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Research Paper

Planned Versus Unplanned Extubation in Opioid Overdose Patients: Does it Have any Effect on the Prognosis? A Cohort Study

Mitra Rahimi[1], Ghafar Ali Mahmoudi[2], Shahin Shadnia[1], Nasim Zamani[3,4], Rebecca McDonald[5], Hossein Hassanian-Moghaddam[3,4], Peyman Erfantalab Evini[1*]

1. Toxicological Research Center, Excellence Center of Clinical Toxicology, Department of Clinical Toxicology, Loghman Hakim Hospital, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran.
2. Department of Internal Medicine, School of Medicine, Lorestan University of Medical Sciences, Khorramabad, Iran.
3. Department of Clinical Toxicology, Loghman Hakim Hospital, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran.
4. Social Determinants of Health Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran.
5. National Addiction Center, Institute of Psychiatry, Psychology and Neuroscience, King's College Hospital, London, UK.

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*** Corresponding author:**
Peyman Erfantalab Evini, PhD.
Address: *Toxicological Research Center, Excellence Center of Clinical Toxicology, Department of Clinical Toxicology, Loghman Hakim Hospital, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran.*
E-mail: *mahmoudi.gh@lums.ac.ir*

ABSTRACT

Background: Tracheal intubation is a life-saving measure in patients poisoned acutely with opioid, and when naloxone treatment is inadequate. This study determined the risk factors for early unplanned extubation in these patients and evaluated the effects on the clinical outcomes.

Methods: At a poisoning center in Tehran, Iran, 165 opioid overdose patients who were admitted to the intensive care unit and intubated between September 2019 and March 2020 were enrolled into this study. Patients were categorized in two groups: a) those extubated based on the physicians' decision, and b) those who were extubated by self or were accidentally. The two groups were compared regarding their clinical outcomes and complications during hospitalization. In addition, the re-intubated patients in both groups were compared to those with successful intubation regarding the predisposing factors and mortality.

Results: Of these patients, 36 (21.8%) died before extubation, and planned extubation was performed in 109 of them (84.5%). Unplanned extubation occurred in 20 patients (15.5%). Agitation, elevated temperature (>38.5ºC), and insufficient nursing care were the independent risk factors for the unplanned extubation. 6(5.5%) and 3(15%) patients died following the planned and unplanned extubation, respectively, and 24 patients required reintubation. Patient transfer, succinylcholine use, aspiration pneumonia, presence of brain injury, and insufficient nursing care were independent risk factors for re-intubation.

Conclusion: Among the patients with high drug dependency, higher doses of sedatives were needed to avoid self-extubation. Infection control and sufficient nursing care were factors that led to better clinical outcomes for extubation in these patients.

Keywords: Emergency medicine, Intensive care unit, Intubation, Opioid analgesics, Poisoning, Airway extubation

Introduction

Tracheal intubation represents a life-saving and supportive measure in patients acutely poisoned with opioid when response to naloxone is inadequate [1]. Intubation is typically needed when such poisoning cases involve severe loss of consciousness [2]. Tracheal intubation is generally considered a safe procedure in these patients. Even under ideal circumstances, intubation may still be accompanied by adverse effects related to adverse events, such as mucosal injury to the trachea. However, avoiding intubation in these patients with low consciousness may lead to graver complications, including aspiration pneumonia, Acute Respiratory Distress Syndrome (ARDS), pulmonary sepsis and even death [1].

Immediate complications are primarily associated with problems during intubation and extubation, while early and late complications represent the short- and long-term effects of epithelial trauma [3]. These complications may be even worse when patients need re-intubation after planned or unplanned self-extubation due to repeated mucosal injuries or severe changes in the pressure within the chest and lungs [4]. The risks of re-intubation in general Intensive Care Units (ICUs) vary between 2-25%, depending on the setting and the quality of nursing care [5]. Inadequate sedation as well as agitation are the major risk factors for self or unplanned extubation, while the need for re-intubation is the major determinant of the patient's clinical outcomes. Both self extubation and re-intubation may lead to serious complications, such as aspiration, laryngeal edema, and increased risk of pneumonia [6]. Nevertheless, no research has been conducted on overdose opioid patients to date. Therefore, we investigated this issue because it contributes significantly to the treatment plan of opioid patients admitted to ICUs.

