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Risk factors and clinical outcomes of ventilator associated pneumonia in neonates in the Neonatal Intensive Care Unit of Dr. Soetomo Hospital Surabaya

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ABSTRACT

Introduction: Ventilator-associated pneumonia (VAP) is a hospital-acquired infection in mechanical ventilation for more than two consecutive days, resulting in increased mortality and treatment costs. This study aimed to analyse the risk factors and clinical outcomes of neonatal with ventilator associated pneumonia in the neonatal intensive care unit (NICU).

Methods: A case-control study was conducted on neonates who had mechanical ventilators installed for more than two consecutive days, from January 2020 to December 2021, at Dr. Soetomo Hospital, Surabaya. The risk factors studied were duration of stay in the NICU, reintubation, duration of ventilation before VAP, rate of prematurity, low birth weight, enteral feeding, and underlying disease. The clinical outcomes studied were the duration of hospital stay and the total ventilation duration.

Results: The study subjects were 135 neonates consisting of 45 cases of VAP and 90 non-VAP. Significant risk factors were duration of NICU stay ($p<0.001$), duration of ventilation before VAP ($p=0.002$), and rate of prematurity ($p=0.024$). Multivariate analysis found no independent risk factors for VAP. Hospital stay duration ($p<0.001$) and ventilation duration were significantly correlated with the incidence of VAP ($p<0.001$).

Conclusion: Risk factors for neonatal VAP were the duration of NICU stay, duration of ventilation prior to VAP occurrence, and degree of prematurity. The impact of VAP was longer duration of hospitalisation and duration of ventilation.

Keywords: ventilator-associated pneumonia, neonates, neonatal intensive care unit.
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INTRODUCTION

Ventilator-associated pneumonia (VAP) is a common and severe complication in mechanically ventilated neonates[1] and the second-most common hospital-acquired infection (HAIs) in neonatal intensive care unit (NICU) patients.[2] Ventilator-associated pneumonia is defined as pneumonia that occurs after two calendar days of being attached to an invasive mechanical ventilator.[3] Ventilator-associated pneumonia in neonates will affect morbidity, mortality, length of stay, and hospital costs.[4] Ventilator-associated pneumonia occurs in one third of cases of nosocomial infection in neonates.[4] The rate of occurrence of neonatal VAP is 6.8% to 79%.[1,5,6] The highest VAP occurrence rate was in the neonatal age group (23.3%) compared to infants aged one month to 1 year (3.2%) and children aged one year to 18 years (8.3%).[1] Studies in developing countries report an incidence even up to 37,25%.[7]

Various study results were also obtained in studies that focused on identifying risk factors. The effect of weight, gestational age, reintubation, enteral feeding, and underlying disease on the incidence of VAP is still different in several studies.[1,3,8,9] Some studies also mention risks associated with intubation frequency, transfusion frequency, and ventilation duration. Only duration of ventilation was consistently identified as a significant risk factor, but the available studies have not been able to distinguish duration of ventilation as a risk factor for VAP or as a clinical outcome.[7,10,11] Based on this background, this study aims to assess the risk factors and clinical outcomes of VAP in neonates.

METHODS

This case-control study was conducted by reviewing the medical records of NICU patients at Dr. Soetomo Hospital from January 2020 to December 2021. The neonatal intensive care unit of Dr. Soetomo Hospital is a tertiary referral NICU in education centre hospital. All neonates mechanically ventilated by artificial airway via endotracheal tube or tracheostomy for more than two calendar days were included in this study. The samples were divided into a case group that experienced VAP and a control group that did not experience VAP. Referral cases with conditions already intubated at referring hospitals and cases with clinical pneumonia before ventilator installation were excluded.

Research data in the form of medical

records, daily clinical developments, and results of laboratory, microbiological, and radiological investigations were obtained from paper and electronic documents. Radiological results were reviewed from the radiology report. The researcher reviewed each medical record to sort out cases where VAP occurred based on PNU-1, 2, and 3 criteria set by the Centers for Disease Control and Prevention (CDC).[3] In both cases of VAP and non-VAP, identification of the risk factor variables studied was carried out, namely duration of stay in the NICU before VAP, reintubation, duration of ventilation before VAP, low birth weight, prematurity, underlying disease. The outcomes were duration of hospital stay, duration of total NICU stay, and duration of total ventilation.

This research adopted study by Thatrimontrichai et al, 2017 with operational definition of duration of ventilation to distinguish duration of ventilation as a risk factor or a clinical outcome.[12] The duration of ventilation before VAP was used in the case group and the duration of total ventilation in the control group.[12] The same method was applied to the variable duration of stay in the NICU. Prematurity was divided into premature, which consists of highly preterm (<28 weeks), very preterm (28-32 weeks), moderately preterm (32-34 weeks), late preterm (34-37 weeks), and term (>37 weeks). Infant birth weight was divided into <1000 grams (extremely low birth weight), 1000-1499 grams (very low birthweight), 1500-2499 grams (low birth weight), and ≥ 2500 grams.

