Risk of Delayed Intubation After Presumed Opioid Overdose in the Emergency Department

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Study objective: The objective of this study was to evaluate the optimal duration of monitoring for patients with presumed opioid overdoses prior to a non-ICU admission, particularly in the context of the increasing prevalence of fentanyl analogs and other potent synthetic opioids. Given the critical role of emergency physicians in managing this public health crisis, the study aims to inform clinical decisionmaking regarding patient disposition after the initial overdose treatment.

Methods: The Fentalog Study, conducted through the American College of Medical Toxicology's Toxicology Investigators Consortium, is a prospective, multi-institutional project designed to identify patients presenting to the emergency department with acute opioid overdose, gather clinical details, and confirm substances through biologic testing. This study is a secondary analysis of the Fentalog Study that assessed the risk of "delayed intubation," defined as any intubation occurring after 4 hours of arrival to the emergency department.

Results: Of the 1,591 patients included, only 9 (0.6%) required delayed intubation. Eight of these patients had nonrespiratory-related conditions contributing to the need for intubation. One patient only had respiratory-related conditions, had respiratory acidosis, and received a total of 6.4 mg naloxone before intubation.

Conclusion: This study provides evidence that delayed intubation after 4 hours of monitoring in patients with presumed opioid overdose is exceedingly rare. [Ann Emerg Med. 2025;85:498-504.]

Please see page 499 for the Editor's Capsule Summary of this article.

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INTRODUCTION

The opioid epidemic has become an omnipresent public health crisis, driving a significant rise in overdose fatalities across the United States.[1] The current phase of the epidemic is largely driven by synthetic opioids, particularly fentanyl and its potent analogs, which are often more lethal than users expect. This has resulted in a sharp increase in overdose deaths, many occurring rapidly after exposure to a lethal dose.[2-5] In addition to the loss of lives, the epidemic has placed tremendous strain on health care systems,[6-8] underscoring the need for comprehensive prevention and treatment strategies.

Emergency medical service providers frequently encounter suspected opioid overdoses, often treating patients with respiratory depression using naloxone in the out-of-hospital setting before transporting them to emergency departments (EDs) for further care.[9-13] Once in the ED, providers must decide whether to discharge the patient, continue monitoring, or admit them for further treatment.

Deciding whether to admit a patient with acute drug overdose to a medical floor or an ICU is complicated by the risk of delayed decompensation. Although patients may experience a recurrence of respiratory depression after naloxone treatment, the timing is unpredictable, particularly in cases of polysubstance overdose, leading general wards to hesitate in accepting such admissions. One study found a 15% risk of adverse events based on assessments conducted 1 hour after naloxone treatment,[14] whereas another reported a 5% risk of delayed complications occurring more than 2 hours after naloxone treatment.[15] Medical floors are cost-effective but ill equipped to manage rapidly deteriorating patients, whereas ICUs, though resource rich, may be unnecessary for those

Editor's Capsule Summary

What is already known on this topic

Opioid overdose often creates prolonged sedation and concerns for delayed hypoventilation.

What question this study addressed

What is the proportion of those with opioid overdose who received endotracheal intubation after 4 hours of emergency department (ED) observation and what are the features?

What this study adds to our knowledge

In an observational study of 1,591 people, intubation after 4 hours of ED observation was rare (9 patients) and due to non-opioid reasons in most patients.

How this is relevant to clinical practice

Patients with opioid overdose rarely need > 4 hours of ED monitoring or ICU care if no respiratory effect noted.

who are stable. Furthermore, there is limited research on the optimal duration of ED monitoring for patients who do not require ICU care before being safely admitted to a non-ICU bed.

The American College of Medical Toxicology's Toxicology Investigators Consortium (ToxIC) established the Fentalog Study to monitor and analyze the evolving threat of fentanyl analogs in the opioid crisis. This prospective study tracks the emergence of these substances, documents their clinical effects, and enhances understanding of their effect on public health. The present study is a secondary analysis of data collected in the Fentalog Study to determine the rate of delayed intubation following suspected opioid overdoses. Understanding the likelihood of delayed intubation can aid in determining the necessary level of care to be provided after treatment in an ED.

METHODS

Study Design and Setting

This is a secondary analysis of the ToxIC Fentalog Study between September 21, 2020, and May 14, 2024. The Fentalog Study is an ongoing observational cohort study of patients with suspected opioid overdose who present to EDs at 10 medical centers across the United States. The Fentalog Study's data collection methods were previously described.[16] The Fentalog Study was approved by the Western Institutional Review Board (WIRB) - Copernicus Group Institutional Review Board and the institutional review boards of all participating sites. This secondary analysis was determined to not be human subjects research by the University of Iowa Institutional Review Board.

