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Original Contribution

Intranasal naloxone delivery is an alternative to intravenous naloxone for opioid overdoses☆

Mark A. Merlin DO, EMT-P[a,b,*], Matthew Saybolt BS[c], Raffi Kapitanyan MD[d], Scott M. Alter BS, EMT-P[c], Janos Jeges MD[d], Junfeng Liu PhD[d,e], Susan Calabrese MICP[b], Kevin O. Rynn PharmD[b,f], Rachael Perritt PharmD[b,f], Peter W. Pryor II MD, MPH[d]

[a]*Department of Emergency Medicine and Pediatrics, University of Medicine and Dentistry of New Jersey-Robert Wood Johnson Medical School, New Brunswick, NJ, USA*
[b]*Robert Wood Johnson University Hospital, New Brunswick, NJ, USA*
[c]*University of Medicine and Dentistry of New Jersey-Robert Wood Johnson Medical School Piscataway, NJ, USA*
[d]*Department of Emergency Medicine, University of Medicine and Dentistry of New Jersey-Robert Wood Johnson Medical School, New Brunswick, NJ, USA*
[e]*Department of Biostatistics, School of Public Health, University of Medicine and Dentistry of New Jersey, Piscataway, NJ, USA*
[f]*Department of Pharmacy Practice, Rutgers University, School of Pharmacy, Piscataway, NJ, USA*

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* Corresponding author. Department of Emergency Medicine, UMDNJ-Robert Wood Johnson Medical School, New Brunswick, NJ 08901, USA. Tel.:+1 732 235 8717.
E-mail address: merlinma@umdnj.edu (M.A. Merlin).

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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.

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 (μ) SD (σ) ratio ($\mu/\sigma = 0.95$) is 100% with sample size, n = 38. We also find that n = 38 (IN, confirmed opioid) can detect a μ/σ 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 (μ) SD (σ) 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 η 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 (Δ) between IN and IV was completed. We tested H_0: $\Delta = 0$ vs H_a: Δ does not equal 0, where Δ 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 (σ) 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 Δ/σ 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 (σ) 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 χ^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

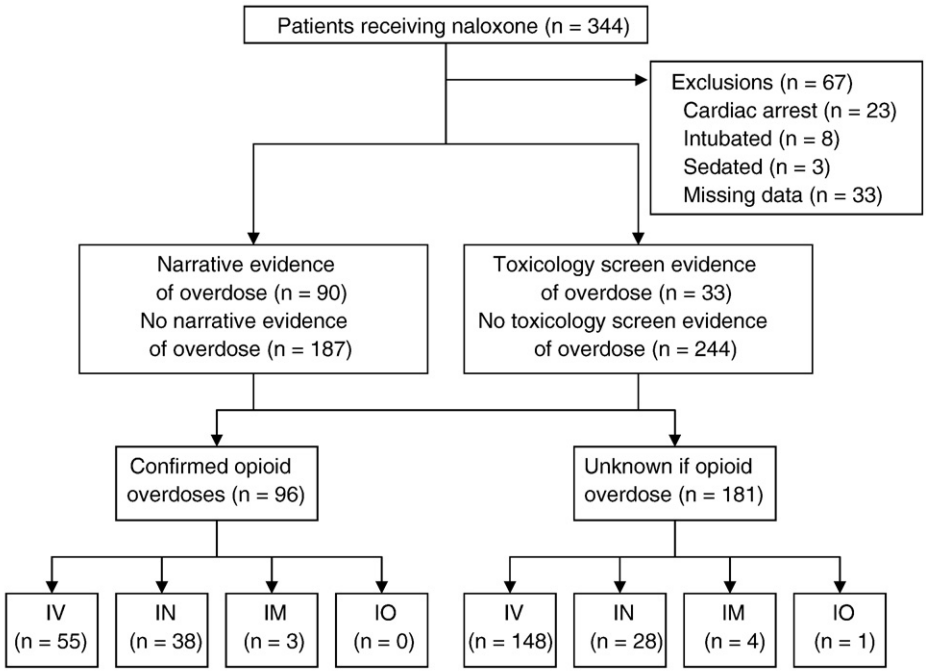

Fig. 1 Flow chart of study design.

