Central Nervous System Depressants Poisoning and Ventilator Associated Pneumonia: An Underrated Risk Factor at the Toxicological Intensive Care Unit

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Abstract

Background: Ventilator-Associated Pneumonia (VAP) is the main cause of nosocomial infection at intensive care units (ICUs), which causes high mortality and morbidity.

Objectives: The objective of the present survey was to identify the VAP risk and prognostic factors among poisoned patients, who were admitted to the toxicological ICU (TICU), especially central nervous system (CNS) depressants due to their prevalence and importance.

Patients and Methods: A case-control study was conducted at the Loghman Hakim hospital between March 2013 and March 2014. Among 300 poisoned patients with mechanical ventilator ≥ 48 hours, 150 patients, who had developed microbiologically-confirmed VAP were considered as the VAP group and 150 without VAP were defined as the control group. The following data were collected; age, gender, type of poisoning, glasgow coma score, Acute physiology and chronic health evaluation (APACHE) II score, length of hospital stay, previous antibiotic use, microbial culture of the trachea, body temperature, leukocyte count, and patients' outcome. Based on the type of poisoning, patients were divided into three groups including: opioid, CNS depressants and others. All data were expressed as means (SD) for continuous variables and frequencies for categorical variables. Logistic regression was used to determine the relationship between risk factors and VAP.

Results: The mean age of the patients was 33.9 ± 14.3 years. The probable VAP incidence and mortality were 22% and 18.6%, respectively. The rate of CNS depressant versus opioid use (odds ratio, 3.74; P < 0.027), APACHE II (odds ratio, 1.28; P < 0.000) and length of hospital stay (odds ratio, 2.15; P < 0.000) were the independent risk factors for VAP. While, the APACHE II score (odds ratio, 1.12; P < 0.044) and length of hospital stay (odds ratio, 2.15; P < 0.000) were the independent predictors of VAP mortality among these patients. The most common microorganisms in VAP cases were Methicillin-Resistant *Staphylococcus aureus* (MRSA) and *Acinetobacter* sp. (56.7% and 12.7%, respectively).

Conclusions: Central nervous system depressant was an important risk factor for VAP among poisoned patients. Hypoventilation due to CNS depression can lead to VAP. The APACHE II and length of hospital stay were shown as independent predictors of VAP and mortality among these patients.

Keywords: Intensive Care Unit, Risk Factors, Ventilator-Associated, Pneumonia, Toxicity

1. Background

Ventilator-associated pneumonia (VAP) as the main cause of nosocomial infections occurs in intensive care unit (ICUs) patients with mechanical ventilation (MV), and results in high mortality and morbidity rates as well as high costs of health care (1). It seems that VAP and hospital-associated pneumonia (HAP) are the reason for sixty percent of deaths in nosocomial-infected patients. More precisely, it has been estimated that hospital mortality rates due to HAP and VAP vary from 20% to 70% based on the definition, study population, and the type of hospi-

tal or ICU (2). According to the literature, the general rate of VAP is 13.6 per 1000 ventilator days (3). Every year, millions of people suffer from poisoning and mortality due to poisoning, which has dramatically increased within the recent years (4). The occurrence of VAP increases the length of hospital stay, life-threatening complications and death due to poisoned patients (5).

Hassanian-Moghaddam et al. evaluated 108265 patients in six years and reported that anti-convulsive and sedative-hypnotics (22.3%) were the most frequent medica-

tions responsible for poisoning, while pesticides and narcotics were the most common causes of mortality with 24.84% and 24.75% rates of mortality, respectively (6).

Various study designs and statistical techniques were used for identifying the specific risk factors predisposing critically ill patients to develop VAP. Accordingly, the risk of VAP increased with several host and treatment factors (7-10). Treatment-related risk factors include male gender, underlying respiratory disease, multiple-organ failure, Acquired Immune Deficiency Syndrome (AIDS), head injury, coma, neurosurgery, monitoring of intracranial pressure, re-intubation, or transportation out of the ICU. Modifiable patient-related risk factors include the flat head of the bed, prior antibiotic exposure and aspiration occurrence before intubation (7-9). Severely poisoned patients frequently require ICU admission and MV, therefore are at the risk for developing VAP (10). Central nervous system (CNS) depression occurs due to poisoning with sedative-hypnotics. In most instances, CNS depression and respiratory depression occurin parallel. However, not all CNS depressants cause significant hypoventilation (11). There are nostudies related to the type of poisoning as a risk factor of VAP.