Inclusion

Patients were eligible for inclusion to the Fentalog Study if they were evaluated in the ED for suspected acute opioid overdose, were 18 years old or more, and had residual or waste serum samples available from blood taken as part of routine clinical care. Suspected opioid overdose was identified by the following aspects: (1) opioid toxicity based on chief complaints or discharge diagnosis; (2) received naloxone for overdose treatment in the out-of-hospital setting or ED; or (3) self-reported opioid use resulting in the present ED visit for overdose. Patients were excluded if their age was less than 18 years, if they were incarcerated persons, or if there had co-occurring significant burns or physical trauma. During the routine data collection for the study, information was gathered on whether a patient was intubated at any point during their hospital stay, intubated within 4 hours of arrival to the ED, or intubated more than 4 hours after arrival. Patients were excluded from this secondary analysis if they were intubated within 4 hours of arrival to a hospital and/or if their comprehensive toxicology analysis was incomplete at the time of this analysis (Figure).

Protocol and Data Collection

Patients at participating sites were screened and assessed for eligibility by research staff (medical toxicology physicians, fellows, or trained research assistants) using the above criteria. Data collection consisted of demographic variables (eg, age, sex, and race or ethnicity), past medical and psychiatric history, suspected exposures to opioids and other substances, clinical characteristics (eg, relevant laboratory data and specific organ toxicity), treatments received (eg, naloxone treatment), and disposition. Deidentified clinical information was collected by medical record review from the patient's electronic medical record by trained research staff at each site and entered into a central REDCap database. Any missing data from the electronic medical record was entered as an "unknown" variable in REDCap. Quality assurances of data entry and data quality were maintained by ToxIC staff according to standardized practices.[17]

Comprehensive Toxicology Analysis

Waste serum samples obtained as part of routine clinical care were transferred to deidentified cryogenic tubes and

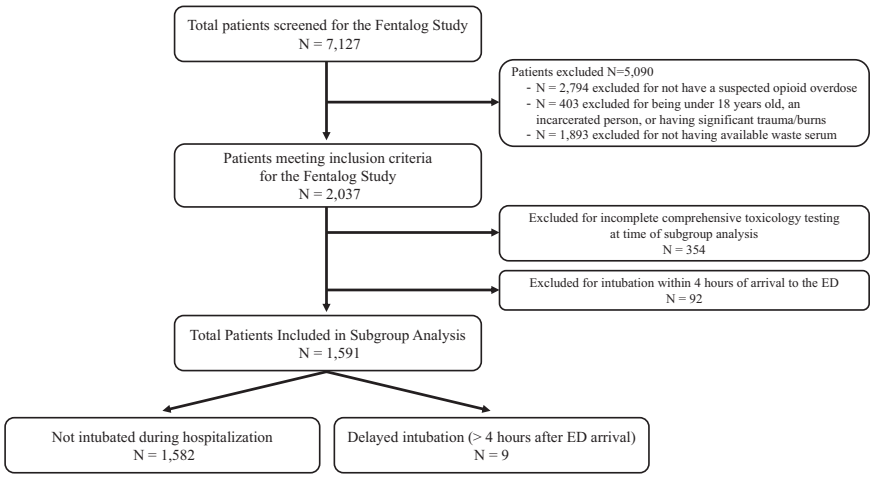

Figure. Patients included in analysis.

stored at temperatures between −4 °C and −80 °C until toxicologic analysis. Toxicology analysis was performed quarterly by the Center for Forensic Science Research and Education. Qualitative molecular identification consisted of liquid chromatography quadrupole time-of-flight mass spectrometry, with secondary analysis using liquid chromatography tandem quadrupole mass spectrometry when necessary (eg, for resolution of molecular isomers). The library used for this testing contains over 1,200 substances, including traditional illicit drugs, pharmaceuticals, novel psychoactive substances, adulterants, metabolites, and other compounds. This validated methodology has been previously described, and the library is updated as the drug market evolves.[18] Toxicologic analysis was performed blinded to clinical outcomes. Deidentified toxicology results were then paired with the clinical database.[16]

Outcomes

The primary outcome of this secondary analysis was whether the patient received delayed intubation following suspected opioid overdose, defined as endotracheal intubation occurring more than 4 hours after arrival at a hospital. Patients were divided into the following 2 groups: (1) delayed intubation and (2) no delayed intubation. A secondary outcome was a description of the cases within the delayed intubation group, and all details within the Fentalog Study were reviewed to identify relevant information that could better explain why these patients might have received delayed intubation.

