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Ventilator-Associated Pneumonia in Hospitalized Newborns in a Neonatal Intensive Care Unit

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Background: Ventilator-associated pneumonia (VAP) develops in mechanically ventilated patients 48 hours after putting the patients on the ventilator. VAP is the second most common nosocomial infection in neonatal intensive care units (NICU).

Objectives: The current study was conducted to determine the rate, microbiological characteristics and outcome of VAP in neonates admitted in the NICU of Shohada-e-Tajrish Hospital.

Patients and Methods: A prospective cross-sectional study was conducted from Oct 2009 to Sep 2010, on all neonates receiving mechanical ventilation for more than 48h in the NICU. Clinical and paraclinical data were documented and tracheal secretions were collected by nonbronchoscopic bronchoalveolar lavage (NB-BAL) method for the smear and culture. Colony count and antibiograms were done on all culture-positive specimens.

Results: From 103 patients admitted in the NICU, a total of 66 patients were intubated for 48h or more. VAP occurred in 33.3% of the mechanically ventilated neonates. Microorganisms associated with VAP included: *Klebsiella* species in 68.1%, *Acinetobacter* spp. and *Enterococcus* spp. in 13.6%, and *Candida* spp. in 4.5%. Lower gestational age and birth weight, longer duration of hospital stay and prolonged ventilator need had a significant relationship with VAP. Mortality rate was 6.8% in the ventilated infants without VAP, while 22.7% of the neonates who developed VAP, died.

Conclusions: VAP was common in mechanically ventilated infants in the NICU of the hospital and was associated with increased mortality. Further studies are needed to investigate the prevention of VAP in mechanically ventilated neonates.

Keywords: Infant; Newborn; VAP; Intensive Care Units, Neonatal; Respiration, Artificial

1. Background

Ventilator-associated pneumonia (VAP) develops in mechanically ventilated patients 48 hours or more after the patient putting on mechanical ventilation, and it is the second most common nosocomial infection in neonatal intensive care units (NICU) (1, 2). Overall, VAP occurs in 3-10% of the ventilated patients in pediatric intensive care unit (PICU) and 6.8-32.3% of the neonates in NICUs. The incidence of VAP in neonates varies according to birth weight, and gestational age especially under 28 weeks (3, 4). Low-birth weight is an important risk factor for prolonged ventilator need and VAP. Ventilator-associated pneumonia is associated with substantially increased hospital stay and hospital costs, and also an increase in the use of antibiotics and ventilators, and also increased morbidity and mortality rates (5, 6).

Empiric antibiotic therapy is the norm for all patients in NICUs especially in all intubated cases (7, 8). One of the

most common infections in Infants admitted to NICUs is ventilator-associated pneumonia, and appropriate diagnosis and treatment increase the chance of survival. On the other hand, over diagnosis is associated with an increase in antimicrobial resistance. Therefore, it is imperative not to diagnose VAP merely on the presence of purulent tracheal discharge.

The gold standard for diagnosis of VAP is lung biopsy, however it is an invasive procedure. Since it is difficult to make a definite diagnosis of VAP in children and adults, centers for disease control and prevention (CDC) has recommended the following criteria for diagnosis of VAP in children under one year of age:

Worsening of gas exchange (e.g. O₂ desaturations [e.g. pulse oximetry < 94%], increased oxygen requirements, or increased ventilator demand) and at least three of the following:

Implication for health policy/practice/research/medical education:

It is recommended to health policy makers that prevention, timely diagnosis, and treatment of VAP (ventilator-associated pneumonia) can improve survival of preterm infants.

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- Temperature instability
- Leukopenia ($< 4,000$ WBC/mm³) or leukocytosis ($> 15,000$ WBC/mm³) and left shift ($> 10\%$ band forms)
- New onset of purulent sputum or change in character of sputum, or increased respiratory secretions, or increased suctioning requirements
 - Apnea, tachypnea, nasal flaring with retraction of chest wall or grunting
 - Wheezing, rales, or rhonchi
 - Cough
 - Bradycardia (< 100 beats/min) or tachycardia (> 170 beats/min) (9)

2. Objectives

Since there is little information available about pneumonia caused by mechanical ventilation in infants and neonates, the current study aimed to investigate the prevalence and risk factors of ventilator-associated pneumonia, to determine the causative microorganisms, and the associated mortality rate.

3. Patients and Methods

The current prospective cross-sectional study was conducted in the NICU of Shohada-e-Tajrish Hospital, affiliated with Shahid Beheshti University of Medical Sciences, from October 2009 to September 2010. This NICU had six beds, 90% bed occupancy, two neonatologists, nine pediatric assistants and the patient to nurse ratio of 3:1. All hospitalized patients mechanically ventilated for more than 48 hours, were included in this study. Newborns with congenital anomalies were excluded. The study modified the CDC criteria for the diagnosis of VAP in the patients of the NICU as following:

- 1-Diagnosis of infection 48 hours after initiation of mechanical ventilation (presence of pathogenic bacteria in the secretion of bronchus by NB-BAL method)
 - 2- New infiltrative lesions on chest radiograph
 - 3- Worsening of blood gas
- Along with three of following criteria:
- a-Temperature instability
 - b- Changes in the quality of oral or tracheal secretions
 - c- WBC less than 5000 or more than 15000 in CBC
 - d- Apnea
 - e- Respiratory symptoms (nasal flaring, retraction, wheezing, rales, rhonchi)
 - f- Tachycardia or bradycardia

Demographic data of patients, underlying disease, duration of mechanical ventilation, hospital stay, and time of taking specimens were documented. Chest X-rays of the patients were interpreted by the attending neonatologist.

