Naloxone therapy in opioid overdose patients: intranasal or intravenous? A randomized clinical trial

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Abstract

Introduction: This study was designed to compare the effects of intranasal (IN) and intravenous (IV) administration of naloxone in patients who had overdosed on opioids.

Material and methods: This randomized clinical trial study was conducted in the Department of Poisoning Emergencies at Noor and Ali Asghar (PBUH) University Hospital. One hundred opioid overdose patients were assigned by random allocation software into two study groups (n = 50). Both groups received 0.4 mg naloxone: one group IN and the other IV. Outcomes included change in the level of consciousness (measured using a descriptive scale and the Glasgow Coma Scale (GCS)), time to response, vital signs (blood pressure, heart rate and respiratory rate), arterial blood O_2 saturation before and after naloxone administration, side-effects (agitation) and length of hospital stay.

Results: Patients who had been administered IN naloxone demonstrated significantly higher levels of consciousness than those in the IV group using both descriptive and GCS scales ($p < 0.001$). There was a significant difference in the heart rate between IN and IV groups ($p = 0.003$). However, blood pressure, respiratory rate and arterial O_2 saturation were not significantly different between the two groups after naloxone administration ($p = 0.18$, $p = 0.17$, $p = 0.32$). There was also no significant difference in the length of hospital stay between the two groups ($p = 0.14$).

Conclusions: Intranasal naloxone is as effective as IV naloxone in reversing both respiratory depression and depressive effects on the central nervous system caused by opioid overdose.

Key words: opioid, intranasal, naloxone, intravenous, overdose.

Introduction

As a competitive antagonist of the mu-opioid receptors [1], naloxone can be used for resuscitating patients who have significant respiratory depression and impaired consciousness due to opioid toxicity. Cannulation is a particular difficulty in intravenous drug users (IDUs). Often pre-existing venous damage can delay or even prevent the administration of an antidote. Additionally, IDUs are also at an increased risk of carrying blood borne infections that could be transmitted to healthcare

workers through needle stick injuries [2]. Whilst patients with altered mental status or multiple narcotic overdose may require intravenous (IV) access for other reasons, those with isolated narcotic overdose who rapidly respond to intranasal (IN) naloxone may not require IV access at all [3, 4]. The problems with the IV route of naloxone administration have led to efforts to find an effective alternative means of delivery.

The IN route has been shown to be clinically effective for a number of medications including analgesics and sedatives [5, 6]. When used with carefully selected medications, this delivery route has the advantage of rapid onset, high plasma bioavailability, direct transport to the central nervous system across the olfactory mucosa, elimination of first pass metabolism and, perhaps most importantly, elimination of the use of needles [7–13].

Some observational studies have suggested that intranasal naloxone may be safely administered for the reversal of opioid intoxication in the pre-hospital and hospital settings. Unfortunately such studies have suffered from several limitations such as lack of randomization or blinding and reliance on the subjective reporting of paramedics who were required to record times, administer medications and assess appropriate patient responses [4, 14–18].

This study was designed therefore to compare the effect of intranasal administration of naloxone with those of intravenous administration in the treatment of suspected opioid overdose patients in a managed clinical environment referring to the limitations pointed out above in previous studies.

Material and methods

Study design and setting

This randomized trial study was conducted in the Department of Poisoning Emergencies at Noor and Ali Asghar (Peace Be Upon Him) University Hospital. The study protocol was approved by the Ethics Committee of Isfahan University of Medical Sciences. The study was also registered at ClinicalTrials.gov (Reference number identifier: NCT01293058).

Patient selection and treatment protocol

Included in the study were all patients with the age range 15–50 suspected of opioid overdoses. This selection was based upon a history of opioid overdose and the display of clinical manifestations including myotic pupils and loss of consciousness (with or without respiratory depression defined by a respiratory rate of less than 12). One hundred eligible patients were divided into two groups (each group containing 50 patients) in addition to basic life support following clinical practice guidelines [19]. One group was administered 0.4 mg naloxone diluted down to a 2 ml nasal spray (1 ml into each nostril) whilst the other received 0.4 mg IV naloxone as a bolus dose. Normal saline was used as the solvent. The intranasal spray was administered to patients in lying position. All patients who failed to respond within 5 min of the initial naloxone administration were given a further 0.4 mg naloxone by the same administration route (IN or IV). Patients failing to respond to the first 0.4 mg naloxone with an increased level of consciousness or a reversal of respiratory depression were excluded from the study. Naloxone hydrochloride was purchased from Tolid Daru Co, Tehran, Iran.

Data collection

The information collected for this study included patients' demographics, the type of opioid used and the means of administration, vital signs (blood pressure, heart rate, respiratory rate), level of consciousness measured with descriptive scales (conscious, lethargic, obtundation, stupor, and coma) and the Glasgow Coma Scale (GCS), time to response, arterial blood oxygen (O_2) saturation before and 5 min after naloxone administration, side-effects (e.g. agitation) and duration of hospital stay. These data were collected from checklists including information on patient history, clinical assessments and records of treatment administered to the patient.

