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Original Research Article

Etiological Risk Factors and Causative Organisms in Ventilator Associated Pneumonia in Newborns: A Prospective Study.

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Conflict of interest: Nil

Abstract:

Background: Ventilator associated pneumonia (VAP) is a common cause of nosocomial infection and accounts for 6.8% to 32.2% of health care-acquired infections among neonates. Mechanically ventilated infants in the neonatal intensive care unit (NICU) are particularly at high risk of developing VAP because of poor host factors, severe underlying diseases, prolonged use of mechanical ventilation, inadequate pulmonary toilet and extensive use of invasive devices and procedures.

Methods. This was a prospective observational study carried out at Zanana Hospital, SMS Medical College, Jaipur over a period of one year from July 2012 to June 2013. A total of 100 neonates fulfilled the inclusion criteria, were included in the study and formed subjects.

Results: Out of total 100 patients 38 patients (38%) developed VAP according to diagnostic criteria based on clinical and radiologic picture and had positive ETA culture. On bivariate analysis of various risk factors for VAP, including birth weight, prematurity (gestational ages 37 weeks), duration of MV, number of re-intubations and length of NICU stay it was found that very low birth weight (OR 0.062; 95%CI 0.019-0.205; P 0.001), duration of Mechanical ventilation (OR 0.333; P value- 0.0276) and number of Re-Intubations were significantly associated with VAP but there were statistically no significant differences between the two groups with respect to SGA.

Conclusion. Endotracheal aspirate can be used to predict the development of VAP by microscopic examination for number of pus cell, gram stain, culture and sensitivity for type of micro-organism.

Keywords: Ventilator-associated pneumonia (VAP),Neonatal intensive care unit,Nosocomial infection, Mechanically ventilated infants.

Introduction

Ventilator associated pneumonia(VAP) is a common cause of nosocomial infection and accounts for 6.8% to 32.2% of health care-acquired infections among neonates and have a large impact on length of hospital stay, cost and neonatal morbidity & mortality [1,2]. Mechanically ventilated infants in the neonatal intensive care unit (NICU) are particularly at high risk of developing VAP because of poor host factors, severe underlying diseases, prolonged use of mechanical ventilation, inadequate pulmonary toilet and extensive use of invasive devices and procedures [3]. Depending upon time period, VAP is classified as early onset or late onset VAP, the importance of this segregation of VAP is because of difference in the pathogenesis, causative microorganisms and outcome in these two categories.

While treating the sick newborns that were on ventilator, we should not rely on routine investigations of systemic infection like septic screen and micro-organism pattern detected by blood culture because, the nature and type of organism causing VAP is different from systemic infection and haematogenous seeding of microorganism are rarely causing VAP [4]. There are two sources of microorganism causing VAP either **Endogenous**, due to aspiration of colonised fluid from nasopharynx, oropharynx and also from tracheal and gastric secretions or **Exogenous**, due to inhalation of colonised secretions from uncleaned hands of health

worker, ventilator circuits and from biofilm of endotracheal tube into lungs. The type of organism and pathogenesis of VAP is entirely different to other systemic sepsis or pneumonia so it can affect the outcome of management of patients on ventilator. So there is a need to identify the causative organism of VAP from secretion of respiratory tract by ETA (Endotracheal aspirate). VAP has been extensively studied in adults but there is great paucity of data of VAP in children especially in neonatal age, so this study was done.

Material and Methods:

This was a Prospective observational study carried out at neonatal intensive care unit, Zanana Hospital, SMS Medical College, Jaipur over a period of one year from July 2012 to June 2013**.** All sick neonates who required ventilator support admitted in the NICU were included in the study but Neonates who required mechanical ventilation for less than 48 hour and those who had infective pneumonia at the time of initiation of Mechanical ventilation were excluded from study.

After taking written informed consent from parents of neonates, detailed history and information of all included newborns was recorded on pre-designed proforma including- antenatal history, risk factors of mother, type of delivery, complication during labour, post natal age, birth weight, maturity, duration of mechanical ventilation, number of re-intubations, length of NICU stay etc.