Samples from tracheal secretions were taken with sterile deep endotracheal aspirations method, (NB-BAL). Bronchoalveolar lavage specimens were assessed for smears and cultures, and the colony count of bacteria

and antibiotic sensitivity. Cultures were sent in two separate media, in eosin methylene blue agar (EMB) for gram negative organisms and in blood agar for gram-positive organisms. Weekly evaluation of VAP was applied in cases with prolonged mechanical ventilation of more than seven days. The changes in quality or quantity of tracheal secretions, the need to change the set-up of ventilator, duration of mechanical ventilation, medications, and complications were recorded.

The primary outcome was the prevalence of VAP and determination of microorganism in colony count and antibiotic sensitivity; the secondary outcome was determination of the association of VAP with duration of mechanical ventilation, other complications of mechanical ventilation, and hospital stay.

The SPSS software version 11 was employed to analyze the data.

4. Results

During the study period, a total of 103 patients were admitted; 66 newborns fulfilled the criteria for enrollment, and 41 (62.1%) were male. The mean gestational age was 32.5 ± 3.7 , (range: 28-40 weeks); 45 infants (68%) were 28-34 weeks, 9 (16%) 34-37 weeks, and 12 (28%) more than 37 weeks (Table 1). Mean birth weight in 29 infants (43%) was less than 1500g, in 26 (39%) 1500-2500 g, and in 11 babies (16%) more than 2500g. Main reasons for admission were: prematurity in 40 infants (60.6%), respiratory distress in 19 newborns (28.8%), asphyxia in 4 babies (6.4%), and metabolic disorders in 3 neonates (4.5%).

In the current study, the incidence of VAP was 26.9% according to CDC criteria, and according to the modified criteria employed in the current study (positive tracheal culture and positive findings in CXR with one of these criteria: change in the nature of secretions, abnormal CBC/ABG or heart rate), it was 33.3%.

The mean days of mechanical ventilation and hospital course were: 10.3 ± 10.1 and 25.9 ± 19.9 , respectively. In 22 patients (33.3%), the NB-BAL culture was positive for pathogens; spp. was isolated in 15 patients (68.2%), *Acinetobacter spp.* in three (13.6%), *Enterobacter spp.* in three (13.6%) and *Candida spp.* in one (4.5%) newborn.

Although all patients with positive findings on tracheal cultures had positive findings on chest X-rays, in three (6.8%) of the cases with positive findings on chest X-rays findings of tracheal cultures were negative. In 95.5% of the cases, positive findings on cultures were accompanied by organisms in smears of secretions; however in 6.8% of positive findings on smears, findings of cultures were negative. 88% of Babies with positive findings on cultures on NB-BAL, (VAP), had rales in lung fields on clinical examinations, leukocytosis was observed in 46.8% and leukopenia in 6.7%; 72.2% had abnormal blood gases. In one patient (4.5%), the same organism (*Candida spp.*) was isolated both in blood and tracheal culture. Outcome of

the patients was significantly different in VAP-positive groups, the mortality rate in VAP group was 22.7% and in the VAP-negative babies was 6.8%.

Table 1. Characteristics of Patients

Characteristics	VAP ^a	
	-, No. (%)	+, No. (%)
Male	31 (46.9)	10 (15.5)
Mean gestational age, wk		
28-34	27 (61.4)	18 (81.1)
34-37	05 (11.4)	04 (18.2)
> 37	12 (27.3)	0
Mean birth weight, g		
< 1500	27 (61.4)	15 (2.68)
1500-2500	05 (11.4)	04 (18.2)
2500 <	12 (27.3)	0
Cause of admission		
Prematurity	23 (52.3)	17 (77.3)
Respiratory distress	16 (36.4)	3 (13.6)
Asphyxia	2 (4.5)	2 (9.1)
Metabolic disorder	3 (6.8)	0
Radiologic finding	3 (6.8)	22 (100)
Positive tracheal smear	3 (6.8)	21 (95.5)
Abnormal CBC		
Leukocytosis	0 (0)	1 (6.7)
Leukopenia	4 (9.1)	1 (4.5)
Positive blood culture	2 (4.5)	16 (72.2)
Microorganism		
<i>Klebsiella spp.</i>	-	68.1%
<i>Acinetobacter spp.</i>	-	13.6%
<i>Enterococcus spp.</i>	-	13.6%
<i>Candida spp.</i>	-	1.5%

^a Abbreviation: VAP, ventilator-associated pneumonia.

