomplete documentation of prehospital dose or route of naloxone. During the study period, naloxone was empirically given to many undifferentiated cardiac arrest patients in the system. As such, patients who expired in the ED were excluded from the study population, as naloxone was not specifically administered for a suspected opioid overdose. Inclusion of these patients would likely skew data in a way that lacks meaningful clinical significance.

Measurements

Data were collected using a standardized data collection form on REDCap. Prehospital data points collected included gender, age, date of naloxone administration, dose and route of each administration, application of supplemental oxygen, performance of chest compressions or ventilations, and medications administered aside from naloxone. PCRs were also reviewed for provider documentation of specific prehospital AEs that occurred after naloxone administration [patient agitation requiring medication or restraints in the setting of being determined to be a harm to themselves/others or without decision-making capacity, seizures, dysrhythmias excluding sinus rhythms, and concern for pulmonary edema (13,14)]. Documentation was also reviewed for any mention of drug paraphernalia on scene, EMS intubation, and return of spontaneous circulation (ROSC) after cardiac arrest. Additionally, the level of provider administering the naloxone (ALS, BLS, police, bystander) was recorded.

An in-hospital, or ED AE, was defined as patient agitation requiring medication or restraints in the setting of being determined to be a harm to themselves/others or without decision-making capacity; seizures; cardiac dysrhythmias excluding sinus rhythms; pulmonary edema confirmed by thoracic ultrasound, chest x-ray study or chest computed tomography scan; documented pulse oximetry reading < 92%, administration of supplemental oxygen; or administration of naloxone during the ED stay (13–15). Although a desaturation or need for a dose of naloxone or supplemental oxygen in the ED are not direct complications of the prehospital dose of naloxone, the occurrences of these events are concerning clinical indicators for medical staff that call into question the possibility of an incomplete history or co-ingestion. As such, these red-flag events may result in changes in overall patient management and resulting disposition.

Hospital data points collected included time of triage and ED disposition, vital signs at triage and time of ED disposition, occurrence and time of recorded supplemental oxygen application, including bilevel positive airway pressure and intubation, occurrence and time of a recorded pulse oximetry (SpO_2) reading of < 92%, occurrence and time of seizure medication administration, occurrence and time of agitation requiring medication or restraints, and occurrence and time of ED intubation. If naloxone was administered in the ED, the time, dose, and route of the first administration was recorded, as well as if the patient received additional doses or required a naloxone infusion. Additionally, the EMR was reviewed for treatment with antibiotics for suspected aspiration pneumonitis, pulmonary edema confirmed by imaging, ROSC achieved in the ED, and dysrhythmias excluding sinus rhythms. Finally, the ED disposition was recorded (discharge, elope/leave against medical advice, transfer to emergency psychiatric unit, admit to General Medicine, admit to intensive care or step-down unit, expired). ED length of stay was defined as time from triage until the time of the disposition order (admit, discharge), and therefore does not include the time that the patient may have spent boarding in the ED.

Analytical Methods

Given nonparametric data, median and interquartile ranges were used to describe naloxone doses, patient ages, and time intervals within the ED. Univariate analysis consisting of Mann–Whitney *U* testing was used for subset analysis of characteristics of patients who did, vs. did not, receive ED naloxone, and patients who were admitted to an intensive care or step-down unit from the ED vs. patients with a different ED disposition (discharge, elope/leave against medical advice, transfer to emergency psychiatric unit, or admit to General Medicine). Multivariate analysis consisting of a forward, stepwise binary logistic regression was used to ascertain the effects of gender (male, female), doses (<1 mg, 1 to < 2 mg, ≥ 2 mg), and routes (i.n., not i.n.) of prehospital naloxone, total dose of prehospital naloxone (<2 mg, 2 to < 4 mg, 4 to < 6 mg, ≥ 6 mg), number of total doses of prehospital naloxone (n = 1, 2, or 3), and occurrence of prehospital AE (yes, no) covariates, on the likelihood that patients have an AE in the ED (yes, no), receive ED naloxone (yes, no), or are admitted to an intensive care or step-down unit (yes, no). For the purpose of the

binary logistical regression, it seemed reasonable to include i.v., i.o., and intramuscular in the same group given their identical dose and dosing interval recommendations on Lexicomp (Hudson, OH), with the extension that medication doses via i.v. and i.o. routes are the same (16,17). Statistical analysis was performed using SPSS Statistics Faculty Pack 25 (IBM Corporation, Armonk, NY), with $p < 0.05$ indicating statistical significance. No formal sample size or power calculation was performed; to include all possible data available, the full calendar years between EMR adoption by the ED and the date of initial institutional review board application were included.

