Intravenous vs Subcutaneous Naloxone for Out-of-hospital Management of Presumed Opioid Overdose

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ABSTRACT

Objective: To determine whether naloxone administered IV to out-of-hospital patients with suspected opioid overdose would have a more rapid therapeutic onset than naloxone given subcutaneously (SQ).

Methods: A prospective, sequential, observational cohort study of 196 consecutive patients with suspected opioid overdose was conducted in an urban out-of-hospital setting, comparing time intervals from arrival at the patient's side to development of a respiratory rate ≥10 breaths/min, and durations of bag–valve–mask ventilation. Subjects received either naloxone 0.4 mg IV (n = 74) or naloxone 0.8 mg SQ (n = 122), for respiratory depression of <10 breaths/min.

Results: Mean interval from crew arrival to respiratory rate ≥10 breaths/min was 9.3 ± 4.2 min for the IV group vs 9.6 ± 4.58 min for the SQ group (95% CI of the difference −1.55, 1.00). Mean duration of bag–valve–mask ventilation was 8.1 ± 6.0 min for the IV group vs 9.1 ± 4.8 min for the SQ group. Cost of materials for administering naloxone 0.4 mg IV was $12.30/patient, compared with $10.70/patient for naloxone 0.8 mg SQ.

Conclusion: There was no clinical difference in the time interval to respiratory rate ≥10 breaths/min between naloxone 0.8 mg SQ and naloxone 0.4 mg IV for the out-of-hospital management of patients with suspected opioid overdose. The slower rate of absorption via the SQ route was offset by the delay in establishing an IV.

Key words: opioid overdose; naloxone; respiratory depression; route of administration; EMS; emergency medical services; out-of-hospital.

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Administration of an opioid antagonist has become an accepted part of the out-of-hospital management of opioid overdose.[1–4] Acute opioid intoxication is characterized by drowsiness, euphoria, miosis, and respiratory depression.[1] In overdose, respiratory depression becomes profound enough to cause anoxia, leading to death. Prior to the 1960s, treatment of opioid overdose consisted of airway support and oxygenation until the effect of the opioid wore off. For out-of-hospital caregivers, this necessitated continuous airway maintenance with bag–valve–mask or endotracheal intubation during transport.

In 1961, Dupont Pharmaceutical synthesized naloxone, the first substance to act as a purely competitive antagonist at mu-receptor sites.[5] Its high lipid solubility allows naloxone to readily cross the blood–brain barrier. Via the IV route, onset of action is within 1–2 minutes. The distribution half-life is 20 minutes to 4 hours,[5–8] and the drug is then metabolized by the liver to naloxone-3-glucuronide and excreted within 72 hours.[9,10]

Naloxone is absorbed not only IV, but also by IM, subcutaneous (SQ), endotracheal, sublingual, intralingual, submental, and nasal routes.[4,11–16] In routine use, IM or SQ injections are acceptable alternate routes of administration if IV access is impossible, but generally have not been advocated for emergency situations due to an unpredictable absorption rate. Although one large, retrospective study of presumed out-of-hospital opioid overdoses found good response to IM naloxone use,[4] animal studies have shown naloxone absorption to be delayed by up to 15 minutes after IM or SQ injection.[17,18]

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In emergency situations, IV administration of naloxone is the route of choice because of its rapid onset. The ability of out-of-hospital caregivers to reverse the respiratory depression of opioids using IV naloxone has greatly decreased the duration of the hypoxic state during which the airway is at risk. Transport of patients at risk for respiratory depression from opioids has become easier and much less physically strenuous. However, venous access can be difficult or impossible to achieve in the chronic IV drug user.

The skin of chronic users is characterized by repeated injection sites, resulting in "track marks," ulcers, and sclerosis of veins. Abscesses and cellulitis commonly overlie venous access sites. The difficulty in obtaining venous access in chronic IV drug users under emergency conditions in the field and the enhanced risk of occupational blood contact[19-25] with patients who have high risk factors for HIV seropositivity and hepatitis B suggest the need for an alternative to the IV route of administration.

We conducted a study of naloxone administered IV vs SQ in patients with opioid overdose. The null hypothesis of this study was that there would be no difference in the time interval from arrival at the patient's side to respiratory rate ≥10 breaths/min when using either 0.4 mg IV naloxone or 0.8 mg SQ naloxone. Based on the literature, we expected that this time interval would be shorter for the IV route than for the SQ route. A secondary objective was to assess the ease of use of SQ vs IV naloxone in the out-of-hospital environment. The SQ route was chosen over the IM route because the attendants were already trained in the administration of SQ injections of epinephrine for the treatment of anaphylaxis.

