



Original Contribution

# Intranasal naloxone delivery is an alternative to intravenous naloxone for opioid overdoses<sup>☆</sup>

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## Abstract

**Introduction:** This study proposes that intranasal (IN) naloxone administration is preferable to intravenous (IV) naloxone by emergency medical services for opioid overdoses. Our study attempts to establish that IN naloxone is as effective as IV naloxone but without the risk of needle exposure. We also attempt to validate the use of the Glasgow Coma Scale (GCS) in opioid intoxication.

**Methods:** A retrospective chart review of prehospital advanced life support patients was performed on confirmed opioid overdose patients. Initial and final unassisted respiratory rates (RR) and GCS, recorded by paramedics, were used as indicators of naloxone effectiveness. The median changes in RR and GCS were determined.

**Results:** Three hundred forty-four patients who received naloxone by paramedics from January 1, 2005, until December 31, 2007, were evaluated. Of confirmed opioid overdoses, change in RR was 6 for the IV group and 4 for the IN group ( $P = .08$ ). Change in GCS was 4 for the IV group and 3 for the IN group ( $P = .19$ ). Correlations between RR and GCS for initial, final, and change were significant at the 0.01 level ( $\rho = 0.577, 0.462, 0.568$ , respectively).

**Conclusion:** Intranasal naloxone is statistically as effective as IV naloxone at reversing the effects of opioid overdose. The IV and IN groups had similar average increases in RR and GCS. Based on our

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results, IN naloxone is a viable alternative to IV naloxone while posing less risk of needle stick injury. Additionally, we demonstrated that GCS is correlated with RR in opioid intoxication.  
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## 1. Introduction

### 1.1. Background

In 1991, the Occupational Health and Safety Administration mandated the implementation of alternative drug delivery systems to minimize needle stick injuries and decrease the exposure of blood borne pathogens to emergency health workers [1]. The risk of exposure to blood borne pathogens is especially high in the emergency medical services (EMS) environment. The annual blood contact for individual EMS providers is estimated to be as high as 12.3 exposures per year in populations with more than 90% of the HIV statuses unknown [2]. In high-risk populations, such as intravenous (IV) drug abusers, alternative practices are vital in maintaining the safety of the EMS personnel while providing adequate care to the patients.

Intranasal (IN) medication delivery is a safe and direct means to provide medication to patients without using needles. Some advantages compared with parenteral include avoidance of painful injection, avoidance of risks associated with IV access, rapid onset, and high levels of patient acceptability [3].

Human studies elucidate naloxone pharmacokinetics [4-6]. The onset of IV naloxone is 1 to 2 minutes; it has a clinical duration of 20 to 90 minutes that varies with dosage and administration route [7]. Intranasal administration of naloxone bypasses hepatic first-pass metabolism because absorption is direct via nasal mucosa, due to richly supplied vasculature and low barrier to drug permeation [8]. Intranasal drug delivery also has the potential to target brain delivery, bypassing the blood brain barrier [9].

Pharmacokinetic data for IN administration in humans is lacking. Currently, data in rats describe 100% bioavailability for IN naloxone, with similar elimination half-life to IV naloxone [10]. In this animal study, peak plasma concentrations for IN naloxone occurred within 3 minutes of administration. This evidence corroborates supporting this route of administration. Clinical outcome data also support the use of IN naloxone in reversing opioid effects in both the overdose setting and for opioid dependency [11-13].

Multiple articles suggest IN naloxone has a strong evidence base as a first-line therapy for people with suspected opioid overdose in the prehospital setting. The 2006 Best Evidence Topic Report [14], published in the *Emergency Medicine Journal*, summarizes the findings in these articles published since 1992. The review concludes IN naloxone has minimal adverse side effects and is a safe route of administration.

From 2002 to 2005, several case series were published on IN naloxone [15,16]. Limitations of these studies included small patient number, variable exclusion/inclusion criteria, differing route and timing of naloxone, and inconsistent methods of response measurement quantified. A 2005 article concluded that IN naloxone was a good first-line therapy for patients suspected of opioid overdose, with findings of rapid reversal of overdose in most patients and a limited risk of needle stick exposures [11]. Two additional studies [12,17]—a randomized control trial and a retrospective case review—both conclude that IN naloxone was effective, but time to onset was prolonged from IV and intramuscular naloxone.