Some clinical and biological parameters are different between survivors and non-survivors or patients with or without VAP recurrence, yet they do not have predictive values for determination of the outcome. The search continues for reliable predictive markers that can distinguish the patients who will have favorable outcomes. Timely identification of the patients at high risk of death or VAP recurrence may give an opportunity to change the treatment plan to improve the outcome (12).

2. Objectives

The objective of the present study was to identify the VAP risk and prognostic factors among poisoned patients, who were admitted to the Toxicological ICU (TICU), especially regarding CNS depressants due to their prevalence and importance.

3. Patients and Methods

3.1. Patients and Study Design

This case-control study was approved by the ethics committee of Shahid Beheshti University of Medical Sciences (code number 1393-1-91-13108). The study was conducted at Loghman Hakim hospital poison center (LHHPC) with l6 toxicological ICU beds, over a period of 12 months from March 2013 to March 2014. The studied hospital is a unique tertiary care teaching and referral poison treatment center in the capital city of Iran (Tehran) with an average of 25000 hospitalized and outpatients, annually.

Those with severe immune-suppression or suspicion of respiratory infection on admission were excluded (n = 39). Also, poisoning and intubation and mechanical ventilation for ≥ 48 hours at the TICU were the inclusion criteria. Among the 675 consecutive, ≥ 48 hours intubated and mechanically ventilated, TICU patients, all 150 cases,who developed microbiologically-confirmed VAP were considered as theVAP group. For each simultaneous VAP diagnosed case, one control patient without VAP was selected randomly from the rest of the patients at the same time (n = 150). Thus, each case and control patient were selected simultaneously.

The acute physiology and chronic health evaluation (APACHE) II score was calculated on the first day of admission to the ICU for all patients (13). All patients received intravenous 40-mg daily dose of pantoprazole (pantozol) for stress ulcer prophylaxis.

3.2. Diagnosis of Pneumonia

Pneumonia diagnosis was based on new or progressive chest radiography infiltrations with at least two of the following criteria:

1) Temperature higher than 38°C or lower than 35°C;
2) Leukocyte count higher than 10000/μL or lower than 4000/μL;
3) New purulent respiratory secretion or any changes in the sputum;
4) Positive blood or pleural effusion cultures;
5) Detection of rales or dullness on chest examination, and/or
6) at least 10% decrease in arterial PO_2 (14).

Non-protected endo tracheal aspiration (NPEA) was obtained for each patient with a suction catheter adapted to a mucus collector without saline instillation, before initiation of the antimicrobial treatment. The diagnostic threshold for NPEA was at least 10^5 colony-forming units/mL. In addition, a positive tracheal aspirate culture was required to confirm the diagnosis of VAP. Two samples of blood culture were collected from different veins with a 15-minute interval.

3.3. Data Collection

A self-made questionnaire was filled for every patient by a trained TICU nurse. The data collected included age, gender, type of poisoning, mental status by the glasgow coma scale (GCS) (15), acute physiology and chronic health evaluation (APACHE) II score (13), length of hospital stay, underlying diseases, previous antibiotic use, microbial culture of the trachea, antimicrobial treatments performed for VAP and their duration, chest X-ray (CXR), body temperature, leukocyte count (using the Sys mex KX-21 N Automated Hematology analyzer at the Loghman hospital laboratory) and patients' outcome (survivor versus non-survivor). Based on the type of poisoning, patients were divided in three groups that included opioid (opium, heroin and methadone), CNS depressants (antidepressant, benzodiazepine and anti-convulsive) and other such as pesticide, methanol, 3, 4-Methylenedioxy-Methamphetamine (MDMA) and multi drugs.

3.4. Statistical Analysis

All data were expressed as means (plus standard deviation) for continuous variables and frequencies (percent) for categorical variables. Normality assumption was checked visually by using normal plots and using the Kolmogorov Smirnov normality test for continuous variables.

Logistic regression was used to determine the relationship between risk factors and VAP. Crude odd ratios and their 95% confidence intervals were first determined. The multivariate model was then used by a stepwise method in logistic regression with age and gender forced into the model. P-values of less than 0.05 were considered statistically significant. The statistical analysis was performed by the SPSS software (version 16, Chicago, IL, USA).

