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Ventilator Associated Pneumonia in an Intensive Care Unit

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Abstract

The aim of this prospective study was to evaluate the incidence, etiologic agents and mortality rate of ventilator-associated pneumonia (VAP). In a six-month period, cases who were 18 years or older, dependent on mechanical ventilator for more than 3 days and without pulmonary infection on first admission were included in this study. In all cases, body temperature recordings, blood and urine culture, microbiological analyses of endotracheal aspirates, and chest X-rays were obtained and used to identify VAP. Apache II scores on admission, duration of mechanical ventilation, length of intensive care unit (ICU) stay and mortality were recorded. This study included 45 cases and 22 developed VAP (48%). The incidence of VAP was 25.34 per 1000 ventilator days. Univariate analyses showed that duration of mechanical ventilation, length of ICU stay, coma and tracheotomy were associated with the development of VAP. The mortality rate of cases with VAP (72.7%) was significantly higher than cases without VAP (39.1%). The most frequent microorganisms were *Acinetobacter* spp., *Pseudomonas aeruginosa and Klebsiella pneumoniae*. In our study, VAP was a very common and important complication of mechanical ventilation and mortality was very high. To reduce mortality, minimize morbidity, shorten the length of stay, and reduce costs, defined risk factors for VAP should be recognized and an effective infection control program for the prevention of VAP should be implemented. Surveillance results should be evaluated regularly and necessary precautions should be taken.

Keywords

Ventilator Associated Pneumonia, Mechanical Ventilation, Intensive Care Unit

1. Introduction

Pneumonia due to mechanical ventilation (VAP) is an important problem in intensive care units. VAP occurs in an average of 9% - 27% of patients who are mechanically ventilated for more than 48 hours in intensive care units [1]. Disruption of defense mechanisms, colonization with pathogenic microorganisms and presence of microorganisms with high virulence have an important place in the pathogenesis of the disease [2]. Bacteria reach the lung tissue by micro aspiration of oropharyngeal secretions, aspiration of esophageal-gastric contents, inhalation of infected aerosols, hematogenous spread, and direct spread in the intubated patient. Even with a diagnostic fiberoptic bronchoscope, the lower respiratory tract can be contaminated.

In mechanically ventilated patients, leakage of pharyngeal flora around the endotracheal cuff, blockage of the sinusoidal ostium and infection of the ostium in nasotracheal intubation, local trauma, impaired clearance of the lower respiratory tract, application of invasive procedures such as bronchoscopy, indirect air contact with other critical patients, and direct contact with the hands of workers are additional entry routes for pathogens. Early onset VAP caused by antibiotic susceptible pathogens develops within 4 days after intubation, while late onset VAP with multidrug-resistant bacteria develops after the fourth day of intubation [1].

As one of the highest-incidence hospital acquired infections in intensive care units [3], VAP is associated with increases in mortality [4] [5]. One meta-analysis found the mean VAP attributable mortality in the ICU to be 32.5% [6], and 33% in another study [7]. VAP increases the length of stay in the intensive care unit and hospital and the time the patient needs ventilator support, which causes an increase in the use of antibiotics in ICU and thus increases the hospital cost [1].

Many factors have been associated with an increased likelihood of developing VAP. Detection of risk factors, close follow-up and early treatment of VAP development will reduce hospital costs as well as affect patient morbidity and mortality. In this prospective study, we aimed to determine the incidence, factors and mortality related to VAP in patients hospitalized in our intensive care unit and treated with mechanical ventilation.

2. Methods

This was a prospective randomized study that took place in the 12 bed-intensive care unit of Haseki Training and Research Hospital, Department of Anesthesiology and Reanimation, İstanbul from April 2010 up to September 2010. This study was approved by the local Institutional Review Board. A total of 45 patients who did not have pneumonia on admission to our unit, older than 18 years and with mechanical ventilation for at least 48 hours were included in the study.

Patients who have received mechanical ventilation for less than 48 hours, pa-

tients with lung infection in the first 48 hours, patients with lung infection on admission to the intensive care unit, and patients under the age of 18 were excluded from the study. Center for Disease Control and Prevention/National Healthcare Safety Network (CDC/NHSN) diagnostic criteria were used to diagnose VAP in our cases [8]. After the patients were admitted to the intensive care unit, they were monitored (ECG, SpO_2, central venous catheter, hourly urine follow-up, invasive-noninvasive arterial pressure).