There are factors in favor or against early extubation in patients poisoned with opioid. These patients are generally young and without background disorders, and are expected to regain consciousness early as the opioid substance is eliminated from the body. On the other hand, the risk of opioid withdrawal, aspiration pneumonia, because of, and respiratory distress is increased in these patients due either to the action of the toxin or antidotes in the body, or abrupt loss of consciousness on a full stomach. Indeed, most clinical toxicologists and intensive care specialists try to extubate these patients as soon as possible, once the opioid is excreted. However, opioid withdrawal, aspiration pneumonia, and dependence on other drugs, such as sedatives and anti-depressants may complicate the intervention.

Most studies on the clinical outcomes of planned and unplanned extubation have been conducted in general ICUs and on internal medicine patients, demonstrating that extubation failure correlate with old age and underlying chronic cardiac or respiratory diseases [7, 8]. No independent studies have been conducted in opioid overdose patients with regard to intubation or extubation.

Aim of the study: To address the above query, we conducted the current study in patients with opioid overdose who were intubated and admitted to the toxicology ICU for two reasons:

a) to determine the possible risk factors for early unplanned extubation and, b) to evaluate the effects of unplanned extubation on re-intubation of these patients on the clinical outcomes.

Materials and Methods

Study population & setting: This prospective, single-center observational cohort study was conducted in 165 patients who were overdoes with opioid alone or multiple substances. They were admitted to the toxicology ICU of a poisoning center at Loghman Hakim Hospital in Tehran, Iran, between September 2019 and March 2020 prior to their enrollment in this study.

Eligibility: Patients were eligible for inclusion in the study if they were at the age of 13 years or older, and intubated due to either, a) loss of consciousness (Glasgow Coma Scale [GCS]<8) or, b) aspiration and acute respiratory failure (Figure 1). The patients who had been intubated at other hospitals and were referred to our center were also included. Patients were excluded if they died before a decision for extubation was reached.

Measures: On admission, a specific form was completed that assessed the patients' demographics (age, gender), vital signs on-arrival an hour before extubation and Acute Physiology and Chronic Health Evaluation II (APACHE-II) score. Also, we documented the patients' PaO_2/FiO_2 (PF ratio), history of background conditions (cardiovascular, hepatic, renal, neurological, addiction, and smoking), and the type of opioid that caused poisoning. Re-intubation was usually carried out for patients in the first 72 hours after extubation [9]. In addition, we documented the following information for each patient:

• Any treatment that the patient had been received to date.

• The location and shift where the intubation had been performed (ward vs ICU).

• The quality of nursing care received at Loghman Hakim Hospital (standard vs non-standard).

• Medications administered to induce and/or maintain sedation during intubation.

• Duration of intubation (number of days).

• The justification for ICU admission.

• The final clinical outcome (death, complete recovery, recovery with sequelae).

• Complications during the patient's hospital stay, such as:

- Aspiration pneumonia

- Ventilator-Associated Pneumonia (VAP)

- Rhabdomyolysis

- Acute renal injury

- Neurologic complications, including seizures

- Patients' vital signs and lab results upon extubation

Also, the mode of extubation (planned vs unplanned), time of extubation (a.m., p.m., night), the time elapsed between extubation and re-intubation, where applicable, the results of Rapid Shallow Breathing Index (RSBI) and the cuff test were recorded. The RSBI was calculated when patients were in spontaneous breathing mode for at least one minute [10, 11]. Based on the weaning protocol, either of the following Spontaneous Breathing Trial (SBT) was used: a) low-pressure support, T-piece or, b) Continuous Positive Airway Pressure (CPAP)

The quality of nursing care was evaluated by a co-author who reviewed their duties in caring for the intubated patients and self-report of issues, e.g. if the nurse forgot to infuse the sedatives, or did not suction the endotracheal tube on-time [11].

Clinical outcomes: The primary outcomes were the instances for re-intubation and the number of patients who died.

Statistical analysis: Patients were categorized into two groups: a) those who were extubated based on the physicians' decision and, b) those who self-extubated and/or extubated accidentally (Figure 1). The extubations were considered as planned if patients were extubated at a scheduled time or if they were planned to be extubated at a definitive time but were self-extubated at the last moment.

Extubations were considered unplanned, if a) patients extubated themselves or were extubated accidentally during in-hospital transfer or, if b) they had been extubated as planned but were re-intubated with the second extubation being unplanned.

Planned versus unplanned extubation and the need for reintubation versus no reintubation were compared regarding their outcomes using Mann-Whitney U-Test for continuous variables, and Chi square/Fisher's exact test for categorical variables. IBM® SPSS® statics version 23 software was used for multivariate analyses to identify the independent variables that could be predictive of the subsequent unplanned extubation and/or re-intubation. A P-value below 0.05 was considered as statistically significant.

