RESEARCH ARTICLE

Factors Influencing Ventilator-Associated Pneumonia in Cancer Patients

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Abstract

Background: With increasing survival periods and diversification of treatment methods, treatment of critically ill cancer patients has become an important factor influencing patient prognosis. Patients with cancer are at high risk of infections and subsequent complications. This study investigated the incidence and factors contributing to the development of ventilator-associated pneumonia (VAP). Materials and Methods: This retrospective study investigated the incidence of VAP and factors leading to infection in patients admitted to the intensive care unit (ICU) of a cancer center from January 1, 2012 to December 31, 2013. Results: The incidence of VAP was 2.13 cases per 1,000 days of intubation, and 13 of 288 patients (4.5%) developed VAP. Lung cancer was the most common cancer associated with VAP (N=7, 53.9%), and longer hospital stays and intubation were associated with increased VAP incidence. In the group using a "ventilator bundle," the incidence was 1.14 cases per 1,000 days compared to 2.89 cases per 1,000 days without its use; however, this difference was not statistically significant (p=0.158). Age (≥ 65, OR=5.56, 95% confidence interval [CI]=1.29-23.95), surgery (OR=3.78, 95%CI=1.05-13.78), and tracheotomy (OR=4.46, 95%CI=1.00-19.85) were significant VAP risk factors. The most common causative organisms were methicillin-resistant *Staphylococcus aureus* (MRSA) and *Pseudomonas aeruginosa* (N=4, 30.8% each), followed by *Acinetobacter baumannii* and *Candida albicans* (N=2, 15.4% each). Conclusions: The incidence of pneumonia among critically ill cancer patients is highest in those with lung cancer, but lower than among non-cancer patients. The length of hospital stay and time on mechanical ventilation are important risk factors for development of VAP. Although not statistically significant, "ventilator bundle" care is an effective intervention that delays or reduces incidence of VAP. Major risk factors for VAP include age (≥ 65 years), surgery, and tracheostomy, while fungi, gram-negative bacteria, and multidrug-resistant organisms were identified as the major causative pathogens of VAP in this study.

Keywords: Cancer cases - pneumonia - ventilator-associated - risk factors

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Introduction

Due to economic development and lifestyle changes, cancer has become an important health concern in Asia. Increased research on patients with cancer has led to significant developments in its treatment and management (Shin et al., 2010). Despite this progress, cancer remains the disease with the heaviest financial burden and highest mortality in Korea (Cho et al., 2013). As the survival period of cancer patients increases and treatment methods become increasingly diversified, treatment of critically ill cancer patients has become an important factor in their prognosis (Wigmore et al., 2013). Patients with cancer have significantly elevated risks of infections and potential complications. Complicated and multimodal cancer treatments, breakdown of physical barriers such as the mucosa and the integumentary system, neutropenia, immunosuppression, splenectomy, central lines, and local tumors increase the risk of infection in patients with cancer. Patients in hospitals are easily infected even by less virulent organisms, leading to increased morbidity and mortality (Danai et al., 2006; Martin et al., 2003; Safdar & Armstrong, 2001). Critically ill cancer patients are significantly effected by successful ventilator care on the treatment. (Kang et al., 2013).

According to a report from the Korean Nosocomial Infections Surveillance System (KONIS), there were a total of 3,757 cases of nosocomial infections between July 2010 and July 2011 at 72 different intensive care units (ICUs) across the country. Pneumonia was the third most common nosocomial infection, with 687 (18%) cases (Jeon et al., 2012).

Among risk factors for development of ventilator-associated pneumonia (VAP), age, severity of underlying disease, and the duration of mechanical ventilation have been associated with incidence of VAP (Lee, 2008). History of antibiotic use, supine position, and transfer aspiration were also identified as risk factors (Kollef et al., 1997). Chastre and Fagon (2002) similarly identified antibiotics and supine patient position as well as antacid

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use, intubation, nasogastric tube insertion and feeding, and use of certain respiratory equipment such as ventilators with humidifying cascades and nebulizers as risk factors for VAP. Additionally, Harris and Miller (2000) reported contaminated respiratory equipment, ventilators, and hands of care providers as well as aspiration of oropharynx or lower respiratory tract secretions, re-intubation attempts, colonization by gastric bacteria, tube feeding, and use of gloves, water, fluids, and antibiotics as risk factors. Hasan et al. (2012), reporting the results of their study conducted from 2003 to 2009, found unplanned extubation, trauma patients, chronic obstructive pulmonary disease, and use of neuromuscular blocking agents to be risk factors, and tracheostomy, duration of intubation, length of ICU admission, and total length of hospital stay to be statistically significant factors for VAP.