Trained medical staff prospectively recorded demographic data and clinical features of patients including measurement of the eye, motor, verbal and GCS scores in an appropriate form. The GCS was determined based on three components: eyes (4 – opens spontaneously, 3 – to verbal command, 2 – to pain, 1 – none), verbal (5 – oriented, 4 – disoriented, 3 – inappropriate words, 2 – incomprehensible sounds, 1 – none), and motor (6 – obeys, 5 – localizes pain, 4 – withdrawal, 3 – abnormal flexion, 2 – abnormal extension, 1 – none) [20].

Key outcome measures

The primary outcome measure was level of consciousness. Secondary outcomes were vital signs, the time interval to response, arterial blood O_2 saturation, the frequency of side-effects (e.g. agitation) and the duration of hospital stay.

Statistical analysis

Randomization was carried out using random allocation software (Saghaei, 2004). Quantitative variables were compared using the independent *t*-test. Qualitative variables were compared using χ^2 and Mann-Whitney tests. Data were analyzed using SPSS version 17.0 (SPSS Inc, Chicago, IL,

USA) with $p < 0.05$ being considered statistically significant.

Results

Age, gender, opioid agent and route of opioid use before naloxone administration between the two groups were not significantly different (Table I).

The results regarding level of consciousness (including descriptive and Glasgow Coma Scales) after naloxone administration are shown in Table II. The mean response time in the IN group and the IV group was 2.56 ±0.64 min and 1.48 ±0.58 min respectively ($p < 0.001$). The IN group had a significantly longer time to response to naloxone than the IV group ($p < 0.001$).

After naloxone administration there was a significant difference in heart rate between the IN and IV groups ($p = 0.003$). However, blood pressure and respiratory rate were not significantly different between the two groups ($p = 0.18$, $p = 0.17$) (Table III).

The mean arterial O_2 saturation before IN and IV naloxone administration was 71.4 ±8.3% and 72.7 ±6.3% ($p = 0.45$) respectively. Arterial O_2 saturation following naloxone administration was 94.4 ±1.3 in the IN group and 94.6 ±1.5 ($p = 0.32$) in the IV group.

The mean length of hospital stay was 1.53 ±0.16 days and 1.2 ±0.15 days in the IN and IV groups respectively ($p = 0.15$). Agitation after naloxone administration was observed in 12 patients in the IV group. No patient in the IN group were observed to become agitated.

Table I. Comparison of demographic, opioid agent and route of exposure between two groups

Variables	Groups		Value of *p*
	Intranasal naloxone	Intravenous naloxone	
Age, mean ± SD [year]	29.9 ±8.4	33.2 ±21.1	0.11*
Males, *n* (%)	39 (78)	37 (74)	0.64**
Opioid agent, *n* (%)			0.06**
Diphenoxylate	0	4 (8)	
Crack***	2 (4)	0	
Buprenorphine	4 (8)	0	
Methadone	8 (16)	10 (20)	
Heroin	14 (28)	12 (24)	
Opium	22 (44)	24 (48)	
Opioid exposure route, *n* (%)			0.68**
Intravenous	13 (26)	10 (20)	
Oral	26 (52)	26 (52)	
Sniffing	11 (22)	14 (28)	

**Independent t-test, **χ^2 test, ***Crack in Iran contains heroin combined with other opioid agents*

Discussion

Intranasal administration of naloxone has been shown to have many advantages [7–13].

Given the necessity for the rapid administration of naloxone in opioid overdose emergencies, the nasal route can offer immediate safe access and can circumvent the difficulties of having to remove clothing to cannulate. This method has been underutilized to date.

This study showed that among opioid overdose patients, IN naloxone is as effective as IV naloxone at reversing the depressive effects on the central nervous system caused by opioids. Although our results showed no significant clinical difference between the two groups after naloxone administration, level of consciousness was higher in patients administered IN naloxone than those in the IV group. This finding may be because of direct transportation of naloxone to the central nervous system across the olfactory mucosa [7]. Although Dowling *et al.* [21] in an open-label crossover volunteer study evaluated the pharmacokinetics of intranasal naloxone and reported that the IN route is the least useful due to its poor bioavailability, major differences existed between their subjects and opioid poisoned patients. They administered IN naloxone to alert healthy volunteers who involuntarily swallowed a significant percentage of the administered drug that pooled in the nasopharynx. Due to the high first pass metabolism of naloxone this may have resulted in the very low bioavailability observed. In patients unconscious due

Table II. Level of consciousness in opioid overdose patients before and after naloxone administration

Level of consciousness	Before naloxone	After naloxone
Intranasal administration, *n* (%)		
Coma	12 (24)	0
Stupor	24 (48)	0
Obtundation	14 (28)	0
Lethargic	0	28 (56)
Conscious	0	22 (44)
Intravenous administration, *n* (%):		
Coma	10 (20)	0
Stupor	28 (56)	0
Obtundation	12 (24)	20 (40)
Lethargic	0	18 (36)
Conscious	0	12 (24)

Table III. Vital signs, arterial O_2 saturation and GCS (Glasgow Coma Scale) in opioid overdose patients before and after naloxone administration between two groups