Results

On-arrival or early data: Among the 2,253 patients who were admitted with a diagnosis of opioid overdose, 165 patients were evaluated and subsequently needed intubation (Figure 1). Among the included patients, the median age was 33 (25, 49) years (range: 13 to 86 years) 153 of whom (93%) were males. Of these patients, 28 (17%) had been intubated at other hospitals before being transferred to our center. Twenty-seven of the patients (16.4%) had received a naloxone treatment before admission to the Emergency Department.

Fatal cases before extubation: Table 1 represents the characteristics of the patients on-arrival compared to those who died before extubation versus those who were extubated, and either discharged from the hospital or died at the hospital. Patients who died before extubation (n=36) were older (median 48 vs. 33 years, P<0.001) and had lower oxygen saturation on-arrival (SpO_2; P=0.012) than non-fatal cases before extubation (Figure 1). Among the fatal cases, tramadol was administered less frequently (3 deaths, 8.3%) than other opioid agents. The time of intubation was the single determinant of survival among cases before the first extubation. The odds of survival were 2.8 times more frequently for

Table 1. Selected on-arrival characteristics of opioid poisoned patients(n=165)

Variables		No. (%)/[IQR](Min-Max)			P	OR(95% CI)
		Total (n=165)	Death before Extubation (n=36)	No Death before Extubation (n=129)		
Vital signs Median	Age(y)	33 [25, 49] (13, 86)	48 [33, 66] (16, 86)	33 [25,49] (13, 84)	<0.001*	
	Glasgow Coma Scale	8 [6, 12] (3, 15)	7 [4, 13] (3, 15)	9 [6, 12] (3, 15)	0.095†	
	SpO_2[a]	94 [90,96] (44,100)	92 [87,96] (61,98)	95 [91,97] (44,100)	0.012*	
	Temperature[a]	37 [37, 37] (36, 39)	37 [36, 37] (36, 39)	37 [37, 37] (36, 38)	0.471*	
	Respiratory Rate[a]	16 [13, 20] (6, 51)	16 [13, 19] (8, 36)	16 [14, 20] (6, 51)	0.401*	
	Pulse Rate[a]	95 [80, 110] (35, 150)	100 [80, 109] (35, 140)	95 [80, 110] (60, 150)	0.648*	
	Systolic Blood Pressure[a]	110 [100, 130] (61, 180)	110 [100, 135] (61, 166)	110 [100, 130] (71, 180)	0.687*	
	Diastolic Blood Pressure[a]	70 [64, 80] (35, 124)	70 [63, 84] (35, 124)	70 [64, 80] (45, 119)	0.875*	
	PO_2/FiO_2	300 [250, 300] (150, 350)	250 [250, 300] (150, 350)	300 [300, 325] (200, 350)	<0.001*	
	APACHE II	11 [8, 16] (3, 34)	16 [13, 18] (8, 33)	9 [7, 14] (4, 27)	<0.001*	
Background diseases	Addiction	94(57)	27(75)	67(51.9)	0.014†	2.8(1.2, 6.4)
	COPD	10(6.1)	6(16.7)	4(3.1)	0.008‡	6.2(1.6, 23.5)
	Diabetes	5(3)	2(5.6)	3(2.3)	0.299‡	-
	CHF	11(6.7)	8(22.2)	3(2.3)	<0.001‡	12(3.0, 48.1)
	Smoking	76(46.1)	19(52.8)	57(44.2)	0.360†	
	CVD	12(7.3)	8(22.2)	4(3.1)	0.001‡	8.9(2.5, 31.7)
	Stroke	3(7.3)	2(5.6)	1(0.8)	0.120‡	
	Seizure	12(7.3)	1(2.8)	11(8.5)	0.466‡	
	Mental Dis	11(6.7)	3(8.3)	8(6.2)	0.706‡	
	Suicide	6(3.6)	1(2.8)	5(3.9)	0.999‡	
	Others	9(5.5)	0	9(7)	0,208‡	
Location of intubation	ED	1(0.6)	1(2.8)	0	0.349†	
	Other centers	28(17)	7(19.4)	21(16.3)		
	Ward	36(21.8)	10(27.8)	26(20.2)		
	Not ward or other centers	1(0.6)	0	1(0.8)		
	Toxicology ED	84(50.9)	15(41.7)	69(53.5)		
	Toxicology ICU	15(9.1)	3(8.3)	12(9.3)		
Intubation time,	Morning	52(31.5)	6(16.7)	46(35.7)	0.037†	2.8(1.1, 7.1) for morning and 0.4(0.2, 0.9) for night
	Afternoon	49(29.7)	10(27.8)	39(30.2)		
	Night	64(38.8)	20(55.6)	44(34.1)		