KONIS data cited by Kwak et al. (2010; 2011) identified gram-negative bacilli, primarily Acinetobacter baumannii, as the most common group of VAP-associated pathogens, accounting for over 50% of cases. Chen et al. (2012) also identified Acinetobacter baumannii as the most common pathogen in cases outside of Korea. Maxima et al. (2006), however, found Pseudomonas aeruginosa to be the most common pathogen associated with VAP.

In an effort to prevent VAP, Resar et al. (2005) implemented the Institute for Healthcare Improvement's (IHI) "ventilator bundle" recommendations at 61 hospitals from 2002 to 2004, and reported a statistically significant reduction of VAP from 6.6 cases in 2002 to 2.7 cases in 2004.

Against this background, the present study investigated VAP-related clinical features of cancer patients and analyzed VAP risk factors. Influential factors, such as causative organisms and infection management, were also studied.

Materials and Methods

In this study, approved by the institutional research board of the National Cancer Center (NCC2014-0008) of Korea, a retrospective review was conducted using medical records of patients admitted to ICUs at a cancer center between January 1, 2012 and December 31, 2013 who underwent mechanical ventilation. As the study sought to monitor development of VAP, patients admitted to the ICU with existing pneumonia diagnoses were excluded. Data for factors related to the occurrence of VAP were collected after 48 h of intubation.

Using a structured data collection sheet, information regarding age, gender, type of cancer, level of consciousness, duration of intubation, antibiotic use, antacid use, surgical intervention, steroid use, survival, length of ICU stay, type of ICU, APACHE II score, presence of tracheostomy, use of ventilator bundle, and occurrence of VAP were recorded.

Data were analyzed using Stata release 12.0 (2011. StataCorp LP, College Station, TX, USA), and frequency and percentage were used for technical analyses. Chi-squared and Fisher's exact tests were used to analyze relationships between patient characteristics and occurrence of VAP, while risk factors for development of VAP in cancer patients were identified using regression analysis.

Results

Patient characteristics

During the study period, 288 patients required mechanical ventilation for more than 48 hours for reasons not related to pneumonia; of these, 13 developed ventilator-associated pneumonia, corresponding to 2.13 VAP cases per 1,000 days of intubation. The mean age was 63.0 (±11.1), mean duration of admission and intubation were 25.6 days (±57.5) and 21.2 days (±53.2), respectively, and the mean APACHE II score was 21.0 (±6.3).

The IHI "ventilator bundle" was introduced to the ICU in March 2013. It implemented IHI recommendations for elevation of the head of the bed, daily assessment of readiness to extubate, prophylaxis for peptic ulcer disease and deep venous thrombosis, and daily chlorhexidine oral care (Bird et al., 2010), as well as hand hygiene, maintenance of ventilator circuits, and aspiration. A checklist was used to evaluate component compliance. The "ventilator bundle" was used for 126 of 288 patients (43.8%) in this study.

Risk factors for ventilator-associated pneumonia

Of 13 patients who developed VAP, 10 (76.9%) were male (p=1.00) and those aged ≥ 65 years (76.9%) outnumbered those under 65 (23.1%) (p=0.046). Among different cancer types, lung cancer was dominant (N=7, 53.9%).

Table 1. General Characteristics

Characteristics		VAP		Non VAP		p
Age	<65	3	(23.1)	146	(53.1)	0.046+
	≥65	10	(76.9)	129	(46.9)	
Type of Cancer	Lung	7	(53.9)	100	(36.4)	0.461
	Liver	1	(7.7)	40	(14.6)	
	Brain & Neuro	1	(7.7)	33	(12.0)	
	Hematologic	0	(0.0)	30	(10.9)	
	Stomach	0	(0.0)	21	(7.6)	
	esophageal	1	(7.7)	12	(4.4)	
	Prostate	2	(15.4)	11	(4.0)	
	Breast	0	(0.0)	10	(3.6)	
	Colorectal	1	(7.7)	8	(2.9)	
Length of stay Hosp.						
	3~10	1	(7.7)	111	(40.4)	0.005
	11~30	6	(46.2)	122	(44.4)	
	>30	6	(46.2)	42	(15.3)	
Duration of device use ventilator						
	3~10	3	(23.1)	149	(54.2)	0.027
	11~30	6	(46.2)	96	(34.9)	
	>30	4	(30.8)	30	(10.9)	
Operation	Yes	7	(53.9)	61	(22.2)	0.009
	No	6	(46.2)	214	(77.8)	
Tracheostomy	Yes	10	(76.9)	81	(29.5)	0.001+
	No	3	(23.1)	194	(70.6)	
Application of VAP Bundle						
	Yes	3	(23.1)	123	(44.7)	0.158+
	No	10	(76.9)	152	(55.3)	
APACHE II	0~24	9	(69.2)	212	(77.1)	0.508
	>24	4	(30.8)	63	(22.9)	
Survive	Survive	5	(38.5)	143	(52.0)	0.34
	Death	8	(61.5)	132	(48.0)	

The length of hospital stay was statistically significant (p=0.005), with increased duration directly associated with increased VAP incidence. Similarly, the duration of intubation was also statistically significant (p=0.027), with prolonged intubation associated with higher VAP incidence.