Endotracheal aspirate samples, simultaneous blood and urine samples were taken from the patients when they were first intubated, at the end of the 2nd day, at the end of the 4th day, then once a week, and when infection was suspected during the follow-up period. Apache II scoring was used for the first 24-hour acute physiological evaluation of our cases. The duration of hospitalization of our patients and whether they used antibiotics were recorded.

Daily arterial blood gas monitoring (PaO_2, $PaCO_2$, pH, HCO_3), complete blood count (hemoglobin, hematocrit, leukocyte, thrombocyte), and PA chest X-ray at 48-hour intervals were recorded. For clinical evaluation, the daily highest temperature, and qualitative and quantitative changes in lung secretion were recorded. Hemoculture was sent for cases whose body temperature was above 38.5˚C. Endotracheal aspiration was performed by the open method and under sterile conditions. Tracheostomy was planned on the 10th day on average if extubating was not considered in the near future. Ampicillin/sulbactam (1 g 3 times a day, i.v.) was routinely started empirically from the moment they were admitted to the intensive care unit. Antibiotic treatment was then rearranged in consultation with infectious diseases, taking into account the results of the culture antibiogram and the patient's clinical status. Ranitidine (50 mg 3 times a day, i.v.), a H_2 receptor blocker, was routinely administered to protect the stomach. By calculating the basal metabolic rates and actual energy consumption of the cases (Harris-Benedict Formula), appropriate nutrition products (primarily enteral) were chosen.

The patients were fed enterally through naso-jejunal or nasoduodenal feeding tubes and parenterally through central venous catheters if enteral feeding was contraindicated and if there was no tolerance. In order to prevent regurgitation in patients who were fed enterally, the patient's head was held up 30 - 45 degrees and gastric residue was followed up at 4-hour intervals.

3. Statistical Analysis

While evaluating the data, a statistical package program was used for statistical analysis. While evaluating the study data, the Kolmogorov-Smirnov distribution test was used to examine normal distribution as well as descriptive statistical methods (frequency, percentage, mean, standard deviation). The Pearson Chi-Square test was used to compare qualitative data.

The Mann Whitney U test was used for comparison of parameters between two groups. In the case of more than two groups, the Kruskal Wallis test was

used to compare the parameters between groups, and the Mann Whitney U test was used to determine the group that caused the difference. The results were evaluated at 95% confidence interval, $p < 0.05$ significance level and $p < 0.01$ forward significance level.

4. Results

In this prospective study, 45 patients receiving mechanical ventilation for at least 3 days during the 6 months were included. VAP developed in 22 of 45 patients. Twenty-three of the cases were female and 22 were male. The ages of the cases were between 19 and 90 years. The length of stay in the intensive care unit was between 4 and 97 days, and the mechanical ventilation periods were between 3 and 95 days. Mortality was 55% in patients who underwent mechanical ventilation. During this 6-month period, the incidence of VAP development in the intensive care unit was found to be 48.88%. Mortality was 72.7% in cases with VAP. Twenty patients were discharged medically. Tracheostomy was performed in 9 of the patients. Patients were admitted to the intensive care unit for different reasons (Table 1).

In this study, the mean duration of stay in the intensive care unit for cases with VAP was 31.14 ± 22.87 days, and the average duration of stay on mechanical ventilation for cases with VAP was 27.77 ± 23.53 days. We found the mean duration of stay in the intensive care unit to be 15.96 ± 15.36 days, and the mean mechanical ventilation time to be 11.17 ± 11.34 days for patients who did not develop VAP.

The mean time of VAP development after initiating mechanical ventilation was 12.22 days. The mean VAP development time was 6.33 ± 2.94 days in surviving patients who developed VAP and 14.44 ± 13.30 days in non-surviving patients who developed VAP. However, there was no statistically significant difference between them. In this study, no significant difference was found between

Table 1. Reasons for hospitalization.