Variable	Before naloxone administration	After naloxone administration	Value of *p*
Systolic blood pressure [mm Hg]:			
Intranasal naloxone	99 ±16	106 ±14.7	*
Intravenous naloxone	97 ±21	112 ±9.6	
Value of *p*	0.68	0.18	
Diastolic blood pressure [mm Hg]:			
Intranasal naloxone	63 ±8.9	78 ±7.1	*
Intravenous naloxone	66 ±11	77 ±4.5	
Value of *p*	0.11	0.18	
Heart rate (per min):			
Intranasal naloxone	90 ±22	90 ±8.3	NS
Intravenous naloxone	89 ±25	97 ±12.9	*
Value of *p*	0.78	0.003	
Respiratory rate (per min):			
Intranasal naloxone	13 ±5.9	18 ±2.4	*
Intravenous naloxone	11 ±2.5	19 ±2.8	
Value of *p*	0.06	0.17	
Arterial O_2 saturation:			
Intranasal naloxone	71.4 ±8.3	94.4 ±1.3	*
Intravenous naloxone	72.7 ±6.3	94.6 ±1.5	
Value of *p*	0.25	0.32	
Glasgow Coma Scale (range: 1–15):			
Intranasal naloxone	9.7 ±1.6	14.3 ±0.73	*
Intravenous naloxone	9.4 ±1.3	13.2 ±1.5	
Value of *p*	0.22	< 0.001	

**P value < 0.05, NS – not significant*

to opioid overdose with consequent depressed oropharyngeal reflexes, less nasally administered naloxone may be swallowed, thus increasing the IN absorption and bioavailability.

Merlin *et al.* [22] reported that the route of administration (IV or IN) of naloxone made no significant difference to its effect on level of consciousness (using GCS). Our findings were incompatible with these results. Previous studies have been criticized for using GCS to quantify the change in level of consciousness following naloxone administration in cases of opioid intoxication [23] but the GCS has previously been used to evaluate non-trauma patients [24–26]. Therefore, in our study we used both descriptive and GCS scores to evaluate the level of consciousness. There is disagreement between physicians over the clinical usefulness of the GCS [27, 28]. The inter-observer variability is high when the scoring systems are not used on a regular basis, thus affecting the accuracy and reproducibility of the data [29–32]. This is potentially relevant in our study, as GCS determination was performed by several different physicians and had not formed a routine part of patient assessment before the study period. We tried to minimize variability by having one person to coordinate the process of data collection and had our anaesthesiologist or toxicologist formally train our emergency physicians in the assessment of GCS prior to the study. All GCS assessments were subsequently made by this group of physicians.

Merlin *et al.* [22] also reported that the route of naloxone administration (IN or IV) made no difference to the effect on respiratory rate. Our findings supported this conclusion. Our study also showed that there was no difference between the two groups in normalization of blood pressure and arterial O_2 saturation after naloxone administration.

There was a difference in the rates of agitation after naloxone treatment between the two study groups, with patients who received IV treatment showing higher rates (n = 12) than those who received IN treatment (n = 0). This may be explained by the difference in rates of naloxone absorption between the two methods of naloxone administration [9] and may be seen as an advantage of

the IN route. However, the higher rate of agitation in the IV group may be due to the higher number of addicted patients in this group.

Since opioid abusers frequently have incomplete, inaccessible or non-existent medical histories, it is impossible to establish how many patients in each group were addicted to opioids (and therefore subject to withdrawal with the administration of naloxone).

Whilst the randomization method used in the study should result in an approximately equal addiction rate between the two groups, it remains impossible to state definitely that IN administration results in a lower likelihood of agitation. To further investigate this area, a limited study of patients with a documented history of addiction would be required.

In a review article Kerr *et al.* [33] demonstrated that there is not enough evidence to support IN naloxone as a first-line intervention by paramedics for the treatment of heroin overdose in the pre-hospital setting. In contrast, in a short-cut review Ashton and Hassan [34] screened 596 papers and concluded that intranasal naloxone is a safe and effective first line, pre-hospital intervention, both in reversing the effects of an opioid overdose and helping to reduce the risk of needle stick injury.

There are also some limitations to our study. Our results should not be extrapolated to other institutions. It is a single-centre study, and may not be representative of all patients. Since not all of the subjects became completely alert after naloxone administration, it remains possible that other toxic agents were present in some patients. However, no toxicological screening was carried out to establish the presence and type of other agents which may have affected the level of consciousness. Alternatively, an insufficient naloxone dosage may have resulted in some of the patients failing to return to full consciousness. In the presented work there was a predominance of male patients – 78% and 74% in the IN and IV groups respectively. Therefore the described results may not be extrapolated to a female population.

In conclusion, IN naloxone is as effective as IV naloxone in reversing both respiratory depression and the depressive effects on the central nervous system caused by opioid overdose. We may therefore suggest using the IN route for administration of naloxone in opioid overdose patients to reverse clinical manifestations with less severe withdrawal, especially in patients with a history of previous addiction.

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