Int J Clin Exp Med 2018;11(5):4695-4701
www.ijcem.com /ISSN:1940-5901/IJCEM0075770

Original Article

Ventilator-associated pneumonia in premature newborns admitted to the intensive care unit

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Received March 10, 2018; Accepted April 7, 2018; Epub May 15, 2018; Published May 30, 2018

Abstract: Objective: To explore the clinical features and prevention measures of ventilator associated pneumonia (VAP) of premature newborns treated with mechanical ventilation (MV). Methods: From June 2010 to June 2017, a retrospective analysis of 200 premature newborns, including 56 critically ill premature newborns with VAP who received MV treatment and 144 premature newborns who received MV treatment but no VAP occurring served as the control. Of the 56 infants, 20 and 36 were treated with and without antibiotic, and the two groups were labeled as the VAP+Ab group and the VAP group, respectively. The gestational age, birth weight, Apgar score and primary disease of the premature were recorded. Additionally, the survival rates, MV days, APACHE II scores, and the hospital stays were compared. Results: The three groups exhibited no significant differences in the gestational ages, birth weights, Apgar scores. The premature newborns without VAP occurring (the control) had a survival rate of approximately 90%, much higher than the VAP group (60%) (P=0.045). Prophylactic use of antibiotics could significantly improve (P=0.032), with the survival rate of the premature newborns with VAP reaching nearly 85%. Compared with the VAP group, the control group exhibited a shorter MV day (P<0.001), hospital stay (P<0.001), and lower APACHEII score (P=0.025). However, prophylactic use of antibiotics significantly shortened the MV day (P=0.001), hospital stays of the VAP-associated premature newborns (P<0.001), and also lowered their APACHE II scores (P=0.034), suggesting the prophylactic use of antibiotics may be a potential way to improve the health status of the infants. Conclusion: As compared to their counterparts without VAP, the premature infants associated with VAP had lower survival rates, longer MV days, and hospital stays. The prophylactic use of antibiotics, however, can significantly improve the survival rate of premature infants associated with VAP, lower their MV days and hospital stays, and improve their health status.

Keywords: Premature infants, neonatal intensive care unit, ventilator-associated pneumonia

Introduction

The most premature infants have a lower body weight than the normal babies, leading to higher incidences of some diseases. The anatomical and physiological characteristics of premature infants may increase their death rates, to 12.7-20.8% [1, 2]. Furthermore, the non-well developed respiratory system and circulatory systems may also increase their vulnerability to the outside adverse stimulus [3, 4].

As a consequence, premature infants need special nursing in Neonatal Intensive Care Unit (NICU) where MV (mechanical ventilation) treatment is generally employed to improve the survival rates of the newborns with respiratory failure [5]. However, MV may cause some infections of lower respiratory tract, generally known as ventilator-associated pneumonia (VAP) [6]. The infections stem mainly from the colonization of some pathogens. In general, the VAP pathogenesis can be outlined as following: when the newborns are treated with MV, tracheal intubation may cause damage of their respiratory tract mucus and the pathogens which originally colonized in their partes oralis are inhaled deep within the respiratory tract and even to the lung. If the defense mechanism of their lungs is not strong enough to resist the pathogens, ventilator-associated pneumonia would occur [7, 8].

According to an international report, the incidence of VAP in premature infants admitted to

Table 1. The basic information of the newborns

	Gestational age (week)	Body weight at birth (kg)	Apgar score at birth
Control (n=144)	34.4±2.4	3.027±0.320	5.2±2.7
VAP (n=36)	35.2±1.8	3.208±0.197	4.7±3.2
VAP+Ab (n=20)	35.0±2.2	3.138±0.218	5.1±2.8
F value	0.113	0.397	0.025
P value	0.895	0.689	0.976

Note: Control: The newborns without VAP diagnosed; VAP: the newborns diagnosed with VAP but not subjected to antibiotics treatment; VAP+Ab: The newborns diagnosed with VAP and subjected to antibiotics treatment.