Patients who underwent surgical interventions were more prone to VAP than those who had not (p=0.009), and 10 patients (76.9%) among those who underwent tracheotomy developed VAP, a statistically significant difference (p=0.001) compared to those without.

APACHE II scores were analyzed for 2 groups (≤ 24 and ≥ 25 points) with a cutoff at a predicted mortality of 40%, and revealed no statistically significant differences in 9 cases (69.2%) in the ≤ 24 group and 4 cases (30.8%) in the ≥ 25 group. Although there were fewer VAP cases in the group implementing the IHI "ventilator bundle" (3 cases, 23.1%) compared to 10 cases (76.9%) in the group without, the difference was not statistically significant (p=0.158).

No statistically significant differences were found between groups using antibiotics or antacids as most patients received these treatments. There were 2 cases (15.4%) of VAP in patients administered a single antibiotic agent versus 11 cases (84.7%) among those using 2 or more antibiotics, but this difference was not found to be statistically significant (p=1.000). No statistically significant difference was observed for steroid use, with 7 cases (53.9%) of VAP in the steroid use group and 6 in the non-steroid group. Although VAP was not a direct cause of death for any study patients, there were 8 deaths (61.5%) among those affected by VAP.

Results of the logistic regression

Logistic regression was performed on variables shown to be significant by univariate analysis. As a result, risk factors for the development of VAP included age (≥ 65, OR=5.56, 95% confidence interval [CI]=1.29-23.95), surgical intervention (OR=3.78, 95%CI=1.05-13.68), and tracheostomy (OR=4.46, 95%CI=1.00-19.85), corresponding to 5.56-, 3.78-, and 4.46-fold VAP incidences, respectively, in these high-risk groups (Table 2).

Table 2. Risk of Factors of VAP

Variables		Coeff.	Std. Err.	p	OR (95% CI)
Age	≥65	2.3	4.14	0.021	5.56 (1.29-23.95)
Length of stay Hospital					
	11-30	0.96	4.74	0.336	3.58 (0.27-48.03)
	>30	1.13	8.13	0.26	5.42 (0.29-102.53)
Duration of device use ventilator					
	11-30	0.47	1.44	0.639	1.55 (0.25-9.61)
	>30	0.36	1.89	0.716	1.55 (0.14-16.79)
Operation	Yes	2.03	2.48	0.043	3.78 (1.05-13.68)
Tracheostomy	Yes	1.96	3.4	0.049	4.46 (1.00-19.85)

Table 3. Logistic Regression

		VAP	Non VAP	p
MRSA		4 (30.8)	52 (18.9)	0.014*
Klebsiella pneumoniae		0 (0.0)	21 (7.7)	
Pseudomnas aeruginosa		4 (30.8)	22 (8.0)	
Acinetobacter baumannii		2 (15.4)	7 (2.6)	
Candida albicans		2 (15.4)	67 (34.4)	
VRE		1 (7.7)	47 (17.1)	
Others		0 (0.0)	41 (14.9)	
Non		0 (0.0)	18 (6.6)	
Positive	1	1 (7.7)	101 (36.7)	0.037*
	≤2	12 (92.3)	174 (62.3)	

Pathogens in VAP

Although C. albicans was most frequently isolated in the study population, MRSA and P. aeruginosa were the most common causative agents of VAP, with 4 cases (30.8%) each. Those with 2 or more isolated strains (12 cases, 92.3%) were associated with increased incidence of VAP compared to those with a single isolated strain (1 case, 7.7%), a statistically significant difference (p=0.037) (Table 3).

Discussion

This study sought to understand the characteristics of patients who developed VAP after intubation at a cancer center and thus identify risk factors for developing VAP. Although numerous studies report VAP incidence, there are significant differences in the reported numbers due to the differences in characteristics among different ICUs and hospitals (Chastre & Fagon, 2002).

Maxima et al. (2006) reported a VAP incidence of 16.6 cases per 1,000 days of intubation, while Hasan et al. (2012) reported only 6.3 cases. This study found a VAP incidence of 2.13 cases per 1,000 days of intubation, lower than the 2012 KONIS reported 2.24 cases per 1,000 days intubation in a medium-sized hospital (400-699 beds).

