ORIGINAL ARTICLE

Early Predictors of Ventilator Associated Pneumonia in Preterm Neonates Admitted in a Special Newborn Care Unit

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ABSTRACT

Objective: To determine the utility of microscopic examination and culture of endotracheal aspirate (ETA) in the early diagnosis of ventilator-associated pneumonia (VAP) in preterm neonates.

Methods: We enrolled 80 consecutive neonates (both inborn and out-born) with gestational age of < 37 weeks admitted in Special Newborn Care Unit (SNCU) and requiring mechanical ventilation (MV) for ≥ 48 hours. The diagnosis of VAP was made using the criteria laid down by the Centers for Disease Control (CDC).

Results: 47 preterm neonates (58.5%) developed VAP; the overall incidence was 74.7/1000 ventilator-days. The mean (SD) time (hours) to ETA culture was less as compared to diagnosis based on CDC criteria [108.9 (8.00 hrs) vs 132.4 (53.24); *P = 0.004*] with sensitivity and specificity of 80.8% and 72.7%, respectively. Outborn delivery was the single most important risk factor for VAP. Multidrug resistant (MDR) *Klebsiella pneumoniae* (63.9%) was the most prevalent organism.

Conclusions: We noticed a very high incidence of VAP among preterm neonates in SNCU. ETA culture can aid in early diagnosis.

Keywords: *Culture, Endotracheal tube, Klebsiella, Special newborn care units*

INTRODUCTION

Excessive and unsupervised use of mechanical ventilation in preterm neonates can predispose to complications like volutrauma leading to chronic lung disease, ventilator associated pneumonia (VAP), air leaks, and subglottic stenosis etc [1]. VAP is defined as hospital acquired pneumonia, developing in patients after 48 hours of initiation of mechanical ventilation (MV) [2]. It is one of the most common nosocomial infections associated with high morbidity, mortality, and medical cost [3]. The incidence of VAP varies greatly from 2.7 to 10.9 episodes per 1000 ventilator days in high income countries and up to 37.2 per 1000 ventilator days in low-and middle-income countries [4,5].

There is paucity of data regarding the early predictors of VAP among preterm neonates from tertiary level special newborn care units (SNCU) in India. The time taken to reach a microbiological diagnosis in suspected VAP is of crucial importance. We could find only one study from India which showed a high sensitivity and specificity of endotracheal aspirate (ETA) microscopy and culture in the early diagnosis of VAP in near term and term neonates [6]. In the current study, we aimed to determine the early predictors of VAP by examining the ETA microscopy, culture and endotracheal tube (ET) tip culture among ventilated preterm neonates in an SNCU. We also determined the incidence, risk factors, causative microbial agents, and outcome of VAP in these neonates.

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METHODS

In this prospective observational study, we included all consecutive neonates (inborn and out-born) with a gestational age of < 37 weeks, who required MV for ≥ 48 hours and admitted in our 12-bedded tertiary level SNCU. The study period was from August 2019 to August 2020. Informed consent was obtained from parents/guardians. All preterm neonates with suspected or diagnosed pneumonia at the time of initiation of MV, major congenital birth anomalies (including antenatally detected critical cyanotic congenital heart disease), pulmonary hemorrhage, outborn neonates intubated at admission and with a

previous history of MV were excluded. Analysis of our unit's previous years admission data, revealed that there were 1000 new admissions in the SNCU out of which 40% were preterm neonates. Assuming that 20% of these would require MV, we decided to enrol a convenient sample of 80 eligible consecutive neonates over a period of 12 months.

Neonates who needed ventilatory support were intubated by orotracheal route in the labor room or NICU. One set of sterile/autoclaved ventilator circuit with heated humidification system was used till extubation. We used open method for suctioning of secretions. The endotracheal (ET) tube was changed only if blocked or displaced for each patient.We continuously recorded vitals and ventilator settings every two hourly in a pre-designed proforma. The clinical diagnosis of VAP was made on the basis of Centers for Disease control (CDC), USA criteria [7]. As per unit's protocol, we extubated the preterm neonates when all of the following criteria were met: *a*) Adequate spontaneous efforts, *b*) hemodynamically stable with no inotropes, *c*) FiO_2 requirement was less than 30% to maintain sPO_2 between 90-95%, *d*) requirement of peak inspiratory pressure (PIP) and peak end expiratory pressure (PEEP) was less than 15 cm and 5 cm of H_2O respectively.

Samples of ETA were collected by open suction after 48 hours of MV, under aseptic precautions. ET tip sample was sent for cultures per standard protocol at first ET replacement or during extubation, whichever was earlier. The samples of endotracheal aspirate (ETA) and ET tip underwent qualitative culture microscopic analysis and quantitative culture within one hour of collection. A smear was prepared from ETA for gram staining. Culture (conventional and BACTEC) was done on blood and MacConkey agar and antibiotic sensitivity was done using Muller Hinton agar.