Variables		No. (%)/[IQR](Min-Max) Total (n=165)	Death before Extubation (n=36)	No Death before Extubation (n=129)	P	OR(95% CI)
Type of opioid	Heroin	1(0.6)	1(2.8)	0	0.002†	3.6(1.1, 12.6) for tramadol and 0.2(0.04, 0.89) for MTD+opium
	Methadone	70(42.4)	12(33.3)	58(45)		
	Tramadol	35(21.2)	3(8.3)	32(24.8)		
	Inhaled opium	46(27.9)	13(36.1)	33(25.6)		
	Oral opium	1(0.6)	1(2.8)	0		
	MTD+Tramadol	2(1.2)	0	2(1.6)		
	MTD+opium	7(4.2)	4(11.1)	3(2.3)		
	Tramadol+opium	1(0.6)	0	1(0.8)		
	MTD+Heroin	1(0.6)	1(2.8)	0		
	3 or more opioids	1(0.6)	1(2.8)	0		

*Mann-Whitney U test; †Pearson Chi-square; ‡Fisher's exact test; ᵃDone-up to one hour before extubation.Italic Bold cases are responsible variables to make Pearson's chi-square analysis significant. IQR: Interquartile range. COPD: Chronic obstructive pulmonary disease. CHF: Congestive heart failure. CVD: Cardiovascular disease. ED: Emergency department. MDT: Multi Drug Toxicity.

morning intubations (95% CI: 1.1, 7.1) while it was 0.4 for the night shifts (95% CI: 0.2, 0.9; P=0.037).

The PO_2/FiO_2 ratio and APACHE-II score differed significantly among the fatal cases before extubation versus non-fatal cases before extubation (250 vs. 300 and 16 vs. 9 respectively, P<0.001). In terms of background diseases, the cases who died before extubation had significantly increased odds of addiction (2.8, 95% CI: 1.2, 6.4; P<0.001), Chronic Obstructive Pulmonary Disease (COPD) (6.2, 95% CI: 1.6, 23.5; P<0.001), Congestive Heart Failure (CHF) (12.0, 95% CI: 3.0, 48.1, P<0.001), and/or cardiovascular disease (CVD; 8.9, 95% CI: 2.5, 31.7; P=0.001).

Extubation & reintubation: Of the 129 extubated cases, 109(84.5%) individuals were extubated by the medical staff, of whom 14(12.8%) were reintubated but six of them (5.5%) died subsequently. Of the 20 patients who had unplanned extubation, 10(50%) were intubated again but 3 individuals (15%) did not survive (Figure 1). Table 2 represents the select variables in the groups of planned vs. unplanned extubation and re-intubated vs. not re-intubated patients during the patients' hospital stay. Compared to the patients who underwent planned extubation, the unplanned extubation cases were younger (25 vs. 32 years) and had higher rates of leukocytosis (10800 vs 9100 White Blood Cells [WBC] per microliter), seizure (20.0% vs. 6.4%), insufficient nursing care (30% vs 1.8%), neuromuscular blockade with atracurium (30.0% vs. 5.5%), brain injury (15% vs 3.7%), tube occlusion (5.0% vs 0), withdrawal syndrome (5.0% vs 0), agitation (60.0% vs 4.6%), and had more frequent intrahospital transfers (25.0% vs 2.7%).

The hospital stay post-extubation was shorter for the unplanned extubation cases (2 vs. 5 days). The reintubation occurred significantly more often (P<0.05) in patients with one of the following conditions: lower SpO_2 values post-extubation (96% vs 98%); higher leukocytosis (12800 vs 9100 WBCs per microliter), inhalational opium overdose (46% vs 21%), neuromuscular blockade with atracurium (24.0% vs 5.7%), rhabdomyolysis (12.0% vs 3.8%), ventilator associated pneumonia (VAP; 64.0% vs 26.6%), higher rapid shallow breathing index (87.0 vs 70.0), gastrointestinal bleeding (12.0% vs 2.8%), temperature above 38.5º Celsius (84.0% vs 54.3%), tachypnea above 20/min (20.0% vs 6.6%), tachycardia above 90 beats/min (32.0% vs 14.3%), intubation time in the morning (50.0% vs 32.0%), not enough nursing care (21.0% vs 3.0%), more tube occlusion (one vs. 0), transferred cases (21.0% vs 3.0%), and bacterial growths in trachea (62.5% vs 36.2%). The odds of mortality in the re-intubated patients were 60% higher than those who did not undergo reintubation (37.5% vs 0; or, 1.6; Interquartile Range (IQR): 1.2, 2.2; P<0.001).