RESULTS

Subject Derivation

From a database query and related chart review of patient encounters from January 1, 2014 through December 31, 2017, 570 encounters (499 unique names) were located involving patients aged ≥ 18 years who arrived via ambulance to SBUH after receiving prehospital naloxone for a suspected opioid overdose. Seventeen patient encounters were excluded from analysis due to missing prehospital naloxone dose and route information, and 40 were excluded due to patient expiration in the ED. There were 513 patient encounters included in the analysis (Figure 1). The median age of patients was 29 years (interquartile range 24–42), and 30.4% were female (Table 1). Two of these patients were confirmed to have additional self-administered exposure to opioids in the ED; AEs resulting from these repeat overdoses were not included in the analysis. During this period of time, fewer than 10 requests for refusal of medical care after naloxone administration were granted in the Suffolk County EMS system.

Of the 40 patient encounters excluded from analysis due to death in the ED, 38 arrived to the ED in cardiac arrest. Two additional patients died in the ED; one due to surgical complications, and one due to a massive intracranial hemorrhage.

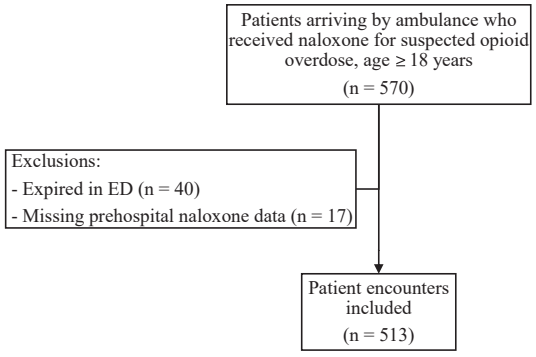

Figure 1. Flow diagram of subject derivation. ED = emergency department.

Prehospital Events

Frequency and quartile data of prehospital events of included patient encounters are described in Table 1. Due to inconsistent and varied prehospital documentation practices, the only prehospital airway management intervention able to be reported with confidence is the occurrence of 22 intubations.

Figure 2 describes the frequency and median doses of prehospital-administered naloxone, grouped by route, organized by first dose, second dose, and third dose. Of the 306 patients who received their first dose of naloxone via the intranasal route, 136 (44%) received multiple doses of prehospital naloxone. In comparison, only 12% of patients who received their first prehospital dose of naloxone by another route (i.v., i.o., or i.m.) then went on to receive additional prehospital doses of naloxone ($p < 0.001$). Of the 57 patients who received their first and second dose of naloxone by the intranasal route, 11 (19%) required a third dose of prehospital naloxone. No patients received more than three doses of prehospital naloxone. Of the 513 patients included in the study, 160 (31%) received multiple doses of prehospital naloxone.

Emergency department events. Frequency and quartile data of ED characteristics of included patient encounters are summarized in Table 2. Table 3 describes, by hours after triage, the number of patients who received ED naloxone or were intubated in the ED.

Seventy of the 76 patients who received ED naloxone had an abnormality documented on their initial ED presentation, most commonly an abnormal neurologic, respiratory, or psychiatric examination finding; offered a complaint, or had abnormal triage vital signs. Of the 6 who had reassuring initial presentations, all admitted to using what they believed to be heroin. Four received naloxone within 2 h of ED triage. The remaining 2 received naloxone 126 and 193 min after ED triage, with the former documented to be hypoxemic 73 min after ED triage, and the latter having admitted to using methadone in addition to heroin.