NICU nursing is in the range of 9% to 70%, with a death rate of 20-71%. In comparison, the VAP incidence in China is reported to be about 48.5% and the death rate is approximately 37.5%. Once diagnosed with VAP, the newborns must be subjected to a longer time of MV treatment, leading to a delayed time of NICU nursing, during which the death rate of the treated newborn may increase [9]. At present, the prophylactic use of antibiotics has been proven to reduce the complications and death rates in some surgery cases. However, whether the use of antibiotics can reduce the VAP incidence in premature infants has been seldom reported. As a result, the study was to investigate the effects of the prophylactic use of antibiotics on the clinical features of the premature newborns with VAP. This study may provide some clinical information to help develop the prophylactic measures to alleviate the VAP symptoms of premature newborns.

Clinical data collection and methods

Clinical data collection

From June 2010 to June 2017, there were a total of 200 premature infants born in Children's Hospital of Shanghai and admitted to conventional mechanical ventilation (CMV) treatment. Among these babies, 56 were diagnosed with VAP, including 25 males and 31 females. In these babies, one group including 8 males and 12 females was subjected to antibiotics treatment while the other group including 17 males and 19 females did not. The 144 premature babies without VAP included 70 males and 74 females, and they served as the control. Moreover, the parents of all the premature babies involved in this study had signed the informed consent form, and the study was approved by the Ethics Committee of Children's Hospital of Shanghai.

Inclusion criteria: (1) The premature infants, (2) The newborns who were critically ill, (3) The newborns who needed MV treatment, (4) The newborns diagnosed with VAP. The diagnostic criteria of VAP was as follows: invasive mechanical ventilation was conducted for at least 48 h until within 48 h after extubation and the patients who were diagnosed with at least two of the following clinical features: (1) The body temperature was at least 1°C higher than the normal value, or the body temperature was ≥38°C; (2) Numeration of leukocyte in peripheral blood was greater than $10*10^9 \cdot L^{-1}$ or lower than $4*10^9 \cdot L^{-1}$; (3) To the smear of the purulent sputum in the airways, there were more than 25 leukocytes and less than 10 pavement-epithelium cells observed in low-power field; (4) Chest x-ray check indicated new or progressive infiltration lesions [10]. Additionally, the patch shadow of the chest x-ray check should be combined with at least two of the three following features: (1) Leukocyte concentration greater than $12*10^9 \cdot L^{-1}$; (2) The body temperature ≥38.3°C; (3) Purulent secretions observed in bronchus. Moreover, diagnostic criteria of VAP also included the etiological diagnosis. In brief, after sampling the pleural-fluid and the blood using a bronchofibroscope, the samples were cultured and the results satisfied at least one of the following features: (1) The count of bacterial colonies was $\geq 10^3$ CFU/mL; (2) When using bronchoalveolar lavag as the culture liquid, the count of bacterial colonies was greater than 10^4 CFU/mL; (3) The count of bacterial colonies was no less than 10^5 or 10^6 CFU/mL when using endotracheal suction fluids as the specimen; (4) The pathogens could be observed after culturing the blood and purulent liquid specimen [11].

Exclusion criteria: (1) The full-term newborns; (2) The premature newborns who were diagnosed with severe cardiopulmonary respiratory and circulatory failure; (3) The MV time was less than 48 h; (4) The newborns who were diagnosed with pneumonia within 48 h of MV treatment; (5) The newborns who died within 48-72 h after endotracheal intubation [12, 13].

MV methods

The breathing machines used in this study were purchased from GALILEO Company (the U.S.A.).