METHODS

Study Design: Prospective data were collected during a historical control period and after a protocol change from IV to SQ naloxone. Comparison with a historical control, rather than use of a concurrent randomized treatment design, was the study design advised and approved by the University of British Columbia Ethics Committee. The Medical Advisory Committee of the British Columbia Ambulance Service approved the protocol change.

Population and Setting: The study was conducted in the Greater Vancouver Regional District (GVRD) of British Columbia, which has a population of approximately 1.6 million. The primary receiving hospital was St. Paul's Hospital, a 420-bed tertiary care facility situated in the downtown core of Vancouver, BC. The ED census is 54,000 patient visits per year, and the unit provides care to the majority of IV drug users in the GVRD. Patients also were received at Vancouver General, Royal Columbian, Mount St. Joseph's, and Burnaby General Hospitals in Vancouver, BC.

Participants in the study were British Columbia Ambulance Service (BCAS) attendants, who are trained to the EMA-I (basic life support), EMA-II (IV), and advanced life support (ALS) levels. The province-wide BCAS is the largest geographic ambulance system in the world, with over 3,300 employees at more than 200 ambulance stations. The 3-tiered system involves simultaneous dispatch of first responder, EMA, and ALS cars. Average ambulance response time for respiratory arrest in the participating stations is 4–6 minutes. The study involved the 11 ambulance stations that fall into the catchment area servicing the most concentrated density of intravenous drug users.

Subjects for the study were out-of-hospital patients with presumed opioid overdose who received naloxone. Inclusion criteria were all patients who fit the BCAS protocol for suspected opioid overdose, which is: decreased level of consciousness, history suggestive of opioid use, and respiratory rate <10 breaths/min. Patients were excluded if they were in cardiac arrest. Since the goal was to measure therapeutic response to naloxone, only those patients who met the criteria for suspected opioid overdose and who received naloxone were entered into the study.

Experimental Protocol: The standard protocol for management of opioid overdose consisted of maintenance of ventilation and oxygenation via bag–valve–mask; obtaining a brief patient history and a baseline set of vital signs prior to establishment of a peripheral IV line of normal saline; and the administration of naloxone 0.4 mg IV. The protocol did not require that a base-station physician be consulted prior to administration of the first dose of naloxone. If, according to crew judgment, no improvement was observed over a period of 5 minutes, orders for an additional 0.4 mg of naloxone could be obtained from an emergency physician via telephone. The protocol also allowed for blood glucose determination and consideration of other contributing factors at that time. It has been the pattern of practice of the BCAS to use ventilatory assist and small doses of naloxone to support patients with respiratory rate <10 breaths/min due to suspected opioid overdose. The intent is to prevent the complications of larger doses of naloxone while protecting the patients from the effects of hypoventilation.

In addition to routine documentation, the attendants completed field data forms each time naloxone was given for suspected opioid overdose. They recorded the time of: crew arrival at the patient's side, IV initiation, drug administration, and start/stop of airway intervention. In addition, they recorded the patient's respiratory rate every 2 minutes. The data form also captured subjective assessments of ease of use and risk of needlestick injury, and open-ended comments on any aspect of the protocol and the study.

Data on ED length of stay, discharge diagnosis, and complications were obtained for those patients for whom identification obtained by paramedics could be cross-referenced with hospital records (a common problem in the IV drug user population).

The study was conducted sequentially in 2 phases, IV and SQ. Funding support was limited to 3 months of data collection. To ensure the collection of adequate information on efficacy or potential problems with SQ naloxone, a 2-month experimental period followed a 1-month control period.

The IV phase was conducted over a 4-week period from June 1 to June 30, 1996. Data on response to the standard IV naloxone protocol were collected for consecutive patients meeting the inclusion criteria. The SQ phase of the study was conducted from July 1 to September 1, 1996. The standard protocol for presumed opioid overdose was changed for the 11 stations involved for the purposes of the study. The experimental protocol began with standard airway management and obtaining history and vital signs. Patients were then given naloxone 0.8 mg SQ into the upper arm or thigh. If, according to crew judgment, no improvement was observed after 5 minutes, the crew defaulted to the IV phase protocol (IV rescue). An IV line was established and 0.4 mg naloxone was administered IV, followed by standard patient care.