Of the 76 patients who received ED naloxone, 41 (54%) received multiple doses in the ED, and 19 (25%) were started on a naloxone infusion. Forty-three (57%) were eventually admitted, 36 (47%) of whom were admitted to an intensive care or step-down unit.

Overall, 252 (49%) of 513 patients were documented to have had an ED AE. Results of the logistical analysis regression analysis indicated that patients with an increased number of prehospital naloxone doses, an occurrence of a prehospital AE, and a route of

Table 1. Prehospital Characteristics of Included Patient Encounters

	Entire Cohort	ED Naloxone			ED Disposition		
Patient Encounter Prehospital Characteristics	n = 513	ED Naloxone n = 76	No ED Naloxone n = 437	*p* Value*	Admitted to Intensive Care or Step-Down Unit n = 108	ED Disposition Other than I CU/Step-Down Unit n = 405	*p* Value*
Gender, n (%)							
Female	156 (30.4)	20 (26.3)	136 (31.1)		36 (33.3)	120 (29.6)	
Age (y)	29 [24–42]	32 [26–48]	29 [24–41]	0.055	37 [26–54]	29 [24–39]	< 0.001
Number of prehospital naloxone doses, n (%)							
1	353 (68.8)	47 (61.8)	306 (70)		68 (63)	285 (70.4)	
2	140 (27.3)	25 (32.9)	115 (26.3)		32 (29.6)	108 (26.6)	
3	20 (3.9)	4 (5.3)	16 (3.7)		8 (7.4)	12 (3)	
Person administering naloxone, n							
ALS	426	64	362		98	328	
BLS	47	10	37		9	38	
Police	82	8	74		12	70	
Bystander	14	1	13		1	13	
Total prehospital naloxone (mg)	2 [2–3]	2 [2–3.75]	2 [2–3]	0.876	2 [2–4]	2 [2–3]	0.147
Prehospital adverse events, n (%)							
Pulmonary edema	4 (0.8)	0	4 (0.9)		4 (3.7)	0	
Seizure	5 (1)	0	5 (1.1)		5 (4.6)	0	
Dysrhythmia	3 (0.6)	0	3 (0.7)		1 (0.9)	2 (0.5)	
Agitation	10 (1.9)	1 (1.3)	9 (2.1)		3 (2.8)	7 (1.7)	
Prehospital intubation, n (%)	22 (4.3)	1 (1.3)	21 (4.8)		22 (20.4)	0	
Prehospital ROSC, n (%)	17 (3.3)	1 (1.3)	16 (3.7)		13 (12)	4 (1)	

Values are reported as median [interquartile range] unless otherwise noted.
ED = emergency department; ALS = Advanced Life Support; BLS = Basic Life Support; ROSC = return of spontaneous circulation; ICU = intensive care unit.
* By Mann–Whitney test.