Data was recorded, collected, and grouped according to research objectives. The relationship between risk factors and clinical outcomes with the incidence of neonatal VAP was analysed using Chi-square analysis. The analysis results were considered statistically significant if the p-value <0.05. Multivariate analysis between the dominant risk factors was carried out using logistic regression analysis.

RESULTS

The research was carried out by reviewing the medical records of NICU patients at Dr. Soetomo Hospital. Data was taken from medical record status by providing data on 310 neonates fitted with ventilators. There were only 279 medical records status that could be found by officers. Of the 279 status, 170 medical records status met the inclusion criteria, 77 did not meet the inclusion criteria, and 32 were excluded. VAP cases that met the inclusion criteria were 45 cases, and the remaining 126 were randomised to take 90 control samples.

Most of the sex in the VAP group were female (62.2%), but in the non-VAP group, most were male (60%). Most of the delivery methods were caesarean sections in the VAP (71.1%) and non-VAP groups (67.8%). Most of the appearance, pulse, grimace, activity, respiration (APGAR) scores in the VAP (82.2%) and non-VAP (56.7%) groups were ≥7. Most amniotic fluids were evident in the VAP (86.7%) and non-VAP (76.7%) groups. The primary characteristics of the research subjects can be seen in Table 1.

The total study duration of NICU stay ranged from 3 to 107 days, with a median of 13 days (SD 15.4). Most of the total duration of care in the NICU was in the VAP group, which was >13 days (84.4%), but in the non-VAP group, which was ≤ 13 days (72.2%). There was a significant relationship between the duration of total stay in the NICU and the incidence of VAP (p<0.001). This study also analysed the duration of stay in the NICU before the onset of VAP to differentiate the total duration in the NICU as a clinical outcome and the duration of stay in the NICU before VAP as a risk factor. The median stay in the NICU before VAP was shorter, namely, ten days. Most of the duration of stay in the NICU before VAP in the VAP group was more than 10 days (64.4%), and conversely, most of the non-VAP group was ≤ 10 days (38.9%). There was a significant relationship between the duration of the NICU stay before VAP and the incidence of VAP (p=0.005).

The duration of ventilation before VAP combined between the two groups ranged from 3 to 84 days with a median of 9 days (SD 12.8). Most of the duration of ventilation before VAP in the VAP group was >9 days (60%), but in the non-VAP group, it was ≤ 9 days (67.8%). There is a significant relationship between the duration of ventilation before VAP and the incidence of VAP (p=0.002). Reintubation frequency in this study was 112 subjects (82.9%). Most were reintubated in the VAP group (73.3%) and non-VAP (82.9%). There was a significant relationship between reintubation and the incidence of VAP (p=0.035).

Most of the babies in the VAP and non-VAP groups were low birth weights. There was no significant relationship between birth weight and the incidence of VAP (p=0.441). Gestational age in this study ranged from 25-42 weeks with a median of 35 weeks (SD 4.3). The majority of the study subjects were premature in the VAP (57.8%) and non-VAP groups (65.6%). There was no significant relationship between prematurity and the incidence of VAP (p=0.381). Follow-up test by classifying gestational age according to the degree of prematurity. Of the 86 babies classified as premature, 9 (6.7%) were extreme preterm, 34 (25.2%) were very preterm, 17 (12.6%) were moderate preterm, and 26 (19.3%) were late preterm. In preterm cases, there is a significant relationship between the rate

Table 1. The basic characteristics of the VAP and non-VAP study subjects.

Variable	VAP (n=45)	Non VAP (n=90)	Total
Gender			
Male	17 (37.8%)	54 (60%)	71 (52.6%)
Female	28 (62.2%)	36 (40%)	64 (47.4%)
Labor method			
Normal	13 (28.9%)	29 (32.2%)	42 (31.1%)
Sectio caesaria	32 (71.1%)	61 (67.8%	93 (68.9%)
APGAR score			
≥ 7	37(82.2%)	51 (56.7%)	88 (65.2%)
< 7	8 (17.8%)	39 (43.3%)	47 (34.8%)
Amniotic colour			
Clear	39 (86.7%)	69 (76.7%)	108 (80%%)
Turbid	6 (13.3%)	21 (23.3%)	27 (20%%)

Table 2. Results of statistical analysis of risk factors associated with the incidence of neonatal VAP.