Analytical Methods and Sample Size Determinations: Field data forms were reviewed for appropriateness of application of the suspected overdose protocol, drug combinations used by the patient, initial and every 5 minute vital signs, dose and route of administration of naloxone, duration of basic airway intervention, total time with patient until spontaneous ventilation ≥10 breaths/min, and total time from drug administration to spontaneous ventilation. The primary outcome of interest was the time interval from arrival at the patient's side until the respiratory rate was ≥10 breaths/min. It was determined prior to commencement of the study that a 2-minute difference between the IV and SQ groups for the primary outcome would be considered clinically significant (based on a 25% difference in documented response time).

Data were analyzed using SPSS (V.7.0, SPSS Inc., Chicago, IL). Comparisons of mean time intervals were done using the unpaired t-test and verified with nonparametric testing. Power calculations using the results from the control arm of the study were performed using an $\alpha = 0.05$, power = 0.90, $\Delta = 2.0$ minutes, and SD = 4.18. Based on these calculations, a sample size of 184 (92 per arm) was required.

Since there is no capability for our ambulance crews to monitor respiration continuously, the every-2-minute recordings were considered to be the smallest feasible interval for manual recording. For analysis, the intervals were treated as continuous variables.

TABLE 1 Subject Populations in the IV and SQ Naloxone Groups

	IV (n = 74)	SQ (n = 122)
Age (mean)	36 yr	33 yr
Gender		
Men	58 (78.4%)	97 (79.5%)
Women	12 (16.2%)	17 (13.9%)
Unknown	4 (5.4%)	8 (6.6%)
Initial respiratory rate (mean)	2.2 breaths/min	2.9 breaths/min
Initial Glasgow Coma Scale score (mean)	4.1	4.6
Initial systolic blood pressure (mean)	141.8 mm Hg	144.5 mm Hg
Initial heart rate (mean)	101.5 beats/min	102.3 beats/min
Initial respiratory rate = 0	39 (53%)	68 (56%)

RESULTS

The total number of subjects enrolled in the study over the 12-week period was 222, 83 of whom were in the IV naloxone phase, and 139 in the SQ phase. Of these, 9 of the IV group and 17 of the SQ group were excluded due to inappropriate use of the protocol (respiratory rate ≥10 breaths/min prior to naloxone administration) (n = 25) or insufficient data (n = 1).

Data concerning age, gender, initial respiratory rate, heart rate, and blood pressure (BP), and initial Glasgow Coma Scale score are shown in Table 1. A post-hoc power analysis was performed and confirmed the adequacy of our sample size.

A summary of calculated time intervals is shown in Tables 2 and 3. Figures 1 and 2 are graphic representations of the primary outcome (time interval from arrival at patient's side to respiratory rate ≥10 breaths/min).

The number of patients requiring at least 2 doses of naloxone prior to hospital arrival was 26 out of 74 (35%) in the IV group and 18 out of 122 (15%) in the SQ group. Sixteen of the 18 patients in the SQ group requiring a second dose were given the second dose via the IV route (IV rescue, 0.4 mg naloxone IV), while 2 received a second dose of 0.8 mg SQ. All patients were included in the analysis.

One patient in each of the 2 study groups had an initial BP of <90 mm Hg. The patient in the SQ group responded well to one dose of SQ naloxone. The patient in the IV group required a second dose.