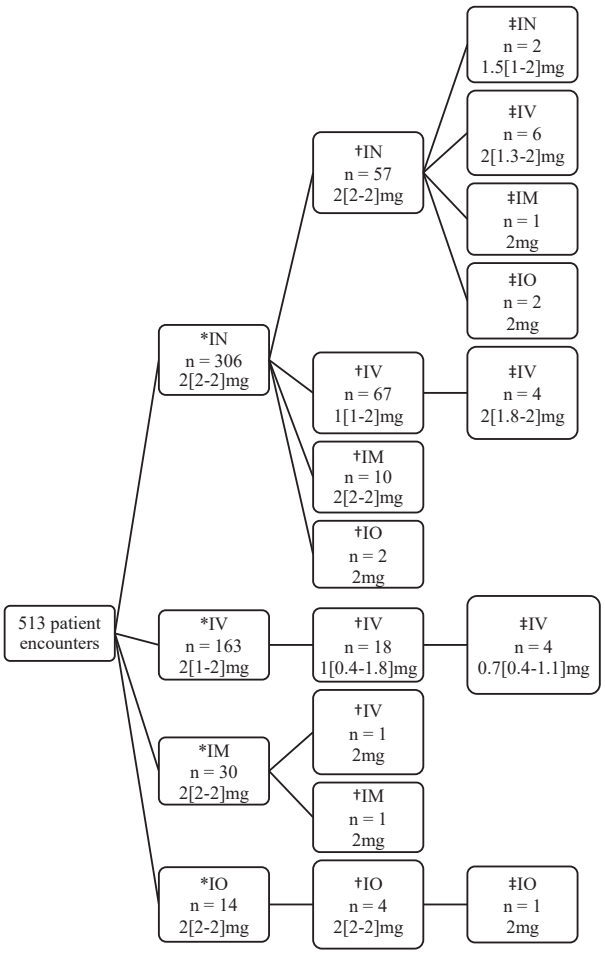

Figure 2. Sequence of individual prehospital naloxone administrations grouped by route, organized by first dose, second dose, third dose. Doses for each route are represented as median [IQR]. IN = intranasal; IV = intravenous; IM = intramuscular; IO = intraosseous; * = first dose; † = second dose; ‡ = third dose.

administration other than i.n. for the first dose of prehospital naloxone were significantly more likely to experience an ED AE (Table 4).

Subset Analysis of Patients Who Received ED Naloxone

Subset analysis of patients who received ED naloxone indicated an association between receiving ED naloxone and the ED length of stay; patients who received ED naloxone had longer ED stays ($p < 0.001$; U = 11,341).

Subset Analysis of Patients Admitted to an Intensive Care or Step-Down Unit

Admission to an intensive care or step-down unit was associated with older patient age ($p < 0.001$, U = 16,712), shorter time in the ED until application of supplemental oxygen ($p < 0.001$, U = 3270), shorter time in the ED until documented hypoxemia ($p < 0.001$, U = 7327), a greater first bolus dose of naloxone in the ED ($p = 0.005$, U = 428), and a shorter ED length of stay ($p < 0.001$; U = 29,157).

Logistical regression analysis of patients who were admitted to an intensive care or step-down unit from the ED indicated that the occurrence of a prehospital AE, and a route of administration other than i.n. for the first dose of prehospital naloxone, were significantly associated with an increased likelihood of admission to an intensive care or step-down unit from the ED (Table 4). Furthermore, patients who received < 2 mg of prehospital naloxone had the least likelihood of being admitted to an intensive care or step-down unit from the ED, whereas patients who received at least 6 mg of prehospital naloxone had a dramatically increased likelihood of intensive care or step-down unit admission from the ED (Table 4).

DISCUSSION

The primary outcome of our retrospective, observational chart review of adult patients who received prehospital naloxone for a suspected opioid overdose suggests that an increasing number of prehospital naloxone doses, an occurrence of a prehospital AE, and a route of administration other than i.n. for the first dose of prehospital naloxone were significantly associated with an increased likelihood of an ED AE. Of note, we do not believe that naloxone itself contributes to these occurrences, rather, its repeated use may be a surrogate marker for overall patient acuity.

Prehospital Events

The percentage of patients who received one, two, or three doses of prehospital naloxone in our study are similar to those observed by Gulec et al. in a cohort of patients who received prehospital naloxone from 2014–2016 in the northeastern United States (6). Gulec et al. compared effectiveness of prehospital naloxone administered by different levels of providers (BLS vs. ALS) in terms of improved mental and respiratory status, though no details regarding hospital course, individual doses, or naloxone concentration were included (6). Interestingly, they noted no significant difference in the need for multiple naloxone administrations between emergency medical technicians (EMTs) and ALS providers, with EMTs exclusively providing i.n. naloxone. In any discussion of multiple naloxone administrations, it is important to consider the time elapsed between doses. Additional, potentially unnecessary doses may be given if the response to an initial dose was reassessed prior to