4. Results

Among 675 patients, 150 cases of VAP were documented in the study period, representing a probable VAP incidence of 22% (per ventilated patient $\geq$ 48 hours/ICU admitted patients). The mean age of the 300 eligible patients was 33.9 ± 14.3 years and 203 patients (67.6%) were male. In the VAP group, CNS depressants were the most common cause of poisoning (Table 1). The mortality rate of the control group was 17.2%, which was not different from the case group (18.6 %) (P > 0.05). History of antibiotic consumption was significantly higher in the VAP patients (Case/Control = 42/9).

4.1. Risk Factors for Ventilator-Associated Pneumonia

The characteristics of the study population (case and control) and crude odds ratio are shown in We We found significant risk associated with age, APACHE I, length of hospital stay, previous antibiotic use and type of poisoning in the univariate analysis.

As shown in Table 2, applying the multivariate analysis for the risk factors, revealed that APACHE II, length of hospital stay and type of poisoning were significant predictors of pneumonia with odds ratios ranging from 1.28 to 3.74.

Table 1. Characteristics of the Study Population (Case and Control) and Crude Odds Ratio

Variables	Cases (n = 150)	Control (n = 150)	Crude OR	CI (95%)	P Value
Age, mean (SD)	36.55 (14.47)	31.40 (13.77)	1.02	1.01 - 1.04	< 0.0001
APACHE II, mean (SD)	17.70 (3.81)	13.16 (5.13)	1.28	1.19 - 1.37	< 0.0001
Length of hospital stay, mean (SD)	14.07 (11.33)	3.24 (1.59)	2.95	2.23 - 3.89	< 0.0001
Gender (male), No. (%)	112 (74.7)	91 (60.7)	1.23	0.93 - 1.63	0.141
Previous antibiotics, No. (%)	42 (28)	9 (6)	0.21	0.04 - 0.26	< 0.0001
Glasgow coma score, No. (%)					
11 - 15	43 (28.7)	46 (30.7)	1	NA	NA
6 - 10	81 (54)	85 (56.7)	1.15	0.69 - 1.92	0.560
3 - 5	26 (17.3)	19 (12.7)	1.92	0.92 - 4.05	0.084
Type of poisoning, No. (%)					
Others[a]	25 (16.7)	65 (43.4)	1	NA	NA
Opioid[a]	51 (34)	41 (27.3)	2.23	1.74 - 5.99	< 0.0001
CNS depressants[a]	74 (49.3)	44 (29.3)	3.37	2.41 - 7.91	< 0.0001

Abbreviation: NA, not available.
[a]Pesticide, Methanol, 3, 4-Methylenedioxy-Methamphetamine (MDMA) and multi drugs; Opium, heroin and methadone; Antidepressant, Benzodiazepine and anti-convulsive.

Table 2. Risk Factors for the Development of Ventilator-Associated Pneumonia in Poisoned Patients (Multivariate Logistic Regression)[a]

Variables	Odds Ratio	95% Confidence Interval	P Value
APACHE II	1.28	1.11 - 1.46	< 0.0001
Length of hospital stay	2.15	1.27 - 3.37	< 0.0001
Type of poisoning			
Opioid	1	NA	NA
CNS depressants	3.74	1.16 - 6.02	0.027
Others	0.70	0.15 - 2.11	0.639

Abbreviation: NA, not available.
[a]The model was adjusted with age and gender.

4.2. Microbiological Results

Microbiological evaluation results of the respiratory sample (tracheobronchial aspirate) in the VAP group are shown in Table 3. Overall, the most frequent pathogens causing pneumonia were Methicillin-resistant *Staphylococcus aureus* (56.7%) and *Acinetobacter* spp. (12.7%). In those who had died, MRSA (39.29%), *Acinetobacter* sp. (21.43%) and *Pseudomonas aeruginosa* (21.43%) were the most frequent pathogens while in the survivors, MRSA accounted for 60.6% of the pathogens followed by *Klebsiella* and *Acinetobacter* spp. There was no association between the pathogens and previously used antibiotics (P = 0.9).

Blood culture was positive in 18 (14.8%) and 4 (14.3%) sur-vivors and non-survivors, respectively (P = 0.9). Furthermore, MRSA was positive in 95.5% of blood cultures in VAP cases. Urine culture was positive in 13 (10.7%) and 5 (17.9%) survivors and non-survivors, respectively (P = 0.2).

4.3. Predictors of Intensive Care Unit Mortality Among Patients With Ventilator Associated Pneumonia

Regarding mortality events, as shown in Tables 4 and 5, we found that APACHE II and length of hospital stay had a significant effect on the ICU mortality in both univariate and multivariate analysis, with odds ratio of 1.13 (P = 0.026) and 1.31 (P = 0.034), respectively.

