Prediction of endotracheal intubation outcome in opioid-poisoned patients: A clinical approach to bispectral monitoring

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BACKGROUND: Some opioid-poisoned patients do not respond appropriately to naloxone; consequently, intubation is required. Although various measures have been used to evaluate the level of consciousness of poisoned patients, no study has assessed the role of the bispectral index (BIS) to ascertain the depth of anesthesia in opioid-poisoned patients who require endotracheal intubation.
OBJECTIVE: To compare BIS scores between opioid-poisoned patients with and without intubation, and to determine the BIS cut-off point for endotracheal intubation in these patients.
METHODS: In the present cross-sectional study, conducted in an Iranian university referral hospital for poisoning emergencies between 2012 and 2013, opioid-poisoned patients (n=41) were divided into two groups according to their requirement for endotracheal intubation. BIS analyses were performed at the time of admission and at the time of intubation for those who required it. In addition, electromyography and signal quality index were evaluated for all patients at the time of admission, and cardiorespiratory monitoring was performed during the hospitalization period. Using ROC curves, and sensitivity and specificity analyses, the optimal BIS cut-off point for prediction of intubation of these patients was determined.
RESULTS: The optimal cut-off point for prediction of intubation was BIS ≤78, which had a sensitivity of 86.7% (95% CI 66.1 to 98.8) and specificity of 88.5% (95% CI 73.9% to 98.8%); the positive and negative predictive values were 81.2 % and 92%, respectively.
CONCLUSIONS: BIS may be considered an acceptable index to determine the need for intubation in opioid-poisoned patients whose response to naloxone is inadequate.

Key Words: *Bispectral index (BIS); Endotracheal intubation; Naloxone; Opioid poisoning*

Prédire l'issue de l'intubation trachéale chez les patients empoisonnés par des opioïdes : une approche de la surveillance bispectrale

HISTORIQUE : Certains patients empoisonnés par des opioïdes ne répondent pas bien au naloxone et doivent être intubés. Diverses mesures sont utilisées pour évaluer le niveau de conscience des patients empoisonnés, mais aucune étude n'a porté sur le rôle de l'index bispectral (IBS) pour déterminer la profondeur de l'anesthésie chez les patients empoisonnés par des opioïdes qui doivent subir une intubation trachéale.
OBJECTIF : Comparer les indices de l'IBS entre les patients empoisonnés par des opioïdes intubés ou non et déterminer le seuil d'IBS pour l'intubation trachéale de ces patients.
MÉTHODOLOGIE : Dans la présente étude transversale menée entre 2012 et 2013 dans un hôpital universitaire iranien spécialisé dans les urgences causées par des empoisonnements, les patients empoisonnés par des opioïdes (n=41) ont été divisés en deux groupes, en fonction de la nécessité qu'ils subissent une intubation trachéale. Les chercheurs ont analysé l'IBS au moment de l'admission et de l'intubation des patients qui devaient la subir. Ils ont aussi évalué l'électromyographie et l'indice de qualité du signal chez tous les patients au moment de l'admission et assuré un monitorage cardiorespiratoire pendant la période d'hospitalisation. À l'aide des courbes ROC et des analyses de sensibilité et de spécificité, ils ont déterminé le seuil d'IBS optimal pour prédire l'intubation de ces patients.
RÉSULTATS : Un IBS de 78 ou moins, d'une sensibilité de 86,7 % (95 % IC 66,1 à 98,8) et d'une spécificité de 88,5 % (95 % IC 73,9 % à 98,8 %), était le seuil optimal pour prédire l'intubation. Les valeurs prédictives positives et négatives s'établissaient à 81,2 % et 92 %, respectivement.
CONCLUSIONS : L'IBS peut être considéré comme un index acceptable pour déterminer la nécessité d'intuber les patients empoisonnés par des opioïdes qui répondent peu au naloxone.

The high prevalence of mortality among individuals who engage in opiate injection drug use remains an ongoing problem in many countries, and needs an effective drug policy and public health action (1). A flood of opioids has resulted in a rising tide of deaths in recent decades (2). In fact, deaths from opiate overdose exceed the number of homicide deaths in New York City (New York, USA), which is estimated to be 900 each year (3). Clinical patterns of opioid intoxication are dependent on the amount of drug taken. The most consistent and important clinical sign of opioid toxicity is respiratory depression, which requires expedient endotracheal intubation in some patients to protect the airway, and to minimize the risk of hypoventilation and subsequent hypoxemia (4). Failure of airway maintenance and protection, or inadequate oxygenation or ventilation, represent the most straightforward criteria for intubation (5). In addition, intubation is required if an opioid antagonist fails to produce an adequate response, especially with evidence of respiratory depression (6).