5. Discussion

Ventilator-associated pneumonia (VAP) is the cause of 6.8-32.3% of nosocomial infections in the NICUs (10). The prevalence of VAP in the current study was 26.9% according to the CDC criteria; however according to the criteria modified for the current study, 33.3% of the neonates on ventilator were diagnosed with VAP. The diagnostic criteria for VAP, as stated by the CDC, rely on a combination of clinical characteristics (apnea, temperature instability, changes on tracheal secretions and heart rate), and para-clinical findings (CBC, chest x-ray, ABG); however, in neonates, these criteria have a low specificity, therefore, for early detection of at risk newborns, more specific criteria are needed (10).

Incidence of VAP has been reported as 20.1% and 30.6% in the studies from China, and India, respectively (11). In the current study, 68.2% of VAP was diagnosed in infants under 1500 g, 27.3% between 1500-2500 g, and 4.5% of neonates who weighed more than 2500 g ($P = 0.025$); it was expected, since the prevalence of VAP increases with lower-birth weight. In Donggun's study, low-birth weight and underlying lung disease were associated with VAP (12).

In the study conducted by Apisarnthanarak (13), the incidence of VAP was 28.3% or 6.5 per 1000 ventilator days at gestational age of 28 weeks which decreased to 4 in 1000 ventilator days in infants over 28 weeks of gestational age (GA). In the current study, the gestational age was lower than 34 weeks in most of the VAP cases (81.8%), and between 34-37 weeks in 18.2% of the cases. Ventilator-associated pneumonia was not observed in neonates over 37 weeks of GA.

Bacteremia or blood stream infection before the onset of VAP is regarded as an independent risk factor for VAP, even though the pathogens isolated from the blood stream, are not usually the same as those detected in the tracheal specimen. In the current study, only in one case, the microorganism found in the blood (*Candida spp.*), was isolated from the tracheal secretions as well. Discordance of microorganisms in blood and tracheal secretions suggests that VAP is not due to hematogenous spread of bacteria from the blood; however, presence of concomitant sepsis can worsen the outcome.

The most common bacterial organisms responsible for nosocomial pneumonias are gram-negative bacilli such as *Klebsiella pneumoniae*, *E. coli*, *Pseudomonas aeruginosa*, and gram-positive cocci such as *S. aureus* (14). In the current study, *Klebsiella spp.* was the most common organism isolated from tracheal secretions in babies with VAP, while the other microorganisms were: *Acinetobacter spp.*, *Enterococci spp.*, and *Candida spp.*

Another Study isolated *staphylococcus spp.* in 28.4%, *Pseudomonas spp.* in 25.2%, and gram-negative bacilli in 26.6% of the infants with VAP; but, similar to the findings in the current study, most of the other researches named gram-negative organisms as the most common pathogens that lead to VA (15).

Most of the studies have reported that VAP increases the duration of hospital stay and vice versa. In the current study, the babies with VAP (VAP-positive) were hospitalized for a much longer period than the VAP-negative patients (mean duration of admission: 33.2 ± 2.4 days vs. 22.4 ± 17.8 days, respectively), similar to Apisarnthanarak's study in which the mean duration of hospitalization for the VAP-positive babies was 138 days and for the VAP-negative patients 82 days (13). Tripathi et al. reported these figures as 32.7 ± 13.7 days vs. 19.7 ± 23.9 days; their research revealed that duration of mechanical ventilation is an independent risk factor for VAP (16). The mean duration of ventilation in the VAP-positive vs. VAP-negative patients was 14.1 ± 11.1 and

8.4 ± 9.1 (P = 0.029), respectively.

The current study had some limitations: the diagnosis of VAP was based on clinical manifestations, radiological findings and also the presence of microorganism in NB-BAL which can be due to colonization of trachea and the colonization is not necessarily associated with infection and VAP. The lung biopsy, which is regarded as the gold standard, was not performed on the patients; however, as lung biopsy is an invasive procedure, most of the other researchers have used cumulative data similar to the ones used in the current study to diagnose VAP. The BACTEC media was not utilized for culturing, which could have increased the yield of the microorganisms. In addition, small sample size in the current study may be a limiting factor to determine the risk factors of VAP; further studies with larger sample sizes are needed.

The findings of the current study emphasize that the duration of hospital stay and mechanical ventilation of neonates admitted to NICUs, have a significant association with ventilator-associated pneumonia, which in turn, leads to an increase in the mortality rate. Prevention and timely treatment of this nosocomial infection are critical for improving the prognosis of these infants.

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Authors' Contribution

1- Study concept and design: Dr. Fallahi, Dr. Sanaee. 2- Acquisition of data: Dr. Naeempour. 3- Analysis and interpretation of data: Dr. Naeempour, Dr. Sanaee, Dr. Fallahi. 4- Drafting of the manuscript: Dr. Fallahi. 5- Critical revision of the manuscript for important intellectual content: Dr. Bassir, Dr. Ghadamlee. 6- Statistical analysis: Dr. Naeempour. 7- Administrative, technical, and material support: Dr. Fallahi, Dr. Bassir, Dr. Naeempour, and Dr. Ghadamlee. 8- Study supervision: Dr. Fallahi, Dr. Sanaee.

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