Original Article

Iran J Pediatr
Dec 2011; Vol 21 (No 4), Pp: 418-424

Ventilator Associated Pneumonia in Critically-Ill Neonates Admitted To Neonatal Intensive Care Unit, Zagazig University Hospitals

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Received: *Oct 02, 2010*; Final Revision: *May 20, 2011*; Accepted: *Jul 16, 2011*

Abstract

Objective: ventilator associated pneumonia (VAP) is defined as nosocomial pneumonia in mechanically ventilated patients. It is considered to be most important cause of infection-related death in intensive care unit. We studied the characteristics and risk factors of VAP in critically-ill neonates.

Methods: Fifty six consecutive neonates with different diagnosis admitted from January to October 2010 to neonatal intensive care unit (NICU), Zagazig University Hospitals who needed mechanical ventilation were included in the study. There were 32 neonates, 18 males and 14 females with proven diagnosis of VAP, and 24 neonates, 11 males and 13 females without VAP served as control group. All studied neonates were subjected to history taking, clinical examination, routine investigations (Complete blood count, C-reactive protein, arterial blood gases, blood culture and liver and kidney function tests), and chest X-ray daily as well as non-bronchoscopic alveolar lavage culture for VAP group only.

Findings: Of 56 neonates who needed mechanical ventilation, 57.1% developed VAP. Prematurity, low birth weight and prolonged duration of mechanical ventilation were risk factors for developing VAP. Increased total leucocytic count, CRP and hypoalbuminemia were significantly presented in VAP-group. There were significant differences between VAP and non-VAP groups regarding hypothermia, mucopurulent endotracheal tube secretion, $PaCO_2$ and PaO_2. Microorganisms associated with blood stream infection in VAP diagnosed group were *Klebsiella* (15.6%), *S. aureus* (12.5%), *Pseudomonas* (9.4%), *E. coli* (6.2%), *Candida* (3.1%); 53.1% of obtained blood cultures were sterile. Of non-bronchoscopic alveolar lavage cultures obtained from VAP patients, 68.6% showed gram negative infection, 21.8% showed gram positive organisms and 9.3% revealed *Candida* infection.

Conclusion: The most important risk factors of VAP are prematurity, low birth weight, prolonged duration of mechanical ventilation, enteral nutrition and umbilical catheterization.

Iranian Journal of Pediatrics, Volume 21(Number 4), December 2011, Pages: 418-424

Key Words: Ventilator Associated Pneumonia; Neonate; Neonatal Intensive Care Unit; low birth weight; Prematurity

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Introduction

Ventilator associated pneumonia (VAP) is defined as hospital acquired pneumonia occurring in patients receiving mechanical ventilation through an endotracheal or tracheostomy tube [1]. VAP that occurs within 48 to 72 hours after tracheal intubation is usually termed early-onset pneumonia which often results from aspiration that complicates the intubation process while VAP that occurs after 72 hours is considered as late-onset pneumonia [2].

VAP accounts for up to 30% of nosocomial infections in NICU patients and complicates the course of 8 to 28% of patients receiving mechanical ventilation [3]. The pathogenesis of VAP involves two processes, bacterial colonization of the aerodigestive tract, then aspiration of contaminated oral secretions into the lower airways because endotracheal tubes used to ventilate neonates are not cuffed [4].

The etiologic agent of VAP may differ according to length of hospital stay, co-morbid conditions and exposition of anti-microbials [5]. Aerobic gram negative bacilli account more than 60% of VAP cases. However, some investigators have reported that gram positive bacteria have become increasingly more common with *S. aureus* being the predominant isolate [6].

The criteria used to diagnose VAP in neonates include mechanical ventilation within 48 hours of onset of suspected VAP; worsening gas exchange with an increase in oxygen or ventilatory requirements; 2 or more chest radiographs that show new infiltrates, consolidation, cavitation, or pneumatoceles; and at least 3 signs and symptoms. Signs and symptoms may include temperature instability, wheezing, tachypnea, cough, abnormal heart rate, change in secretions, or an abnormal leukocyte count. The criteria have not been validated in neonates, and they are often open to subjective interpretation because they overlap with other diseases [7].