Table 2. In-Hospital Characteristics of Included Patient Encounters

	Entire Cohort	ED Naloxone			ED Disposition		
Patient Encounter in Hospital Characteristics	n = 513	ED Naloxone n = 76	No ED Naloxone n = 437	*p* Value*	Admitted to Intensive Care or Step-Down Unit n = 108	ED Disposition Other than Intensive Care or Step-Down Unit n = 405	*p* Value*
ED adverse events							
Oxygen administration, n (%)	196 (38.2)	54 (71.1)	142 (21.1)		96 (88.9)	100 (24.7)	
Time in ED until oxygen admin. (min)	2 [0–33]	7 [0–49]	0 [0–31]	0.222	0 [0–2]	24 [0–71]	< 0.001
Documented SpO_2 < 92%, n (%)	135 (26.3)	43 (56.6)	92 (32.5)		62 (57.4)	73 (18)	
Time in ED until hypoxemia (min)	0 [0–56]	24 [0–63]	0 [0–31]	0.114	0 [0–2]	19 [0–85]	< 0.001
Additional naloxone administered in ED, n (%)	76 (14.8)	76 (100)	0		36 (33.3)	40 (9.9)	
Time in ED until ED dose (min)	90 [41–167]	90 [41–167]			87 [12–183]	99 [57–167]	0.193
First bolus dose of naloxone in ED (mg)	0.2 [0.04–0.4]	0.2 [0.04–0.4]			0.35 [0.18–1.4]	0.2 [0.04–.4]	0.005
Multiple doses of naloxone in ED, n (%)	41 (8)	41 (53.9)			21 (19.4)	20 (4.9)	
Naloxone infusion in ED, n (%)	19 (3.7)	19 (25)			13 (12)	6 (1.5)	
Agitation, n (%)	18 (3.5)	4 (5.3)	14 (3.2)		7 (5.6)	11 (2.7)	
Time in ED until agitation (min)	22 [10–87]	36 [16–81]	20 [7–108]		21 [5–65]	22 [11–93]	
Pulmonary edema, n (%)	9 (1.8)	4 (5.3)	5 (1.1)		8 (7.4)	1 (0.2)	
Dysrhythmia excluding sinus rhythm, n (%)	3 (0.6)	0	3 (0.7)		3 (2.8)	0	
Seizure, n (%)	2 (0.4)	0	2 (0.5)		2 (1.9)	0	
Time in ED until seizure (min)	2.5		2.5		2.5		
Suspected aspiration pneumonitis, n (%)	62 (12.1)	21 (27.6)	41 (9.4)		41 (38)	21 (5.2)	
ED intubation, n (%)	55 (10.7)	16 (21.1)	39 (8.9)		53 (49.1)	2 (0.5)	
Time in ED until intubation (min)	19 [11.8–48]	23 [14–70]	18 [10–40]	0.246	19 [10–53]	16	0.739
ED ROSC, n (%)	11 (2.1)	0	11 (2.5)			11 (10.2)	
ED length of stay (min)	332 [213–496]	477 [309–676]	315 [207–470]	<0.001	243 [159–374]	363 [242–537]	<0.001
ED disposition, n (%)							
AMA/eloped	54 (10.5)	5 (6.6)	49 (11.2)		0	54 (13.3)	
Discharge	279 (54.4)	24 (31.6)	255 (58.4)		0	279 (68.9)	
EPU	25 (4.9)	4 (5.3)	21 (4.8)		0	25 (6.2)	
Admit	155 (30.2)	43 (56.6)	112 (25.6)		108 (100)	47 (11.6)	
Telemetry or regular floor bed	47 (9.2)	7 (9.2)	40 (9.2)		0	47 (11.6)	
Step-down Unit	7 (1.4)	1 (1.3)	6 (1.4)		7 (6.5)	0	
ICU	101 (19.7)	35 (46.1)	66 (15.1)		101 (93.5)	0	

Values are reported as median [interquartile range] unless otherwise noted.
ED = emergency department; ROSC = return of spontaneous circulation; EPU = emergency psychiatric unit; AMA = against medical advice; ICU = intensive care unit.
* By Mann–Whitney test.