Table 2. Selected variables in two groups of extubated and re-intubated patients

Variables		No. (%)/[IQR](Min-Max)		P	OR (95% CI)	No. (%)/[IQR](Min-Max)		P	OR(95% CI)
		Planned Extubation (n=109)	Unplanned Extubation (n=20)			Re-Intubation (n=24)	No Re-Intubation (n=105)		
Median	Age	32 [25, 46] (15, 75)	25 [25, 34] (13, 84)	0.026*		30 [22, 44] (13, 65)	30 [24, 41] (13, 84)	0.865*	
	RSBI	77 [60, 80] (28, 100)	N/A	N/A		87 [77, 100] (60, 100)	70 [60, 80] (28, 95)	0.001*	
	SpO_2 post extubation	97 [96, 98] (78,100)	96 [94, 99] (66, 100)	0.971*		96 [92, 98](66, 99)	98 [96, 98] (78, 100)	0.015*	
	Hospital stay post extubation	5 [2, 7] (1, 40)	2 [1, 6] (1, 23)	0.022*		3.5 [1, 8] (1, 23)	5 [2, 7] (1, 40)	0.562*	
	Hgb	11.8 [10.5, 13.3] (7.2, 16.6)	12.5 [9.8, 13.7] (7.2, 17.5)	0.646*		11.4 [9.1, 12.5] (7.2, 15.3)	12.2 [10.6, 13.6] (7.2, 17.5)	0.045*	
	ALT	33 [17, 55] (10, 2177)	35 [21, 54] (12, 221)	0.70*		33 [17, 55] (10, 2177)	41 [33, 68] (12, 362)	0.049*	
	Seizure	7(6.4)	4(20)	0.046‡	3.643 (0.957, 13.867)	3(12)	8(7.6)	0.440‡	1.7 (0.4, 7.1)
	Suicide	4(3.66)	1(5)	0.808‡	1.382 (0.146, 13.044)	3(12)	2(2)	0.066‡	7.357 (1.157, 46.777)
	Gastric washing	8(7.4)	5(25)	0.031‡	4.208 (1.215, 14.572)	3(12)	10(9.5)	0.662‡	1.357 (0.343, 5.62)
Pain relief (Pre-intubation)	Etomidate	66(60.5)	6(30)	0.011†	0.279 (0.100, 0.783)	10(40)	62(59)	0.122†	.495 (0.201, 1.218)
	Midazolam	74(67.9)	13(65)	0.800†	0.878 (0.322, 2.395)	17(70)	70(66.6)	0.694†	1.214 (0.461, 3.201)
	Propofol	5(4.6)	0	0.329‡	0.954 (0.916, 0.994)	0	5(20.8)	0.276‡	0.806 (0.740, 0.879)
Blockage pre-intubation	Succinylcholine	4(3.6)	0	0.384‡	0.963 (0.929,.999)	1(4)	3(2.85)	0.738‡	1.478 (0.147, 14.862)
	Atracurium	6(5.5)	6(30)	0.001†	7.357 (2.083, 25.984)	6(24)	6(5.71)	0.003†	5.500 (1.595, 18.968)
Complications during hospitalization	Rhabdomyolysis	2(1.8)	2(10)	0.053‡	5.944 (0.787, 44.926)	3(13)	1(0.95)	0.003‡	14.9 (1.5, 149.9)
	Brain Injury	4(3.67)	3(15)	0.040‡	4.632 (0.952, 22.540)	3(12)	4(3.8)	0.090‡	3.607 (0.751, 17.321)
	Aspiration Pneumonia	70(64)	13(65)	0.947†	1.035 (0.381, 2.809)	19(76)	64(60.95)	0.093†	2.434 (0.843, 7.028)
	VAP	38(34.9)	6(30)	0.673†	0.801 (0.285, 2.253)	16(64)	28(26.6)	0.001†	5.500 (2.122, 14.258)
	Gastrointestinal bleeding	4(3.67)	2(10)	0.217‡	2.917 (0.497, 17.115)	3(12)	3(2.85)	0.044‡	4.857 (0.916, 25.745)
Intubation Shift	Morning	37(33.9)	9(45)			12(50)	34(32)		
	Afternoon	34(31)	5(25)	0.634†		8(33.3)	31(29.5)	0.109†	
	Night	38(34.9)	6(30)			4(16.6)	40(38)		
Extubation Shift	Morning	90(82.5)	7(35)			15(62.5)	82(78)		
	Afternoon	13(11.9)	6(30)	0.001†		7(29)	12(11.5)	0.366†	
	Night	6(5.5)	7(35)			2(8.2)	11(10.5)		