The diagnosis of VAP was made on the basis of criteria given by National Nosocomial Infection Surveillance system (1996), the pediatric modification of the original guidelines given by Centre for Disease Control and Prevention (CDC). All patients were ventilated by orotracheal tube, which was changed only if, blocked or displaced, Patients were ventilated in SIMV/CMV/ACV mode using 'Babylog 8000-plus Dragger' ventilator with heated humidification system. Patients were placed on Servo controlled warmer with skin temperature set on 37.0C with an audio-visual alarm. No prophylactic topical Oropharyngeal antibiotics and selective gut decontamination was done in any of the patients. Baseline total leukocyte count, differential leukocyte count and chest X ray PA view were done in all patients at the time of initiation of Mechanical Ventilation and subsequent blood counts were done on day 3 and day on which pneumonia was suspected by the new chest signs and increasing ventilator requirements. After Baseline chest X-ray, next chest X-ray was done after 48 hours of mechanical ventilation on suspicion of pneumonia or any other pulmonary complication. Routinely X-ray was done only once weekly if no pneumonia was detected. Under all aseptic precautions endotracheal secretions were collected at the time of intubation then after 48 hours of ventilation and later if required, after instilling 1-2ml of sterile normal saline into the endotracheal tube in-situ and then collecting it back and was sent immediately to laboratory for both cytological analysis and culture and antibiotic sensitivity. 10 [5] CFU/ml of endotracheal aspirate was the cut off between organisms causing VAP and colonization [?]. Blood cultures were collected whenever there was a suspicion of VAP. All babies were examined thoroughly daily and monitored for vitals, urine output, temperature, cyanosis, chest retraction, shock, seizure, bleeding or any other complication.

Data were analysed using statistical software package SPSS 22. Proportions were compared using Chi squire statistics and were supported by 95% confidence limits wherever required. Fisher's exact p-value to see the difference between the mean of two different groups if data was normally distributed. If data was not found to be normally distributed, a non-parametric equivalent of two-sample t-test, the Mann Whitney test used to test the level of significance between two values. The difference between any two groups was considered to be significant if p value was < 0.05. The method for multiple regression analysis was 'Enter' method.

Results:

A total of 180 patients were enrolled in the study, but at last 100 neonates fulfilled the inclusion criteria, were included in the study and formed subjects. Among these 38 patients (38%) developed VAP according to diagnostic criteria based on clinical and radiologic picture and had positive ETA culture. Baseline demographic characteristics including age on admission, birth weight, sex, gestational age, haemoglobin, presence of premature rupture of membrane at birth (PROM), indication of mechanical ventilation were comparable in both groups.

Table 1: baseline demographic characteristics of infants with and without VAP:

Variables	**VAP (38)**	**Non VAP (62)**	**p-value**
Age on admission (days)	1.24±0.74	1.32±0.9	
Birth weight(kg)	2.01±0.65	2.15±0.7	0.065
Sex	24/14	34/28	0.413
SGA/AGA/LGA	10/27/1	16/44/2	0.985
Mean haemoglobin (gm%)	16.9	16.4	
PROM(present/absent)	13/25	22/40	0.896
Degree of asphyxia(severe/ moderate)	7/20	20/18	0.056

Indication of MV			
Apnoea	8	12	0.402
Poor respiratory effort	13	29	
HMD	11	11	
Others	6	10	

On bivariate analysis of various risk factors for VAP, including birth weight, prematurity (gestational ages < 37 weeks), duration of mechanical ventilation, number of re-intubations and length of NICU stay it was found that very low birth weight, duration of MV, number of re-intubations and length of NICU stay were significantly associated with VAP but there were statistically no significant difference between the two groups with respect to prematurity, sex and SGA. Multiple logistic regression analysis revealed that duration of MV (OR 0.062; 95%CI 0.019-0.205; P < 0.001), birth weight (OR 0.333; 95% 0.571-0.88; P value-0.0276) and number of re-intubation (OR 0.145; 95%CI 0.05-0.396; P value- < 0.001) were statistically significant independent risk factors for development of VAP.

