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**Introduction:**

Opioids are a highly addictive class of drugs, which include heroin and morphine, prescription pain relievers such as oxycodone and fentanyl, and drugs used to treat opioid addiction, such as methadone and buprenorphine.[1] Opioids inhibit the perception of pain and produce sensations of euphoria. However, they also produce a number of unpleasant effects, including drowsiness, mental confusion, and nausea.[2] In cases of opioid overdose, there can be serious medical complications including respiratory depression and arrest, coma, and death.[1]

Opioid abuse and addiction is a serious problem that affects the social and economic welfare and the health of communities in the United States and around the world. It is estimated that between 26.4 million and 36 million people globally abuse opioids.[3] According to the National Institute on Drug Abuse, the number of heroin users in the United States doubled from 380,000 to 670,000 between 2005 and 2012.[4] In Vermont, annual overdose deaths from opioids including prescription opioids, heroin, and fentanyl, have nearly doubled between 2010 and 2015, rising from 41 to 76 deaths across the state.[5] Vermont Emergency department visits for opioids have risen by 340% between 2010 and 2014, although prescription opioid related emergency department visits have remained roughly level since 2012.[6] Between 2014 and 2015, there were 2,618 emergency medical system (EMS) responses to potential opioid overdoses, which comprised approximately 1.5% of all EMS calls in Vermont.[5]

When EMS personnel encounter a patient with potential opioid overdose, they typically administer the direct opioid antagonist naloxone. Naloxone is designed to rapidly reverse opioid overdose by binding to opioid receptors to reverse and block the effects of opioids.[7] Between 2014 and 2016, VT EMS agencies administered 1,999 doses of naloxone to 1,421 patients suspected of opioid overdose, utilizing different routes of administration.[8,9] Routes included intramuscular (IM), intravenous (IV), subcutaneous (SQ), intraosseous (IO), and intranasal (IN).[10] Advanced Life Support (ALS) personnel, which includes Advanced and Intermediate Emergency Medical Technicians (A-EMT and EMT-I), and Paramedics, are able to utilize all (including injectable) routes of administration. However, Basic Life Support (BLS) personnel, which includes Emergency Medical Technicians (EMTs) without advanced training, are able to utilize only the intranasal route of administration.

In addition to the ability to be handled by individuals with less or no medical training, intranasal administration has several benefits, including the potential to reduce the risk of needle-stick injuries and blood-borne pathogen transmissions.[10,11] Many early studies suggest that the intranasal route of administration is of similar effectiveness to the injectable routes.[11-19] The main objective of our study was to compare the efficacy of intravenous and intraosseous (IV/IO) routes of naloxone administration to the intranasal (IN) route in suspected opioid overdoses in Vermont. Additionally, we aimed to examine the influence of provider level, incident cardiac arrest at the time of treatment, and of naloxone dosage on patient outcomes in cases of suspected opioid overdose.

In order to conduct our analysis, we used data from the Statewide Incident Reporting Network (SIREN), "a comprehensive prehospital patient care data collection, analysis and reporting system" that all Vermont EMS agencies have used to collect data since 2010.[20] Annually, Vermont EMS agencies add 87,000 to 89,000 emergency and non-emergency calls into SIREN.[20] Our goal in this research was to utilize this data set with the hopes of influencing Vermont EMS best practices as well as reducing EMS-associated costs.

## Methods:

### *Study Design*

We reviewed retrospective data from Vermont EMS calls that were entered into SIREN by roughly eighty Vermont-based ambulances and 15 first response agencies (exact numbers were not available.) We used data that was de-identified by another IRB-approved research study and stored through the Vermont Department of Health. The state-wide data was collected between April 2014 and August 2016. We stored the data on a personal computer with password protection. This project was approved by the University of Vermont Institutional Review Board.