Variables		No. (%)/[IQR](Min-Max) Planned Extubation (n=109)	No. (%)/[IQR](Min-Max) Unplanned Extubation (n=20)	P	OR (95% CI)	No. (%)/[IQR](Min-Max) Re-Intubation (n=24)	No. (%)/[IQR](Min-Max) No Re-Intubation (n=105)	P	OR(95% CI)
Cause of Unplanned Extubation,	Not enough sedation	4(3.7)	9(45)	0.001‡	21.477 (5.672, 81.332)	4(16.7)	9(8.6)	0.235‡	2.133 (0.598, 7.616)
	Insufficient nursing care	2(1.8)	6(30)	0.001‡	22.929 (4.212, 124.819)	5(21)	3(3)	0.001‡	8.947 (1.97, 40.62)
	Withdrawal syndrome	0	1(5)	0.02‡	0.148 (0.098,.225)	1	0	0.36‡	0.180 (0.124, 0.260)
	Agitation	5(4.6)	12(60)	0.001†	31 (8.8, 110.8)	4(16.7)	13(12.4)	0.575†	1.415 (0.418, 4.797)
	In-hospital transfer	3(2.75)	5(25)	0.001‡	11.778 (2.550, 54.396)	5(21)	3(3)	0.001‡	8.947 (1.971, 40.62)
	Not restraining	4(3.7)	6(30)	0.001‡	11.250 (2.823, 44.834)	2(8.3)	8(7.6)	0.906‡	1.102 (219, 5.554)
Bacterial growths and death in two groups	Trachea	46(42.2)	7(35)	0.547†	0.737 (0.273, 1.993)	15(62.5)	38(36.2)	0.018†	2.939 (1.174, 7.354)
	Urine	5(4.6)	3(15)	0.076‡	3.671 (0.802, 16.790)	2	6(5.7)	0.631	1.500 (0.284, 7.934)
	Death	6(5.5)	3(15)	0.125‡	3.029 (0.691, 13.279)	9(37.5)	0	0.001	1.6 (1.174,2.181)

N/A: Not Applicable; ALT: Alanine Transaminase, RSBI: Rapid Shallow Breathing Index, VAP: Ventilator Associated Pneumonia; *Mann-Whitney U test; †Pearson's Chi-square, ‡Fisher's exact test

Discussion

The results of this study demonstrated that pulmonary complications were among the most frequent reasons for re-intubation in the opioid overdose patients. Bacterial growth in the trachea, leukocytosis, VAP, tachypnea, and fever were the main factors accounting for the correlation between the respiratory problems and unplanned extubation or re-intubation. Thus, it is evident that despite short-term intubation, respiratory complications may still occur after the intubation procedure in patients with opioid poisoning.

In a study conducted by Megarbane et al. [1] in intubated patients with acute poisoning, the median intubation time was 24hr (13–52hr). Unplanned self-extubation occurred in 27% of the cases, post-extubation laryngeal dyspnea in 9%, with mandatory reintubation in 2%. Over the 24hr period following extubation, complaints of dysphonia (59%), pharyngeal pain (57%), dysphagia (44%), and dyspnea (18%) were reported often [1]. However, it should be kept in mind that some of our patients developed sequelae and underwent tracheostomy, suggesting that our patients had more severe poisoning than those in the results reported by Megarbane et al. [1]. This may explain the higher rates of re-intubations and respiratory complications that occurred at our setting, although the quality of nursing care could be considered as the contributing factor.

The significance of nursing care & shifts: Consistent with our results, previous studies have indicated that the quality of nursing care could be one of the possible causes of unplanned extubation [12, 13]. Although our patients were extubated by senior physicians (attending physicians or fellows), higher prevalence of re-intubation that occurred on evening and night shifts suggests that a shortage of nursing care could account for inadequate care, hence the reason for re-intubation in these patients [14]. This further suggests that patients' extubation at our hospital should be performed during the morning shifts when the nursing care is more readily available.

