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Clinical significance of ventilator-associated event☆,☆☆

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ABSTRACT

Purpose: A novel surveillance algorithm of ventilator-associated event (VAE) was introduced to overcome the subjectivity of conventional ventilator-associated pneumonia. We investigated the risk factors and prognostic values of VAE.

Methods: We conducted a retrospective study of 869 patients treated with mechanical ventilation for greater than or equal to 2 calendar days from January 2013 to June 2014. We compared the episodes of mechanical ventilation with or without VAE and analyzed risk factors and clinical outcomes of VAE.

Results: Among 1031 episodes of mechanical ventilation, 92 episodes were complicated with VAE. VAE occurred more frequently when the initial causes of mechanical ventilation were trauma (odds ratio [OR], 2.7; 95% confidence interval [CI], 1.1-6.3) and pulmonary edema (OR, 2.4; 95% CI, 1.2-4.7). VAE was significantly associated with prolonged mechanical ventilation (5 vs 12 days; $P < .001$), reduced rate of successful extubation (50.1% vs 17.5%; $P < .001$), and increased 30-day mortality (35.6% vs 74.2%; $P < .001$). VAE was a significant risk factor of 30-day mortality on multivariate regression analysis (OR, 3.6; 95% CI, 2.0-6.6; $P < .001$).

Conclusions: Patients treated with mechanical ventilation due to pulmonary edema or trauma had increased risk of VAE, with its development indicative of adverse clinical outcomes.

1. Introduction

Respiratory insufficiency is the leading cause of intensive care unit (ICU) admission in adult patients, with more than one third of critically ill patients requiring mechanical ventilation. Hence, appropriate management of mechanically ventilated patients is important to improve patient prognosis in clinical practice and to evaluate the competence of each ICU [1]. Ventilator-associated pneumonia (VAP) is a major complication of critically ill patients who depend on mechanical ventilation. Internationally, the overall rate of VAP is 15.8 events per 1000 ventilator-days [2], and the occurrence of VAP increases as the duration of mechanical ventilation continues [3]. The mean durations of mechanical ventilation and ICU stay of patients with VAP are about twice those of patients without VAP. More hospitalization costs are involved for patients with VAP than patients without VAP [4]. Although there have been some debates, a recent study revealed that the overall attributable mortality of VAP reached up to 13% [5]. Because of its deleterious effects on ICU patient outcomes, several preventive and therapeutic strategies were developed and integrated as a VAP bundle approach. In spite of significant reduction of VAP after implementation of this bundle approach [6], there are still many problems. One of them is the difficulty to diagnose VAP.

Different diagnostic criteria for VAP exist due to the lack of a criterion standard. However, the degree of agreement for each criterion is poor [7], and the incidence, the time of diagnosis, and the mortality vary according to the selected criteria [8]. All previously well-known and conventional criteria for VAP include the presence of pneumonic infiltration on chest radiograph [9–12]. Despite the universal use of chest radiograph in ICU, it has low accuracy and reliability for VAP diagnosis. Therefore, the diagnosis of VAP is highly dependent on the choice of VAP criteria and the clinician's interpretation of chest radiographs. To overcome inaccuracy, subjectivity, and variation in the diagnosis of VAP, the Centers for Disease Control and Prevention developed a new surveillance algorithm of ventilator-associated event (VAE) in 2013 [13]. It uses numerical and objective parameters, such as fraction of inspired oxygen (F_{IO_2}) and positive end-expiratory pressure (PEEP), to detect oxygenation deterioration for patients on mechanical ventilation. These

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conditions encompass various complications related to mechanical ventilation besides pneumonia. Most importantly, chest radiographic findings are not included in the VAE system, in contrast to traditional VAP criteria.

There are 3 definition tiers within the VAE system. The first tier is ventilator-associated condition (VAC), which represents the worsening of oxygenation. It is defined by an increase in daily minimum PEEP of greater than or equal to 3 cm H_2O or FIO_2 of greater than or equal to 0.2, sustained for 2 or more calendar days, after 2 or more calendar days of stable or decreasing daily minimum PEEP or FIO_2. Daily minimum values must be maintained for at least 1 hour. The second tier is infection-related, ventilator-associated condition (IVAC), which represents concurrent infection within 2 calendar days before or after the onset of VAC. It requires change in temperature or white blood cell count: temperature greater than 38°C or less than 36°C or white blood cell count greater than or equal to 12 000 cells/mm^3 or less than or equal to 4000 cells/mm^3. In addition, a new antimicrobial agent should be started and continued for 4 or more days. The third tier is VAP, which represents the laboratory evidence of respiratory infection in the case of IVAC. Ventilator-associated pneumonia was classified to possible VAP (PoVAP) and probable VAP (PrVAP). Possible VAP required one of the following: purulent respiratory secretions or positive culture of respiratory specimen. Meanwhile, PrVAP required one of these following criteria: purulent respiratory secretions and positive culture of respiratory specimen, positive pleural fluid culture, positive lung histopathology, positive diagnostic test for *Legionella* or respiratory virus [14].