Table 3. Microbiological Identification in 150 Patients With Ventilator-Associated Pneumonia[a]

Microorganisms	Survivors (n = 122)	Non-Survivors (n = 28)	Total (n = 150)	P Value
MRSA	74 (60.7)	11 (39.3)	85 (56.7)	0.012
MSSA	1 (0.8)	0	1 (0.7)	0.012
Pseudomonas aeruginosa	9 (7.4)	6 (21.4)	15 (10)	0.012
Klebsiella pneumoniae	17 (13.9)	1 (3.6)	18 (12)	0.012
Acinetobacter sp.	13 (10.7)	6 (21.4)	19 (12.7)	0.012
Escherichia coli	2 (1.6)	3 (10.7)	5 (3.3)	0.012
polymicrobial	6 (4.9)	1 (3.6)	7 (4.7)	0.012

Abbreviations: MRSA, Methicillin resistant *Staphylococus aureus*; MSSA, Methicillin sensitive *Staphylococus aureus*.
[a]Values are expressed as No. (%).

Table 4. Characteristics of Survivors and Non-Survivors in the Ventilator-Associated Pneumonia Group and Their Crude Odds Ratio

Variables	Survivors (n = 122)	Non Survivors (n = 28)	Crude OR	CI (95%)	P Value
Age, mean (SD)	35.94 (14.01)	39.21 (15.60)	1.02	0.98 - 1.04	0.282
APACHE II, mean (SD)	17.36 (3.62)	19.21 (4.31)	1.12	1.02 - 1.25	0.023
Length of hospital stay, mean (SD)	12.99 (9.68)	18.78 (16.14)	1.03	1.01 - 1.07	0.021
Length of antibiotic treatment, mean (SD)	7.04 (3.77)	8.42 (4.87)	1.08	0.98 - 1.18	0.105
Temperature, mean (SD)	38.05 (0.59)	38.27 (0.75)	1.74	0.91 - 3.36	0.095
Leukocyte count, mean (SD)	11725 (3870)	12414 (3691)	1.01	0.99 - 1.03	0.391
Gender (men), No. (%)	89 (73)	23 (82.1)	1.70	0.59 - 4.85	0.317
Previous antibiotics, No. (%)	32 (26.2)	10 (35.7)	0.64	0.26 - 1.53	0.316
Glasgow coma score, No. (%)					
11 - 15	35 (28.7)	8 (28.6)	1	NA	NA
6 - 10	67 (54.9)	14 (50)	0.91	0.35 - 2.38	0.855
3 - 5	20 (16.4)	6 (21.4)	1.31	0.39 - 4.32	0.655
Type of poisoning, No. (%)					
Others[a]	21 (17.21)	5 (17.86)	1	NA	NA
Opioid[a]	37 (30.32)	13 (46.43)	1.00	0.31 - 2.99	0.964
CNS depressants[a]	64 (52.47)	10 (35.8)	0.51	0.16 - 1.53	0.224

Abbreviation: NA, not available.
[a]Pesticide, methanol, 3, 4-methylenedioxy-methamphetamine (MDMA) and multi drugs; Opium, heroin and methadone; CNS depressants, antidepressant, benzodiazepine and anti-convulsive.

Table 5. Prognostic Factors for Mortality Among Patients With Ventilator-Associated Pneumonia (Multivariate Logistic Regression)[a]

Variables	Odds Ratio	95% Confidence Interval	P Value
APACHE II	1.13	1.01 - 1.25	0.026
Length of hospital stay	1.31	1.01 - 1.08	0.034

[a]The model was adjusted with age and gender.

5. Discussion

In the present study, CNS depressants, APACHE II and prolonged length of hospital stay were identified as independent risk factors for VAP development. Among these, CNS depressants was the most important risk factor, which increased the risk of VAP 3.7 folds higher than opioid. Also, we adjusted for gender and age in the models. There was no similar finding in the literature review about CNS depressant as a risk factor of VAP, yet it is obvious that CNS depressants have an effect on respiratory depression (11). Some CNS depressants such as clozapine may induce aspiration pneumonia as one of the side effects (16).

Also, acute respiratory failure is known as a frequent problem of drug abuse. It is more likely to develop in the setting of chronic lung disease or in those with limited respiratory reserve. Wilson KC and Saukkonen JJ reported that drug-related respiratory failure, when due to CNS depression alone, may be predictable, but in patients with drug-related significant pulmonary pathology, a course of illness may be predictable (17).

