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PII: S0736-4679(22)00640-0
DOI: https://doi.org/10.1016/j.jemermed.2022.10.017
Reference: JEM 13332

To appear in: *Journal of Emergency Medicine*

Received date: 29 April 2022
Revised date: 6 October 2022
Accepted date: 21 October 2022

Please cite this article as: Kirstin Acus , Jessica Krizo , Spencer Prete , Thomas Langlois , Ashley Pajela , Caroline Mangira , Erin Simon , Amy Raubenolt , Do Higher Doses of Naloxone Increase the Risk of Pulmonary Complications?, *Journal of Emergency Medicine* (2022), doi: https://doi.org/10.1016/j.jemermed.2022.10.017

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This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

This research was presented at the American College of Emergency Physicians Annual Meeting October 26, 2021 and the National Association of EMS Physicians Annual Meeting January 10, 2022.

Do Higher Doses of Naloxone Increase the Risk of Pulmonary Complications?

Abstract

Background: Though naloxone has proven to be an effective opioid reversal agent, concern that high doses of naloxone can cause pulmonary edema may prevent healthcare providers from administering it in initial high doses.

Objective: To determine if increased dosages of naloxone are correlated with an increase in pulmonary complications in patients presenting to the emergency department (ED) following an opioid overdose.

Methods: This was a retrospective study of patients treated with naloxone by emergency medical services (EMS) or in the emergency department (ED) at an urban level 1 trauma center and three associated free-standing EDs. Data were queried from EMS run reports and the medical record and included demographics, naloxone dosing,

administration route, and pulmonary complications. Patients were grouped by naloxone dose received, defined as low (≤ 2 mg), moderate (>2 mg to ≤4 mg), and high (> 4 mg).

Results: Of the 639 patients included, 13 (2.0%) were diagnosed with a pulmonary complication. There was no difference in the development of pulmonary complications across groups (p=0.676). There was no difference in pulmonary complications based on the route of administration (p=0.342). The administration of higher doses of naloxone was not associated with longer hospital stays (p=0.0327).

Conclusion: This study suggests that the reluctance held by many healthcare providers to administer larger doses of naloxone on initial treatment may not be warranted. In this investigation, there were no poor outcomes associated with an increase in naloxone administration. Further investigation is warranted to examine this in a more diverse population.

Keywords

Naloxone, Narcan, opioid; fentanyl, carfentanil, edema, overdose

1. Introduction

Since the late 1990s, the opioid epidemic has posed challenges for emergency medicine providers. Timely administration of naloxone is an important treatment for opioid overdose. Naloxone is a highly lipophilic, non-selective, and competitive opioid receptor antagonist. It readily crosses the blood-brain barrier and rapidly displaces opiates from the mu-opioid receptor. It is one of the most effective agents available to rapidly reverse the fatal effects of opioids on the respiratory system (1, 2).

There are approximately 115 opioid-related deaths daily in the United States. The Centers for Disease Control and Prevention credits the trend in increasing death rates from years prior to higher availability and use of illicitly manufactured synthetic

opioids, such as fentanyl and carfentanil (3). Despite naloxone's efficacy, many healthcare providers hesitate to administer it in high doses for opiate overdose. Animal studies have shown that doses of naloxone typically effective in reversing morphine toxicity are less effective in the reversal of fentanyl analogs (4). The number of patients requiring multiple naloxone administrations by emergency medical service (EMS) providers has been trending upwards, further suggesting an increase in the potency of opioids involved in modern-day overdoses (5). Despite this data, physicians may refrain from administering high doses of naloxone early in cases due to concerns related to an unsubstantiated theory that naloxone leads to pulmonary complications.

Pulmonary edema and other pulmonary complications have been reported in patients who have received naloxone. Whether the patients developed pulmonary edema secondary to the naloxone or the opiate intoxication itself is undetermined. One of the most frequently discussed theories which discourages the use of high doses of naloxone proposes that large amounts of centrally mediated catecholamines are released from the rapidly reawakened patient in the form of a stress response. Subsequently, a sympathetic vasoactive response is initiated that could lead to pulmonary capillary extravasation (6, 7). On the other hand, decreased respiratory drive, perhaps the most well-known complication of opiate intoxication, also causes pulmonary edema. Inspiration against a closed glottis decreases intrathoracic pressure, leading to fluid extravasation. Theoretically, this would be exacerbated by prolonged time and pressure against the closed glottis. Therefore, from this aspect, rapid reversal of this process by high doses of naloxone would be beneficial.