### *Population & Sample Size*

The patient population selected for this study included all patients that were entered into the SIREN database and administered naloxone during the study period. For this study, we assumed that any patient that was administered naloxone had clinically suspected opiate overdose. Exclusion criteria consisted of failure to be treated with naloxone. We did not exclude any cases based on patient age. In the cases where a patient received multiple doses of naloxone, we analyzed only the first dose of naloxone administered. We separately analyzed second and total doses given in our secondary analysis. The sample size was limited by the availability of data from SIREN.

### *Key Variables*

Our main predictor variables were route of administration (intravenous/intraosseous or intranasal), medication dosage (in milligrams), provider level (advanced life support, basic life

support, or unknown), and cardiac arrest (whether or not a patient had a documented cardiac arrest at the time of the EMS response.) Data cleaning information and expanded variable definitions are described in Appendix 1. The primary outcome variable was patient response to medication, which was categorized as improved or no change/worsened.

We converted all medication administration doses into milligrams. We excluded data that was missing dose or had a first dose of naloxone that was not inside the normal therapeutic range of 0.1-2 mg (n = 11).[10] We also excluded data with an unknown provider level (n = 3) or with a route of administration that was not IV/IO or nasal (n = 49).

### *Data Quality Verification*

To verify that data quality was preserved across all transformations, we took a random sample equal to 10% (n = 119) of all of our cases (n = 1139) and found that all cases in the random sample were correctly included or excluded, and were correctly coded. We then used SPSS and Microsoft Excel analytics as well as a manual review to verify our sample results.

### *Analytical Methods*

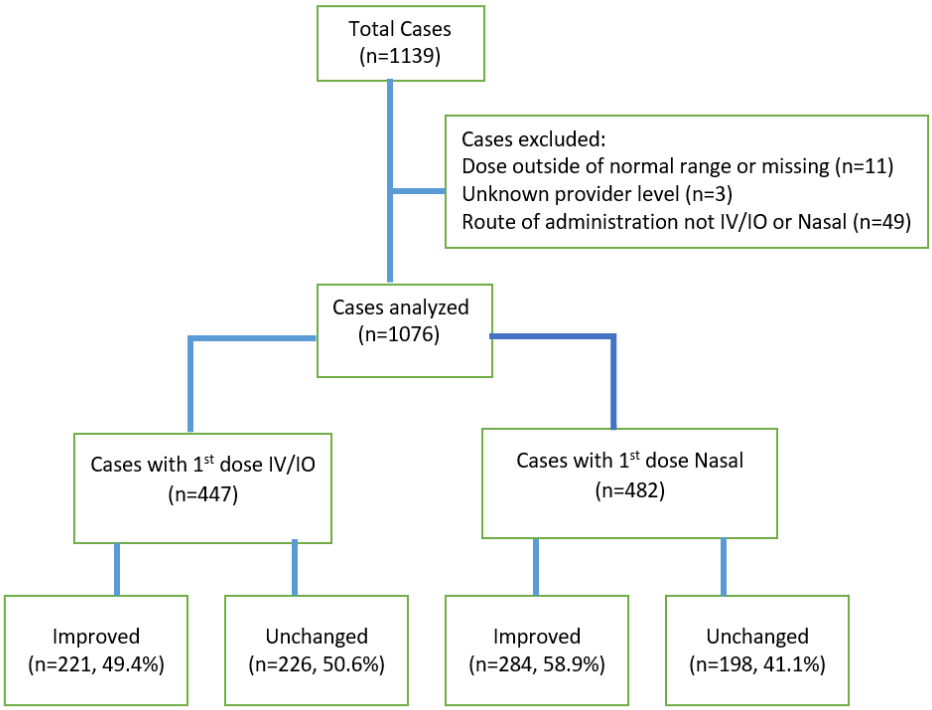
We conducted a binary logistic regression in SPSS to predict improvement in condition (patient to response medication). A p-value <0.05 was the threshold to define statistical significance. Our logistic regression model is shown below:

$$y = B_0 + B_1*(AdminRoute) + B_2*(AdminDose) + B_3*(Crew\_Member\_Level) + B_4*(Cardiac\_Arrest)$$

## Results:

Our sample consisted of 1139 cases of first-dose naloxone administration, and 1076 cases met inclusion criteria and were included in the primary analysis. Figure 1 shows inclusion and exclusion criteria applied to our sample. Sex, gender, age, and other demographic information were not available in the de-identified data.

