

Comparison of the efficacy of an infusion pump or standard IV push injection to deliver naloxone in treatment of opioid toxicity

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Background: The optimal goal of naloxone infusion in intensive care units is to ameliorate opioid-induced side effects in therapy or eliminate the symptoms of opioid toxicity in overdoses. Accurately monitoring and regulating the doses is critical to prevent adverse effects related to naloxone administration. The present study aimed to compare treatment outcomes when using two methods of intravenous naloxone infusion: an infusion pump or the standard method.

Methods: This study involved 80 patients with signs and symptoms of opioid overdose. The patients were randomly assigned into two groups with respect to intravenous infusion of naloxone by either an infusion pump or the standard method.

Results: Comparison of study parameters between the two groups at 12 and 24 hours after intervention showed significantly more compensatory acid-base imbalance in the naloxone infusion pump group. In the group that received naloxone by pump, only one patient experienced withdrawal symptoms, but withdrawal symptoms appeared in 12 patients (30.0%) in the standard intravenous infusion group within 12 hours and in seven additional patients (17.5%) within 24 hours of intervention. In the group receiving pump-based naloxone infusion therapy, no other complications were reported; however in the standard infusion group, the 12-hour and 24-hour complication rates were 55.0% and 32.5%, respectively. The length of hospital stay was 2.85 ± 1.05 and 4.22 ± 0.92 days for the pump and standard infusion groups, respectively ($P < 0.001$).

Conclusions: Naloxone infusion using an infusion pump may be safer with regard to hemodynamic stability, resulting in shorter hospitalization periods, and fewer posttreatment complications.

Key Words: Acid-base imbalance; Infusion pumps; Intensive care unit; Naloxone; Opioid; Treatment outcome

INTRODUCTION

The establishment of pragmatic, yet personalized, approaches for the management of opioid toxicity remains a priority: these approaches should consider both the benefits as well as the safety of therapeutic regimens, while also allowing for precise monitoring of the dosages of antidotal agents. Naloxone is the primary therapeutic agent administered to opioid overdose

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patients worldwide and is used in both addiction treatment clinics and emergency centers [1,2]. With the aim of successfully eliminating opioid toxicity, the first step in patient management is to establish an accurate history of their opioid usage, and the second step is to schedule appropriate naloxone therapy by monitoring the infusion dose [3]. Naloxone is a highly effective antidote, the use of which is potentially lifesaving [4-6]: however, its use may also introduce potential risks [7]. According to the current guidelines, naloxone treatment regimens should be based on balancing the need for treatment against the risk of inappropriate use. In this regard, continuous titration of the naloxone dose is considered ideal. As a rule, when addressing toxicity due to opioids with long half-lives or high receptor affinity, continuous naloxone infusion may be required to prevent a relapse into sedation following initial treatment of acute toxicity [8,9]. One of the drawbacks of the standard naloxone infusion method is lack of confidence in the calculated hourly rate, which if not determined accurately, can lead to under-dosing and consequent withdrawal symptoms and reappearance of symptoms of drug poisoning, and occasionally may also result in prolonged hospitalization or even death. The lack of certainty and consistency with respect to naloxone dosage can be the result of a variety of factors, including the manipulation of the patient's serum access, or lack of available time for nurse to administer intravenous naloxone at an appropriate rate [10]. In this regard, we postulated that using an infusion pump to administer naloxone may prevent these problems and ensure the patient receives the appropriate dose of naloxone with the highest accuracy. The present study aimed to compare the outcomes of treatment of opioid poisoning using two methods of naloxone infusion: an infusion pump or the standard method.

MATERIALS AND METHODS

This study involved 80 patients with the signs and symptoms of opioid overdose (with different doses and routes of exposure) that were scheduled for naloxone therapy in the Clinical Toxicology Department of Payambaran Hospital in Tehran from January to September 2019. The sample size was calculated with Cochran's sample size formula: the parameters for this calculation were $p=q=0.5$, $d=0.11$, and $z=1.96$. All patients were admitted to the intensive care unit. In this study, patients with any history of systemic disorders, such as cardiovascular or cerebrovascular disorders, or respiratory problems, such as pneumonia or chronic obstructive pulmonary disease, and who had positive urinary tests for amphetamines,

KEY MESSAGES

- Optimal goal of naloxone infusion in intensive care units is to ameliorate opioid-induced side effects in patients administered opioids as analgesic agents or to eliminate the symptoms of toxicity in cases of opioid overdose.
- Infusion of naloxone using an infusion pump can be safer with regard to achieving proper hemodynamic stability, reducing the duration of hospitalization, and limiting posttreatment complication.