In 2015, the VAE system was modified, and PoVAP and PrVAP were replaced by possible VAP (PVAP). The VAE system made the objective assessment of quality of health care institutions possible, and more than 1500 hospitals in the United States currently use the VAE system [15]. The application of the VAE system is expected to expand due to its objectivity, comprehensiveness, and clinical significance. The authors investigated the incidence, risk factors, and prognostic values of VAE.

2. Methods

2.1. Study population and data collection

We conducted a retrospective observational study of mechanically ventilated patients admitted to the ICU of Korea University Guro Hospital, Seoul, Korea, from January 2013 to June 2014. There were 2 mixed ICUs with a total of 50 beds. Patients aged younger than 18 years or who were treated with mechanical ventilation for less than 2 consecutive calendar days were excluded. We reviewed the data of eligible patients, including baseline demographics (age, sex, underlying conditions, and severity index), primary causes of mechanical ventilation, formal chest radiograph readings, antibiotics history, microbiological data of respiratory specimens, and mechanical ventilation settings. The Charlson comorbidity score [16] and the Acute Physiology and Chronic Health Evaluation (APACHE) II score were used to represent underlying conditions and severity, respectively.

We identified the primary cause of mechanical ventilation in each episode. At first, primary causes were collected in detail. For example, if 2 patients needed mechanical ventilation due to loss of consciousness caused by subdural hemorrhage and epidural hemorrhage, each diagnosis was registered. Then, they were sorted as intracranial hemorrhage. Finally, intracranial hemorrhage and cerebral infarction were classified as central nervous system disorder. By this process, we listed 10 primary causes of mechanical ventilation (Table 1). The primary cause was decided by the consensus of 2 dedicated investigators in the vague case.

If bilateral opacity was documented in the formal chest radiograph readings, accompanied by positive fluid balance preceding 3 days without clear evidence of cardiac or renal failure, then mechanical ventilation was thought be caused by volume overload. If there were medical records concerning acute respiratory distress syndrome (ARDS); bilateral opacity in chest radiograph; and compatible values of PEEP, FIO_2, and arterial oxygen pressure, ARDS was considered as the primary cause of mechanical ventilation. Although we tried to differentiate volume overload and ARDS in patients showing bilateral opacity in chest radiographs, there was a wide gray zone. We considered both volume overload (hydrostatic pulmonary edema) and ARDS (permeability edema) as pulmonary edema in this study.

This study was approved by the Institutional Review Board (IRB) of the Korea University Guro Hospital (KUGH15096-001). Informed consent was waived by the IRB.

Table 1
Causes of mechanical ventilation

Primary causes	Detailed causes	n
CNS disorder	Mental change	29
	Intracranial hemorrhage	88
	Cerebrovascular accident	10
	Seizure	16
Cardiovascular disorder	Acute myocardial infarction	14
	Congestive heart failure	39
	Cardiac arrest of any cause	92
Respiratory disorder	COPD acute exacerbation	27
	Asthma acute exacerbation	2
	ILD acute exacerbation	8
	Aspiration	18
	Pulmonary embolism	8
	Hemoptysis	5
Sepsis	Respiratory sepsis	197
	Nonrespiratory sepsis	73
Gastrointestinal bleeding	Gastrointestinal bleeding	25
Renal disorder	Renal disorder	20
Trauma	Trauma	36
Postoperative care	Cardiac surgery	68
	Noncardiac surgery	104
Pulmonary edema	ARDS	17
	Volume overload	50
Others	Others	85

CNS indicates central nervous system; COPD, chronic obstructive pulmonary disease; ILD, interstitial lung disease.

2.2. Detection of VAE

We checked the parameters for each episode of mechanical ventilation, such as duration of certain mode, FIO_2 and PEEP, and entered them into the VAE calculator version 2.1, to verify the occurrence of VAC [17]. Ventilator-associated condition was additionally analyzed to detect IVAC and VAP. Our hospital grades the quality of respiratory secretion by the Murray-Washington method [18] and reports culture results qualitatively. Grade 5 or 6 and moderate or severe colony correspond to the purulent secretion and the positive culture results suggested by the VAE surveillance system, respectively [14]. We diagnosed PoVAP and PrVAP based on this relationship.

2.3. Outcome measures

In this study, we did not compare patient to patient, but episode to episode. An episode of mechanical ventilation is defined as a period of days during which the patient was on mechanical ventilation [14]. If a patient is free of mechanical ventilation for at least 1 full calendar day and then depends on mechanical ventilation again, a new episode begins.

Therefore, there can be multiple episodes of mechanical ventilation in 1 patient during a single ICU admission. The same APACHE II score and Charlson comorbidity score were applied to different episodes during a single ICU admission. We examined the incidence of VAC, IVAC, and VAP and compared the baseline characteristics, duration of mechanical ventilation, rate of weaning and extubation, and 30- and 60-day mortality in episodes with or without VAE. Weaning was considered successful when a patient breathes without mechanical ventilation for more than 48 hours. Extubation was considered successful when a