Analyses

Sociodemographic and clinical characteristics were stratified for patients with delayed intubation and for patients who were not intubated during hospitalization. We had determined, a priori, that we would conduct only descriptive assessments if the prevalence of our outcome was rare (<10%) while conducting multivariate logistic regression to identify demographic (eg, sex, age at consultation, and geography) and clinical characteristics if the prevalence of delayed intubation was higher in this sample.

RESULTS

A total of 1,591 patients were included in this subanalysis (Figure). Demographics, initial vital signs, laboratory results, and naloxone administrations are shown in Table 1. In total, 9 patients (0.6%) were intubated more than 4 hours after arrival at an ED (delayed intubation). Tables 2 and 3 provide more detailed information for these patients. Naloxone was administered to 78% (n=7) of the patients with delayed intubation, all of whom required multiple doses. Four patients received 3 or more doses. Eight patients with delayed intubation had indications for intubation outside of hypoventilation-induced respiratory failure. Of the initial 1,591 patients, only one (0.1%) necessitated delayed intubation without other indications for intubation. This patient received 5 doses of naloxone for a total of 6.4 mg, and their blood gas revealed respiratory acidosis (pH 7.21, pCO_2 68 mmHg, HCO_3 26 mmol/L).

Within the delayed intubation group, at least 2 substances were present in every patient on comprehensive toxicology testing, with 1 patient having 13 substances identified. None of the patients with delayed intubation had heroin (diacetylmorphine) or heroin metabolites confirmed. The following substances were identified in these patients, presumably through illicit use: fentanyl,

Table 1. Demographics, vital signs, laboratory results, total naloxone received, and the number of analytes confirmed for patients necessitating delayed intubation versus patients who were not intubated.

	Intubated > 4 h		Not Intubated	
Characteristics	**n**	**Median (q1, q3)**	**n**	**Median (q1, q3)**
Total	9		1,582	
Sex				
Male	6		1,142	
Female	3		431	
Transgender	0		9	
Age (y)				
18-29	2		321	
30-39	1		447	
40-49	4		288	
50-59	1		247	
60-69	1		204	
70+	0		56	
Unknown	0		19	
Race				
American Indian/ Alaska Native	0		15	
Asian	0		25	
Black	4		419	
Non-Hispanic White	2		657	
Hispanic	3		355	
Native Hawaiian/ Pacific Islander	0		3	
Mixed	0		2	
Unknown	0		106	
Initial ED vital signs				
MAP	8	108 (95, 125)	1,440	100 (88, 111)
PR	8	103 (95, 113)	1,456	94 (81, 108)
RR	8	23 (18, 34)	1,428	18 (16, 20)
O_2 Sat	8	96 (91, 98)	1,449	97 (94, 99)
Laboratory results				
pH*	7	7.2 (7.2, 7.3)	573	7.3 (7.2, 7.4)
pCO_2*	7	60 (49, 75)	574	54 (47, 63)
Bicarbonate*	8	23 (21, 26)	1,402	25 (22, 27)
Creatinine*	8	1.2 (1.0, 1.3)	1,406	1.0 (0.8, 1.3)
Lactate*	6	2.3 (2.1, 2.5)	564	2.2 (1.4, 3.7)
Ethanol	1	26†	211	116 (46.5, 194.1)†
Naloxone (mg, total)				
Bolus	7	4.4 (2.24, 6.7)	1,168	2.5 (1.55, 4.4)
Infusion	1	1.8†	136	4 (1.62, 10)
Number of analytes present‡	9	9 (7, 9)	1,582	6 (4, 9)

PR, pulse rate (beats/min); *MAP*, mean arterial pressure (mmHg); *O_2 Sat*, oxygen saturation through pulse oximetry (%); *RR*, respiratory rate (breaths/min).
*Within 2 h of ED arrival.
†When ethanol was present in the patient's system; if serum ethanol concentration was undetectable, they were not included in this row. Bicarbonate from basic metabolic panel in mmol/L; creatinine in mg/dL; lactate in mmol/L; pH and pCO_2 from venous blood gas; pCO_2 in mmHg; ethanol (serum ethanol concentration) in μg/L.
‡Inclusion of all analytes identified (parent compounds, metabolites, and iatrogenic).

fentanyl analogs (despropionyl fentanyl [4-ANPP] and para-fluorofentanyl), a σ-receptor agonist (noscapine), an illicit benzodiazepine (flualprazolam), methamphetamine, methylenedioxymethamphetamine, and multiple adulterants (levamisole, quinine, and xylazine).