Table 2. The numbers of the premature newborns with primary diseases

Name of the primary diseases	Control (n=144)	VAP (n=36)	VAP+Ab (n=20)	X^2	*P* value
Pulmonary hyaline membrane disease	52	11	9	3.844	0.986
Pneumorrhagia	12	3	1		
Intracranial hemorrhage	16	6	2		
Central nervous system infections	7	4	1		
Meconium aspiration syndrome	22	6	3		
Apnea	28	8	4		
Asphyxia of newborn	3	1	1		

Note: Control: The newborns without VAP diagnosed; VAP: the newborns diagnosed with VAP but not subjected to antibiotics treatment; VAP+Ab: The newborns diagnosed with VAP and subjected to antibiotics treatment.

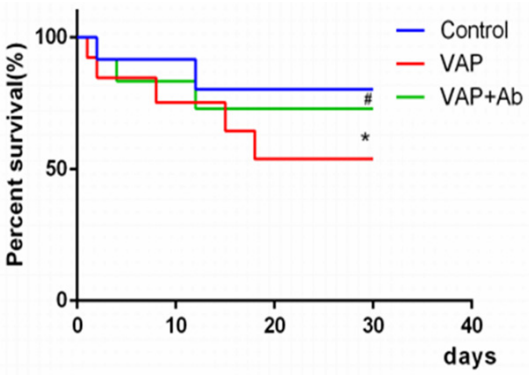

Figure 1. Survival rate of the premature infants within a month of NICU. Control: The newborns without VAP diagnosed; VAP: The newborns diagnosed with VAP but not subjected to antibiotics treatment; VAP+Ab: The newborns diagnosed with VAP and subjected to antibiotics treatment. *P<0.05 means a significant difference between the control group and the VAP group; #P<0.05 represents a significant difference between the VAP group and the VAP+Ab group.

The ventilation models and parameters were regularly adjusted according to the body weights and conditions of the newborns. The original parameters were set as following: 30-50% of oxygen inhalation concentration; a breathing rate of 25-30 times per min. Also, the inspiratory-to-expiratory ratio was 1:1.5-1:2. Ventilator weaning and antibiotic treatments were performed according to changes in the condition of the newborns.

Statistical analysis

All the data were analyzed by using SPSS 19.0 software. As for the measurement data, LSD-t test was carried out to analyze the differences between the groups. When it came to the enumeration data, Chi-square test (X^2 test) was performed to analyze the differences between the groups.

Results

Baseline characteristics

From June 2010 to June 2017, a total of 200 premature newborns were hospitalized in Children's Hospital of Shanghai. Their basic information was summarized in **Tables 1**, **2**. After MV treatment, there were 144 newborns who were not diagnosed with VAP (the control group), including 70 males and 74 females. Among these newborns, the average gestational age was 34.4±2.4 weeks, and the average body weight was 3.027±0.320 kg. The Apgar score was 5.2±2.7. Additionally, there were 56 premature newborns diagnosed with VAP, including 25 males and 31 females. Among these newborns, 20 were treated with antibiotics (VAP+Ab), including 8 males and 12 females. Their average gestational age, body weight and Apgar score were 35.0±2.2 weeks, 3.138±0.218 kg and 5.1±2.8, respectively. In comparison, 36 newborns (17 males and 19 females) were not subjected to the antibiotics treatment, and their average gestational age, body weight and Apgar score were 35.2±1.8 weeks, 3.208±0.197 kg and 4.7±3.2, respectively. However, there were no significant difference observed between the VAP+Ab group and the VAP group in terms of average gestational age, body weight, and Apgar score. As shown in **Table 2**, the primary diseases of the 200 newborns included 72 cases of hyaline membrane disease, 16 cases of pulmonary hemorrhage, 24 cases of intracranial hemorrhage, 12 cases of central nervous system infection, 31 cases of meconium aspiration syndrome, 40 cases of apnea and 5 cases of asphyxiation, with no difference in primary disease (P=0.986).