methamphetamines, or tetrahydrocannabinol were all excluded from the study. Also, patients who required intubation upon admission to the hospital emergency department were not included in the study. The family members of the patients gave written informed consent on admission, and the study protocols were approved by the hospital-based institutional ethics committee. The baseline characteristics, including patient demographics and the type and route of exposure of the drug used, were collected by reviewing the hospital records and by interviewing the family members. Using a computerized random number generator, the patients were randomly assigned into two groups with respect to intravenous infusion of naloxone using either an infusion pump or the standard method (direct intravenous infusion: naloxone added into the crystalloid fluids or through the infusion Microset). A 0.04-mg naloxone dose is considered a reasonable starting intravenous dose in most patients, with additional 0.04-mg doses administered as necessary (up to a maximum dose of 0.12 mg); throughout naloxone infusion, patient ventilation and oxygenation are supported as required. In patient who fail to respond to the standard initial treatment, the dose may be increased by 0.2- or 0.4-mg increments up to a total dose of 2 mg. Typically, hourly administration of two-thirds of the total bolus dose of naloxone that initially resulted in reversal will maintain the desired effect [11].

On admission to the intensive care unit, the level of consciousness of our study patients was assessed according to the Richmond agitation sedation scale (RASS) as +4 (combative), +3 (very agitated), +2 (agitated), +1 (restless), 0 (alert and calm), -1 (drowsy), -2 (light sedation), -3 (moderate sedation), -4 (deep sedation), or -5 (unarousable). Prior to naloxone intervention, as well as 12 and 24 hours after, the doses of naloxone used, continuing requirement for orotracheal intubation, arterial blood gas measurements, and probable complications, such as opioid withdrawal symptoms, were all assessed. In addition, the total duration of naloxone infusion, total hospi-

tal stay, improvement without further complications, or in-hospital death were evaluated in both groups. In this study, the complications of naloxone therapy considered were as follows: opioid withdrawal symptoms, subsequent return of symptoms of opioid toxicity and apnea.

The results were summarized as the mean \pm standard deviation for quantitative variables and as absolute frequencies and percentages for categorical variables. Normality of data was analyzed using the Kolmogorov-Smirnoff test. Categorical vari-

ables were compared using the chi-square test, or using Fisher's exact test when more than 20% of cells with expected counts of less than 5 were observed. Quantitative variables were also compared with Student t-test or the Mann-Whitney U-test. Multivariable regression modeling was used to determine the differences in study outcomes between the two groups. For the statistical analyses SPSS ver. 16.0 (SPSS Inc., Chicago, IL, USA) was used. P-values of 0.05 or less were considered statistically significant.

Table 1. Clinical characteristics of the study patients

Variable	Pump infusion (n=40)	Direct infusion (n=40)	P-value
Male sex	32 (80.0)	36 (90.0)	0.210
Mean age (yr)	44.62 \pm 15.80	48.18 \pm 17.71	0.347
Type of substance			0.852
Opiate	12 (30.0)	11 (27.5)	
Methadone	25 (62.5)	27 (67.5)	
Heroin	3 (7.5)	2 (5.0)	
Chronic use	28 (70.0)	32 (80.0)	
Amount of use (mg)	1,668 \pm 2,679	1,226 \pm 1,874	0.394
Route of administration			0.999
Oral	37 (92.5)	38 (95.0)	
Injection	3 (7.5)	2 (5.0)	
RASS score, point (%)			0.314
-5	2 (5.0)	0	
-4	7 (17.5)	4 (10.0)	
-3	13 (32.5)	18 (45.0)	
-2	15 (37.5)	17 (42.5)	
-1	3 (7.5)	1 (2.5)	
Vital sign			
Blood pressure (mm Hg)	112.19 \pm 24.32	111.39 \pm 17.80	0.867
Heart rate (/min)	71.32 \pm 16.91	66.58 \pm 16.29	0.205
Respiratory rate (/min)	8.78 \pm 2.10	8.40 \pm 2.57	0.477
Body temperature ($^{\circ}$ C)	36.70 \pm 0.45	36.57 \pm 0.44	0.195
Arterial blood gas analysis			
pH	7.24 \pm 0.04	7.25 \pm 0.04	0.577
HCO ₃ (meq/L)	18.80 \pm 2.00	18.10 \pm 1.93	0.116
PaCO ₂ (mm Hg)	62.32 \pm 5.11	62.75 \pm 5.00	0.708
PaO ₂ (mm Hg)	70.52 \pm 8.12	68.60 \pm 6.18	0.237
Naloxone doses administered			
Initial dose (mg)	0.83 \pm 0.71	0.77 \pm 0.65	0.635
Maintenance dose per hour (mg)	0.54 \pm 0.50	0.54 \pm 0.48	0.953

Values are presented as number (%) or mean \pm standard deviation.
RASS: Richmond agitation sedation scale.