### 1.2. Purpose

The intent of this study was to investigate whether IN naloxone was noninferior compared to IV naloxone in increasing respiratory rates (RRs) and mental status in patients presenting with suspected opioid overdose in the prehospital setting. Our primary outcome measures were changes in Glasgow Coma Scale (GCS) and unassisted RRs after administration of IN and IV naloxone. We also attempt to demonstrate that GCS is correlated with RR in opioid overdose.

### 1.3. Hypothesis

We hypothesize that in patients presenting with opioid overdoses, IN naloxone will be noninferior to IV naloxone in increasing RR and GCS.

## 2. Methods

### 2.1. Design

The study is a retrospective cohort conducted by chart review.

### 2.2. Setting

The study was conducted at a university-based level I trauma center in an urban setting. The EMS system contain 6 advanced life support (ALS) units that perform 6920 ALS treats per year within a context of approximately 30 000 dispatches per year (including basic life support units). Only ALS may administer naloxone in our study's site. All ALS personnel received training in IN and IV naloxone

administration during paramedic class, and this procedure is frequently performed throughout our state.

### 2.3. Selection of participants

Testing the hypothesis requires determination of opioid intoxication. Criteria created to ensure acute opioid overdose includes documentation of one of the following: patient admission of illegal or nontherapeutic opioid use to paramedics or emergency department (ED) physician, witness testimony to paramedics or ED physician, evidence of opioid use observed by paramedics (eg, heroin, prescription narcotics, or used paraphernalia found on person), or positive urine toxicologic screen for opioids.

Participant exclusion criteria included patients in cardiac arrest, intubation before naloxone administration, sedation by paramedics before naloxone administration, or patients with end point data missing from patient care reports (PCRs).

### 2.4. Interventions

From a database of ALS responses, patients who received naloxone between January 1, 2005, and December 31, 2007, were selected as participants. As per state standing orders, patients with altered mental status received IV naloxone at an initial dose between 0.4 and 2.0 mg or IN naloxone at 1 mg per nostril at the discretion of the paramedics.

### 2.5. Methods of measurement

Paramedics recorded data on standard ALS PCRs while treating their patients. Vital signs, including RR and GCS, were assessed and recorded upon initial evaluation and after any treatment or intervention. Any illegible handwritten values were confirmed with the paramedic who wrote the PCR.

### 2.6. Data collection and processing

The study was approved by our institutional review board. All data were collected by an investigator trained in Microsoft Access and the Emergency Department Information Management database. The investigators who collected data were 2 medical students. The investigators had to both agree independently if records were clear that the patient received IV as well as proper determination of opioid abuse. After students documented these findings, the principal investigator reviewed all material. From an Access database of EMS responses, a query was performed to list all patients who were administered naloxone between January 1, 2005, and December 31, 2007. Referring to the original PCRs, the investigators recorded date, destination hospital, route of naloxone delivery, dosage, time to reassessment, participant age and sex, and positive narrative identification of acute opioid intoxication. Data were extracted from the PCRs onto

a Microsoft Excel spreadsheet. In addition, the investigators recorded patients' RR and GCS values documented immediately before and after administration of a single dose of naloxone. After enrolling qualified participants, patient records were cross-referenced with ED records in Emergency Department Information Management to obtain additional confirmation of opioid intoxication by ED physician progress notes or participant urine toxicologic screens. The admitting or discharge diagnosis was also obtained when available. Among the participants with confirmed opioid overdoses, PCRs and physician progress notes were reevaluated to determine any coingestion in addition to opioids. All data were entered into a standardized abstraction form. End points were reconfirmed 3 times for each patient by reinspection of PCRs by the investigators. The investigators met bimonthly to discuss progress and review discrepancies.