Reason for admission	n	%
Intracranial hemorrhage	7	15.55
Acute respiratory failure	6	13.33
Malnutrition	4	8.88
Myocardial infarction	4	8.88
Sudden cardiopulmonary arrest	3	6.66
Cerebrovascular disease	3	6.66
Abdominal surgery	3	6.66
Cranial surgery	2	4.44
Trauma	2	4.44
Pulmonary embolism	2	4.44
Other	9	19.98

the mean age, gender distribution and Apache II score of the cases with and without pneumonia ($p > 0.05$) (Table 2).

The mean age and Apache II score of the surviving patients with VAP and surviving patients without VAP were found to be significantly lower than the average age and Apache II score of the non-surviving patients with VAP and non-surviving patients without VAP ($p < 0.05$) (Table 3). The average length of stay in the intensive care unit and mechanical ventilation in cases with pneumonia were found to be significantly higher than the average length of stay in the intensive care unit and mechanical ventilation in cases without pneumonia ($p < 0.01$) (Table 2).

The mortality rate of patients with pneumonia (72.7%) was found to be significantly higher than the mortality rate of patients without pneumonia (39.1%) ($p < 0.05$) (Table 4). There was no significant difference between the rates for presence of DM, ischemic heart disease (ICD), congestive heart failure (CHF), coma (GCS < 7), previous antibiotic use, previous hospitalization and advanced age (>60) in cases with and without pneumonia ($p > 0.05$). The rate of COPD in cases with pneumonia (9.1%) was significantly lower than the rate of COPD (43.5%) in cases without pneumonia ($p < 0.05$). The tracheostomy rate in patients with pneumonia (36.4%) was found to be significantly higher than the tracheostomy rate (4.3%) in patients without pneumonia ($p < 0.05$). No significant

Table 2. Demographic Characteristics, Apache II score, duration of mechanical ventilation, and length of stay in ICU New Roman or the Symbol font (please no other font).

	Without VAP (n = 23)	With VAP (n = 22)	p
Age (year)	64.26 ± 19.08	66.27 ± 18.95	0.716
Gender (f/m)	9/14	14/8	0.100
Apache II	22.83 ± 8.37	28.82 ± 12.67	0.080
Duration of mechanical ventilation (days)	11.17 ± 11.34	27.77 ± 23.53	P < 0.001
Length of stay in ICU (days)	15.96 ± 15.36	31.14 ± 22.87	0.001**

**p < 0.01 Comparison of cases that developed pneumonia with cases that did not develop pneumonia.

Table 3. Distribution of age and apache II score.

	Surviving without VAP		Non-surviving without VAP		Surviving with VAP		Non-surviving with VAP		p
	Mean	Sd	Mean	Sd	Mean	Sd	Mean	Sd	
Age	59.93	21.12	72.38	11.71	48.83	19.18	72.81	14.58	0.025μ
Apache II	20.40	7.83	27.38	7.84	20.17	11.79	29.44	8.94	0.017μ

μ: p < 0.05 Comparison of surviving cases with and without VAP and non-surviving cases with and without VAP.

Table 4. Mortality findings.

		Without VAP		With VAP		p
		n	%	n	%	
Mortality	No	14	60.9%	6	27.3%	0.023*
	Yes	9	39.1%	16	72.7%	

*: $p < 0.05$ Comparison of cases that developed pneumonia with cases that did not develop pneumonia.

correlation was found between early-late development of pneumonia and mortality ($p > 0.05$).

5. Discussion

VAP is observed as the second most common nosocomial infection in intensive care units, and it is the most common infection in mechanically ventilated patients [2]. In studies conducted, the incidence of VAP was reported at rates ranging from 14.8 to 28/1000 ventilator days [9] [10]. Similar rates were observed in studies conducted in Turkey [11] [12]. In this study, we found the incidence of VAP development in our intensive care unit was 25.34/1000 ventilator days in 6 months. As the incidence of VAP differs in each intensive care unit, there are differences in incidence rates at different times for the same intensive care unit. Therefore, regular assessment of the incidence helps provide information about the flora of the intensive care unit, the measures to be taken and how they will change the outcomes.

Prolonged duration of mechanical ventilation is an important risk factor for VAP. It was observed that VAP increases the length of hospital stay and the duration of mechanical ventilation, and the increase in the length of stay of patients in the intensive care unit and prolonged duration on the mechanical ventilator increases the incidence of VAP [11] [12] [13] [14] [15].