Documented case reports exist supporting both of these theories. Several case reports have been published suggesting that patients developed pulmonary edema secondary to the administration of naloxone (6, 8, 9). However, pulmonary edema has

also been found before administering naloxone in many patients with opioid overdoses (10, 11).

Given the substantial impact the opioid epidemic has on society, the goal of this study is to evaluate adverse pulmonary events when naloxone is utilized to treat overdoses. This study aimed to determine whether higher doses of naloxone are associated with pulmonary complications (pulmonary edema or pneumonia) and whether this impacted admission rates and hospital length of stay (LOS). In addition, we sought to determine if the route by which naloxone was administered (intravenous (IV) versus intranasal (IN)) was associated with a difference in outcomes.

2. Methods

This was a retrospective chart review of adult patients 18 years of age and older who presented to an urban tertiary care hospital ED or one of three affiliated free-standing EDs and received at least one dose of naloxone between January 1, 2018, and December 31, 2019. It included patients who arrived via ambulance and those who arrived via other means. Patients were excluded if they fell outside the specified age range, received CPR, or were declared dead upon arrival. Our primary objective was to determine if pulmonary complications were associated with increased naloxone dosage. Patients were grouped by naloxone dose received, which was defined as low (≤ 2 mg), moderate (>2 mg to ≤4 mg), or high (> 4 mg). Pulmonary complications included pulmonary edema or pneumonia (including aspiration pneumonia). Our secondary objectives included evaluating the impact of the route of naloxone administration on pulmonary complications and the association of naloxone dosage on admission rate and hospital LOS. The study was approved by the hospital's Institutional Research Review Board.

Patient information including age, gender, insurance status, naloxone dosage, route of naloxone administration, chief complaint, pulmonary complications, ED disposition, and hospital LOS were abstracted from the electronic medical record Epic®. EMS data were abstracted from electronic and paper records from a large urban fire department. Data were maintained in REDCap®

Categorical variables are presented as frequency and percentages and analyzed using the chi-square test or Fisher's exact test. Continuous variables are presented as median and interquartile range, and differences between groups were tested using Wilcoxon rank sum test. Multiple regression analyses were fit to assess the effect of naloxone dosage on LOS and hospital complications. The significance level was set at 0.05. Analyses were performed using SAS® Software (version 9.4; Cary, NC).

3. Results

A total of 639 patients met the inclusion criteria for this study. Patients had a mean age of 45.8 ± 17.9 years, were evenly distributed between male (53%) and female (47%), were predominantly white (70%), and non-Hispanic (92%) (Table 1). Chief complaints included drug ingestion/overdose (49.6%), altered mental status (14.4%), respiratory-related complaints (5%), or presenting to the ED unresponsive (4%). Most patients (66%) received a low dose of naloxone, with the rest receiving moderate (22%) and high (12%) doses of naloxone. Naloxone administration was intravenous (54%), intranasal (30%), intraosseous (<1%), or included multiple administration methods (15%)

A total of 13 (2.0%) subjects were diagnosed with pulmonary complications. These complications included pneumonia (6), aspiration pneumonia (4), and pulmonary edema (3). The administration of higher doses of naloxone was not associated with a greater

risk of developing pulmonary edema (p=0.7106), aspiration pneumonia (p=0.5507), or pneumonia (p=0.2712) compared to the administration of low and moderate doses. Furthermore, the administration of higher doses of naloxone was not associated with a greater risk of developing pulmonary complications overall (p=0.6764) (Table 2).

There was no significant difference in the development of pulmonary complications when comparing the administration of naloxone through IV or intranasal route exclusively (p=0.3422). (The number of patients who received the medication exclusively through IO access was too low to assess significance) (Table 3).