Table 2: Risk factors in infants with and without VAP:

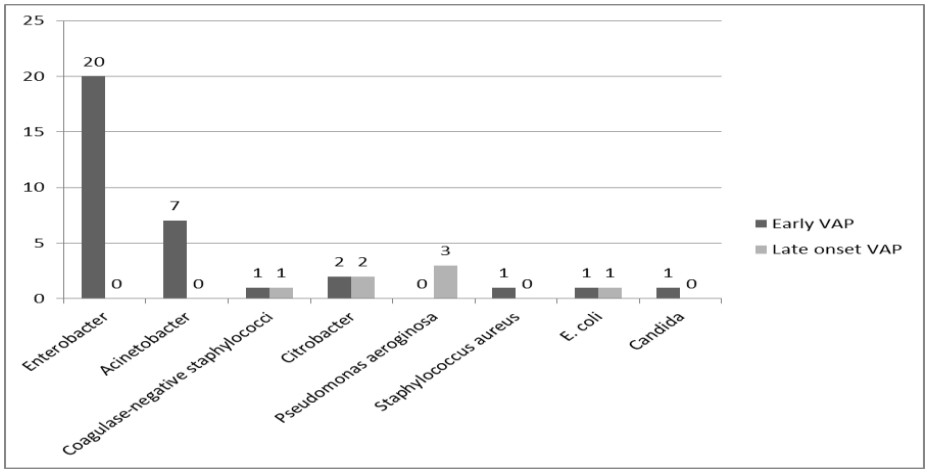
Variables	**VAP(n=38)**	**Non-VAP (n=62)**	**P value**
Very low birth weight (birth weight<1.5 kg)	10 (26.3%)	6(9.6%)	**0.0276**
Prematurity(EGA<36 weeks)	22(57.8%)	28(45.1%)	**0.2164**
Small for gestational age(SGA)	10(26.3%)	16(25.8%)	**0.9551**
Length of NICU stay in days(mean ± SD)	14.24±7.12	7.71±2.98	**<0.001**
Number of re-intubation(mean ±SD)	12.16±3.6	8.87±2.97	**<0.001**
Duration of MV(days) (mean ± SD)	6.02±2.28	3.87±0.924	**<0.001**

Out of total 100 patients 27 showed growth in blood culture, out of total 27 bacteria isolated, Enterobacter species-10 isolates (37%), Coagulase negative Staphylococcus -7 isolates (25.9%), Staphycococcus aureus-5 isolates (18.5%) were the most common organisms isolated followed by Escherichia coli, Pseudomonas species each accounting for 2 isolates (7.4%) and Acinetobacter species accounting 1 bacteria (3.7%).

Out of 38 clinical suspected VAP cases a total of 41 bacteria were isolated because of 2 multiple isolated growth patterns. So in VAP group out of total 41 bacterial isolates, *Enterobacter species* were in 20 isolates (48.8%), *Acinetobacter species* in 8(21%), *Citrobacter species* in 4(9.7%), *Pseudomonas species* in 3 isolates (7.3%) were the most common organisms followed by *E. coli*, and *coagulase negative Staphylococcus* each accounting for 2 bacteria (4.8%) and *S. aureus* and *candida* each accounting for 1 bacteria (2.4%).

Incidence of VAP was 81 cases per thousand ventilator days. 31(81.5%) cases developed VAP within 5 days of mechanical ventilation and were classified as early onset VAP and rest 7(18.4%) cases developed pneumonia after 5 days of ventilation and were categorized under late onset VAP.

On segregation of organisms on basis of onset of VAP, it was found that early onset VAP was most commonly caused by *Enterobacter (52.6%)* whereas *Pseudomonas species* (42.8%) were the causative agent of late onset VAP.



Graph 13: Organism causing early and late onset vap:

It was found that Gram negative organisms were the major cause of VAP in this study. Microorganisms were isolated in 41 specimens from endotracheal aspirate culture, where Enterobacter (20), Acinetobacter species (8) and Citrobacter species (4) were predominant organisms. Polymicrobial infection was found in 2 specimens from endotracheal aspirate culture.

In 27 specimens (27%) from hemoculture, *Enterobacter species, coagulase negative staphylococcus* and *Staphylococcus aureus* were predominant organisms.

Discussion:

Nosocomial pneumonia is a major cause of morbidity and mortality in hospitalized patients especially in mechanically ventilated infants in Neonatal ICU[2].

Average incidence of VAP varies from place to place (9% and 70%) [13]. This variation may be due to difference in use of aseptic precautions in intensive care unit, different diagnostic methods with different sensitivity and specificity, sample size and underlying disease state requiring ventilator support [6,13]. The incidence of VAP in our study was 38%, comparable to earlier studies such as **Bauer et al [11]** in 2000 in which the overall incidence of VAP varies between 9% and 70%, **Petdechai et al [12]** (40.6%), **Apisarnatharak et al [9]** (28.3%).