Variable	VAP (n=45)	Non-VAP (n=90)	Total	P-value by univariate analysis
Duration of NICU stay before VAP				
≤ 10 days	16 (35.6%)	55 (61.1%)	71 (52.6%)	0.005
>10 days	29 (64.4%)	35 (38.9%)	64 (47.4%)	
Reintubation				
Yes	33 (73.3%)	79 (87.8%)	112 (82.9 %)	0.035
No	12 (26.7%)	11 (12.2%)	23 (17.1 %)	
Ventilation duration before VAP				
≤ 9 days	18 (40%)	61 (67.8%)	79 (58.5%)	0.002
> 9 days	27(60%)	29 (32.2%)	56 (41.5%)	
Birth weight				
<1000 gram	6 (13.3%)	18 (20%)	24 (17.8%)	0.441
1000-1499 gram	8 (17.8%)	21 (23.3%)	29 (21.5%)	
1500-2499 gram	17 (37.8%)	23 (25.6%)	40 (29.6%)	
≥2500 gram	14 (31.1%)	28 (31.1%)	42 (31.1%)	
Prematurity				
Yes	27 (57.8%)	59 (65.6%)	86 (63.7%)	0.381
No	18 (42.2%)	31 (34.4%)	49 (36.3%)	
Prematurity				
Extremely preterm	0 (0%)	9 (10%)	9 (6.7%)	0.024
Very preterm	8 (17.8%)	26 (28.9%)	34 (25.2%)	
Moderate preterm	10 (22.2%)	7 (77.8%)	17 (12.6 %)	
Late preterm	9 (20%)	17(18.9%)	26 (19.3 %)	
Full-term	18 (40%)	31(34.4%)	49 (36.2%)	

Table 3. Results of multivariate analysis of risk factors associated with neonatal VAP.

Variable	VAP (n=45)	Non-VAP (n=90)	Total	P-value by multivariate analysis
Duration of NICU stay before VAP				
≤ 10 days	16 (35.6%)	55 (61.1%)	71 (52.6%)	0.570
>10 days	29 (64.4%)	35 (38.9%)	64 (47.4%)	
Reintubation				
Yes	33 (73.3%)	79 (87.8%)	112 (82.9 %)	0.222
No	12 (26.7%)	11 (12.2%)	23 (17.1 %)	
Ventilation duration before VAP				
≤ 9 days	18 (40%)	61 (67.8%)	79 (58.5%)	0.117
> 9 days	27(60%)	29 (32.2%)	56 (41.5%)	
Prematurity				
Extremely preterm	0 (0%)	9 (10%)	9 (6.7%)	0.129
Very preterm	8 (17.8%)	26 (28.9%)	34 (25.2%)	
Moderate preterm	10 (22.2%)	7 (77.8%)	17 (12.6 %)	
Late preterm	9 (20%)	17(18.9%)	26 (19.3 %)	
Full-term	18 (40%)	31(34.4%)	49 (36.2%)	

Table 4. Results of statistical analysis of clinical outcomes related to the incidence of neonatal VAP.

Variable	VAP (n=45)	Non-VAP (n=90)	Total	P- value
Duration of hospital stay				
≤14 days	9 (20%)	65 (72.2%)	74 (54.8%)	<0.001
>14 days	36 (80%)	25 (27.8%)	61 (45.2%)	
Total ventilation duration				
≤ 9 days	6 (13.3%)	61 (67.8%)	67 (49.6%)	<0.001
> 9 days	39 (86.7%)	29 (32.2%)	68 (50.4%)	
The total duration of stay in the NICU				
≤ 13 days	7 (15.6%)	65 (72.2%)	79 (58.5%)	<0.001
> 13 days	38 (84.4%)	25 (27.8%)	56 (41.5%)	

of prematurity and the incidence of VAP (p=0.024). The results of the statistical analysis of risk factors associated with the incidence of neonatal VAP can be seen in Table 2.

Multivariate analysis with logistic regression was performed on risk factors that had a significant relationship with the incidence of VAP: duration of stay in the NICU before VAP, reintubation, ventilation before VAP and prematurity. The analysis results concluded that there were no independent risk factors for VAP, as shown in Table 3.

The clinical outcomes examined in this study were the duration of hospital stay, total ventilation, and total care in the NICU. The duration of hospital stay ranged from 3-107 days with a median of 14 days (SD=19.6). Most of the duration of hospitalisation in the VAP group was > 14 days (80%), but in the non-VAP group, it was ≤ 14 days (72.2%). Statistical analysis showed a significant relationship between the duration of hospital stay and the incidence of VAP (P<0.001). Total ventilation duration ranged from 3-84 days with a median of 9 days (SD 12.8). Most of the duration of total ventilation in the VAP group was > nine days (86.7%), but in the non-VAP group, it was ≤9 days (67.8%). Statistical analysis showed a significant relationship (p<0.001). The results of the statistical analysis of the relationship between clinical outcomes and the incidence of VAP can be seen in Table 4.