The survival rates of the premature newborns

After the premature newborns received NICU nursing, their survival rates were regularly recorded within a month. As shown in **Figure 1**,

Table 3. The multiple comparison (LSD) of MV days of different groups

(I) group	(J) group	Mean difference (I-J)	SD	Significance	95% confidence intervals	
					The lower limit	The upper limit
1.00	2.00	-21.10000*	1.77012	<0.001	-25.4313	-16.7687
	3.00	-7.80000*	1.77012	0.005	-12.1313	-3.4687
2.00	1.00	21.10000*	1.77012	<0.001	16.7687	25.4313
	3.00	13.30000*	1.77012	<0.001	8.9687	17.6313
3.00	1.00	7.80000*	1.77012	0.005	3.4687	12.1313
	2.00	-13.30000*	1.77012	<0.001	-17.6313	-8.9687

Note: Means a significant difference (*P<0.05). 1.00: The control group; 2.00: The VAP group; 3.00: The VAP+Ab group.

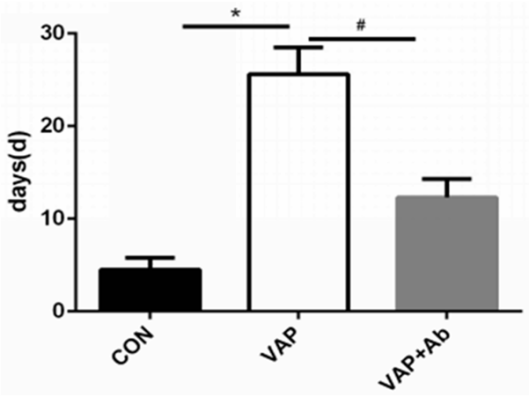

Figure 2. Significance comparison of MV days between different groups. Con: The newborns without VAP diagnosed; VAP: The newborns diagnosed with VAP but not subjected to antibiotics treatment; VAP+Ab: The newborns diagnosed with VAP and subjected to antibiotics treatment. *P<0.05 means a significant difference between the control group and the VAP group; #P<0.05 represents a significant difference between the VAP group and the VAP+Ab group.

after a month, the survival rate of the newborns in the control group was 90%, significantly higher (P=0.045) than that in the VAP group (only 60%). However, the VAP+Ab group had a survival rate of approximately 85%, much higher than the VAP group (P=0.032).

MV days

After the premature newborns were subjected to NICU nursing, the MV days were regularly recorded, and the results and their multiple comparisons are shown in **Table 3**, **Figure 2**, respectively. The MV day of the control group was the lowest, with a value of 4.5±1.3 days, followed by the VAP+Ab group (12.3±2.0 days) and the VAP group (25.6±2.9 days). It was also observed that the MV day of the control group was shorter than that of the VAP group (P<0.001). Furthermore, when treated with antibiotics, the newborns with VAP needed significantly shorter MV day than the VAP group (P=0.001).

APACHE II evaluation

The APACHE II evaluation was composed of three parts including the acute physiology evaluation, age and chronic health evaluation. The final result was the combination of the three parts: the higher the APACHE II score was, the more severe the condition of a patient was. Acute Physiology Score (APS) include 12 physiological parameters, among which, the body temperature, heart rate, breathing rate, and blood pressure are generally regarded as the fundamental vital signs of patients. In this section, therefore, APACHE II was employed to evaluate the vital signs of the newborns and the multiple comparison analysis results are listed in **Table 4**, **Figure 3**. The APACHE II score of the control group was 8.8±3.6, significantly lower (P=0.025) than that of the VAP group (17.2±3.8). As expected, the VAP+Ab group had a significantly lower (P=0.034) APACHE II score (9.4±3.0), indicating the prophylactic use of antibiotics had a marked alleviation effect on the VAP associated premature newborns.