In this study, the duration of stay in the intensive care unit and mechanical ventilator was significantly longer in patients who developed VAP (**Table 2**). The mean time to develop VAP after intubation was 3.3 days and the risk of VAP development was highest in the first five days of mechanical ventilation (3%) [13] [16] [18]. In this study, it was observed that this period was prolonged. Our first priority in preventing the development of VAP should be to avoid invasive mechanical ventilation. Although noninvasive mechanical ventilation is an alternative, it is not suitable for every patient and it is important to extubate the patient as early as possible in cases where intubation and mechanical ventilation are required [1].

Microorganisms in the etiology of VAP vary according to the hospital, the microbial flora of the intensive care unit and the characteristics of the patients [19]. Studies showed that 60% of VAP agents are gram-negative bacteria [15]. In different studies, it was determined that *Acinetobacter* spp., *P. aeruginosa*, *K. pneumoniae*, *MSSA* (*methicillin-sensitive Staphylococcus aureus*), *MRSA* (*me-*

thicillin resistant Staphylococcus), *Enterobacter* spp., *C. albicans* and polymicrobial agents were observed at different rates [10] [13] [16] [18] [20] [21] [22]. In this study, 95% of the agents were gram-negative bacteria. *Acinetobacter* spp. was the most common cause of VAP (36.36%), followed by *P. aeruginosa* (27.27%), *K. pneumoniae* (9.09%), *E. auregenes* (4.54%), *H. influenza* (4.54%), *and MRSA* (4.54%). Among cases, 13.63% of VAP agents were polymicrobial. The VAP agents found in this study and in the literature are similar, but the percentages differ due to the techniques used in the diagnosis and changes in the patient population (**Table 5**).

Many studies have shown that advanced age alone increases the risk of developing VAP [11] [17] [23] [24]. However, some studies found no significant difference between the two groups with or without VAP in terms of VAP development [12]. Age did not have any effect between the cases with and without VAP, even when they were divided into two groups as those over and under 70 years of age [12]. In this study, we divided the patients into two groups as those over and under 60 years of age, and we did not observe any difference in the development of VAP in the two groups.

Age does not appear to be particularly associated with risk of pneumonia in ventilated patients. A secondary analysis of a European cohort study [25] is unable to identify a higher risk of VAP among elderly patients [25]. In contrast, studies showed that VAP develops more in males and independent risk factor [18] [23] [26]. However, as many studies have shown, gender had no effect on the development of pneumonia in this study [12] [14] [22]. This may be due to the sample size. However, the most important risk factor for mechanical ventilation is the underlying medical condition, comorbidities, and disease severity of the patients.

The Apache II scoring system is a scoring system developed to measure the severity of disease in the intensive care unit [27]. High Apache II score is thought to be a risk factor for the development of VAP [24]. While there are studies that found an APACHE II score over 20 indicates the severity of disease [28], and that a high APACHE II score was an independent risk factor for the development of VAP [12], there are also studies that found APACHE II score was not

Table 5. Causative agents in cases with pneumonia.

Agents	n	%
Acinetobacter spp.	8	36.36
P. aeruginosa	6	27.27
K. pneumonia	2	9.09
E. aerogenes	1	4.54
H. influenza	1	4.54
MRSA	1	4.54
Polymicrobial	3	13.63

a risk factor for nosocomial infection but was a risk factor for mortality [22]. In this study, we found that Apache II score was not an independent risk factor for the development of VAP, but whether VAP develops or not is a risk factor for mortality (**Table 3**).

Predisposing risk factors for the development of the disease are diverse in relation to the host, the course of hospitalization, and drug therapy (**Table 6**). There are studies showing that the use of antibiotics previously increases the probability of developing infection with resistant agents [17] [22], as well as studies showing that it does not [14] [21]. In this study, no statistically significant difference was found regarding the increase in the development of VAP in cases with a history of previous antibiotic use. Tracheostomy bypasses normal respiratory defense mechanisms such as oropharynx and cilia and contribute to VAP. Tracheostomy was performed in 36.4% of our cases who developed VAP. Compared to our cases who did not develop VAP (4.3%), tracheostomy was significantly higher, consistent with previous studies [12] [28]. Comorbidities like

Table 6. Comparison of risk factors with mortality.