Table 3. Patients Who Received ED Naloxone or Were Intubated in the ED by Hours After ED Triage

Intervention	> 2 h	> 3 h	> 4 h
ED naloxone, n (%)	27 (5.3%)	18 (3.5%)	8 (1.6%)
Intubation in ED, n (%)	8 (1.6%)	6 (1.1%)	5 (1%)

ED = emergency department.

naloxone's onset of action, which is variably dependent upon the route and dose of ingested opioid as well as the route and dose of naloxone (3,9,18). Furthermore, co-ingestions of substances other than opioids may confound a patient's expected response to naloxone. Often this co-ingestion information may not be available to prehospital providers, who may continue to treat the patient with additional doses of naloxone. A recent study demonstrated that patients with polysubstance use had higher odds of requiring multiple doses of naloxone, though these doses were administered in the prehospital setting and within the ED (7). At the same time, it is likely that providers should not be discouraged from administering multiple doses of naloxone to "non-responding" patients, as it not only has been shown that there has been an increase in multiple naloxone administrations by EMS nationally, but the odds of multiple administrations are higher in areas of the country found to have greater rates of synthetic opioid detection (5). Our study was not structured to exclude patients found to have co-ingestions, or patients who overall did not respond to naloxone, as these details are often not immediately known, nor is there a universally accepted definition for naloxone response (19). Furthermore, because obtaining a serum or urine drug screen on all patients presenting after a suspected opiate ingestion is not common practice in our department, this information was not consistently available for retrospective analysis.

Table 4. Statistics from Multivariate Analysis Using Binary Logistic Regression

	Odds Ratio	95% CI
ED adverse event		
Prehospital adverse event	3.7	1.2–11.8
Number of prehospital naloxone doses	1.9	1.3–2.7
Route of administration besides intranasal for first prehospital dose	1.7	1.2–2.5
Admission to intensive care or step-down unit from ED		
Prehospital adverse event	8.7	3–25.4
Route of administration besides intranasal for first prehospital dose	3.8	2.3–6.4
Total dose of prehospital naloxone (mg)		
< 2	Reference	–
2 to < 4	2.7	1.4–5.4
4 to < 6	3.7	1.6–8.6
≥ 6	27.2	3–25.4

$p < 0.05$ for significance.
ED = emergency department; CI = confidence interval.

Of the 513 patients in our study, 35% received their first dose of naloxone i.v./i.o. It is possible that the association between route of administration other than i.n. for the first dose of prehospital naloxone and increased likelihood of ED AE is related to naloxone pharmacokinetics. Intravenous naloxone provides a near-immediate therapeutic serum concentration of naloxone, followed by a rapid decline (10). Recent pharmacokinetic studies of concentrated naloxone suggest that when delivered as 2 mg/0.1 mL, naloxone i.n. has approximately 50% bioavailability relative to i.v., and although the time to peak serum concentration is approximately 15–30 min, therapeutic plasma levels are maintained for 2 h (9–11). Interestingly, 20 min after administration, naloxone 1.6 mg/0.2 mL i.n. has been shown to result in higher serum naloxone concentrations than naloxone 1 mg i.v. (11). Although our study used a 2 mg/2 mL concentration and thus is not directly comparable, it is possible that the more sustained effect of i.n. naloxone was a protective factor against ED AE. These pharmacokinetics may also help explain the observation that 44% of patients who received naloxone i.n. went on to receive multiple prehospital doses, which was a significantly greater percentage of patients than those initially receiving naloxone via alternate routes. Reported percentages of patients requiring additional naloxone after a first dose of intranasal naloxone range from 6% to 42%, which could be attributed to a longer onset of action than prehospital providers expect, inconsistent definitions of clinical response, or variable provider discretion in naloxone dosing (6,8,12,19–26). Finally, it is also important to consider that providers may have chosen to use non-i.n. routes for patients who initially seemed sicker, in anticipation of the need for vascular access for additional medications (22).

Emergency Department Events

One of the secondary outcomes included a subset analysis of patients receiving ED naloxone. A majority of patients who received ED naloxone had an abnormal initial examination. Of those who did not, only 2 received ED naloxone at least 2 h after ED triage, with one admitting to also ingesting methadone. Based on our observations, we would echo the sentiments of Heaton et al. in emphasizing physician awareness of possible polysubstance use when considering patient discharge after 2–3 h of ED observation (7).