In our study duration of mechanical ventilation required for seven or more than seven days was highly significant for the prediction of VAP (P-value <0.05) with Multiple logistic regression analysis (OR 0.062; 95%CI 0.019-0.205; P < 0.001) also revealed duration was an independent and statistically significant risk factors for development of VAP. **Tripathi et al [13]** (2009) also reported the same result with multiple regression analysis (OR 1.10; 95% CI 1.02, 1.21; P = 0.021) established this variant as an independent and statistically significant risk factors. **Apisarnthanarak et al [9], Petdachai et al [12]** , **Patra et al [**24], **Yuan et al [25]**, **Bauer et al [11]** , **Badr et al [26]** , **Casado et al [27]** and **Kawanishi F et al [30]** in 2014 also observed similar result in their studies.

In our study number of re-intubation was highly significant for the prediction of VAP (p-value <0.05) and also revealed by multiple logistic regression analysis (OR 0.145; 95%CI 0.05-0.396; P < 0.001). In a similar study done by **Tripathi et al [13]** (2009) found that number of re-intubation is an independent and statistically significant risk factors for predicting ventilator associated pneumonia by multiple regression analysis (OR 5.3; 95% CI 2.0,14.0). and others i.e. **Yuan et al [25]** (2007), **Patra et al [24]** (2007), **Zhang et al [14] (2013), Liu et al [28] in 2013** and **Kawanishi F et al [30]** were also found similar result.

In this study multiple logistic regression analysis revealed that very low birth weight (birth weight < 1500 gram) (OR 0.333; 95% 0.571-0.88; P = 0.0276) independent and statistically significant risk factors for development of VAP, In similar study **Tripathi et al [13], Petedechai et al [12], Badr** et al [26], **Zhang et al [14] in 2013, Thatrimontrichal-A et al [29]** and **Kawanishi F et al [30]** were also found the low birth weight significant risk factors for development of VAP.

In our study we found that the length of NICU stay was significantly associated with VAP as observed by bivariate analysis (p-value<0.001).

In similar study **Tripathi et al [13]**, P**etedechai et al [10] in 2000, Apisarnthanarak** et al [9] (2003), **Petdachai et al [12]** in 2004, **Zhang et al [14] in 2013** and **Thatrimontrichal-A et al [29] in 2017** also found that the length of NICU stay was significantly associated with VAP.

As far as etiological organisms are concerned, Gram-negative bacilli comprised major isolates from cultures of specimens obtained from endotracheal aspirate and blood. Aerobic gram-negative bacilli are implicated in a wide spectrum of nosocomial infections in the ICU. Their emergence as significant pathogens seems to be related partly to the widespread use of broad-spectrum antibiotics, and partly to their ability to develop resistance rapidly to the major groups of antibiotics [18]. Gram negative predominance was also observed in our study similar to previous neonatal studies [14,16,20] but due to increased use of advanced diagnostic techniques and interventional procedures emergence of *Enterobacter* and *Acinetobacter* species in most of neonatal ICUs is common now a days that is creating a significant therapeutic problem because of resistance of these organisms to most of antibiotics.

Conclusion:

There are few limitations in our study. We could not send the blood culture simultaneously with endotracheal aspirate culture after 48 hours of intubation which could help to identify the microorganism in ETA and blood culture simultaneously. Our small sample size limits the statistical power to detect other possible independent risk factors for VAP and for mortality. Our data did not include the indication for reintubation which also may be a relevant risk factor for VAP. Because many of the NICU patients had concurrent nosocomial infections during their NICU stay, the attributable morbidity and mortality associated with VAP cannot be determined from our study.

Recommendations:

1. Till date the treatment of VAP is generally with antibiotics used for neonatal sepsis as guided by blood culture so paediatricians should understand the epidemiology that micro-organism pattern causing VAP is different from that of blood stream infection as evidenced by our study and line of treatment of neonates on mechanical ventilation should be based on ETA culture report.

2. Endotracheal aspirate (ETA) can be used to predict the development of VAP by microscopic examination for number of pus cell, gram stain, culture and sensitivity for type of micro-organism. Its use should be encouraged in NICU to predict VAP as it is very simple, safe, non-invasive and inexpensive method.

3. The treating paediatrician should try to extubate the baby as early as possible and avoid repeated intubation of neonates as far as possible as both are significant risk factor for development of VAP. There is great paucity of study data on VAP in children especially in neonatal age, so further studies are required on neonates to develop universal and definite guideline for prevention and management of Ventilator Associated Pneumonia.

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