Use of a modified Clinical Pulmonary Infection Score (CPIS) has improved the diagnostic utility of clinical diagnosis [8]. Modified CPIS is an accepted tool for clinical estimation of VAP, encompassing five components: temperature, blood leukocytes, tracheal secretions, oxygenation index and chest roentgenogram [9]. The detection of the causative organism in VAP is imperative for guiding an appropriate therapy as there is strong evidence of the adverse effect of inadequate empirical treatment on outcome [10]. Microbial diagnosis of VAP is based on the culture of samples obtained from lower respiratory tract by tracheal aspirate which is considered a less invasive method that may have an acceptable diagnostic accuracy [11].

The aim of this work is to determine characteristics and risk factors of VAP in critically ill newborn infants admitted to NICU, Zagazig University Hospitals.

Subjects and Methods

This is a prospective observational study conducted over a period of one year from January to October 2010 in a Neonatal Intensive Care Unit of a tertiary care teaching hospital, Zagazig University Hospital, Egypt. NICU of the hospital was 26 bedded with 11 ventilators at that time

The study included 56 neonates who received mechanical ventilation by orotracheal tube for a period of >48 hrs because of different illnesses. Neonates requiring mechanical ventilation for less than 48 hours and those who had pneumonia at the time of initiation of mechanical ventilation were excluded from study.

Patients were classified into 2 groups:

Group I (VAP-group): included 32 neonates (18 males and 14 females) of ages ranged from 6 to 18 (X±SD: 10.9±5.2) days who were clinically diagnosed with VAP according to CPIS [12]. Their weight ranged from 0.9 to 2.5 (X±SD: 1.5±0.87) kg, gestational age ranged from 28 to 38 (X±SD: 33.62±3.2) weeks and were subjected to mechanical ventilation of duration ranged from 4 to 8 (X±SD: 6.3±1.67) days.

Group II (non-VAP group): included 24 neonates (11 males and 13 females) of ages ranging from 6 to 11 (X±SD: 8.4±2) days who did not develop VAP. Their weight ranged from 2.0 to 3.0 (X±SD: 2.65±0.38) kg, gestational age ranged from 33 to 38 (X±SD: 35.7±1.6) weeks and were on mechanical ventilation of duration ranged from 3 to 5 (X±SD: 4.7±1.1) days.

Parents of all neonates gave an informed written consent prior to the study. All neonates were subjected to the following:

1. Clinical history including type of labor, diagnosis at admission and drug therapy.
2. Physical examination with recording vital signs, gestational age determination using modified Ballard score [13], and clinical evidence of sepsis and pneumonia (e.g. lethargy, temperature instability, decreased peripheral perfusion and auscultatory chest findings).
3. Routine laboratory investigations including complete blood count (CBC) with differential leukocyte count, according to Malik et al [14] , C-reactive protein (positive test above 6 mg/l)[15], kidney and liver functions, blood culture[16] and arterial blood gases monitoring.
4. Chest X-ray was done as base line then 48 hours after mechanical ventilation to look for new persistent or progressive lung infiltrates. Otherwise routinely once weekly if no pneumonia was detected
5. Non-bronchoscopic bronchoalveolar lavage culture [17].

Sample collection

An end hole suction catheter size 8F was used for ETT of size 3.5mm, whereas 6F was used for tubes 3mm or smaller. 0.5-1 ml sterile water was directly injected into the endotracheal tube via a sterile disposable syringe. The suction catheter was then advanced immediately into ETT until 1cm beyond the tube tip and the sterile water from the lower airways was suctioned back.

Sample examination

The obtained samples were examined microscopically for micro-organisms and then centrifuged and the pellet was inoculated into blood, chocolate and MacConkey agars.

Statistical Analysis

Data were presented as mean±standard deviation (X±SD) or percentage (%). All statistical comparisons were performed using Student's t-test or chi-square (χ^2). Data were carried out with the Statistical Package for Social Sciences (SPSS), version 14 software. *P*-values less than 0.05 were considered statistically significant.

Findings

Our results are summarized in the following four tables. VAP and non-VAP groups differ significantly regarding gestational age and weight. Duration on mechanical ventilation was highly significantly longer in VAP patients than in non-VAP. Meanwhile, there were non-significant differences regarding gender, mode of delivery and indication of NICU admission (Table 1).