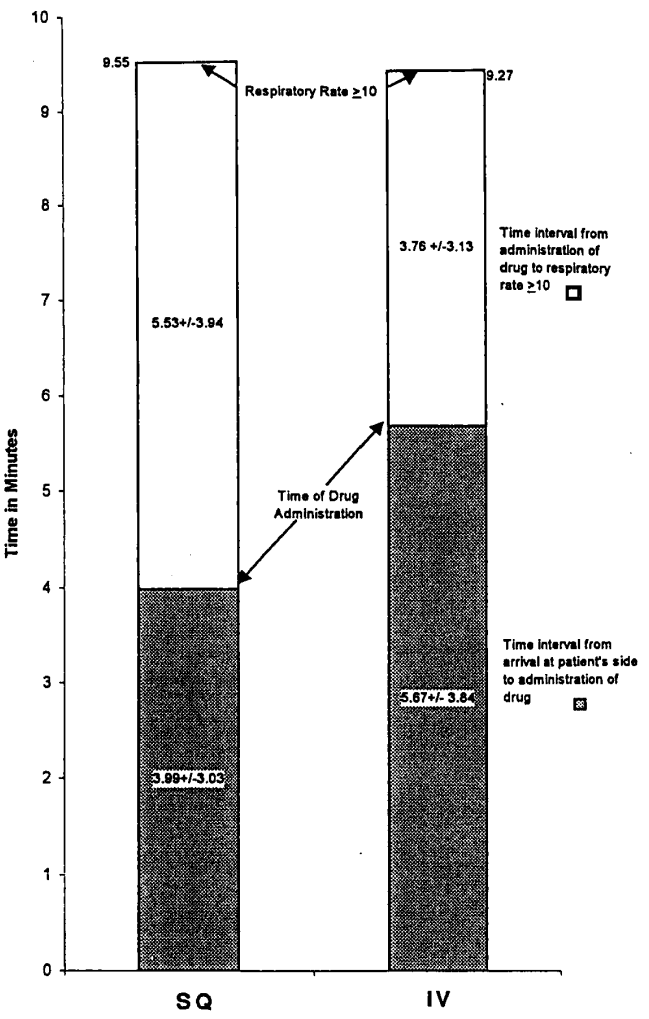

FIGURE 1. Comparison of time intervals (group mean ± SD) from arrival at patient's side to respiratory rate ≥10 breaths/min for patients receiving naloxone 0.4 mg IV vs naloxone 0.8 mg subcutaneous (SQ) in the out-of-hospital setting.

In their anecdotal comments, the attendants indicated that they preferred the SQ to the IV route. Reasons given included less spillage of blood compared with IV initiation; perceived reduced risk of needlestick injury with the use of spring-loaded safety needles; and the impression that emergence was more gradual, resulting in less violence and aggression at the scene.

ED data were available for only 110 (56%) patients overall (58% of the IV and 55% of the SQ subjects). Of those for whom data were available, the ED final diagnosis for almost all patients was heroin overdose. Of the SQ group, one patient was admitted with a diagnosis of pneumonia, and one patient had rhabdomyolysis diagnosed, but was subsequently released. Of the IV group, one patient was diagnosed as having pneumonia, and one as having "vomiting." Neither patient was admitted to hospital. The mean duration of stay in the ED was 3.3 hours for the IV group, and 3.5 hours for the SQ group.

The cost of materials to administer naloxone via the IV route is $12.30 Canadian (0.4 mg naloxone, needle/syringe, IV catheter, IV tubing, and normal saline 250-mL bag), compared with $10.70 Canadian for the SQ route (0.8 mg naloxone plus needle/syringe). These are actual costs to the BCAS based on bulk pricing from the BCAS distributor. This difference increases to an average of $2.20 per patient if the need for additional naloxone (35% of the IV group—0.4 mg naloxone; vs 15% of the SQ group—IV tube, catheter, second syringe, and 0.4 mg naloxone) is taken into consideration.

DISCUSSION

It has been previously established that paramedical personnel involved in out-of-hospital care have an increased risk of exposure to blood-borne disease (HIV and hepatitis B) due to occupational blood contact.[19,20] Procedures that contribute to the risk of percutaneous exposure include wound care, IV starts, and syringe handling.[21] Despite the use of gloves and universal precautions, blood contact still

TABLE 2 Time Intervals for Patients Receiving Naloxone 0.4 mg IV vs Naloxone 0.8 mg SQ in the Out-of-hospital Setting

	IV (n = 74)	SQ (n = 122)	p-value	95% CI of the Difference
Time interval from arrival at patient's side to drug administration	5.7 ± 3.8 min	4.0 ± 3.0 min	0.002	0.6, 2.7
Time interval from drug administration to respiratory rate ≥10 breaths/min	3.8 ± 3.1 min	5.5 ± 3.9 min	0.001	−2.7, 0.8
Time interval from arrival at patient's side to respiratory rate ≥10 breaths/min	9.3 ± 4.2 min	9.6 ± 4.6 min	0.67	−1.6, 1.0
Duration of bag–valve–mask ventilation	8.1 ± 6.0 min	9.1 ± 4.8 min		

occurs during patient treatment in a considerable number of cases.[22]

The risk of HIV exposure is dependent on the prevalence of the pathogen in the patient population, the nature and frequency of blood contact, and the risk of infection transmission for a single blood contact. It has been estimated that the risk of HIV seropositivity among IV drug users ranges from 6.7% to 18.7%, depending on the area surveyed.[21,23] The patient population at highest risk for seropositivity is 15–44-year-old males, the same population at highest risk for opioid overdose.[23–25] The Centre for Disease Control in British Columbia estimates that the number of IV drug users infected with HIV was approximately 1,500 at the end of 1997.

