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IMPACT OF INTENSIVE-CARE-UNIT(ICU)-ACQUIRED VENTILATOR-ASSOCIATED PNEUMONIA(VAP) ON HOSPITAL MORTALITY: A MATCHED-PAIRED CASE-CONTROL STUDY

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ABSTRACT

The effect of ICU-acquired ventilator-associated pneumonia (VAP) on hospital mortality is still a controversial issue in many countries. The aim of this study was to evaluate the effect of ICU-acquired VAP on hospital mortality in a Japanese university hospital. Our study population was comprised of patients aged 16 years or older who were admitted to our ICU and received mechanical ventilation for more than 48 hours during a period of 42 months as of December 2003. To evaluate whether VAP was an independent risk factor for hospital mortality after controlling for other clinical factors, patients with fatal outcomes (cases) were compared to those who survived (controls). From 587 eligible patients, we analyzed 75 cases and 150 controls who were successfully matched on sex, age, and the Acute Physiology and Chronic Health Evaluation II (APACHE II) score using conditional logistic regression models. Univariate analysis demonstrated that hemodialysis (odds ratio [OR], 2.24; 95% confidence interval [CI], 1.21–4.15; p=0.01), surgical site infection (OR, 2.45; 95% CI, 1.22–4.91; p=0.01), and VAP (OR, 2.69; 95% CI, 1.55–4.69; p<0.001) were significantly associated with hospital mortality. After adjusting for confounding factors, multivariate conditional logistic regression analysis showed that hemodialysis (OR, 2.05; 95% CI, 1.06–3.94; p=0.03) and VAP (OR, 2.20; 95% CI, 1.10–4.39; p=0.03) were independently associated with hospital mortality. In conclusion, these data suggest that ICU-acquired VAP significantly affects hospital mortality.

Key Words: Matched-paired case-control study, Ventilator-associated pneumonia (VAP), Intensive care unit (ICU), Hospital mortality

INTRODUCTION

Ventilator-associated pneumonia (VAP) is the most common intensive-care-unit (ICU)-acquired nosocomial infection all over the world.[1-3] However, whether VAP increases hospital mortality or not remains controversial due to the difficulty of VAP diagnosis as well as to a number of factors possibly associated with VAP.[4-13] If ICU-acquired VAP affects patient mortality, all the

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health care workers in ICU share a responsibility for preventing it. If not, to prevent other and different risk factors should be placed emphasis on.

In Japan, few reports have evaluated the impact of VAP focusing on the outcome of a Japanese patient cohort. We previously assessed the impact of VAP on patient outcomes, using the database of the Japanese Nosocomial Infection Surveillance (JANIS) system and found that VAP caused by drug-resistant pathogens increased ICU mortality.[14] In this study, we assessed the impact of ICU-acquired VAP on hospital mortality in Nagoya University Hospital, which is one of the participating hospitals in the ICU surveillance component of JANIS.

METHODS

Study design and subjects

This study was performed in the ICU of Nagoya University Hospital, which is a 1035-bed university-affiliated teaching hospital. The ICU has 8 beds and receives patients from all departments of the hospital including the emergency room as well as other regional hospitals. During a 42-month period (July 2000 to December 2003), about 4500 patients were admitted to the ICU and recorded as complying with the JANIS system.[14] A total of 2095 patients received mechanical ventilation, among whom we excluded 44 aged 15 years and under, 1448 who were on mechanical ventilation for less than 48 hours, and 6 with no hospital discharge record. The remaining 597 patients in the JANIS database were initially enrolled in the study for subsequent sampling in order to collect further clinical information.

Consequently, we performed a frequency-matched stratified sampling of cases and controls from these 597 patients. Cases were defined as patients who died during their hospital stay (n=100), and controls were those who survived their hospitalization (n=497). Case patients were classified into subgroups by sex, age (16–35, 36–55, 56–75, >75), and the Acute Physiology and Chronic Health Evaluation (APACHE) II score[15,16] (0-10, 11-20, 21-30, >30). Control patients were then taken from the corresponding subgroups in proportion to the number of cases with a case: control ratio of two. Among 100 cases, 75 were successfully matched to the 150 control patients. The final sample included 225 patients. Compared to the 75 case patients included, the 25 excluded patients were more critically ill (the mean APACHE II score: 30.2 ± 5.3 vs 20.4 ± 5.8, $p < 0.001$). Although not statistically significant, excluded cases tended to be younger (57.5 ± 21.6 vs 62.4 ± 15.5, p=0.31). The study was approved by the Ethics Review Committee of the Nagoya University Graduate School of Medicine.