LIMITATIONS

This study was one of the first to investigate delayed intubation use among suspected opioid-related overdose patients; however, there are some limitations that should be considered. First, data collected in the Fentalog Study come from several sites throughout the United States, but those are not nationally representative. This may have implications for generalizability. Second, the limited number of patients with delayed intubation restricted the statistical analyses that could be conducted in this study. Third, there was a significant percentage of patients in the Fentalog Study who were excluded for various reasons, which could introduce bias to all subsequent secondary analyses. Future studies with larger samples should consider additional analyses and should consider controlling for various potential confounding variables, including the use of only larger hospitals, which could be skewed toward receiving more critically ill patients.

DISCUSSION

This study provides evidence to suggest that a patient presenting after presumed opioid overdose may be safely managed outside of an ICU after 4 hours of ED monitoring if the patient does not continue to need additional doses of naloxone and there are no other life-threatening conditions present. This is a conservative

Table 2. Demographic data, naloxone administration, and laboratory results from patients with intubation performed more than 4 hours after arrival to hospital

		Naloxone							Laboratory Results						
			Out-of hospital		Hospital			Total		<2 h					>2 h*	
Case	Age (y)/Sex	Administered	Dose #	Total (mg)	Bolus/infusion	Bolus dose #	Total (mg)	Dose #	Total (mg)	Bicarbonate	Creatinine	Lactate	pH	pCO_2	Creatinine	Lactate
1	23/F	Yes	2	4		0	0	2	8	25	1.2	2.6	7.24	54	1.3	6.0
2	26/M	No	0	0		0	0	0	0	NP	NP	NP	NP	NP	0.9	NP
3	32/F	No	0	0		0	0	0	0	21	3.1	2.0	7.30	44	5.5	3.0
4	40/M	Yes	3	6	Bolus	2	0.4	5	6.4	26	1	2.3	7.21	68	0.9	2.2
5	41/M	Yes	3	7		0	0	3	7	17	1	NP	NP	NP	0.9	3.0
6	42/M	Yes	0	0	Bolus + infusion	1	2.4	1	2.4	19	3.1	11.0	6.94	116	1.3	4.5
7	43/M	Yes	2	1	Bolus	2	0.8	4	1.8	30	0.6	2.2	7.33	60	0.4	1.3
8	54/F	Yes	2	4.4		0	0	2	4.4	26	1.3	NP	7.17	82	1.3	2.3
9	63/M	Yes	2	2	Bolus	2	0.08	4	2.08	21	1.1	2.0	7.33	44	1.0	1.6

Bicarbonate from basic metabolic panel in mmol/L; creatinine in mg/dL; lactate in mmol/L; pH and pCO_2 from venous blood gas; pCO_2 in mmHg.
NP, not performed.
Case 5 had a serum ethanol concentration of 25 μg/L. All other cases had undetectable serum ethanol concentrations.
*No cases of delayed intubation had recorded bicarbonate, pH, and pCO_2 >2h after arrival.

recommendation based on the 4-hour time point used for this registry.

Delayed intubation appears to be exceedingly rare, mostly in the setting of critical medical illness aside from opioid intoxication. There was a low overall rate of delayed intubation (0.6%) and an even lower rate of delayed intubation due to hypoventilation (0.1%) alone. Furthermore, the majority (78%) of these cases received at least 1 dose of naloxone, but not all, consistent with previously published articles from the Fentalog Study.[16] These findings reveal that delayed intubation is often associated with factors beyond simple hypoventilation-induced respiratory failure, with the majority of cases having significant nonrespiratory indications for intubation. The presence of multiple substances, including potent synthetic opioids and other illicit drugs, may contribute to the complexity of these cases. Although rare, this finding suggests that clinical practice primarily focused on respiratory depression may not adequately address the broader risks associated with toxicity from present-day overdoses from illicit substances.