Table 1 Baseline characteristics of subjects by confirmation of opioid overdose

	Opioid overdose, median (interquartile range)		Difference estimation (95% CI [a])	*P* of comparison [b]
	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 [c]
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

[a] The confidence interval for the median is slightly greater than 95%, as there is no assumption of distribution.
[b] By Wilcoxon rank sum test unless otherwise noted.
[c] By Pearson's χ^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 [a])	*P* of comparison [b]
	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 [c]
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 [c]
Narrative evidence of opioid overdose, n (%)	51 (92.7)	36 (94.7)	−2.0 (−11.9 to 7.9)	.70 [c]
Toxicologic screen evidence of opioid overdose, n (%)	21 (38.2)	12 (31.6)	6.6 (−13.0 to 26.2)	.51 [c]

[a] The confidence interval for the median is slightly greater than 95%, as there is no assumption of distribution.
[b] By Wilcoxon rank sum test unless otherwise noted.
[c] By Pearson's χ^2 test.

3.2. Main results

Within the IV and IN-confirmed opioid overdose groups, the paired Wilcoxon signed rank test was used to compare initial and final median values of RR and GCS. Naloxone was successful in elevating the RR and GCS in each of the 4 comparisons, as the final values were significantly higher than the initial values (Table 3). For the IV group, RR increased from 10 to 18 ($P < .0001$), and the GCS score increased from 4 to 15 ($P < .0001$). Similarly, for the IN group, RR increased from 10 to 16 ($P < .0001$), and the GCS score increased from 3 to 12 ($P < .0001$).

Naloxone redosing, defined as at least one additional naloxone dose, occurred in 11 (20%) of the IV patients and 16 (42%) of the IN patients. Of the 16 IN patients, 9 received the repeat dose IV at the decision of the paramedic. One patient in the IV group received 3 doses, and one patient in the IN group received 3 doses.

Neither the median initial RR (IV, 10 vs IN, 10) nor the median initial GCS scores (IV, 4 vs IN, 3) were significantly different between the 2 route groups. The median final RR was higher for the IV group than the IN group (18 vs 16; $P = .001$). The median final GCS score was also higher in the IV group than the IN group (15 vs 12; $P = .01$).

Statistically significant differences in final RR and GCS, as well as differences in the change in RR or GCS between the IV and IN groups are noted (Table 3). The median change in RR for the IV group was 6 breaths per minute (95% CI, 4-10) and for the IN group was 4 (95% CI, 2-6). Hodges-Lehmann estimation of the median difference in these changes was 2 (95% CI, −0.001 to 5). The median change in GCS score was 4 for the IV group (95% CI, 3-8) and 3 for the IN group (95% CI, 0-5). Hodges-Lehmann estimation for change median difference was 1 (95% CI, −0.001 to 3). This inconsistency between final scores and improvement may be because the nonparametric Wilcoxon test is used to test the location shift between 2 continuous distributions of identical shapes, and GCS has an upper bound of 15, which is an assumption limitation.

For sample size (n) justification for Wilcoxon signed rank test, we denote $\eta = P(Z_1 + Z_2 > 0)$ η), that is, 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) [20]. Sample size discussion is based on using probability difference as effect size other than distribution locations that have been extensively estimated. Because we are not interested in testing the null hypothesis vs a specific alternative hypothesis in location shift or probability difference, sample size determination and power analysis are not the focus in this article.

Correlations examined the effectiveness of naloxone depending on the initial RR and GCS score. Because the data are not normally distributed and GCS is an ordinal categorical variable, Spearman's rank correlation coefficient was used. Among confirmed opioid overdoses, the correlation between initial RR and change in respiratory rate was $\rho = -0.749$. The correlation between initial GCS score and change in GCS score was $\rho = -0.558$. These values, significant at the 0.01 level, indicate that the lower the initial RR and GCS score, the larger the increase will be in response to naloxone.