Various indexes have been evaluated to determine the need for intubation in critically ill patients (6-8). Not only is a Glasgow Coma Scale (GCS) score ≤8 a useful guide for endotracheal intubation in patients with brain injury resulting from respiratory compromise, it also indicates the need for intubation in cases for which the cause of unconsciousness is poisoning (9,10).

Another index used to measure the level of consciousness and depth of anesthesia and sedation is the bispectral index (BIS) (11). In 1996, The United States Food and Drug Administration approved a novel measure of the level of consciousness by algorithmic processing of a patients' electroencephalographic data for assessing the hypnotic effects of general anesthetics and sedatives (12,13). BIS monitoring was initially used primarily during operative anesthesia. Recently, however, BIS monitoring has become a reasonable approach used in intensive care unit (ICU) patients to assess the depth of sedation, especially among individuals receiving neuromuscular paralysis

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TABLE1
Demographic data and clinical characteristics of the study patients

Characteristic	Patients: Intubated (n=15)	Patients: Nonintubated (n=26)	P
Age, years, mean ± SD	41.93±3.21	33.69±2.40	0.046
Sex			
Male	10 (66.7)	22 (84.6)	0.25*
Female	5 (33.3)	4 (15.4)	
Marital status			
Single	5 (33.3)	10 (38.5)	0.74†
Married	10 (66.7)	16 (61.5)	
Employment status			
Employed	7 (46.7)	21 (80.8)	0.038†
Unemployed	8 (53.3)	5 (19.2)	
Route of poisoning			
Oral	13 (86.7)	24 (92.3)	0.62*
Nonoral	2 (13.3)	2 (7.7)	
Cause of poisoning			
Unintentional (accidental)	6 (40)	18 (69.2)	0.07†
Intentional	9 (60)	8 (30.8)	
Type of opioid			
Methadone	12 (80)	21 (80.8)	0.09*
Heroin	3 (20)	1 (3.8)	
Other opioids	–	4 (15.4)	
Using concomitant medication			
Yes	11 (73.3)	8 (30.8)	0.008*
No	4 (26.7)	18 (69.2)	
Time to first treatment modality, h, mean ± SD	6.38±1.65	2.52±0.65	0.025
Length of hospitalization, h			
≤48	6 (40)	26 (100)	0.001*
>48	9 (69)	0 (0)	

*Data presented as n (%) unless otherwise indicated. *Fisher's exact test; †χ^2 test*

(14-16). The BIS ranges from 0 (equivalent to electroencephalogram silence) to 100. A manufacturer-recommended value between 40 and 60 is suitable for general anesthesia (17).

Several studies have shown a positive correlation between BIS values and GCS and Acute Physiology And Chronic Health Evaluation (APACHE II) scores (11,18,19). A previous review article (8) discussed the different methodologies used to monitor the depth of anesthesia and described potential applications of the BIS for such a purpose.

An incomplete or inadequate response to naloxone and the inability to restore normal breathing predisposes opioid-poisoned patients to decreased consciousness and loss of protective airway reflexes, which may result in respiratory failure and aspiration injury (20). As a result, the decision to intubate poisoned patients is very important because, instead of a maintenance opportunity, any inappropriate delays in airway protection can cause a 'crash' airway scenario and hypoventilation (21).

Despite the potential application of the BIS for monitoring the depth of anesthesia, to our knowledge, its role has yet to be evaluated in opioid-poisoned patients who require endotracheal intubation. Accordingly, the present observational study aimed to compare BIS scores between opioid-poisoned patients with and without endotracheal intubation, and to determine the optimal BIS cut-off point for endotracheal intubation.

METHODS

The present cross-sectional study was conducted at the Noor and Ali Asghar [PBUH] University hospital affiliated with Isfahan University of Medical Sciences (Isfahan, Iran) between 2012 and 2013. This centre, the major referral medical centre for toxicological emergencies in central Iran, is facilitated, staffed and designed for the management of poisoning patients, of whom approximately 400 are admitted monthly.

Patients included in the present study were all opioid-poisoning individuals who were admitted to the ward during the study period. Patients hospitalized for opioid poisoning were randomly selected using a random number table and their identification number. The study protocol was approved by the Institutional Board of Human Studies at Isfahan University of Medical Sciences. In addition, after the study was accurately explained to the patients, informed consent for inclusion was obtained. Discharge and/or death before study commencement were considered to be exclusion criteria.

Forty-one patients hospitalized for opioid poisoning were recruited for the present study and were followed to measure outcomes. Initially, adequate supportive primary care was performed for all opioid-poisoned patients and treatment to facilitate the recovery process was continued. Demographic data and clinical findings from the patients, including vital signs, hemodynamic parameters, routine blood biochemistry analysis, clinical history at admission, amount of ingested opioids, performed treatment modality (eg, gastric lavage, activated charcoal) and length of hospitalization, were recorded for further analysis. If intubation was necessary to control airway and oxygenation, time of intubation was also documented. This information was collected from patient charts and documented reports of emergency services. Expedient endotracheal intubation was performed for patients who were unable to protect their airway despite naloxone administration (6).