The absence of heroin or its metabolites in the Fentalog Study cohort has been previously reported as follows: Shastry et al[19] found 15% of the presumed opioid overdoses overall and 27% of patients who attempted to use "heroin" were found to have heroin identified in their system. This further emphasizes the shift in the opioid crisis from heroin to more potent synthetic opioids, such as fentanyl and its analogs as well as other adulterants. The high prevalence of fentanyl analogues and other substances (especially methamphetamine and xylazine) in this patient population indicates a need for ED practices that are tailored to the evolving landscape of polysubstance overdose. Currently, neither physicians nor patients can be certain of the contents of illicit drugs, making it important to treat these cases as polysubstance overdoses. As such, patients should be monitored and reassessed until they are asymptomatic for a period of time, with this subanalysis suggesting that a minimum of 4 hours of monitoring is appropriate.

This study provides evidence to suggest that there may be exceptionally low likelihood for the need for delayed intubation due to hypoventilation for a patient with presumed opioid overdose. Almost all the cases necessitating delayed intubation had significant co-occurring clinical conditions. Although further investigations with larger samples are needed, these findings support longstanding recommendations that still hold true despite a change in the illicit drug supply, which are as follows: clinicians should perform a thorough clinical assessment on these patients, which should include serial examinations, close monitoring of ventilation (eg, through end tidal monitoring or blood gas

Table 3. Clinical information, substances that patients believed they used, and confirmed substances via biologic testing for patients with intubation performed more than 4 hours after arrival to hospital

Case	Other Clinical Information	Other Substances Admitted	Substances Confirmed Through Comprehensive Toxicology Testing*
1	Received CPR in ED; intracranial subcutaneous gas present	Benzodiazepines, cannabis	Alprazolam, despropionyl fentanyl (4-ANPP), doxylamine, fentanyl, hydrocodone, naloxone, oxycodone, quinine
2	Recurrent vomiting and incontinence	Methamphetamine	Diazepam, hydroxyzine, morphine
3	Preexisting dilated cardiomyopathy and end-stage renal disease; had fluid overload requiring hemodialysis and intubation		Amphetamine, cocaine, 4-ANPP, fentanyl, hydroxyzine, levamisole, lidocaine, methamphetamine, noscapine, para-fluorofentanyl, quinine, tramadol, xylazine
4			Carboxy-tetrahydrocannabinol, cocaine, 4-ANPP, fentanyl, methylenedioxymethamphetamine, naloxone, tadalafil
5	Massive hematemesis for EMS, which recurred in ED		Acetaminophen, cocaine, fentanyl, lidocaine, methamphetamine, midazolam, quinine
6	STEMI necessitating emergent cardiac catheterization		Flualprazolam, lidocaine
7	Subdural hematoma	Amphetamine, cocaine, ethanol	Amphetamine, lidocaine, methadone, methamphetamine, naloxone, quinine
8	Received CPR through EMS with ROSC; was on BIPAP in ED but vomited with large aspiration		Citalopram, 4-ANPP, fentanyl, para-fluorofentanyl, naloxone, naproxen, quinine
9	Numerous white matter hypodensities and irregularities noted		Acetaminophen, carboxy-tetrahydrocannabinol, fentanyl, glimepiride, haloperidol, midazolam, risperidone

BIPAP, bilevel positive airway pressure; *CPR*, cardiopulmonary resuscitation; *EMS*, emergency medical services; *ROSC*, return of spontaneous circulation; *STEMI*, ST-segment elevation myocardial infarction.
*All substances identified on comprehensive toxicology analysis may include iatrogenically administered medications. Metabolites were not included if the parent compound was also identified in the sample.

evaluation), basic laboratory evaluation, and consideration for comorbid health conditions (cardiac disease, obesity, vascular disease, etc). If this workup is reassuring and the patient remains clinically stable after 4 hours of monitoring, we believe a non-ICU disposition would be proper. Future studies are needed to determine the shortest period of ED monitoring needed.

In conclusion, this study found an extremely low rate of patients requiring intubation for respiratory failure after 4 hours of monitoring, provided they initially presented with presumed opioid overdose. The low rate of delayed intervention (delayed intubation) suggests that opioid overdose disposition should continue to be based on comprehensive clinical assessments and ongoing reassessments, emphasizing the efficient use of resources. Accordingly, patients should be monitored and reassessed until they are asymptomatic, with this subanalysis recommending a minimum of 4 hours of monitoring. Future research should focus on developing and validating clinical tools that can help stratify patients based on their risk of delayed decompensation, with the ultimate goal of improving outcomes for this vulnerable population while limiting unnecessary resource utilization.

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