Administration of adequate sedatives and physical restraint have been shown as the important factors for the prevention of self or unplanned extubation in previous studies [15, 16]. Although all of our patients were treated with multiple sedating medications and physical restraint was routinely practiced at our ICU, some of them managed to self-extubate. This may be explained by the high prevalence of opioid addiction in our patients, resulting in withdrawal and agitation and predisposing them to self-extubation. Mousavi et al. found that most unplanned extubations happened during the evening or night shifts or when shifts were staffed by nurses with less work experience and education, while 80% of the self-extubated patients were physically restrained [17]. Interestingly in the current study, the unplanned extubation cases had shorter hospital stays post-extubation compared to those with planned extubation. This may suggest that our delayed decision for extubation, less se-

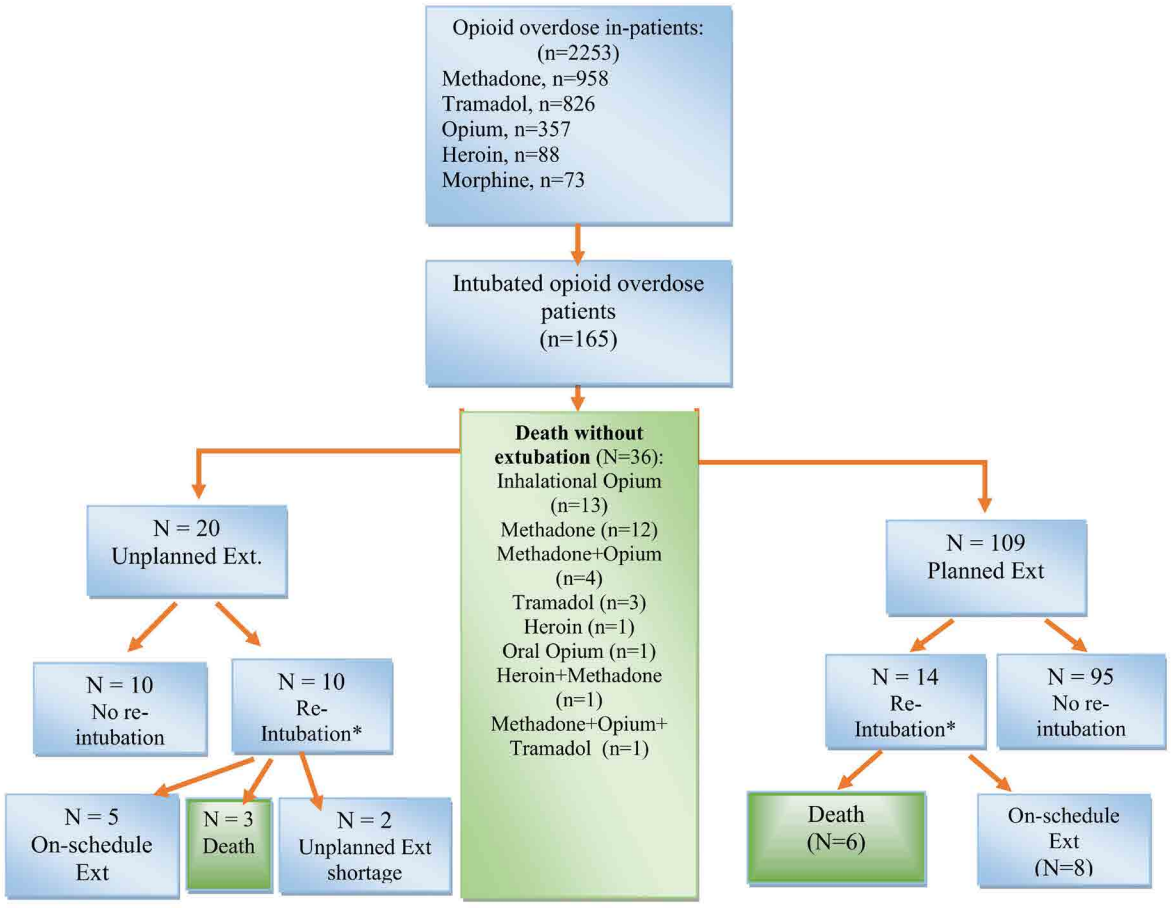

Figure 1. Diagram of the patients with opioid overdose, enrolled between Sept. 2019 and March 2020.

vere poisonings, or the young age of patients might be responsible for self-extubation. Also, the findings may suggest that in settings similar to ours, and in patients with high risk of opioid dependence and withdrawal, significantly higher doses of sedatives are needed to keep them free of agitation and withdrawal symptoms. However, we did not evaluate the severity of withdrawal symptoms in our patients by using the Clinical Opioid Withdrawal Scale (COWS). Thus, it is not possible to comment on the potential causes of withdrawal symptoms, which is a major limitation of the current study.