Variables

In JANIS, the following information was obtained: age, sex, underlying disease, ICU admission and discharge record (date, time, route and outcome), operation record (elective or urgent), device used (ventilator, urinary catheter, central venous catheter), infection (pneumonia, urinary tract infection, catheter-related bloodstream infection, sepsis, surgical site infection, others), and hospital discharge record (date and outcome).[14] For the selected patients, we collected information by referring to the charts on other interventions that may have been associated with VAP and were not obtained in JANIS, such as tracheostomy, hemodialysis, and reintubation.

Definition of VAP

The diagnosis of nosocomial infections was made based on the JANIS definitions, which were modified from those of the National Nosocomial Infections Surveillance (NNIS) system of the Centers for Disease Control and Prevention (CDC).[17] The diagnosis of pneumonia was

defined as either (1) rhonchus or dullness of percussion along with at least one of the following: purulent sputum or change in character of sputum, positive growth in blood culture, and identification of causative pathogen from lower respiratory tract specimens (endotracheal aspiration or bronchoalveolar lavage) or (2) new or progressive infiltrate or other abnormal shadow on chest radiographs along with at least one of the following: purulent sputum or change in character of sputum, identification of causative pathogen from sputum or biopsy specimens, positive growth in blood culture, positive detection of viral antigen or antibody from sputum, and diagnostic single antibody titer (IgM) or 4-fold increase in paired sera (IgG) for pathogen. Newly developed pneumonia at least 48 hours after initiation of mechanical ventilation during ICU stay was defined as ICU-acquired VAP.

Statistical analysis

We performed a matched-paired case-control study. Baseline characteristics of case and control patients were compared by two-way analysis of variance controlling for a matching variable for continuous variables. Categorical variables were compared using χ^2 tests ignoring the matching in data sets instead of applying the Mantel-Haenszel procedure that is applicable to frequency matching data with a case: control ratio of two, since disregarding matching will produce only a slight bias which is often obscured by random variation.[18,19] We then performed logistic regression analysis, conditioned on the matching variables such as sex, age, and APACHE II score. Odds ratios and their confidence intervals were calculated for evaluations of significance. Multivariate analysis simultaneously included all the variables listed in Table 2. For all statistical tests used here, a p-value less than 0.05 was considered statistically significant. All reported P-values were two-sided. Statistical calculations were performed using the SPSS statistical package for Windows version 11.0 (SPSS, Inc., Chicago, IL, USA).

RESULTS

Table 1 shows the baseline characteristics of 75 cases and 150 matched control patients. There were more male than female patients. Three quarters of the patients were older than 56 years, the mean age was 61.8 ± 15.0 years. The mean APACHE II score was 19.1 ± 5.9. The mean duration of mechanical ventilation for case patients was 5.6 ± 10.7 days compared with 4.7 ± 5.5 days for control patients.

As shown in Table 2, the incidence of case patients who developed VAP was 24.0% vs. 4.7% in control patients ($p < 0.001$). Similarly, the incidence of case patients for tracheostomy, hemodialysis, reintubation, surgical site infection and sepsis was higher than those of control patients (respectively, $p = 0.16$, < 0.01, 0.53, < 0.01, 0.03) except for emergency surgery. No patients were diagnosed as both urinary tract infection and catheter-related bloodstream infection.

Univariate comparisons using logistic regression analyses conditioned on the matching variables exhibited slightly attenuated p values from those calculated by simple χ^2 tests (Table 3). In these analyses, history of hemodialysis, surgical site infection, and VAP significantly differed between case patients and control patients. Multivariate logistic regression analysis that was simultaneously adjusted for all the variables revealed that only hemodialysis and VAP were independently and significantly associated with hospital mortality.