Of the included subjects, 314 (49.1%) were admitted, 233 (36.3%) were discharged, 32 (5%) left against medical advice (AMA), 14 (2.2%) eloped, 23 (3.6%) were transferred to another facility, 14 left without being seen by a physician (2.2%), 4 were transferred to the labor and delivery unit (0.6%), 3 (0.47%) were transferred to the operating room,, and2 had no documented disposition. High doses of naloxone were not associated with increased admission rates; in fact, patients who received low doses of naloxone were statistically more likely to be admitted than the those who received moderate or high doses (p<0.0001) (Table 2). For all admitted patients, the average LOS (including ED and inpatient stay, where applicable) was 3.40 days. The administration of high doses of naloxone was not associated with patients experiencing a longer LOS. Similar to the admission rates, patients who received low doses of naloxone were found to have longer LOS than the other two groups (p=0.0327) (Table 2).

4. Discussion

The results of this study suggest that the fear held by many front-line health care providers that high doses of naloxone lead to pulmonary complications, such as

pneumonia, aspiration pneumonia, and pulmonary edema, is misguided. Our study did not detect a significant difference in the development of pulmonary complications when comparing the patients who received low, moderate, or high doses of naloxone. Moreover, administering higher doses of naloxone was not associated with increased admission rates or longer hospital LOS. A 2 mg dose of naloxone is often considered an "empiric dose", thus many of the patients in the "low dose" group may not have had opioid intoxication. This may also explain why this group of patients had increased admission rates and longer hospital LOS.

Although there are many case reports (referencing from 1 to 10 patients) (9, 13-16) on naloxone and its association with pulmonary complications, to our knowledge a 2019 study performed by Farkas, et. al. was the only large, retrospective study similar to ours. The authors of that study evaluated the relationship between out-of-hospital naloxone dosage and subsequent pulmonary complications. Our study evaluated pulmonary complications related to cumulative naloxone dosing regardless if received in the in-hospital or out-of-hospital setting. Farkas et. al. found patients who received high doses of naloxone in out-of-hospital settings were 62% more likely to have a pulmonary complication after an opioid overdose. In contrast, we found no difference in pulmonary complications for patients who received a high dose of naloxone. One possible explanation for why patients in Farkas et al.'s study who received high doses of naloxone pre-hospital were more likely to be diagnosed with pulmonary edema is that patients who required higher initial doses of naloxone by EMS may have experienced prolonged downtimes with corresponding intervals of decreased respiratory drive. Under those circumstances, patients may have developed pulmonary edema before they received their first dose of naloxone. Farkas et. al. also evaluated opioid overdose vs non-opioid etiologies and only considered pre-hospital naloxone administration.

Our study also evaluated if there was an association between the route of naloxone administration and development of pulmonary complications. We compared patients who received naloxone exclusively through an IV or exclusively intranasally. (Patients who received the medication exclusively via IO access were not factored into our study given the small sample size. There was no significant difference in the development of pulmonary complications between groups who received naloxone exclusively through an IV or exclusively intranasally. Our results resemble a meta-analysis performed by Yousefifard et al., which failed to detect a significant difference in complications experienced by patients who received naloxone via the intranasal route compared to those who received it by IV or intramuscular routes (12).

4.1. Limitations

There are several limitations that may limit the generalizability of this study. Given the retrospective nature of this study, we were unable to assess providers' clinical decision-making for the quantity of naloxone to administer or the providers' clinical impressions. We did not specifically seek to confirm whether patients who received naloxone had evidence of opioid use/overdose. We were also unable to assess details related to imaging timing after naloxone had been administered. Finally, a significant number of patients in this study left the ED within hours of receiving naloxone. Though the onset of pulmonary edema in this setting is often sudden, these patients could be considered lost to follow-up (and in particular to the development of the other pulmonary complications studied including pneumonia and aspiration pneumonia). This could include patients who were discharged from the ED, as we did not evaluate length of stay between the different groups of patients who were not admitted.