Hospital stay

After the premature newborns received MV and antibiotics treatments in NICU, the hospital stays of the babies were recorded, and multiple comparison results are shown in **Table 5**, **Figure 4**. The hospital stay of the control group was 16.3±3.2 days, and that of the VAP group and VAP+Ab group were 56.3±4.9 and 27.8±3.2 days, respectively. The finding suggest that prophylactic use of antibiotics could ameliorate the condition of the premature newborns with

Table 4. The multiple comparison (LSD) of APACHEII scores of different groups

(I) group	(J) group	Mean difference (I-J)	SD	Significance	95% confidence intervals	
					The lower limit	The upper limit
1.00	2.00	-8.40000*	2.84410	0.025	-15.3593	-1.4407
	3.00	-0.60000	2.84410	0.840	-7.5593	6.3593
2.00	1.00	8.40000*	2.84410	0.025	1.4407	15.3593
	3.00	7.80000*	2.84410	0.034	0.8407	14.7593
3.00	1.00	0.60000	2.84410	0.840	-6.3593	7.5593
	2.00	-7.80000*	2.84410	0.034	-14.7593	-0.8407

Note: Means a significant difference (*P<0.05). 1.00: The control group; 2.00: The VAP group; 3.00: The VAP+Ab group.

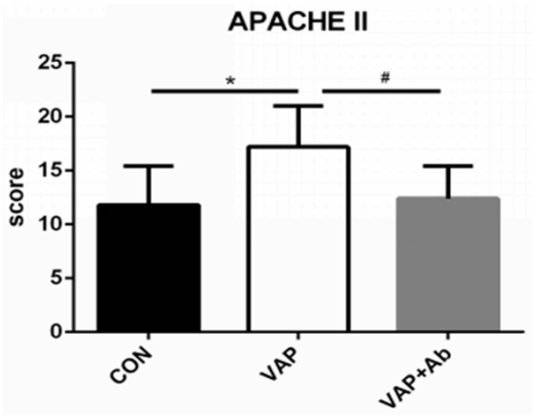

Figure 3. Significance comparison of APACHE II scores between different groups. Con: The newborns without VAP diagnosed; VAP: The newborns diagnosed with VAP but not subjected to antibiotics treatment; VAP+Ab: The newborns diagnosed with VAP and subjected to antibiotics treatment. *P<0.05 means a significant difference between the control group and the VAP group; #P<0.05 represents a significant difference between the VAP group and the VAP+Ab group.

VAP, thereby significantly reducing their hospital stays (both P<0.001).

Discussion

As an important treatment in NICU, MV has saved thousands of lives of critically ill newborns. Sometimes, however, MV may cause some serious complications. At present, there are mainly three theories of the mechanism of ventilator-induced lung injury, including pulmonary barotrauma and volotrauma, atelectrauma, and lung bio trauma [14-16]. The pulmonary barotrauma is possibly due to the improper use of respirators, thus leading to the rupture of pulmonary alveoli and further causing interstitial emphysema, mediastinal emphysema, spontaneous or tension pneumothorax [17, 18]. One of the prophylactic measures is to maintain the blood gas on the normal levels by using a relatively low pressure of MV. Additionally, a report suggested that MV may cause additional strain and stress on the lung, causing some damage of alveolar epithelial cells and capillary endothelial cells, further triggering wide biological response such as the cascade activation of proinflammatory factors, which could aggravate lung injury and even lead to multiple organ dysfunction syndrome [19]. These proinflammatory factors can aggravate the lung damage and even induce the multiple organ dysfunction syndrome. For example, some pathogens originally existing in the upper airway can be transferred to lower airways through trachea cannula, thus causing lung infections. Generally, these pathogens mainly stem from the unclean sputum-absorbking tubes, apparatuses, etc. They are mostly bacilli and streptococcus or other gram-negative bacilli, with strong resistance against drugs [20]. Thus, the significantly increased survival rate, decreased MV days, and hospital stays of the premature newborns were probably because the use of antibiotics greatly inhibited the pathogens which were responsible for respiratory infections.