British Columbia has been experiencing an increase in IV drug use. In 1996 there were 125 deaths attributed to unintended overdose of illicit drugs in Vancouver, compared with 67 in 1991.[24] Opioids, primarily heroin, account for 54.8% of overdose deaths.[25] The prevalence of synthetic opioids (e.g., pentazocine, fentanyl) in Vancouver, BC, is much lower than in most large U.S. cities.

This increase in illicit drug use, along with the risk of blood-borne infection, reinforces the need for an alternative to the IV route of naloxone administration for the treatment of patients with suspected opioid overdose in the out-of-hospital setting. A small pilot study performed in Vancouver in 1995 indicated that naloxone 0.4 mg given SQ was ineffective, but 0.8 mg SQ produced a good response. These results encouraged us to repeat the study on a larger scale using naloxone 0.8 mg SQ.

TABLE 3 Time Intervals for Patients in the Naloxone 0.8 mg SQ Group Who Received IV Rescue (n = 16)

Time interval from arrival at patient's side to respiratory rate ≥10 breaths/min	13.1 ± 4.5 min
Duration of bag–valve–mask ventilation	14.3 ± 5.5 min

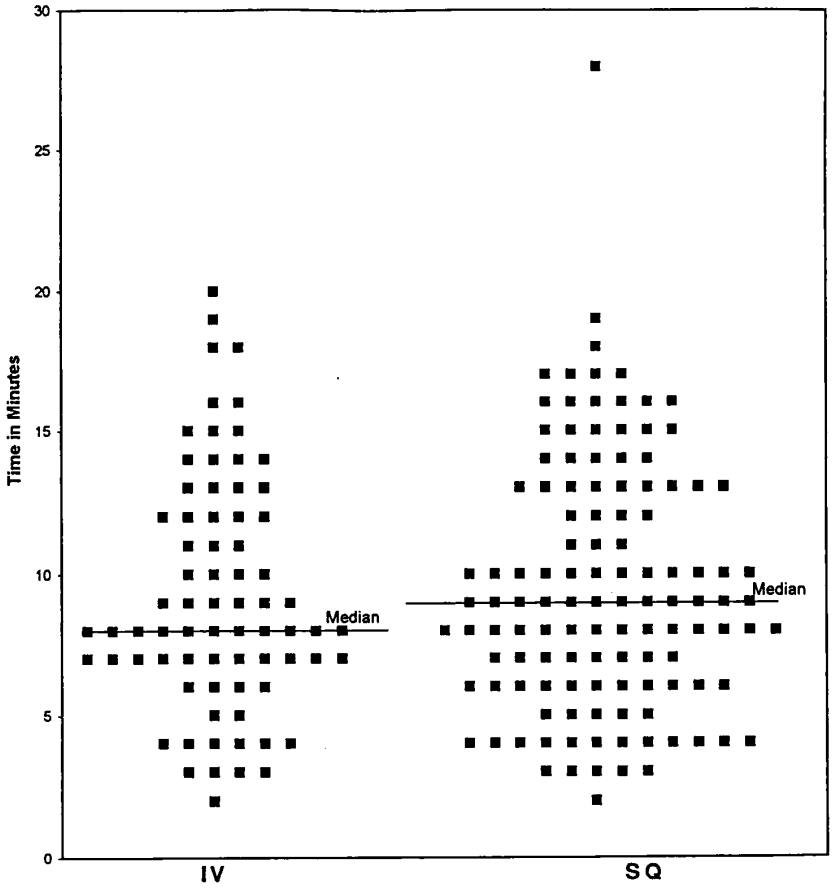

FIGURE 2. Actual vs median time intervals from arrival at patient's side to respiratory rate ≥10 breaths/min for patients receiving naloxone 0.4 mg IV vs naloxone 0.8 mg SQ in the out-of-hospital setting.

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