### 2.7. Outcome measures

Glasgow Coma Scale and RR values recorded on the PCR immediately before administration of the first dose of naloxone determined "initial measurement;" values recorded immediately following the first administration of naloxone defined "final measurement." *Naloxone redosing* was defined as subsequent doses naloxone. The accepted scoring system was used to determine composite GCS values.

### 2.8. Data analysis

Our hypothesis tests the noninferiority of IN. A power calculation for RR improvement was calculated. We assumed the type I error rate to be less than 5%. From the confirmed group (IN,  $n = 38$ ), RR mean change is 4.37 and Standard deviation (SD) is 4.58. The approximate power for detecting such a mean ( $\mu$ ) SD ( $\sigma$ ) ratio ( $\mu/\sigma = 0.95$ ) is 100% with sample size,  $n = 38$ . We also find that  $n = 38$  (IN, confirmed opioid) can detect a  $\mu/\sigma$  ratio as small as 0.55 with 95% power and type I error rate 5% or less.

A power calculation for GCS improvement was completed. The IN group GCS mean change is 4.29 and SD is 4.61. The approximate power for detecting such a mean ( $\mu$ ) SD ( $\sigma$ ) ratio ( $\mu/\sigma = 0.93$ ) is 100% with sample size  $n = 38$ .

A sample size calculation for RR and/or GCS improvement was calculated. We use  $\eta$  to stand for the probability that sum of 2 independently and identically distributed random variables from a continuous symmetric distribution is greater than zero ( $\eta = 0.5$  represents median = 0). For our retrospective study, the hypothesized comparison between  $\eta = 0.5$  and  $\eta = 0.80$  is reasonable, and sample size  $n = 38$  suffices for this specific test.

A power calculation for RR improvement comparison ( $\Delta$ ) between IN and IV was completed. We tested  $H_0: \Delta = 0$  vs  $H_a: \Delta$  does not equal 0, where  $\Delta$  represents the median shift between 2 improvement size distributions (IN and IV). We

assume the type I error rate to be less than 5%, from confirmed group (IN, n = 38; IV, n = 55). The RR change SD ( $\sigma$ ) is around 4.6 for IN group; the approximate power for detecting location shift ( $\Delta = 2$ ) with ratio ( $\Delta/\sigma = 0.44$ ) to be 66% with sample size n = 38, m = 55. We also found that n = 38 and n = 55 (IN and IV, confirmed opioid) can detect a  $\Delta/\sigma$  ratio as small as 0.70 with power 95% and type I error rate 5% or less.

A power calculation for GCS improvement comparison between IN and IV was completed. The GCS change SD ( $\sigma$ ) is 4.6 for IN group; the approximate power for detecting location shift ( $\Delta = 1$ ) with ratio ( $\Delta/\sigma = 0.22$ ) is 27% with sample size n = 38, n = 55. The smaller GCS change difference is more difficult to detect compared with RR change difference, which are approximately 2.

The confirmed opioid overdose group is subdivided based on IV or IN administration. Subjects who received intramuscular naloxone were excluded because of their limited number and irrelevance to study's purpose. Distributions of initial, final and change in RR, and GCS score were examined with graphical methods as well as by Shapiro-Wilk's *W* statistic for normality test. The nonnormal distribution of RR and GCS values necessitated nonparametric methods in the analysis [3,18,19]. Within IV and IN confirmed opioid overdose groups, the Wilcoxon signed rank test was used to compare initial and final values of RR and GCS. Associated with Wilcoxon signed rank test, medians are estimated by Hodges-Lehmann estimator [19] along with Tukey distribution-free confidence interval (CI). Between the IV and IN-confirmed opioid overdose groups, the Wilcoxon rank sum test was used to compare initial, final, and average change in