**Figure 1: Inclusion and Exclusion Criteria**




A total of 1592 doses of naloxone were administered in our sample. Of these, 1497 were administered by advanced life support (ALS) providers, 91 were provided by basic life support (BLS) providers, and 4 were provided by an unknown level provider. Of these doses, 853 doses were administered IV/IO, 678 were administered via a nasal route, 33 were administered subcutaneously or intramuscularly, and 28 were administered by a different or unknown route. Of the cases analyzed there were 1076 cases in which at least one dose of naloxone was administered, 324 cases in which at least two doses were administered, 72 cases in which at least three doses were administered, 21 cases in which at least four doses were administered, 7 cases in which at least five doses were administered, and one case in which 6 doses were administered.

Of all first-dose administrations of naloxone, 6.6% (n = 71) were given by basic life support (BLS) providers, whereas 93.4% (n = 1005) of the first administrations of naloxone were given by advanced life support (ALS) providers. In cases where the first dose of naloxone was given IV or IO, 49.4% improved. In cases where the first dose of naloxone was given via nasal administration, 58.9% improved.

Our primary analysis examined the first dose of naloxone recorded for each unique identifier alongside provider level (ALS or BLS), medication dosage (in mg), route of administration (IV/IO or Nasal), and Cardiac Arrest (yes/no) and patient outcome (improved or unchanged/worse). Results of our primary analysis are shown in Table 1. We found that neither route of administration nor dosage had a statistically significant effect on a patient's response to

naloxone. However, we found that patients who experienced a cardiac arrest were statistically less likely to respond to naloxone (OR 10.8, 95% CI (5.908-19.694)). The Hosmer-Lemeshow goodness of fit test yielded a p-value of 0.374, suggesting the model was sufficiently well calibrated.

**Table 1: Results of Binary Logistic Regression Model Analyzing the Relationship Between Medication Route of Administration (1st dose) and Patient Outcome**

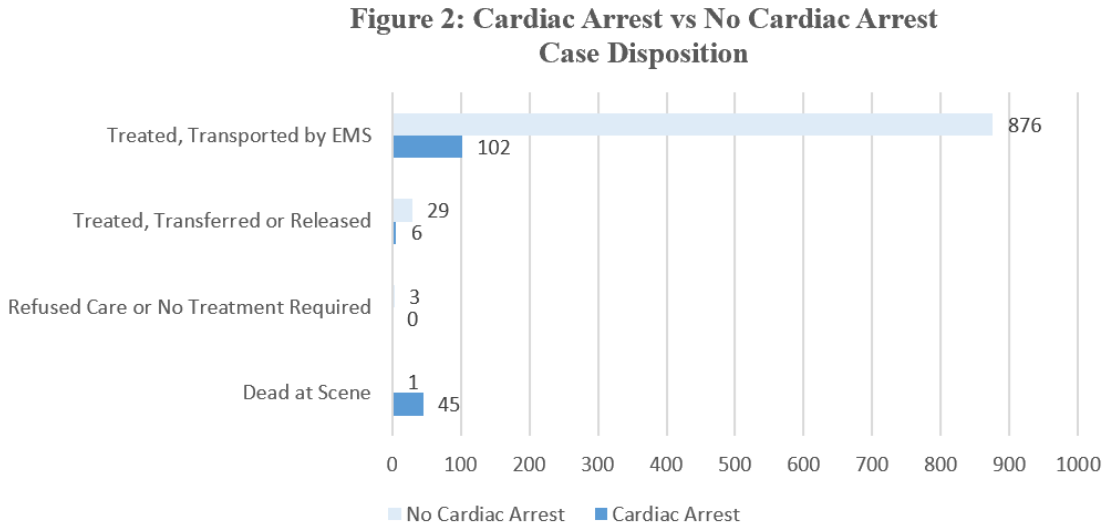
| Variable | Coefficient (β) | Standard Error | Wald $X^2$ | P value | Odds Ratio | 95% CI |
|---|---|---|---|---|---|---|
| Intercept | -1.924 | 0.356 | 29.145 | 0.000 | 0.146 | --- |
| Route | 0.029 | 0.155 | 0.035 | 0.851 | 1.030 | 0.760-1.395 |
| Dosage | -0.046 | 0.120 | 0.147 | 0.701 | 0.955 | 0.755-1.208 |
| Provider Level | 0.308 | 0.287 | 1.153 | 0.283 | 1.361 | 0.775-2.390 |
| Cardiac Arrest | 2.378 | 0.307 | 59.952 | 0.000 | 10.786 | 5.908-19.694 |