When comparing RR and GCS score, the correlations for initial, final, and change were $\rho = 0.577$, 0.462, and 0.568, respectively, and were each significant at the 0.01 level. The correlation between final values is expected to be lower because as the GCS gets higher, it approaches its maximum value. In a healthy population, the GCS score is constant and therefore not possible to be correlated with another variable. In comparison, the unknown opioid overdose group had correlations between RR and GCS score of $\rho = 0.288$, 0.248, and 0.246 for initial, final, and change, respectively, each significant at the 0.01 level. These lower values indicate that in a population of mixed medical conditions, there is only a small correlation between RR and GCS score.

3.3. Study limitations

A limitation of our study is that it is a nonrandomized, nonblinded, retrospective chart review from EMS PCRs. Although our initial intention was to randomize patients, certain legal informed consent laws in our state made this unobtainable.

Table 3 Comparison of response to naloxone by route of administration

		Route of administration, median (95% CI[a])		Difference estimation (95% CI[a])	*P* of comparison[b]
		IV (n = 55)	IN (n = 38)		
RR, per min	Initial	10 (6-12)	10 (6-12)	0 (−2 to 4)	.60
	Final	18 (16-18)	16 (12-16)	4 (2 to 6)	.001
	Change	6 (4-10)	4 (2-6)	2 (−0.001 to 5)	.08
GCS score	Initial	4 (3-9)	3 (3-6)	0 (0 to 1)	.37
	Final	15 (14-15)	12 (8-14)	1 (0 to 3)	.01
	Change	4 (3-8)	3 (0-5)	1 (−0.001 to 3)	.19

[a] The confidence interval for the median is slightly greater than 95%, as there is no assumption of distribution.
[b] By Wilcoxon rank sum test.

Another limitation is that the ED records could only be obtained for patients who were transported to our hospital. Had records from other hospitals been obtained, it is possible that more patients in the unknown group could have been confirmed by either narrative evidence or urinary drug screen. In addition, physician discharge/admitting diagnoses would have provided a greater sample to determine other reasons for the patients' acute illness. Despite this, the results of the study have not been diluted, as only confirmed opioid overdoses were analyzed. This limitation prevented us from having a larger analyzable sample size.

Relying on paramedics' subjective decisions of how to treat a patient introduces possible biases in choosing dose and route of naloxone administration. In addition, time constraints in the prehospital environment may complicate the accuracy of reporting. For example, there is no standard time to reassess a patient after administration of naloxone, and this study assumes that paramedics recorded patients' actual initial GCS and RR exactly at the time of naloxone administration. This in fact is usually impossible, and therefore, there is a degree of inaccuracy in setting the beginning of intervention at time zero. However, we believe that this represents "real-life" scenarios where paramedics decide when a patient is altered and when to reassess.

The use of RR by prehospital personnel is subjective. Experience suggests that EMS professionals do not always document RR correctly. Oftentimes RR are just thought of as hypoventilating or hyperventilating. Our system requires both paramedics to agree on the RR before documentation evidenced by both signing the PCR. We believe that much of the inherent bias of this poorly documented vital sign is eliminated by confirmation of a second ALS provider.

Previous studies indicate naloxone dose should be 1 mg per nostril (total of 2 mg) [9]. It is difficult to determine whether our primary outcomes measures would have changed if 2 mg per nostril was used and if this change would be dose-dependent. Limitations to the use of IN naloxone focus on barriers to absorption. Many factors such as nasal mucociliary clearance [21], metabolic degradation in the nasal cavity, IN use of vasoactive agents, nasal trauma, epistaxis, ambient temperature, and mucosal inflammation influence systemic absorption of nasally administered drugs [5].

Despite an existing policy encouraging paramedics to attempt IN delivery initially, sicker patients may have received IV naloxone rather than IN. Our subjective experience in dealing with paramedics suggests biases toward one method or another based on personal experience and not degree of patient intoxication.

Furthermore, our study used urinary drug screens, when available, to confirm opioid abuse. Certain synthetic opioids and opioid-like substances, such as tramadol and propoxyphene, have a dose-dependent response to naloxone and escape detection from our standard urine toxicologic screens [21]. Conversely, 6 patients had positive urinary drug screens but no narrative evidence on the prehospital patient care report or ED progress notes. These patients may have been on opioids in therapeutic doses but were altered secondarily to other causes, such as sepsis or cerebrovascular accident. However, most initial vital signs were consistent with central nervous system and respiratory depression.