5. Conclusion

The opioid epidemic has taken a devastating toll on society, and with the ever-increasing prevalence of more potent, synthetic opiates, such as fentanyl and carfentanil, the importance of delineating a safe dose of naloxone has never been more important. The patients in our study who received high doses of naloxone did not experience an increased rate of pulmonary complications, hospital admissions, or longer hospital LOS compared to patients who received low or moderate doses. Further investigation is warranted, preferably in the form of prospective randomized trials. We also encourage other hospitals to replicate this to study to yield an increase both power and generalizability. By working together to investigate the association between naloxone and pulmonary complications, the emergency medicine community can establish a new naloxone dosing regimen that will adequately treat patients in the setting of increasing synthetic opioid use.

Article Summary

Why is this topic important?

The number of patients requiring multiple naloxone administrations by providers has been trending upwards, further suggesting an increase in the potency of opioids involved in modern-day overdoses. Despite this data, physicians may defer from administering high doses of the naloxone early on in overdose cases due to concerns that naloxone leads to pulmonary complications.

epidemic grows across the country.

What does this study attempt to show?

This study attempts to show that at our institution increased dosages of naloxone administration are not associated with an increase in pulmonary complications.

What are the key findings?

The key findings are that patients with increased naloxone administration were no more likely to develop pulmonary complications than moderate or low dose naloxone patients, there was no impact of naloxone administration route, and there was no impact of naloxone dose on patient hospital length of stay.

How is patient care impacted?

Increasing provider comfort with potentially providing increased naloxone dosing may lead to a shorter time to reversal in opioid overdose, which can impact the immediate outcomes following reversal and hospitalization.

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Table 1: Subject Demographics, (n=639)

Variable	**Number or mean**	**Percent or median**
Age	45.8	17.87
Gender		
Female	296	46.32
Male	338	52.9
Unknown	5	0.78
Race		
White	449	70.27
Black	153	23.94
Other	6	0.94
Unknown	31	4.85
Ethnicity		
Hispanic	5	0.78
Not-Hispanic	586	91.71
Unknown	48	7.51
Insurance		
Medicaid	295	46.17
Medicare	147	23
Private	84	13.15
Unavailable/Self Pay	113	17.68
Naloxone Group		
High	78	12.21
Low	423	66.2
Moderate	138	21.6

Table 1. Subject demographics and group assignment.

	High Dose Naloxone (n=78)	Moderate Dose Naloxone (n=138)	Low Dose Naloxone (n=423)	*p*-Value
All Pulmonary Complications				
No	77 (98.72)	134 (97.10)	415 (98.10)	0.6764
Yes	1 (1.28)	4 (2.90)	8 (1.89)	
Pulmonary Edema				
No	78 (100.00)	137 (99.28)	421 (99.53)	0.7106
Yes	0 (0.00)	1 (0.72)	2 (0.47)	
Aspiration Pneumonia				
No	77 (98.72)	138 (100.00)	420 (99.29)	0.5507
Yes	1 (1.28)	0 (0.00)	3 (0.71)	
Pneumonia				
No	78 (100.00)	135 (97.83)	420 (99.29)	0.2712
Yes	0 (0.00)	3 (2.17)	3 (0.71)	
Average Hospital Length of Stay (Days)	2.60 (1.46 – 4.97)	2.81 (1.77 – 7.21)	4.61 (2.00 – 8.87)	0.0327
ED Disposition Admit Discharge Other	 28(35.90) 39(50.00) 11(14.10)	 40(28.99) 74(53.62) 24(17.39)	 276(65.56) 120(28.50) 25(5.94)	<0.0001

Table 2. Pulmonary complications rates between low, moderate, and high naloxone dosage groups.

	Intranasal (n=193)	**Intraosseous (n=4)**	**Intravenous (n=347)**	**Mixed or Unknown Route (n=95)**
Pulmonary Complications (Overall)				
Yes	5(2.59)	1(25.00)	5(1.44)	2 (2.11)
No	188(97.41)	3(75.00)	342(98.56)	93 (97.89)

Table 3. Pulmonary complications in subjects receiving naloxone via intraosseous, intravenous, or mixed/unknown routes. Statistics presented as frequency (%).