In this study, we investigated the prophylactic effects of the antibiotics on the reduction of the VAP symptoms of premature newborns. However, it is worth noting that the use of antibiotics for a long time can induce the resistance of the pathogens. So far, there has been no report demonstrating the effects of antibiotics on newborns. As a result, this study for the first time used antibiotics to clinically prevent the VAP symptoms of the premature newborns. However, although the effects of the prophylactic use of antibiotics on the premature new-

Table 5. The multiple comparison (LSD) of hospital stays of different groups

(I) group	(J) group	Mean difference (I-J)	SD	Significance	95% confidence intervals	
					The lower limit	The upper limit
1.00	2.00	-40.00000*	3.14431	<0.001	-47.6938	-32.3062
	3.00	-11.50000*	3.14431	0.011	-19.1938	-3.8062
2.00	1.00	40.00000*	3.14431	<0.001	32.3062	47.6938
	3.00	28.50000*	3.14431	<0.001	20.8062	36.1938
3.00	1.00	11.50000*	3.14431	0.011	3.8062	19.1938
	2.00	-28.50000*	3.14431	<0.001	-36.1938	-20.8062

Note: Means a significant difference (*P<0.05). 1.00: The control group; 2.00: The VAP group; 3.00: The VAP+Ab group.

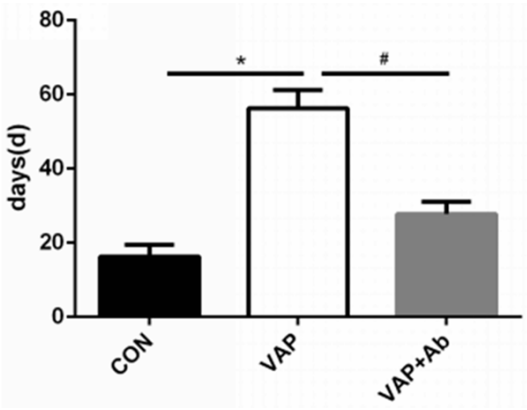

Figure 4. Significant comparison of hospital stays between different groups. Con: The newborns without VAP diagnosed; VAP: The newborns diagnosed with VAP but not subjected to antibiotics treatment; VAP+Ab: The newborns diagnosed with VAP and subjected to antibiotics treatment. *P<0.05 means a significant difference between the control group and the VAP group; #P<0.05 represents a significant difference between the VAP group and the VAP+Ab group.

borns with VAP were well investigated, it needs further exploration of whether the prophylactic use of antibiotics should be approved to be applied in NICU nursing. Because it is still unclear whether the prophylactic use of antibiotics has adverse effects on the function of the liver and lung of the newborns.

Moreover, in this study APACHE II evaluation was employed to assess the vital signs of the premature newborns. APACHE II consists of the acute physiology evaluation, age and chronic health evaluation. The overall evaluation score can be obtained through summing the individual score of the three parts. In acute physiology score evaluation, body temperature, heart rate, breathing rate, and blood pressure can represent fundamental vital signs of patients, therefore, they were widely regarded as main indicators of a patient's condition [21]. Due to the reliability and prevalence of APACHE II, this study used APACHE II evaluation to reflect the condition of the premature newborns: the higher the APACHE II score was, the more severe the condition of a newborn was. Compared with the control group, the VAP group had a significant higher APACHE II score, indicating VAP significantly increase the death risk of the premature newborns, which was in line with a study of Kim [22].

In NICU nursing, the premature newborns diagnosed with VAP had a higher death rate as compared to those newborns without VAP occurring. Moreover, the occurrence of VAP significantly prolonged the MV and hospital stays of the premature newborns, and worsened their primary diseases. However, prophylactic use of antibiotics could markedly decrease the death rate of the VAP-associated premature newborns, shorten the MV days and hospital stays, and ameliorate the related primary diseases. Overall, prophylactic use of antibiotics exhibits a great potential in alleviating the VAP symptoms of the premature newborns receiving MV treatment.

Disclosure of conflict of interest

None.

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