Previous studies have demonstrated similar results in accordance with the duration of hospitalization (18-21). The study of Lahoorpour et al. showed that mechanical ventilation, antibiotic exposure, duration of hospitalization, and fever were significant independent VAP risk factors (18). Afjeh et al. reported that endotracheal tube repositioning was an independent risk factor for VAP in adult ICU patients (19). These results are in accordance with Broughton et al. study in which fever and length of hospital stay were related to acquisition of VAP, and Baran et al. study which noted that nosocomial infections were associated with length of hospital stay (20, 21).

Pesticides were the most common cause of poisoning among other drugs of control patients. It is important to note that some toxicities, such as pesticide poisoning does not have prolonged hospital stays yet accompanies a high mortality rate for its severity (22). In the study of Hassanian-Moghaddam et al. pesticides were the most common cause of death (24.84%) (6).

In the present study, the probable incidence and mortality rate were 22% and 18.6 % at the TICU, respectively. This is while in our previous study the incidence was 8% (2007 - 2008) suggesting an increasing trend of VAP incidence in TICU.

The mortality rate of VAP has also increased slightly compared to our last study, while it is still lower than that reported by most previously published articles sug-gesting 32.1%, 48.33% and 47.3% rates (2, 10, 23, 24). It seems that the young age of our patients as well as their short hospital stay had caused such differences.

The role of systematic antibiotics in the development of VAP is not well known. We found that history of antibiotic consumption was significantly higher in VAP patients. Likewise, the study of Kollef MH indicated that previous antibiotic therapy had an adjusted OR of 3.1 (95% CI, 1.4 - 6.9) for development of VAP. On the contrary, prior antibiotic exposure was protective for VAP in another study (7, 8).

In our study, male gender was predominant in the VAP group but not significant, a finding that is in accordance with the previous literature (8, 25). Mean age and APACHE II scores of the VAP group were higher than the controls. In comparison to other studies, our patients were younger but had higher APACHE II scores (26, 27).

The most frequently involved pathogens were MRSA and Acinetobacter spp. Association of *S. aureus* with poisoning was previously described; however, the notable change during seven years in our ICU was that the sensitive *S. aureus* (58.7%) has been resisted and replaced by MRSA (60.7%) (10, 28). Mgahed et al. reported that MRSA and MSSA species were the most prevailing organisms in the pathogenesis and accounted for about 41.6% and 25% of the infections, respectively (29). In the present study, there was no association between the type of pathogens and previous use of antibiotics. However, antibiotic use was one of the major determinants of resistance.

We used pantozol as a stress ulcer prophylaxis, therefore we could not discriminate it as a predictor or a risk factor. Both H2-antagonists and antacids were considered as independent risk factors for VAP due to gastric colonization and aspiration by declining intragastric acidity and raising its volume (30).

In the present study, APACHE II and prolonged length of hospital stay were detected as prognostic factors for mortality among VAP patients. This is compatible with the study of Mgahed et al. in which one of the related factors with significant correlation to mortality rate of late onset pneumonia was severity of disease, using the APACHE score (29). Also they noted that the existence of pneumonia, inhalational injury, enlarged burn size, and old age were related with increased mortality (30). Furthermore, hypoxemia, hypercapnia and acidosis were reported as significant predictors of mortality among burn patients with pneumonia (29). There was no similar study on out-

comes of patient with VAP and poisoning. Smoking, cardiac disease, and total body surface area were reported as remarkable prognostic variables in pneumonic burn patients as reported by Germann et al. (31). An American survey considered chronic obstructive pulmonary disease (COPD) as one of the risk and prognostic factors of nosocomial pneumonia in mechanically-ventilated burnt patients; however, in our study only one patient had COPD beside his young age (32).

It seems that this is the first study that worked on the association between poisoning and VAP risk factors and since Loghman Hakim hospital is a unique referral poison center (TICU), our samples may be representative of the Iranian population. On the other hand, there were two limitations in our study. Firstly, because many types of poisoning could not be assessed as risk factors of VAP, therefore we categorized them in three groups: opioid, CNS depressants and others. Secondly, there were some predictable variables, which we did not mention and may have to be justified.

In conclusion, CNS depressant was an important risk factor for VAP among poisoned patients. Hypoventilation due to CNS depression can lead to VAP. The APACHE II and length of hospital stay were shown as independent predictors of VAP and mortality among these patients. Consequently, more studies are suggested to expand knowledge on the association between VAP and poisoning.

Acknowledgments

Footnotes

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