In this study, age, length of hospital stay, duration of intubation, surgical intervention, and tracheostomy were found to be risk factors for VAP. Patients aged 65 years or more were at 5.56-fold risk for developing VAP. A previous study (Lee, 2008) identified the 45-64 year age bracket as the group most likely to develop VAP; a foreign report (Tablan et al., 2004) also identified infants and the elderly (≥ 65 years) as groups most vulnerable to VAP, also consistent with the results of this study, although this study included only patients greater than 18 years of age. In this study, patients aged 65 years or more were found to be have risk of VAP in 5.56 times(p=0.021), patients with lung cancer were found to be 5.81 times(Wang et al., 2014) compared to patients aged 60 years or more (p=0.018).

VAP incidence increased with increased duration of hospital stay and intubation (p<0.05), consistent with a previous report that the risk of VAP increases by 1% for every day a patient remains on mechanical ventilation (Harris & Miller, 2000).

VAP occurred more readily when the duration of intubation exceeded 10 days. In contrast to a previous study that found a mean intubation duration until VAP onset of 4.6 days (Cook, 2000), the mean was 39.5 days in this study. Compared to previous studies that estimated the average duration of intubation to be 3-4 days (Seo, Choi & Kim, 2011; Lee, 2008), this study estimated the mean duration to be 21.2 days, significantly higher than

previous reports. Those who did not receive "ventilator bundle" care developed VAP an average of 31.7 days after being placed on mechanical ventilation, while the mean duration of intubation until onset of VAP was 65.7 days in the group that received "ventilator bundle" care.

Hasan et al. (2012) implemented the IHI "ventilator bundle" to reduce the incidence of VAP in their study from 2003 to 2009, and reported a reduced VAP incidence from 19.1 cases per 1,000 days of intubation in 2003 to 6.3 cases in 2009. Bird et al. (2010) implemented the "ventilator bundle" in surgical and trauma ICUs from 2006 to 2009 and found a statistically significant decrease in VAP incidence, from 12 cases per 1,000 days of intubation in 2006 to 4.9 cases in 2009. Ban (2007) conducted a study in Korea to develop and evaluate a program to prevent VAP and reported an intervention program effectiveness that reduced VAP incidence from 17.38 cases per 1,000 days before intervention to 11.04 cases after 3 months of intervention, although these reductions were not statistically significant. The present study also found a reduced incidence of VAP in the group that received "ventilator bundle" care compared to the group that did not (1.14 vs. 2.89 cases per 1,000 days of intubation), but this difference was not statistically significant (p=0.158). Despite differences in the absolute number of VAP cases between the "ventilator bundle" and non-"ventilator bundle" groups (3 and 10 cases, respectively), more exact comparisons could not be made because of differences in the number of participants and the duration of observation for those who received the "ventilator bundle" care (126 participants, 43.8%) and those who did not (162 participants, 56.3%). A longer-term comparative observation study is necessary for a more detailed analysis of the effects of "ventilator bundle" care.

While existing studies reported that use of antibiotics, antacids, and steroids influenced development of VAP (Chastre& Fagon, 2002; Lee, 2008), no significant differences were found in the current study.

APACHE II is a scoring tool used to predict prognosis and mortality of patients admitted to the ICU (Bufalo & Morelli, 1995; Shin et al., 1998). This study used a cutoff predicted mortality rate of 40% to compare the incidence of VAP in 2 APACHE II score groups (≤ 24 and ≥ 25). No statistically significant intergroup difference was observed, in contrast to a previous study reporting an increased incidence of VAP with higher APACHE II scores (Alok et al., 2011).

A cancer type-dependent comparison of the likelihood of developing VAP resulted in the finding of 7 cases (53.9%) of VAP in patients with lung cancer. This finding agrees with previous research findings that pre-existing cardiopulmonary disease is a risk factor for VAP (Fagon, 2002), and that 90% of advanced lung cancer patients require mechanical ventilation and are associated with poor treatment outcomes (Kim et al., 2014). Lung cancer is reported to have higher mortality compared to other types of cancers (Jung et al., 2010), and further research is warranted to investigate this increased mortality and its possible relationship with VAP.

With 69 cases (24.0%), C. albicans was most commonly isolated pathogen in this study; however, the most common causative agents for VAP were MRSA and P. aeruginosa with 4 cases (30.8%) each, followed by A. baumannii and C. albicans with 2 cases (15.4%) each. KONIS data cited by Kwak et al. (2010 and 2011) and Jeon et al. (2012) reported 28% of all nosocomial infections to be fungal in origin, and C. albicans to be a main causative organism for urinary tract infections. Candida species are the most common pathogen associated with fungal pneumonia, which occurs at a rate of 0.9-2.6%, although the number is decreasing. In this study, however, C. albicans pneumonia was responsible for 15.4% of VAP cases, greater than the reported KONIS prevalence. Given the high number of fungal organisms such as C. albicans isolated in this study, measures against cross-infection need to be established.

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