The median number of doses of naloxone given in our sample was 1.0 (IQR 1.0 – 2.0, mean 1.4, SD 0.7). The range of first doses of naloxone was 0.1 mg – 2 mg. Table 2 shows the dosages (in mg) of Naloxone that patients were administered on the first dose.

**Table 2: Dosages (in mg) of Naloxone Administered on the First Dose**

| Dose (in mg) | # of Cases | Percentage |
|---|---|---|
| 0.10 | 1 | 0.09% |
| 0.20 | 3 | 0.28% |
| 0.40 | 70 | 6.50% |
| 0.50 | 111 | 10.32% |
| 0.60 | 1 | 0.09% |
| 0.70 | 1 | 0.09% |
| 0.80 | 13 | 1.21% |
| 1.00 | 193 | 17.94% |
| 1.20 | 1 | 0.09% |
| 1.25 | 1 | 0.09% |
| 1.50 | 18 | 1.67% |
| 1.90 | 1 | 0.09% |
| 2.00 | 662 | 61.52% |
| | 1,076 | 100.00% |

Figure 2 shows the disposition of cardiac arrest patients. The majority of patients (69.9%) were treated and transported by advanced life support (ALS). 29.2% of cardiac arrest patients were found dead at scene.




**Discussion:**

We found that whether naloxone was administered IV/IO or intranasal did not have an effect on a patient's response to naloxone, and within the normal therapeutic range (0.1-2 mg), dosage did not make a difference in patient response to medication. Based on these findings, which corroborate findings from similar studies, intranasal naloxone appears to be an effective alternative to the intravenous and intraosseous routes in a prehospital setting.[11-19]

One advantage of using IV/IO routes of administration is the ability to more accurately titrate dosage of naloxone, which can be useful to avoid potential negative physical and behavioral side effects due to reversal of opiate effect. Furthermore, IV administration can provide more rapid naloxone exposure and opioid reversal than routes with an absorption phase, including intranasal administrations.[21] However, IV administration can produce more adverse events as well as more severe withdrawal symptoms, which must be balanced with the rapidity of opioid reversal.[21]

On the other hand, obtaining vascular access can prove difficult among intravenous drug users, prolonging the time required to administer naloxone.[16] Furthermore, hypotension or restrictive clothing may further complicate IV access. Agitation, confusion, and combativeness are not uncommon among patients awakening from an opioid overdose, which can increase the risk of needle-stick injury to emergency medical personnel.[16] The intranasal route circumvents the need to establish vascular access and can reduce the risk of needle-stick injuries and blood-

borne pathogen transmissions. Additionally, intranasal naloxone can be handled by individuals with varying degrees of medical training.[10]

Because we found that patients in cardiac arrest were significantly less likely to respond to treatment with naloxone, we suggest that providers focus more on treatments proven to benefit a cardiac arrest, such as CPR, and proper ventilation/oxygenation, which corroborates other research and recommendations on treating cardiac arrest in cases of suspected opioid overdose.[22, 23] Furthermore, this finding supports the updated 2015 American Heart Association guidelines for cardiac arrest in patients with known or suspected opioid overdose, which recommend that standard resuscitative measures (including CPR and ventilation) should take priority over naloxone administration.[24]

There were several limitations to our data. Due to our study design, we were unable to control or examine many variables. Notably, we could not control for dose and type of opiate taken, which could both have an effect on the effectiveness of naloxone. Additionally, we could not control for the severity of overdose or the time between overdose and administration of naloxone, or for any exacerbating medical conditions.