Patients who received ED naloxone had a longer overall ED length of stay than those who did not receive ED

naloxone. This is likely owing to continued observation to determine if additional bolus doses of naloxone or an infusion were needed, prior to determining their ED disposition. Several operational components of our ED are pertinent in regards to this. Patients who receive prehospital naloxone are automatically triaged to our 25-bed ED Resuscitation and Critical Care Unit (RACCU) to allow for continuous end-tidal waveform capnography and close clinical monitoring. Although an ED Observation Unit is available, not all beds are equipped with continuous end-tidal waveform capnography, therefore, almost all patients who receive prehospital naloxone stay in the RACCU. Also, ED length of stay in this study refers to the duration of time under which emergency physicians are directing patient care. Once an admission order is placed, care is transferred over to hospitalists. Depending on hospital census, these patients may board in the ED until an inpatient bed is available. We were not able to quantify patient boarding hours within this study.

Although we noted that the occurrence of ED naloxone administration and ED intubation declined with additional time in the ED, 1.6% of patients received their first dose of ED naloxone at least 4 h after ED triage. This is greater than the 0.7% of patients described by Heaton et al., as well as what was observed by Christenson et al. during their derivation of the St. Paul's Early Discharge Rule, and then by Clemency et al. during their validation of the rule (7,8,15). Additionally, we noted more ED intubations (11% vs. 2–9%) (4,7). We believe this could be attributed to polysubstance use, which our study was not structured to exclude. We did observe similar numbers of patients treated for suspected aspiration pneumonitis (12% vs. 2–25%) and instances of radiographically demonstrated pulmonary edema (2% vs. approximately 1%), as others have recently reported (4,7). Finally, our occurrence of prehospital intubations (4%) was also relatively similar to the recently reported 5–7% (7,12).

For patients receiving ED naloxone, the median initial bolus dose was 10-fold lower than the median total prehospital dose. A review of numerous commonly used references revealed great variability in recommended naloxone dosing, especially depending upon the composition of ingested opioids (27). Notably, the American Heart Association changed their recommendations in 2015 for the initial dosing of naloxone for a suspected opioid overdose from an empiric dosing of 0.04–0.4 mg i.m. or i.v., to 0.4 mg i.m. or 2 mg i.n. given the changes in overdose patterns (3,28). This further illustrates the need for a universally accepted definition for naloxone response, as well as pharmacokinetic and pharmacodynamic studies of naloxone in the setting of complicated opioid overdoses, to encourage more consistent clinical decision-making about naloxone doses and titrations.

Admission to an Intensive Care or Step-Down Unit

The other secondary outcome of this study included a subset analysis of patients who were admitted to an intensive care or step-down unit from the ED.

Interestingly, patients who received the lowest total doses of prehospital naloxone had the least likelihood of being admitted to an intensive care or step-down unit from the ED, whereas patients who received the most prehospital naloxone (at least 6 mg of total prehospital naloxone) had a dramatically increased likelihood of admission to an intensive care or step-down unit. This relationship between higher doses of naloxone and the need for the highest level of inpatient care could reflect factors described earlier in the discussion, such as the presence of a co-ingestion or synthetic opioids. It is also possible that these patients were believed to be obtunded, hypoxic, or bradypneic due to opioids, when, in fact, it was a different underlying etiology.

Additionally, patients admitted to an intensive care or step-down unit had an increased likelihood of a prehospital AE and route of administration other than i.n. for the first dose of prehospital naloxone. Again, it is possible these patients appeared sicker to prehospital providers, who decide to place an i.v. for medication administration instead of using the i.n. route. In keeping with this sentiment, many of these patients arrived to the ED in need of an urgent intervention, as evident by their significantly shorter time until supplemental oxygen administration and desaturation events. Their ED length of stay was also significantly shorter, which suggests that emergency physicians determined their disposition and required level of care shortly after their arrival in the ED. As discussed previously, this time period refers to how long the patient was under the direct care of an emergency physician, and does not take patient boarding into account.

All patients who had a serious ED AE including seizure, dysrhythmia, or intubation, as well as most patients with pulmonary edema, and two-thirds of patients being treated for aspiration pneumonitis were admitted to an intensive care or step-down unit. Other indications for these levels of care could have included recommendations from Poison Control, or the clinical determination that a patient requires continuous end-tidal waveform capnography, which is limited to inpatient intensive care units. Of the rare prehospital serious AEs, all patients concerning for pulmonary edema, seizures, or requiring prehospital intubation were admitted to an intensive care or step-down unit.