4. Discussion

Among subjects with confirmed opioid overdoses, IN naloxone is as effective as IV naloxone at reversing the central nervous system-depressing effects caused by opioids. Subjects were compared by route of naloxone administration, using RR and GCS score as indicators of opioid intoxication. In addition to having similar baseline characteristics, both the IV and IN groups had significant increases in RR and GCS score. Furthermore, the data shows both IV and IN naloxone significantly increases both the RR and GCS of patients with confirmed opioid intoxications.

Previous studies have been criticized for using GCS to quantify the degree of improvement in opioid-intoxicated patients after naloxone administration [9]. Although GCS has been questioned in nontrauma patients [22-24]. Opioids are central nervous system depressants that, among other actions, lower patients' RRs. Therefore, we sought to correlate RR and GCS scores to validate the use of GCS for quantification of patient improvement. In confirmed opioid overdose patients, we found correlations between RR and GCS, indicating evidence of a relationship between RR and GCS. For comparison, correlations between RR and GCS were performed in subjects who received naloxone but were not confirmed opioid overdoses (the unknown group). In this group of subjects with a heterogeneous mixture of medical problems, we showed very weak correlations between RR and GCS. The strong correlations between RR and GCS in the confirmed group together with the large difference in degree of correlations between the confirmed opioid abuse group and the unknown group indicate that increases in GCS is a sign of opioid overdose reversal. This demonstrates the prognostic value of GCS for evaluation of opioid overdoses.

Among confirmed opioid intoxications, there was a strong negative correlation between initial RR and change in RR, as well as a similar negative correlation between initial GCS and change in GCS. This indicates that the lower the initial RR and GCS, the larger the increase will be in response to naloxone. This leads us to believe that there is a physiologic ceiling on both values among the entire study population. We conclude that this occurs for 1 of 2 reasons. Portions of the study population may have demonstrated a maximal response to naloxone or rather a maximal elevation of RR and GCS in the context of an unknown quantity of systemic opioid. On the contrary, there may be an average physiologic ceiling of RR and GCS values among the entire population that is unrelated to drug administration but rather is a portrait of the population's basal RR.

Naloxone redosing was at the discretion of the paramedics under physician order. Twice as many patients in the IN group were given second doses, as compared with the IV group. The decision to redose is very subjective and may represent the inability to wait for the full desired clinical response. Alternately, this finding may represent the need for a higher naloxone dose when given IN, rather than IV, to achieve similar increases in RR and GCS. However, the 1 mg per nostril dose may be adequate because the ultimate prehospital goal is to avoid hypoventilation-induced hypoxemia. In our study, paramedics were using naloxone for decreased GCS without hypoventilation, so perhaps the typical IV dose should be lowered to provide an adequate rise in RR without an excessive increase in GCS, which could cause a patient to become fully awake and possibly violent.

We were surprised by the number of patients excluded secondary to administration during cardiac arrest. Naloxone treatment in cardiac arrest is not validated and would have only been given under physician order. We are further investigating this use of naloxone among prehospital providers.

We anticipated the initial patient RRs to be lower than what was found in our results. Although we believe that this would not necessarily change our results, a repeat study that evaluates RR with a protocol that administers naloxone with a more significant degree of hypoventilation would be interesting. It is noteworthy that our paramedics are treating opioid overdoses based on lower GCS and not hypoventilation, following a protocol for altered mental status. As a teaching point, we generally instruct the use of prehospital naloxone when hypoventilation is accompanied by hypoxemia or hypercapnia.

Upon further evaluation of patients from the unknown group, we demonstrate that most subjects were not acutely intoxicated with an opioid, indicating that the study's inclusion criteria and methods of confirmation of opioid overdose were adequate. The results of this study have established the noninferiority of IN naloxone in comparison to its traditional IV delivery. Without sacrificing patient care or intervention response, the prehospital environment should consider the routine use of IN naloxone.

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