We observed significant differences between the planned vs. unplanned extubation groups regarding their Blood Urea Nitrogen (BUN) and creatinine, and the serum magnesium, calcium, and sodium. This may be due to the fact that many poisoned patients are receiving sodium bicarbonate to alleviate their rhabdomyolysis symptoms. These patients may experience electrolyte disturbances, which complicate their extubation, although most of them were young and otherwise healthy individuals who were intubated for short periods only. Rhabdomyolysis is found to be more prevalent in patients with opioid poisoning than in non-opioid cases, which may explain the high rates of withdrawal symptoms in the former group [18-20].

The RSBI is the ratio of respiratory frequency to tidal volume (f/VT), i.e., an RSBI less than 105 breath/minute/L indicates that a patient is likely to fail weaning while a patient with an RSBI greater than 105 breath/minute/L is likely to be weaned successfully [11]. However, in some studies, it has been suggested that a cut-off point, ranging from 76.5 to 80 breaths/min/L, provides a reasonable predictive value in special populations [21-23]. Our cases of successful extubation were consistent with the suggested cut-off range. Although patients with opioid poisoning regain their consciousness as soon as the opioid is excreted from the body and tend to have shorter intubation duration compared to general ICU patients, Rapid Shallow Breathing Index (RSBI) test is still useful in similar populations, considering the high rates of infection that occurred in our intubated patients [24, 25]. However, some studies have challenged the efficacy of these tests even in general ICU patients who are going to be weaned and subsequently extubated [25, 26].

Multivariate analyses have shown that using succinylcholine may independently increase the risk of re-intubation. This drug may paralyze the diaphragm and prolong the intubation period, causing more respiratory complications [26]. Not surprisingly, aspiration pneumonia was a risk factor for re-intubation in our sample. Insufficient nursing care was another independent risk factor which led to early unplanned extubation and further re-intubation. Consistent with the findings of the study conducted by Eskandar, et al. [22], the results of the current study indicated that the risk of death was higher in the patients who underwent reintubation.

Conclusions

In the ICUs specialized in caring for patients suffering from poisoning, increased duration of intubation and/or mechanical ventilation, and re-intubation are complications of unplanned extubation. Based on the finding of the current study, the RSBI and cuff tests are not acceptable tests to determine which patient may be a good candidate for weaning and extubation. These patients are usually more likely to be drug-dependent and; therefore, routine sedation doses administered to them may not be adequate. Infection control and sufficient nursing care are factors that result in desirable clinical outcomes after extubation and prevent unplanned extubation in patients with opioid poisoning. Patients' transfer and agitation may accompany unplanned extubation. Therefore, providing adequate nursing care during transfer is highly important. Also, the night shift is an important risk factor for unplanned extubation, because of the inadequate observation and insufficient healthcare practitioners' presence compared to the morning shifts when nursing care is readily available. The mortality rate significantly increases in the patients who undergo reintubation due to prolonged ventilation, aspiration pneumonia and damage to other organs.

This is the first study to specifically follow up on hospitalized patients with opioid poisoning, with a focus on failures of extubation protocol. There were several potential limitations in our study. No systematic long-term follow-up, i.e., post-hospitalization, was feasible in our patient population. Examinations of ear, nose and throat were not performed by specialists to identify possible vocal cord injuries. The findings of our study also require replication at another multicenter setting.

Future studies should investigate if the administration of higher doses of sedative or even re-initiation of the patients' own therapeutic regimen, e.g. methadone, may help avoid agitation and self-extubation in patients with opioid overdose.

Ethical Considerations

Compliance with ethical guidelines

The study was approved by the Ethics Committee for Medical Research at Shahid Beheshti University of Medical Sciences, Tehran, Iran, and was issued the following approval (Code: IR.SBMU.RETECH.REC.1398.356). Written and oral information about the study purpose and protocol were shared with the patients and their families

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Authors' contributions

Conceived the study, and participated in its design, data collection, and coordination: Peyman Erfantalab Evini and Ghafar Ali Mahmoudi; Participated in data interpretation: Shahin Shadnia and Mitra Rahimi; Helped to draft the manuscript: Nasim Zamani and Hossein Hassanian-Moghaddam; Participated in data analysis, data interpretation, and statistical analysis and helped to draft the manuscript: Rebecca McDonald; Read and approved the final manuscript: All authors.

Conflict of interest

The authors declared no conflict of interest.

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