The outcomes were followed based on BIS measured at admission and before intubation of the included patients. The BIS ranges from 0 (equivalent to electroencephalogram silence) to 100, which indicates complete alertness (17).

In addition, electromyography and signal quality index were evaluated for all patients at the time of admission; cardiac and respiratory monitoring were also performed during the hospitalization period.

All data were analyzed using SPSS version 16 (IBM Corporation USA) and Med-Calc (Med-Calc Software Inc, Belgium) statistical software.

The χ^2 or Fisher's exact test was applied to compare categorical data between patients with and without endotracheal intubation; $P<0.05$ was considered to be statistically significant. In addition, significant differences in continuous data were determined using the Mann-Whitney U test or an independent-samples *t* test where appropriate. ROC curves were used for discrimination by comparison of areas under the curve (AUC) (22). Acceptable and excellent discrimination were defined as AUC 0.7 to 0.8, and 0.8 to 0.9, respectively (23). Therefore, according to the result of ROC curve analyses, sensitivity, specificity and the optimal cut-off point were determined (24). This BIS cut-off point was used to determine predicted and observed endotracheal intubation in poisoned patients.

RESULTS

Endotracheal intubation was required in 15 of the 41 opioid-poisoned patients evaluated in the present study. No patient died during the study and, among patients who completed the study, 10 (66.7%) in the intubation group and 21 (80.8%) in the nonintubation group experienced improvement without complications (P=0.45). In contrast, five patients in each group showed improvement but experienced complications (33.3% versus 19.2%; P=0.45).

Demographic data and clinical findings of patients, including route and cause of poisoning, type and amount of ingested opioid, use of concomitant medication, time to first treatment modality and length of hospitalization, were compared between intubated and nonintubated patients (Table 1). Fisher's exact test and χ^2 analyses showed significant differences in employment status, use of concomitant medication, and length of hospitalization between intubated and nonintubated patients (P=0.038, 0.008 and 0.001, respectively). In addition, independent sample *t* tests showed a longer time to first

TABLE 2
Laboratory results and arterial blood gas values of the study patients

Parameter	Patients		P*
	Intubated (n=15)	Nonintubated (n=26)	
BUN, mmol/L	7.27±0.96	14.21±7.21	0.08
Creatinine, µmol/L	116.69±9.72	111.38±10.61	0.63
Serum Na^+, mEq/L	129.86±0.76	137.50±1.17	0.21
Serum K^+, mEq/L	4.37±0.24	5.05±0.30	0.09
ALT, U/L	25.72±5.40	41.75±10.88	0.03
AST, U/L	22.81±2.95	95.00±36.22	0.01
PT, s	17.45±1.80	24.62±8.88	0.14
PTT, s	40.20±8.89	50.00±17.51	0.59
Glucose, mmol/L	7.04±1.17	5.26±0.28	0.31
Hematocrit, %	43.31±1.26	41.71±1.68	0.61
Platelets, $\times 10^9$/L	232.24±31.18	213.67±29.46	0.64
INR	3.10±0.70	2.76±0.31	0.86
HCO_3, mEq/L	21.25±0.88	26.63±1.48	0.03
BE, mmol/L	−12.4±0.60	−9.12±0.88	0.02
SaO_2, %	77.28±6.05	90.00±5.70)	0.17
PCO_2, mmHg	48.07±3.39	51.21±4.49	0.39
pH	7.24±0.51	7.32±0.02	0.11
PaO_2, mmHg	55.33±5.84	39.04±4.45	0.02

*Data presented as mean ± SD unless otherwise indicated. *Mann-Whitney U test. ALT Alanine aminotransferase; AST Aspartate aminotransferase; BE Base excess; BUN Blood urea nitrogen; INR International normalized ratio; PaO_2 Partial pressure of arterial oxygen; PCO_2 Partial pressure of carbon dioxide; PT Prothrombin time; PTT Partial thromboplastin time; SaO_2 Oxygen saturation*

TABLE 3
Hemodynamic indexes, bispectral index (BIS), electromyography (EMGA) and signal quality index (SQI) of the study patients