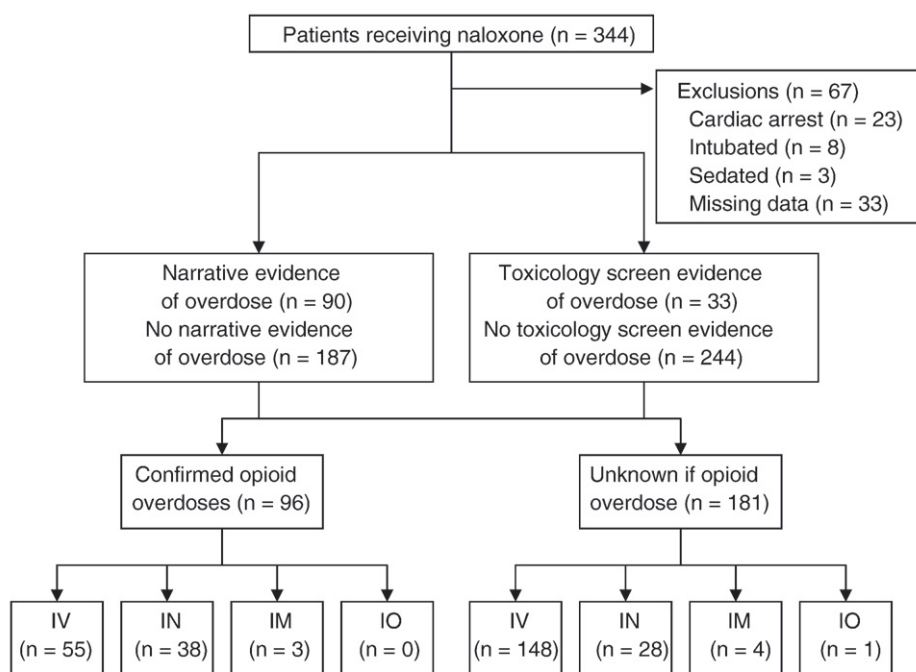
RR and GCS. Associated with Wilcoxon rank sum test, median differences are estimated by Hodges-Lehmann estimator along with Moses' distribution-free CI [19]. Spearman's rank correlation coefficient was used to measure the association between RR and GCS, initial and change in RR, and initial and change in GCS. Proportions were compared by the Pearson's  $\chi^2$  test. All tests were 2-sided. Statistical analysis was carried out using SAS 9.1 TS level 1M0, XP\_PRO platform (SAS Institute Inc, Cary, NC) and Minitab 15 (Minitab Inc, State College, PA).

### 3. Results

#### 3.1. Characteristics of study subjects

From a database of advanced life support emergency medical calls, 344 patients received naloxone. These patients were assessed for eligibility for enrollment in the study. Patients excluded from the study were 23 in cardiac arrest, 8 intubated before naloxone administration, and 3 sedated before naloxone administration. An additional 33 patients were excluded due to missing data on PCRs. Of these 33 patients, 11 (3 IN, 8 IV) were confirmed acute opioid intoxications. The data points missing from the 11 PCRs were as follows: GCS (7 patients), RR (5), and route of administration (1). Two hundred seventy-seven patients remained for enrollment in the study.

Participants were divided into 8 groups based on evidence of opioid overdose (confirmed, unknown) and route of



Abbreviations: IM, intramuscular; IN, intranasal; IO, intraosseous; IV intravenous.

Fig. 1 Flow chart of study design.



**Table 1** Baseline characteristics of subjects by confirmation of opioid overdose

	Opioid overdose, median (interquartile range)		Difference estimation (95% CI <sup>a</sup> )	P of comparison <sup>b</sup>
	Confirmed (n = 96)	Unknown (n = 181)		
Age, y	40 (29-50.8)	51 (37.5-74.5)	-12 (-17 to -6)	<.0001
Male sex, n (%)	61 (63.5)	99 (54.7)	8.8 (-3.2 to 20.9)	.16 <sup>c</sup>
Initial RR, per min	10 (6-16)	16 (14-20)	-6 (-8 to -6)	<.0001
Initial GCS score	3.5 (3-11)	9 (4-13)	-2 (-3 to 0)	.0002
Naloxone dose, mg	2 (2-2)	2 (1-2)	0 (0 to 0)	.19
Reassessment time, min	5 (2-8)	4 (2-7)	0 (-1 to 1)	.71

<sup>a</sup> The confidence interval for the median is slightly greater than 95%, as there is no assumption of distribution.