Table 1 Baseline characteristics of study participants*

Characteristic	Cases (n = 75)	Controls (n = 150)	p value
Sex			
Male	51 (68.0)	102 (68.0)	1.00
Female	24 (32.0)	48 (32.0)	
APACHE II score category			
31–	1 (1.3)	2 (1.3)	1.00
21–30	29 (38.7)	58 (38.7)	
11–20	42 (56.0)	84 (56.0)	
0–10	3 (4.0)	6 (4.0)	
Age category, y			
76–	11 (14.7)	22 (14.7)	1.00
56–75	45 (60.0)	90 (60.0)	
36–55	12 (16.0)	24 (16.0)	
16–35	7 (9.3)	14 (9.3)	
Duration of mechanical ventilation, mean (±SD)	5.6 (10.7)	4.7 (5.5)	0.49

APACHE = the Acute Physiology and Chronic Health Evaluation; SD = Standard deviation.
*Data are presented as No. (%) unless otherwise indicated.

Table 2 Treatment and infections

Factor		Cases (n = 75)	Controls (n = 150)	p value
Treatment				
Emergency surgery	Yes	7 (9.3)	15 (10.0)	0.87
	No	68 (90.3)	135 (90.0)	
Tracheostomy	Yes	13 (17.3)	16 (10.7)	0.16
	No	62 (82.7)	134 (89.3)	
Hemodialysis	Yes	15 (20.0)	10 (6.7)	<0.01
	No	60 (80.0)	140 (93.3)	
Reintubation	Yes	5 (6.7)	7 (4.7)	0.53
	No	70 (93.3)	143 (95.3)	
Infections				
Surgical site infection	Yes	10 (13.3)	4 (2.7)	<0.01
	No	65 (86.7)	146 (97.3)	
Sepsis	Yes	5 (6.7)	2 (1.3)	0.03
	No	70 (93.3)	148 (98.7)	
Ventilator-associated pneumonia	Yes	18 (24.0)	7 (4.7)	<0.001
	No	57 (76.0)	143 (95.3)	

Data are presented as No. (%).

Table 3 Effect of treatment and ICU-acquired infections on hospital mortality

Factor	Univariate analysis				Multivariate analysis			
	OR	95% CI		p value	OR	95% CI		p value
Emergency surgery	0.95	0.43	2.10	0.89	0.93	0.41	2.10	0.86
Tracheostomy	1.46	0.78	2.75	0.24	1.13	0.53	2.40	0.75
Hemodialysis	2.24	1.21	4.15	0.01	2.05	1.06	3.94	0.03
Reintubation	1.31	0.50	3.47	0.59	0.83	0.26	2.63	0.75
SSI	2.45	1.22	4.91	0.01	1.43	0.56	3.65	0.46
Sepsis	2.51	0.93	6.75	0.07	1.25	0.34	4.57	0.74
VAP	2.69	1.55	4.69	<0.001	2.20	1.10	4.39	0.03

ICU = intensive care unit; OR = odds ratio; CI = confidence interval; SSI = surgical site infection; VAP = ventilator-associated pneumonia.

DISCUSSION

In this case-control study, we took VAP, other types of nosocomial infections, ventilator-related factors such as reintubation and tracheostomy, as well as hemodialysis into account to determine the risk factors for hospital mortality, except for urinary tract infections and catheter-related bloodstream infections, which were not diagnosed among patients in the study. Our results demonstrated that VAP and hemodialysis were independently associated with hospital mortality.

