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Brief Report

Case-control study investigating parameters affecting ventilator-associated events in mechanically ventilated patients

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We analyzed a set of clinical parameters using Cox proportional hazard regressions to yield significant factors associated with the development of ventilator-associated events. In our study, intubation site, certain comorbidities, morphine, prednisone, and nutrition emerged as factors. Additionally, we presented potential mechanisms that require further research to validate.

Ventilator-associated pneumonia (VAP) is a relatively rare but serious complication of mechanical ventilation. In 1 study, patients who were placed on mechanical ventilation and developed VAP showed a 15% mortality rate.[1] Because VAP is considered preventable, multiple efforts have been implemented for prevention.[2] In 2013, the Centers for Disease Control and Prevention developed guidelines to categorize certain ventilated patients into 3 categories under 1 umbrella term: ventilator-associated events (VAEs). The first category is a ventilator-associated condition (VAC), followed by infection-related ventilator-associated complication (IVAC), and eventually possible ventilator-associated pneumonia (PVAP).[3] There are multiple factors that can be related to the development of VAEs.[4] VAEs in the clinical environment could be reduced by eliminating or managing circumstances that lead to the increased chance of an event. The objective of this study was to explore the effect of a wide variety of factors on the development of VAEs among mechanically ventilated patients.

METHODS

Data were collected from May 2013 to August 2016 by the infection prevention department as part of their responsibility for daily VAE surveillance. Using an electronic tool developed in-house, we were able to query medical records to collect patient demographics, biometrics, comorbidities, medication administration, ventilator data, and other important variables. Using the variables collected, we then created a clinical database and populated it with patients who were mechanically ventilated during the study period.

Cases were matched 1:1 with controls based on age, sex, unit of intubation, use of vasopressors while intubated, and total ventilator days. For the purpose of this study, the unit of intubation refers to the unit where the ventilated patient stayed during the encounter rather than where the patient was initially intubated (ie, site of intubation). Furthermore, controls were randomly selected among patients who were mechanically ventilated for at least 3 days, to meet the VAE definition. We considered only 2 groups for the analysis: VAC, in which patients reached only the first stage of the VAE spectrum, and IVAC-plus, which combined cases from both the IVAC and PVAP categories. This categorization has previously been used in the literature and limits the overlap between the subcategories.[5] From the dataset, the "time to event" for the VAE group was considered as the interval between the date of intubation and the date of the event. Because the control group did not experience any VAEs, a comparable time period was considered to be total ventilator days.

Statistical analysis

A Cox proportional hazards regression model was used to analyze the risk factors for each VAE group. All collected variables from the database, with exception of those used for matching, were entered into the regression analysis. Through backward selection, factors with

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P values greater than .05 were removed from the model. Using only the significant risk factors identified from the Cox regression, we constructed a final model for each VAE group. All analyses were performed using R 3.3.2 (R Foundation for Statistical Computing, Vienna, Austria), and a *P* value less than .05 was considered statistically significant.

RESULTS

From May 2013 to August 2016, 3,303 invasively ventilated patients were surveyed (16,575 total ventilator days). Using the VAE definitions released by the Centers for Disease Control and Prevention, we reported 99 VACs and 87 IVAC-plus events (47 IVACs and 40 PVAPs). The cases were matched with 186 non-VAE controls, with total ventilator days at 5,282. The median time to event for all cases was 5.0 days (VAC, interquartile range 6.0 days; IVAC-plus, interquartile range 4.5 days).

Cox proportional hazards regression analysis

Associations between each factor and VAEs are summarized in Table 1. Among VACs, patients intubated in the hospital ward were associated with significantly higher hazards. Additionally, a history of CAD or COPD was associated with higher hazards. Likewise, patients who were on TPN were associated with higher hazards. Conversely, patients with CHF were associated with lower hazards. Likewise, patients who were administered morphine while intubated were associated with lower hazards (HR, 0.42, 95% CI, 0.27-0.65, *P* = .000).

Among IVAC-plus events, patients with COPD were associated with higher hazards. Likewise, patients who were either tube fed or on TPN were associated with higher hazards. Conversely, patients with a history of CHF were associated with lower hazards. Similarly, patients intubated in either the ICU or the operating room (OR) were associated with lower hazards. In addition, patients who were administered either morphine or prednisone over the course of intubation were associated with lower hazards.

DISCUSSION

In this study, we identified 10 significant factors that were associated with the development of VAEs. These factors can be grouped into site of intubation, comorbidities, medications, and nutrition. The site of intubation affected the possibility of developing VAC in the hospital ward, and both the ICU and the OR were associated with lower likelihood of IVAC-plus development. This may be related to the events surrounding hospital ward intubations, such as volume status of the patient, possible use of noninvasive ventilation, and level of distress. Furthermore, there is added risk of aspiration, because hospital wards are not ideally equipped for intubation compared with ICU and OR environments.