Statistical analysis: We compared quantitative variables between the VAP and non-VAP groups using Student t-test and Mann Whitney U test. For comparing categorical data, Chi square (X^2) test and Fisher's exact test was used. Sensitivity, specificity, positive (PPV) and negative predictive values (NPV) for ETA microscopy and culture were also calculated. For risk factor analysis, both univariate and multivariate logistic regression analyses were included. A probability value (*P* value) less than 0.05 was considered statistically significant. All statistical calculations were done using Statistical Package for the Social Science 21 version (SPSS Inc.).

RESULTS

Out of 193 mechanically ventilated preterm neonates, 122 were ventilated for more than 48 hours. Of these, six families refused consent, and 36 were excluded (congenital anomalies 9; congenital pneumonia 14; congenital heart disease 6; and, pulmonary hemorrhage 7), and 80 were finally enrolled. 47 (58.5%) neonates developed VAP with an overall incidence of 74.7/1000 ventilator-

Table I Factors Associated With Ventilator-associated Pneumonia

Factors	*VAP group (n = 47)*	*Non-VAP group (n = 33)*	*Odds ratio (95% CI)*	*P value*
Gestational age (< 32 weeks)	15 (31.9)	9 (27.3)	1.25 (0.47-3.34)	0.656
Birth Weight (< 1500 grams)	20 (42.6)	10 (30.3)	1.71 (0.67-4.37)	0.265
Female sex	16 (34.0)	14 (42.4)	0.70 (0.28-1.75)	0.446
Leaking for more than 24 hours	15 (31.9)	11 (33.3)	0.94 (0.36-2.42)	0.894
Vaginal delivery	33 (70.2)	15 (45.5)	2.83 (1.12-7.15)	0.037
Outborn delivery	25 (53.2)	5 (15.1)	6.32 (2.09-19.32)	0.001
Need of resuscitation at birth	14 (29.8)	11 (33.3)	0.85 (0.33-2.21)	0.736
Need for PRBC transfusion	36 (76.6)	16 (48.5)	3.47 (1.33-9.08)	0.009
Opiate therapy	6 (12.8)	10 (30.3)	0.34 (0.11-1.05)	0.087
Invasive procedure (PICC line/UVC)	34 (72.3)	8 (24.2)	8.17 (2.94-22.68)	0.001
Duration of mechanical ventilation in days[a]	9.87 (4.37)	5.00 (1.56)	-	< 0.001
Duration of NICU stay in days[b]	12 (8-15.5)	8 (5-10)	-	< 0.005
No. of ET changes (≥ 2)	37 (78.7)	6 (18.2)	16.65 (5.39-51.39)	< 0.001
ET suctions per day (≥ 3)	12 (25.5)	1(3.0)	10.97 (1.35-89.19)	0.011
Duration of MV (days) (≥ 7)	32 (68.1)	3 (9.1)	21.33 (5.61-81.14)	< 0.001

Values expressed as n(%), [a]mean (SD) or [b]median (IQR). VAP: Ventilator acquired pneumonia; PICC: Peripheral inserted central catheter; UVC: Umbilical venous catheter; ET: Endotracheal tube; MV: Mechanical ventilation; PRBC: Packed red blood cell transfusion; 95% CI: 95% Confidence Interval.

days. The mean gestational age (weeks) in the VAP and non-VAP group was comparable [32.2 (2.9) vs 32.9 (2.6); $P = 0.25$]. The mean (SD) birth weight (g) was less in the VAP group compared to the non-VAP group but the difference was statistically non-significant [1567.2 (469.8) vs 1714.5 (498.1); $P = 0.18$]. There was no significant difference between the rate of mortality between the two groups (57.4% in VAP group vs 63.6% in non-VAP group; $P = 0.72$). The various causes of mortality are compared in **Table II**.

On univariate analysis, delivery through vaginal route, out-born delivery, greater need of blood transfusion, use of invasive procedures (peripherally inserted central catheter and umbilical venous catheter), a greater number of ET changes and suctioning per day, longer duration of MV and NICU stay were significantly associated with the development of VAP as shown in **Table I**. On multivariate analysis, only out-born delivery, as a risk factor was independently associated with the development of VAP (Odds Ratio:13.77; 95% CI: 2.257-84.134; $P = 0.004$).