Limitations

First and foremost, this study was a nonblinded, retrospective chart review of documentation not originally

intended to be analyzed in such a fashion. Results and conclusions are dependent on the timely, accurate, and complete documentation by prehospital and hospital providers. Patient encounter inclusion in the study was dependent upon EMS provider compliance with county regulations that administration of medication be reported to Suffolk County EMS Medical Control, for subsequent inclusion in their database. Furthermore, the majority of PCRs reviewed were handwritten and scanned into the EMR; documentation practices and readability were poor at times.

Additionally, certain data points, such as time to supplemental oxygen administration and time to documentation of hypoxemia were limited to the documentation contained within nursing notes and vital signs. Oxygen may have been administered reflexively given the chief complaint and not necessarily based on clinical presentation; often times, supplemental oxygen administration or desaturation event were not explicitly mentioned in the physician notes. It is also possible that supplemental oxygen administration was confused for the nasal end-tidal capnography, which is routinely applied to patients presenting to the SBUH ED after naloxone administration. Of note, pulse oximetry was used in this study instead of capnography, as pulse oximetry seems to be a historically used marker of respiratory status, is often more widely available, and on our review of records, more consistently documented. Finally, the decision to administer naloxone in the ED, as well as the subsequent doses and dosing interval, were dependent upon attending physician clinical judgment—many notes commented that naloxone was administered for somnolence, not necessarily bradypnea or hypoxemia. It was very difficult to determine the exact indication for each dose of naloxone administered in the ED and would be based largely on speculation.

CONCLUSION

Our study suggests that an increasing number of prehospital naloxone doses, the occurrence of a prehospital AE, and a route of administration other than i.n. for the first dose of prehospital naloxone were significantly associated with an increased likelihood of an ED AE. Overall, the majority of patients who required further ED management or admission presented with abnormalities noted either in triage or shortly thereafter. Future work is needed to prospectively validate these findings; to create a universally accepted definition of response to naloxone, which could perhaps involve using trends in continuous end-tidal waveform capnography to evaluate for immediate, objective changes in ventilatory rate and, to some extent, tidal volume; and to better elucidate the pharmacokinetics and pharmacodynamics of naloxone when used to reverse the effects of unknown opioids, especially when administered i.n. or in the setting of a polysubstance use.

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ARTICLE SUMMARY

1. Why is this topic important?

A dramatic rise in overdose deaths related to synthetic narcotics has raised questions about the ideal dose, concentration, route, and number of administrations needed to achieve clinical efficacy of prehospital-administered naloxone. In current literature, papers that highlight the route, dose, or sequence of individual prehospital naloxone administrations lack evaluation of emergency department (ED) outcomes, whereas papers that focus on ED outcomes do not offer specific details of the prehospital administrations, or are not inclusive of all patients receiving prehospital naloxone for a suspected opioid overdose.

2. What does this study attempt to show?

The primary objective was to retrospectively evaluate if the individual dose, individual route, total dose, number of prehospital naloxone administrations, or occurrence of a prehospital adverse event were associated with the occurrence of adverse events (AE) in the ED. Secondary objectives included a subset analysis of patients who received additional naloxone while in the ED or were admitted to an intensive care or step-down unit from the ED.

3. What are the key findings?

An increasing number of prehospital naloxone doses, an occurrence of a prehospital adverse event, and a route of administration other than intranasal for the first dose of prehospital naloxone were significantly associated with an increased likelihood of an ED adverse event.

Patients who received the lowest total doses of prehospital naloxone had the least likelihood of being admitted to an intensive care or step-down unit from the ED, whereas patients who received the most prehospital naloxone (at least 6 mg of total prehospital naloxone) had a dramatically increased likelihood of admission to an intensive care or step-down unit.

4. How is patient care impacted?

Extra attention should be paid to patients arriving to the ED who received several prehospital doses of naloxone, especially if the total dose is over 6 mg.

In general, patients who require intensive care unit care or additional naloxone arrive to the ED appearing unwell.