However, other studies which attempted to evaluate the effect of VAP on hospital mortality demonstrated contradictory results. To evaluate the attributable mortality caused by VAP, Bregon and colleagues matched 108 nonsurvivors and 108 survivors for underlying diseases, age, sex, length of ICU stay, APACHE II score, and duration of mechanical ventilation. They found that VAP was not an independent risk factor for hospital mortality.[9] Rello and colleagues assessed the risk factors and outcomes of VAP, using a large US database. 816 patients with VAP were matched with 2243 patients without VAP on the basis of duration of mechanical ventilation, severity of illness on admission, type of admission (medical, surgical, trauma), and age. However, no difference was found in hospital mortality between patients with and without VAP.[6]

On the other hand, other investigators reported a significant association between VAP and hospital mortality. Fagon and colleagues demonstrated that nosocomial pneumonia was an independent risk factor for hospital mortality in two different studies with different study designs and different patient populations.[7,12]

Such disparate results among previous studies may be caused by inaccuracies in VAP diagnosis, particularly in ICU settings. Many investigators have stressed the difficulties in making an accurate diagnosis of VAP, while others have reported that attributable mortality was similar, regardless of the diagnostic approach.[8,20,21]

We endeavored to overcome the above difficulty by using the following study design. First, a matched-paired case-control study was chosen because we were addressing hospital mortality. Most of the previous case-control studies compared the difference between the mortality rates of cases (patients with VAP) and controls (patients without VAP). In our study, matched-case patients were those who died, while control patients were those who survived. This study design was the same as that of Bregon and colleagues' first study.[9] Such a design has the major advantage of avoiding the ambiguity of a precise VAP definition. Additionally, our data were

compiled using uniform criteria based on the JANIS definition. Because the minimization of matching variables could avoid overmatching, we matched the study patients taking only three major potential confounding factors (APACHE II score[12], age[22] and sex) into account, factors which were strongly correlated with patient outcome. However, many investigators took account of more factors such as original disease, duration of mechanical ventilation, comorbit disease, and so on. The average APACHE II score of the patients studied was about 20, which was equivalent to those of previous studies. However, the average age was almost 60 and higher. The average ICU stay was about 5 days, which was shorter than those of other studies but within the duration range of the ICU stay of the participating ICUs of JANIS.[8] Moreover, we only enrolled patients who were mechanically ventilated for more than 2 days. Secondly, we used multiple logistic regression analysis to evaluate the independent risk factors for hospital mortality. This technique helped us to eliminate the interrelated factors which may independently influence patient outcome.[23]

However, our analysis had several potential limitations. Although we observed a statistically significant association of VAP with hospital mortality, the statistical power would have been even stronger if all the eligible subjects in the JANIS database could have been analyzed by multivariate procedure.[24] Practical considerations prompted us to limit the number of control patients because clinical information had to be collected that might confound the association between VAP and hospital mortality other than that in the JANIS system. An additional consequence of this sampling procedure was that the case patients selected for analysis were comparably less critically ill. Thus, the present results might not apply to patients whose general condition on admission as measured by the APACHE II score is more serious, suggesting that further study of these patients groups is warranted.

Additionally, the following risk factors which may be associated with patient outcomes were not included in this study. First, the underlying disease, which some studies suggested was an important determinant of hospital mortality. Heyland and colleagues examined the attributable ICU stay and mortality of the patients who acquired VAP and found that attributable mortality was higher for medical patients than for surgical patients,[8] while Baker and colleagues reported that no attributable mortality of VAP was found in trauma patients.[25] Although we did not incorporate underlying disease as a risk factor for hospital mortality, the severity of illness APACHE II score was used, where a variety of underlying diseases had already been taken into account. Second, we did not take the causative organisms of VAP into account when assesing patient outcomes. Some studies have reported that VAP due to gram-negative bacilli and antibiotic-resistant pathogens worsens the prognosis of patients.[1,26-28] We did not take the causative pathogens into account because no pathogen was identified in many cases of VAP. Third, since the optimal initial antimicrobial treatment for VAP appears to be an important determinant of hospital mortality,[1,29,30] the behavior of antibiotic administration should be taken into account. However, since most causative pathogens were not identified, the optimal use of antibiotics was not thoroughly evaluated. Therefore, further studies should be done to obtain more detailed data on underlying patient diseases, as well as on causative pathogens or antibiotic use, especially in relation to pneumonia or VAP.

In conclusion, despite the above limitations, our data suggest that ICU-acquired VAP significantly increased the risk of hospital mortality. Therefore, efforts to prevent ICU-acquired VAP are important to improve the prognosis of the patients admitted to ICUs.

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