The mean (SD) time to diagnosis of VAP by ETA microscopy and culture was 57.79 (4.43) and 108.9 (8.0) hours, respectively, which were significantly shorter ($P < 0.001$ and $P = 0.004$, respectively) than time to clinical diagnosis by CDC criteria at 132.4 (53.2) hours. We also found that ETA microscopy was positive in 59.5% neonates of VAP group and 12.1% neonates of non-VAP group. ETA culture was positive in 80.9% neonates of VAP group and 27.3% neonates of Non-VAP group. The sensitivity, specificity, PPV and NPV of ETA microscopy in our study was 59.5%, 87.8%, 87.5% and 60.4%, respectively; whereas for ETA culture, it was 80.8%, 72.7%, 84.4% and 72.7%, respectively. In ETA culture, gram negative organisms like *Klebsiella pneumoniae* (63.9%) and *Citrobacter freundii* (10.7%) were the most predominant. Among the isolated organisms, the antibiotic resistance was very high with 33 out of 38 (86.8%) being multidrug resistant and showing sensitivity to polymyxin group of antibiotics only. The most common cause of mortality in both the groups was sepsis (55.5% vs 52.4%). The pathogens detected in blood culture were *Klebsiella pneumoniae* (5 in VAP group; 3 in Non-VAP group), *Candida albicans* (4 in VAP group, 2 in Non-VAP group), Methicillin resistant *Staphylococcus aureus* (3 in VAP group), Methicillin resistant coagulase negative *Staphylococcus aureus* (3 in Non-VAP group).

DISCUSSION

The incidence of VAP in other studies ranges from 13.2-57.1% and 7.1 to 70.3 per 1000 ventilator days [8-10]. This variation may be due to difference in diagnostic criteria used for defining VAP and the level of asepsis maintained at various centers. We assume that important factors contributing to a higher incidence of VAP in our study could be limited resources such as low nurse to patient ratio and low hand hygiene compliance based on the previous study's data from our unit [11]. Previous authors [5,8,9] also did not find any difference between the VAP and the non-VAP groups with respect to mortality. Our study population comprised of sick preterm neonates with a mean gestational age of around 32 weeks, so the rate of mortality was very high in both the groups. The reasons of mortality in both the groups were causes other than VAP.

Previous authors did not find any difference in the demographic profile between the two groups [10,12]. In our study, the outborn neonates could possibly be at greater risk of VAP as compared to those who were inborn because of severity of sickness; issues related to transportation such as thermoregulation; level of asepsis maintained during delivery, particularly home delivery and type of antibiotics received before reporting to us. However, Afjeh et al [13] did not find any difference between the two groups with respect to place of delivery.

In a recent study, the mean (SD) time of result of ETA microscopy and culture was 55.7 (4.3) h and 108.3 (19.7) h, respectively [7]. The clinical diagnosis was made much later using CDC criteria [7]. In the study conducted by Gupta et al the sensitivity, specificity, PPV and NPV of ETA culture was 75%, 90%, 84% and 83.7% respectively [6].

Table II Causes of Mortality in Preterm Neonates Receiving Mechanical Ventilation

Cause	*VAP group (n = 47)*	*Non-VAP group (n = 33)*	*P value*
Hypoxic ischemic encephalopathy	4 (14.8%)	3 (14.3%)	0.958
Extreme prematurity	3 (11.1%)	4 (19.0%)	0.439
Respiratory distress syndrome.	5 (18.6%)	3 (14.3%)	0.696
Early onset sepsis	9 (33.3%)	6 (28.6%)	0.724
Late onset sepsis	6 (22.2%)	5 (23.8%)	0.897
Total	27 (57.4%)	21 (63.6%)	0.724

Values in n (%). VAP:Ventilator-associated pneumonia

WHAT THIS STUDY ADDS?

- We noticed a very high incidence of VAP (74.7/1000 ventilator days) among ventilated preterm neonates along with very high incidence of multidrug resistant bugs.
- ET aspiration culture and microscopy provides an opportunity for early diagnosis of VAP as compared to CDC clinical criteria.

We could not collect data on human related factors like percentage of hand hygiene compliance before and after ET suctioning, and percentage of health care staff wearing sterile gloves while suctioning and intubation. This could have affected the incidence of VAP in our neonates.

In our unit with a high incidence of VAP among ventilated preterm neonates, ET aspiration culture and microscopy provided an opportunity for early diagnosis of VAP.

Ethics clearance: Institutional ethics committee, Guru Gobind Singh Medical College, Faridkot, Punjab; No. BFUHS/2K19p-TH/893 dated May 29, 2019.
Contributors: SP: Conceptualized and designed the study, analyzed data and drafted the manuscript; AS: Conceptualized and designed the study, supervised data collection and drafted the manuscript; GK: Conceptualized and designed the study and supervised the sample collection and manuscript; SKD: Supervised data and samples collection and provided inputs for writing the manuscript; NJ: Supervised sample collection and analysis of samples in the microbiology department; SR: assisted in sample collection, data analysis, and writing of manuscript; SJ: Assisted in sample collection, data analysis, and writing of manuscript. All authors approved the final version of manuscript, and are accountable for all aspects related to the study.
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