RESULTS

In total, 40 patients who suffered opioid toxicity randomly received naloxone using pump infusion and the remaining 40 were treated using direct intravenous infusion. Table 1 summarizes the baseline characteristics of the study population. The two groups were matched for demographics, type, amount and route of exposure of the substance used, initial hemodynamic status, arterial blood gas analysis results, as well as initial dose of naloxone used. Both groups were followed up for 12 and 24 hours after naloxone infusion. Comparison of study parameters between the two groups at 12 and 24 hours after naloxone intervention (Table 2) indicated acid-base imbalance was significantly worse among patients who received naloxone by infusion pump than in those who received naloxone by the standard direct intravenous infusion method. The mean dose of naloxone infused per hour was also significantly lower in the direct infusion group. In the group that received naloxone by infusion pump, only one patient experienced withdrawal symptoms, but in the group that received naloxone by intravenous infusion, withdrawal symptom appeared in 12

patients (30.0%) within 12 hours and in seven patients (17.5%) within 24 hours of intervention. No other complications were reported in the infusion-pump-based naloxone therapy group; however in the direct infusion group, 12-hour and 24-hour complication rates were 55.0% and 32.5%, respectively. In this regard, the complications appearing within 12 hours of intervention included restlessness in 10 patients (25.0%), drowsiness or loss of consciousness in 11 patients (27.5%) and need for intubation in one patient (2.5%). Within 24 hours of naloxone administration, restlessness, or loss of consciousness, and need for intubation were evident in three (7.5%), seven (17.5%), and three (7.5%) of patients, respectively. The mean total duration of naloxone treatment was significantly longer in those who were administered naloxone by direct infusion than in the infusion pump group (28.70 ± 11.32 hours as compared to 40.65 ± 10.56 hours, respectively; $P < 0.001$). The length of hospital stay was also longer in the group receiving standard treatment than in the infusion pump group (2.85 ± 1.05 days as compared to 4.22 ± 0.92 days, respectively; $P < 0.001$). The complication-free improvement of opioid toxicity was shown to be 100% and 92.5% respectively ($P = 0.241$). In addition, in-hospital death was reported in 5.0% of patients who received naloxone by direct intravenous infusion, but no patients in the infusion pump group died during their hospital stay ($P = 0.494$). Using multivariable linear regression modeling (Table 3), the use of an infusion pump to administer naloxone was found to be associated with shorter in-hospital stays following treatment of opioid toxicity ($\beta = 0.559$, $P < 0.001$). In a multivari-

Table 2. Outcomes of naloxone infusion 12 and 24 hours after initial infusion

Variable	Pump infusion (n=40)	Direct infusion (n=40)	P-value
12 Hours after infusion			
Orotracheal intubation	0	2 (5.0)	0.494
ABG analysis			
pH	7.33 ± 0.02	7.30 ± 0.03	<0.001
HCO ₃ (meq/L)	23.02 ± 2.06	19.68 ± 1.65	<0.001
PaCO ₂ (mm Hg)	48.65 ± 3.69	53.98 ± 4.43	<0.001
PaO ₂ (mm Hg)	87.78 ± 4.16	80.55 ± 5.62	<0.001
Dose of naloxone per hour (mg)	0.25 ± 0.33	0.47 ± 0.43	0.014
Complication	1 (2.5)	22 (55.0)	<0.001
24 Hours after infusion			
Orotracheal intubation	0	3 (7.5)	0.120
ABG analysis			
pH	7.38 ± 0.02	7.32 ± 0.05	<0.001
HCO ₃ (meq/L)	23.62 ± 1.33	20.10 ± 2.22	<0.001
PaCO ₂ (mm Hg)	41.75 ± 3.05	51.08 ± 6.74	<0.001
PaO ₂ (mm Hg)	92.68 ± 2.85	83.55 ± 7.81	<0.001
Dose of naloxone per hour (mg)	0.07 ± 0.15	0.34 ± 0.40	<0.001
Complication	1 (2.5)	16 (40.0)	<0.001

Values are presented as number (%) or mean \pm standard deviation. ABG: arterial blood gas.

Table 3. Multivariable linear regression analysis to assess the difference in length of hospital stay between the two methods of infusion of naloxone

Factor	Unstandardized coefficient		Standardized coefficient	t	P-value
	B	Standard error	Beta		
(Constant)	3.245	1.497		2.168	0.034
Method	1.333	0.221	0.559	6.038	<0.001
Sex	-0.406	0.378	-0.121	-1.073	0.287
Age	0.008	0.010	0.117	0.854	0.396
Type	0.557	0.481	0.255	1.158	0.251
Chronic	0.487	0.361	0.177	1.350	0.181
Amount	2.166	0.001	0.042	0.255	0.800
Route	-1.708	0.820	-0.346	-2.084	0.041
RASS	-0.099	0.131	-0.071	-0.753	0.454

R-square=0.424.