Parameter	Patients*		P
	Intubated (n=15)	Nonintubated (n=26)	
Systolic blood pressure, mmHg			
At admission	97.18±8.50	113.00±3.33	0.001
At intubation	97.18±28.22	113.33±5.77	0.36
Diastolic blood pressure, mmHg			
At admission	67.71±3.41	63.13±6.66	0.21
At intubation	67.71±9.03	63.33±11.55	0.53
Temperature, °C			
At admission	36.82±0.88	36.07±0.92	0.51
At intubation	37.08±0.17	37.01±0.10	0.96
Heart rate, beats/min			
At admission	77.73±6.42	84.04±2.47	0.31
At intubation	73.18±10.78	77.00±4.58	0.86
Respiratory rate, breaths/min			
At admission	11.72 ±1.47	22.92±4.75	0.03
At intubation	14.28±3.93	16.00±2.00	0.83
EMGA, %			
At admission	41.2±89.29	74.68±6.46	0.01
At intubation	51.40±15.72	47.50±47.50	0.92
BIS			
At admission	67.26±2.67	85.50±1.70	<0.001
At intubation	71.61±1.92	83.00±10.44	0.08
SQI			
At admission	100.00±0.00	100.00±0.00	1
At intubation	100.00±0.00	67.00±33.00	0.05

*Data presented as mean ± SD unless otherwise indicated. *Parameters measured at two time points: on admission and at the time of intubation for patients who required endotracheal intubation; 'At intubation' parameters in nonintubated patients were measured at the same time as those for intubated patients*

treatment modality among intubated compared with nonintubated patients. Moreover, Mann-Whitney U test analysis was used to compare the mean values of blood biochemistry parameters during the first two days of admission between the two groups (Table 2). This analysis showed significant differences in some factors of arterial blood gases including HCO_3, base excess and PaO_2 (P=0.03, 0.02 and 0.02, respectively). Finally, mean values of hemodynamic indexes, electromyography and BIS were compared between groups using *t* tests at admission and at intubation (Table 3). The related results demonstrated that mean systolic blood pressure (SBP), electromyography results, signal quality index and BIS were significantly lower among intubated compared with nonintubated patients.

A ROC analysis of data to evaluate the best point of BIS for prediction of intubation was performed. According to this analysis, BIS ≤78 was the best point for intubation prediction, with 86.7% sensitivity (95% CI 66.1% to 98.8%) and 88.5% specificity (95% CI 73.9% to 98.8%), with associated positive and negative predictive values of 81.2% and 92%, respectively.

DISCUSSION

Endotracheal intubation may prevent respiratory failure and aspiration in opioid-poisoned patients who fail to respond to naloxone and meet the criteria for intubation (25). The primary purpose of the present study was to determine the optimal BIS cut-off point to predict the need for endotracheal intubation in opioid-poisoned patients. Among the 41 patients (age range 24 to 50 years) recruited during the study period, 36.6% underwent intubation. According to the results of the present study, patient age was a significant factor for intubation. Previous studies have reported that vital signs and hemodynamic parameters are dependent on patient age, and that older patients may experience more acute signs of poisoning (26). Although the reason for poisoning did not significantly affect patient intubation status in the present study, intubated patients had a more prevalent history of intentional poisoning (n=9) than nonintubated patients (n=7). In the current study, time to first treatment modality had an impact on patient intubation. As expected, the first treatment modality was conducted earlier in nonintubated patients (mean [± SD] 2.54±0.65 h versus 6.38±1.65 h). In addition, coadministration of other medications with opioids was another factor that influenced the need for intubation. It appears that this factor was associated with a greater severity of poisoning and predisposed patients to require endotracheal intubation (73.3% in intubation versus 30.8% in nonintubation). Moreover, a previous study showed that the time elapsed from taking the poisoning agent to undergoing the first treatment was one of the most important factors to affect prognosis, morbidity and mortality (8). This result appears to be reasonable because the more time elapsed to initiate treatment leads to greater absorption of the poison and more severe adverse reaction (8,26).

In contrast, arterial blood gas analysis of patients showed significant differences in PaO_2, serum bicarbonate level and SBP at ICU admission between intubated and nonintubated patients. Serum bicarbonate levels were significantly lower at admission in individuals who required intubation during the study period. This result demonstrates that patients with more severe opioid toxicity and lower serum bicarbonate levels would require intubation. In addition, SBP was also lower in this group, which showed worse hemodynamic values on admission in those who required intubation. Lower blood pressure may cause metabolic acidosis and lower serum bicarbonate levels. In contrast, PaO_2 at ICU admission was lower in patients who did not require intubation during their hospital stay. This may have occurred because these patients may have adequately responded to naloxone, which led to improvement in respiratory distress, thereby obviating the need for intubation.

BIS analysis showed that BIS was significantly lower in intubated patients at both admission to the ICU and at intubation. The present study showed that BIS ≤78, with specificity of 88.5% and sensitivity of 86.7%, was an appropriate criterion to predict the need for intubation in opioid-poisoned patients. Another study reported that correlation between GCS and BIS analysis is highest when BIS <80 and GCS score <8 are used as cut-off points (19).

CONCLUSION

Because coadministration of other sedatives with opioids occurred in some poisoned patients, they did not respond adequately to naloxone and, consequently, intubation was required. Our study showed that BIS may be an acceptable index to determine the need for intubation in these patients.

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