<sup>b</sup> By Wilcoxon rank sum test unless otherwise noted.

<sup>c</sup> By Pearson's  $\chi^2$  test.

naloxone administration (IV, IN, intramuscular, intraosseous) (Fig. 1). Table 1 shows the comparison of baseline characteristics between the confirmed (n = 96) and the unknown (n = 181) groups. Compared to the unknown group, the RR median rate was 10 vs 16 breaths per minute and the GCS median score was 3.5 vs 9. Further exploration of medical records was required to determine if subjects in the unknown opioid overdose group were unconfirmed opioid overdoses or if the patients presented with acute illnesses secondary to other medical conditions. Of the 181 subjects in the unknown group, 97 were transported to our hospital and 89 diagnoses could be obtained. The 8 subjects who could not be accounted for probably left the ED before being registered. Of these patients with unconfirmed opioid overdoses, the treating physician gave only 3 (3%) patients a diagnosis of suspected (unconfirmed) opioid overdose, which indicates that most patients in the unknown group had a different acute illness. The remaining diagnoses were alcohol intoxication (18%), nonopioid drug overdose (18%), cerebrovascular accident/transient ischemic attack/intracranial bleed (15%), altered mental status of unknown etiology (10%), respiratory failure/asthma (7%), seizure (7%), sepsis

(6%), trauma (6%), hypoglycemia (3%), dehydration (2%), syncope of unknown etiology (2%), anxiety (1%), dementia (1%), and hyperglycemia (1%). Considering all of the patients transported to our hospital, excluding the 8 in the unknown group who did not register (n = 158), 86 patients (54%) received naloxone with a medical condition, other than opioid intoxication, that potentially accounted for their acute presentations.

Within the confirmed opioid overdose group, characteristics of subjects were compared by route of naloxone administration (Table 2). The 2 routes of administration were similar except for evidence of coingestions and dose of naloxone given. Subjects in the IV group had a higher percentage of coingestion confirmations than those in the IN group (median, 32% vs 13%;  $P = .02$ ; 95% CI for proportion difference is 4% to 44%). Although the median naloxone dose for both groups was 2 mg, subjects receiving IN naloxone received a higher dose than those receiving naloxone intravenously (mean, 1.95 vs 1.71 mg;  $P = .01$ ). This is because of EMS protocols, where IV naloxone may be titrated to effect from 0.4 to 2 mg, and IN naloxone is usually given as 2 mg, 1 mg in each nostril.

**Table 2** Baseline characteristics of subjects with confirmed opioid overdoses by route of naloxone administration

	Route of administration, median (interquartile range)		Difference estimation (95% CI <sup>a</sup> )	P of comparison <sup>b</sup>
	IV (n = 55)	IN (n = 38)		
Age, y	42 (31-47)	38 (27-54)	3 (-4 to 9)	.44
Male sex, n (%)	37 (67.3)	23 (60.5)	6.8 (-13.1 to 26.6)	.50 <sup>c</sup>
Initial RR, per min	10 (6-16)	10 (4-14.5)	0 (-2 to 4)	.60
Initial GCS score	4 (3-11)	3 (3-9.25)	0 (0 to 1)	.37
Naloxone dose, mg	2 (1-2)	2 (2-2)	0 (n/a)	.02
Reassessment time, min	4 (2-8)	5 (2.8-7.3)	0 (-2 to 1)	.66
Coingestion evidence, n (%)	32 (58.2)	13 (34.2)	24.0 (4.0 to 43.9)	.02 <sup>c</sup>
Narrative evidence of opioid overdose, n (%)	51 (92.7)	36 (94.7)	-2.0 (-11.9 to 7.9)	.70 <sup>c</sup>
Toxicologic screen evidence of opioid overdose, n (%)	21 (38.2)	12 (31.6)	6.6 (-13.0 to 26.2)	.51 <sup>c</sup>

<sup>a</sup> The confidence interval for the median is slightly greater than 95%, as there is no assumption of distribution.

<sup>b</sup> By Wilcoxon rank sum test unless otherwise noted.

<sup>c</sup> By Pearson's  $\chi^2$  test.

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