Furthermore, we had no way to track clinical reasoning of the EMS provider for choosing a particular route of administration over another (i.e. patients who appear to be in a more severe condition may have been given naloxone IV by the EMS responder, and due to their more severe condition may be less likely to show improvement.) We were unable to assess the cumulative effect of multiple doses on patient outcome. In cases where multiple doses of naloxone were administered, patients may have received naloxone from different levels of providers (first dose by ALS, second dose by BLS, etc.) Thus, we were also unable to examine if and how other variables impacted patient outcome in cases where multiple doses were given.

Finally, our data was limited due to missing data points and erroneous entries, which are common issues among retrospective studies.[25] For example, the data set was missing demographic variables such as sex, age, location, and incident date. Multiple erroneous entries were found. For example, the respiratory rate was frequently not recorded before and/or after naloxone administration, and in other instances, “No Treatment Required” was recorded in the patient disposition field when naloxone was subsequently administered. These errors demonstrate inconsistencies that limit potential data analysis from SIREN data. Lastly, we were unable to confirm our data with hospital records.

**Conclusions:**

We found that whether naloxone was administered IV/IO or intranasal it did not have an effect on patient response to naloxone, and dosage (within the normal therapeutic range) did not make a difference in patient response to naloxone. Our findings, in conjunction with other recent research, suggest that intranasal administration is an effective route when compared with intravenous and intraosseous routes. Furthermore, intranasal administration has several distinct advantages over injectable routes, including the potential to reduce the risk of needle-stick

injuries and blood-borne pathogen transmissions and to be handled by individuals with less medical training. In cases of cardiac arrest, we suggest that providers focus on treatments with proven benefit, such as CPR and proper ventilation and oxygenation. We recommend that EMS providers improve the accuracy and consistency of their data entry in order to increase opportunities for future research and SIREN data analysis. Lastly, we recommend that similar research be replicated in a larger system and in a prospective manner, due to the rural setting and limitations of this study design.

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## Appendix 1: Data Cleaning Notes and Variable Information

We created the variable Medication_Response to classify patient responses to naloxone administration. We categorized responses to medication entered as unchanged or worse together as Unchanged/Worse. Blanks were left blank and not included in our analysis.

We created the variable Medication_Route to classify routes of naloxone administration and regrouped all data entries for administration route as Intravenous/Intraosseous (IV/IO), Nasal, Subcutaneous/Intramuscular (SubQ/IM), Other, and Unknown. IV/IO consisted of all data entered as IV or IO, and are considered pharmacologically equivalent in clinical practice. Nasal consisted of data entered as inhalation, nasal, or intranasal. SubQ/IM consisted of data entered as subcutaneous or intramuscular. Other routes consisted of data entered as other/miscellaneous, inhalation via nebulizer, and nasogastric. Unknown consisted of data entered as Not Recorded or left blank.

We classified crew member levels that provided the first dose of naloxone as Advanced Life Support (ALS), Basic Life Support (BLS), or Unknown. "ALS" included crew member levels A-EMT, ALS, EMT-intermediate-03, and Paramedic. "BLS" included BLS, Emergency Medical Technician (EMT), EMT, EMT Basic, and EMT-Basic. We classified all crew member levels that were Unknown, Other HCP, or left blank as Unknown.

We created the variable Cardiac_Arrest based on whether or not the patient had "Cardiac Arrest" documented in primary or secondary impression or "Cardiorespiratory Arrest" documented as a primary symptom. Cases with Cardiac Arrest or Cardiorespiratory Arrest were classified as Cardiac Arrest.

We converted the data to a 24-hour time scale, and we subtracted one hour from each vital time and medication administration time where the record crossed midnight. We completed this adjustment to appropriately analyze the time interval between recordings.

*Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.*