Mortality		No		Yes		p
		n	%	n	%	
Gender	Male	13	65.0	9	36.0	0.053
	Female	7	35.0	16	64.0	
Previous hospitalization	No	12	60.0	16	64.0	0.783
	Yes	8	40.0	9	36.0	
Previous antibiotic use	No	14	70.0	16	64.0	0.671
	Yes	6	30.0	9	36.0	
Tracheostomy	No	18	90.0	18	72.0	0.260
	Yes	2	10.0	7	28.0	
Diabetes mellitus	No	16	80.0	19	76.0	0.748
	Yes	4	20.0	6	24.0	
Ischemic heart disease	No	18	90.0	20	80.0	0.437
	Yes	2	10.0	5	20.0	
Congestive heart failure	No	17	85.0	18	72.0	0.473
	Yes	3	15.0	7	28.0	
Coma (GCS < 7)	No	16	80.0	11	44.0	0.014*
	Yes	4	20.0	14	56.0	
COPD	No	14	70.0	19	76.0	0.651
	Yes	6	30.0	6	24.0	
Advanced age (>60)	No	12	60.0	5	20.0	0.006*
	Yes	8	40.0	20	80.0	

*: $p < 0.05$.

COPD and diabetes were also found to be risk factors for the development of VAP in studies [11] [17] [28]. The lack of any effect of diabetes and COPD on the development of VAP in our study can be attributed to the low number of patients with COPD. Considering that patients with COPD need longer mechanical ventilation, VAP should be expected to be higher in these patients.

Coma, which is one of the situations in which mechanical ventilation is inevitable, is also defined as another risk factor. In these patients, changes in the defense mechanisms of local airways cause microorganisms to settle and colonize the mucosal surface more easily. In addition, the probability of aspiration and related VAP increases with the suppression of consciousness [17]. In this study, although there was no statistical difference in the rate of VAP in terms of coma, when the values are examined, VAP developed in 12 (66.6%) of 18 patients admitted with a pre-diagnosis of coma.

Despite advances in diagnosis, treatment and prevention, VAP is still an important cause of nosocomial morbidity and mortality [28]. Mortality rates due to VAP are reported to be between 25% and 76% [10] [12] [13]. In this study, the mortality rate in patients with VAP was 72.7%, while it was 39.1% in patients without VAP and mortality rate was significantly higher in patients with pneumonia (**Table 4**). When we look at early and late VAP, there was no significant difference in mortality. Consistent with our findings, İbrahim *et al*. [18] also found no significant difference when comparing mortality in early and late VAP. The mortality rate of patients over 60 years of age is higher than those under 60 years of age among patients who develop VAP [15]. When we compare the mean age values of the cases with mortality, the mean age of the surviving patients with VAP was found to be significantly lower than the non-surviving patients with VAP and non-surviving patients without VAP. According to this result, age is not an independent risk factor for the development of VAP but is a factor that increases mortality (**Table 3**). Although we did not find the Apache II score to be a risk factor for the development of VAP in our study, the mean Apache II scores of the surviving patients with and without VAP were found to be significantly lower than the mean score of the non-surviving patients with and without VAP. This suggests that the Apache II score is not an independent risk factor for the development of VAP but is an independent risk factor for mortality whether or not pneumonia develops (**Table 3**).

The high mortality rates in patients who developed VAP in our study showed us the importance of necessary precautions to reduce the development of VAP. Precautions such as avoiding orotracheal intubation of the patient as much as possible, evaluating the patient for weaning every day, preventing unnecessary patient transfer, raising the head of the bed, providing subglottic secretion drainage and oral hygiene will be effective in reducing and preventing VAP development.

In conclusion, to prevent VAP, patients should be evaluated with anamnesis and laboratory characteristics, potential risks should be determined from the time they enter the intensive care unit, infection control programs should be ap-

plied, surveillance results should be evaluated regularly in each unit and appropriate measures should be taken.

Limitations

There are some limitations in our review. This study was carried out on a small sample in only a short period of time. This research has focused only on the incidence, some risk factors and mortality related to VAP. Other risk factors affecting the development of VAP and VAP treatment methods were not discussed.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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