RASS: Richmond agitation sedation scale.

Table 4. Multivariable logistic regression analyses to assess the difference in 24-hour complication rate between the two methods of infusion of naloxone

Factor	B	Standard error	OR (95% CI)	P-value
Method	-3.825	1.260	0.022 (0.002– 0.258)	0.002
Sex	-0.341	1.542	0.711 (0.035–14.610)	0.825
Age	-0.014	0.033	0.986 (0.925–1.051)	0.663
Type	0.923	1.876	2.517 (0.064– 99.411)	0.623
Chronic	2.036	1.463	7.662 (0.436–134.800)	0.164
Amount	0.001	0.001	1.000 (0.999–1.001)	0.451
Route	-3.125	3.385	0.044 (0.001– 33.439)	0.356
RASS	0.805	0.529	2.237 (0.793–6.315)	0.128
Constant	13.283	6.131	5.872	0.030

Hosmer-Lemeshow goodness of fit: chi-square=9.431, P=0.307.

OR: odds ratio; CI: confidence interval; RASS: Richmond agitation sedation scale.

able logistic regression model (Table 4), the use of an infusion pump was associated with lower 24-hour complication rates following naloxone therapy as compared to naloxone administration by direct infusion (odds ratio, 0.022; P=0.002).

DISCUSSION

The optimal goal of naloxone infusion in intensive care units is to ameliorate opioid-induced side effects in patients administered opioids as analgesic agents or to eliminate the symptoms of toxicity in cases of opioid overdose. The opioid antagonist naloxone is used both as a therapeutic agent for opioid toxicity and also as low-dose adjuvant treatment administered together with opioids in patients requiring analgesic interventions in order to limit undesirable side effects. In general, accurately regulating and monitoring the dose of naloxone infused is very necessary to prevent potentially life-threatening side effects related to its use. The use of an infusion pump to administer naloxone at a continuous and consistent dose may help achieve treatment goals while limiting adverse effects. The present study examined our hypothesis that the use of infusion pumps may lead to greater hemodynamic stability, as well as fewer posttreatment complications in patients treated with naloxone for opioid toxicity. We were able to demonstrate that administration of naloxone using an infusion pump resulted in faster re-establishment of hemodynamic stability, less severe acid-base imbalances within the first 24 hours after treatment, and shorter durations of hospitalization, as compared to infusing naloxone by the standard method (directly

infusing naloxone intravenously). As noted above, the aims when using an infusion pump are first to precisely monitor the dose of naloxone infused and second to reduce the need for the involvement of hospital staff or the patient's companions in the treatment process. In other words, the use of an infusion pump can effectively reduce treatment-related complications leading to shorter hospital stays and thus lower medical expenses for patients admitted for opioid toxicity.

Our study was the first to assess the efficacy of infusion pumps in achieving better therapeutic outcomes after naloxone therapy for opioid toxicity. Although some previous studies have assessed the use of similar pumps for infusion of naloxone in individual cases, such protocols had not been tested in randomized clinical trials and thus could not directly demonstrate the efficacy of using infusion pumps on posttreatment outcomes. Some previous studies have recommended intermittent infusion of small doses of naloxone when using an infusion pump to deliver postsurgical intravenous patient-controlled analgesia in order to minimize some of the side effects of morphine. In some trials in which the antagonist was ineffective, morphine and naloxone were mixed together in saline and delivered via an infusion pump [12-15]. Infusion of low-dose naloxone using an infusion pump may therefore help to improve patient outcomes while minimizing drug-related side effects. More recently, computer-based perfusion pumps have been developed to maximize the efficacy of drugs [16,17]. These measures make it possible to precisely control the overall doses of drugs administered or to compare the predictive performance of such protocols which differ in either general approach. The utility of such devices for delivery of antidotal therapies such as naloxone should be examined further in future studies.

Our study demonstrates that the infusion of naloxone using an infusion pump can be safer with regard to achieving proper hemodynamic stability, reducing the duration of hospitalization, and limiting posttreatment complication. In fact, this approach can prevent unintentional and nontherapeutic interventions by both staff and patient companions.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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AUTHOR CONTRIBUTIONS

Conceptualization, Data curation, Formal analysis, Methodology, Project administration, Visualization, Writing - original draft, review & editing: all authors.

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