Although there is no clear explanation for CAD as a risk factor, this could be related to host risk factors and the fact that CAD patients may have undergone coronary artery bypass surgery during their hospital stay. One randomized controlled trial showed that coronary artery bypass surgery patients had an 8.2% incidence of VAP.[6] This could be related to more generous pain control, anxiolytics, and the effect of thoracotomy and surgery on aspiration risk, effective cough, and atelectasis.

However, patients with CHF were at reduced risk of developing both VAC and IVAC-plus events. This proves more difficult to explain, because a clinician would expect the opposite. Nevertheless, CHF patients will receive diuretic therapy, which will improve oxygenation. This line of events will apparently reduce the likelihood of patients developing VAC and, subsequently, IVAC-plus events. Lewis et al[4] have demonstrated a similar finding VAE patients in which positive fluid balance was a risk factor for VAC. The last comorbidity we identified was COPD, which was expected to be a risk factor for a variety of reasons explained in the following. A study in 2014 by Rouzé et al[7] has also demonstrated this finding for VAP specifically. Patients with COPD differ in terms of the dysfunctional local immunity in their airways and the regular use of inhaled or sometimes systemic steroids. Furthermore, they more commonly also fail to wean, which poses a risk for aspiration and prolonged mechanical ventilation.

Remarkably, patients administered morphine were less likely to develop both VAC and IVAC-plus events compared with controls. The venodilatory effect of morphine, along with its benefits in pulmonary edema, is well established in the literature. Vismara et al[8] have demonstrated venous pressure and tone measurements in patients with pulmonary edema, and the subsequent improvement after morphine administration. They concluded that there are other mechanisms also involved, such as splanchnic pooling and afterload reduction.

In our study, prednisone was found only to be associated with less risk in the IVAC-plus group. It appears that the anti-inflammatory effects of prednisone have suppressed the development of IVAC-plus. Whether it is protective against infection itself is debatable. In the study performed by Lewis et al,[4] prednisone did not significantly affect the rates of both VAE categories.

We found patients on TPN were at risk of developing both VAC and IVAC-plus events. Both enteral nutrition and parenteral nutrition are associated with an increased risk of IVAC-plus events. It has been well demonstrated in the literature that both methods of nutrition are associated with an increased risk of infection,

Table 1
Hazard ratios (95% CIs) of factors associated with ventilator-associated events

Risk factor	VAC (n = 99) Hazard ratio	95% CI	*P*	IVAC-plus (n = 87) Hazard ratio	95% CI	*P*
Site of intubation						
Intensive care unit	0.74	0.46-1.18	NS	0.52	0.30-0.88	.016
Operating room	0.83	0.45-1.52	NS	0.50	0.26-0.96	.037
Hospital ward	3.10	1.30-7.38	.011	1.42	0.60-3.36	NS
Comorbidities						
Congestive heart failure	0.56	0.32-0.97	.038	0.50	0.26-0.94	.032
Coronary artery disease	1.75	1.16-2.65	.008	1.27	0.78-2.06	NS
Chronic obstructive pulmonary disease	1.54	1.06-2.32	.042	1.94	1.20-3.14	.007
Medications						
Morphine	0.42	0.27-0.65	.000	0.55	0.35-0.87	.011
Prednisone	1.06	0.58-1.92	NS	0.30	0.11-0.78	.013
Nutrition						
Tube feeding	1.84	0.88-3.86	NS	2.95	1.15-7.54	.024
Total parenteral nutrition	2.45	1.08-5.54	.032	3.24	1.23-8.55	.018

CI, confidence interval; *IVAC*, infection-related ventilator-associated complication; *NS*, not significant; *VAC*, ventilator-associated condition.

particularly pneumonia and fungal infections. In addition to volume overload, there is a need for central venous access and a longer hospital stay.[9,10]

LIMITATIONS

The data was gathered from a single institution and retrospectively collected. Considering this sample size, we opted to create the IVAC-plus category to differentiate between patients with hypoxemia alone versus those with evidence of hypoxemia and some infectious process. Since VAE classifications are nested, unique characteristics of the VAC group may be seen among IVAC-plus categorization.

CONCLUSIONS

Our study identified several risk factors for the development of VAEs, some of which are new to the literature: intubation site, certain comorbidities, morphine, prednisone, and nutrition. This study invites further exploration of predictive models to improve risk assessments for VAEs among mechanically ventilated patients, as well as further investigation regarding the new risk factors and their mechanisms in the evolution of VAEs.

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