DISCUSSION

This study showed that the median duration of NICU stay before VAP was higher than the median duration of NICU stay in the VAP group, which was 13 days (SD=13.7) versus ten days (SD=10.0). There was a statistical correlation between the duration of total NICU stay and the duration of NICU stay before the onset of VAP with the incidence of VAP. The exact correlation was also shown by other studies in the form of mean and median duration of treatment for the incidence of VAP.[7,12-14] This study defined the duration of NICU stay before the onset of VAP as a risk factor compared to the total duration variable. Total duration of NICU was determined as clinical outcome, and similar to study by Thatrimontrichai et al, 2017 that it was related significantly with event of VAP.[12]

This study showed a high frequency of reintubation, namely as many as 112 cases (82.9%). Reintubation in the non-VAP group was more than in the VAP group, with p=0.035. The impression is that there is a protective factor from reintubation against VAP, contrary to other studies.[2,7,12] Based on the data, we assumed reintubation with the right indications and strict standard procedures can have a lower risk of VAP. Study by Deng et al, 2011 also offered an explanation for this anomaly. Reintubation frequency was a superior variable to predict VAP compared to reintubation variable alone. Their studies found that reintubation more than three times was associated with VAP. Deng et al, 2017 also offered a more precise methodology for assessing the correlation with the occurrence of VAP as a risk factor by setting a detailed timeline in the form of a variable number of reintubations before the onset of VAP.[13]

This study showed a longer median duration of ventilation before VAP in the VAP group, namely nine days (SD=8.83) compared to 5.5 days (SD 8.51) in the non-VAP group. Only a few studies have focused on the variable duration of ventilation before the onset of VAP. This study adopted the method of study by Thatrimontrichai et al, 2017 in comparing the variable duration of ventilation before onset of VAP in the VAP group and the variable duration of total ventilation which ranges from intubation to extubation in the non-VAP group. The study by Thatrimontrichai et al, 2017 reported a longer median duration of ventilation in the non-VAP group, but statistically not significant.[12] Study by Raycheva et al, 2022 also showed results longer duration of ventilation in the VAP group without conducting statistical analysis.[15] We assessed that the variable duration of ventilation before VAP was more appropriate to be used as a risk factor predictor than the duration of total ventilation, primarily used in other studies. Duration of total ventilation is more representative of the clinical outcome of VAP than a risk factor for VAP. A total duration of ventilation or prolonged use of a ventilator as a clinical outcome can be interpreted as a predictor of mortality. This study did not show a significant association between low birth weight and the incidence of VAP. These results are the same as those obtained by other studies.[9,16] The study by Kawanishi et al, 2014 and study by Thatrimontrichai et al, 2017 found a correlation between low birth weight and VAP in the very low birth weight group.[2,12]

The median gestational age in this study was 35 weeks (SD=4.3). Statistical analysis failed to show a significant association between prematurity with VAP. Follow-up tests by classifying gestational age according to the range of rates of prematurity managed to show a significant relationship. Lower gestational age in the VAP group was also found in several studies.[5,14,17,18] In this study, the duration of hospital stays correlated significantly with the incidence of VAP. Similar results were shown by other studies.[12,13,15,18-20] Total ventilation duration in this study also correlated significantly with the clinical outcome of VAP. These results are similar to the majority of other studies.[2,5,7,15]

The weakness of this study is that it did not include detailed risk factor variables such as frequency of reintubation before VAP, surfactant administration, congenital abnormalities, congenital heart defects, surgery, presence of sepsis and central venous access, as well as microbiological variables such as bacteremia and sputum culture results. From this study, the future study is needed to determine the risk factors in neonatal VAP for preventive purposes of mortality.

CONCLUSION

Duration of stay in the NICU before VAP, reintubation, duration of ventilation before VAP, and prematurity were significant risk factors for VAP. However, none of these were independent risk factors for VAP. The incidence of VAP increased the duration of hospital stay, total ventilation, and total stay in the NICU.

CONFLICT OF INTEREST

The authors affirmed that there were no conflicts of interest in this study.

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The authors were responsible for all research funding without obtaining financial support.

ETHICAL CLEARANCE

This study has obtained ethical clearance from the Research Ethics Committee of Dr. Soetomo Hospital Surabaya with reference letter number 0867/LOE/301.4.2/IV/2022.

AUTHOR CONTRIBUTION

All authors contributed equally in this research and publication of this manuscript.

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