Analysis of clinical and radiological characteristics revealed that hypothermia, muco-purulent secretions from ETT and presence of

Table 1: Demographic characteristics of the studied groups

Variables	*VAP- group* (*n*=32)	*Non-VAP group* (*n*=24)	*t*	$\chi 2$	*P* value
Gestational age (weeks) [Mean (SD)]	33.6 (3.2)	35.7 (1.6)	2.1	-	0.04
Weight (kg)	1.5 (0.9)	2.6 (0.4)	2.4	-	0.01
Sex Male	18 (56.25%)	11 (45.8%)		0.1	0.75
Female	14 (43.75%)	13 (54.2%)	-		
Duration on MV (days) [Mean (SD)]	6.3 (1.7)	4.7 (1.1)	4.1	-	0.001
Diagnosis at time of admission					
Respiratory Distress Syndrome	12 (35.9%)	10 (41.7%)			
Congenital Pneumonia	9 (28.1%)	8 (33.3%)		0.86	0.8
Meconium Aspiration Pneumonia	7 (21.9%)	3 (12.5%)			
Hypoxic Ischemic Encephalopathy	4 (12.5%)	3 (12.5%)			
Mode of delivery					
Normal Vaginal Delivery	19 (59.4%)	13 (54.1%)		0.49	0.5
Cesarean Section	13 (40.4%)	11 (45.8%)			

VAP: Ventilator associated pneumonia / SD: Standard Deviation / MV: Mechanical Ventilation

Table 2: Clinical, radiological and historical data of studied patients

Clinical findings		*VAP-group* (*n*=32) No (%)	*Non-VAP group* (*n*=24) No (%)	$\chi 2$	*P* value
Temperature	Hypothermia (< 36.5°)	18 (5)	7 (4)	1.26	0.04
	Hyperthermia (> 38.5°)	56.2 (15.6)	29.1 (16.6)		
Auscultatory chest finding		12 (31.2)	7 (29.1)	0.61	0.5
Mucopurulent ETT secretions		24 (75.0)	3 (12.5)	1.4	0.001
Radiological finding(s)		32 (100)	0	56.0	0.001
Medications	Inotrops (Vasopressors)	28 (87.5)	12 (50)	0.32	0.02
	Antacids (H2-blockers)	27 (84.3)	15 (62.5)	3.5	0.06
	Surfactant	7 (21.9)	4 (16.6)	0.02	0.9
Feeding	Enteral	17 (53.1)	6 (25.0)	0.48	0.03
	Total parenteral nutrition	10 (20.8)	7 (29.1)	0.21	0.2
Invasive maneuvers	Chest tubes	8 (25.0)	2 (8.3)	4.53	0.001
	UVC	24 (75.0)	6 (25)	13.78	0.001

ETT: endotracheal tube UVC: umbilical vein catheterization

infiltration in chest X-ray were significantly more prevalent in VAP patients. Inotropic drugs were significantly more used in VAP patients who also needed more invasive procedures than non-VAP group (Table 2).

A significant rise of TLC, CRP and $PaCO_2$ level in blood gases with significant decrease in albumin level and PaO_2 were observed. Sterile blood cultures were displayed in 17 patients with VAP (53.1%) and 20 of non-VAP group (83.3%) (Table 3).

The most prevalent organism isolated from NB-BAL fluid in VAP patients was *Klebsiella* (34.3%) while *Pneumococci* were the least ones (Table 4).

Table 3: Laboratory investigations in studied groups

Variable	*VAP-group* (*n*=32)	*Non-VAP group* (*n*=24)	*T or* $\chi 2$	*P* value
Total leucocytic count ($\times 10^3$ c/mm^3) **[Mean (SD)]**	19.1 (7.8)	10.5 (10.4)	3.49	0.001
C-Reactive Protein (mg/l) **[Mean (SD)]**	54.5 (40.6)	28.0 (41.9)	1.18	0.03
Renal function tests [Mean (SD)]				
Urea (mg/dl)	33.4 (13.2)	34.4 (8.3)	0.32	0.7
Creatinine (mg/dl)	0.7 (0.3)	0.5 (0.2)	1.78	0.07
Liver function tests [Mean (SD)]				
Aspartate transaminase (U/L)	19.4 (12.5)	15.3 (6.1)	1.48	0.1
Alanine transaminase (U/L)	35.9 (11.1)	33.3 (8.4)	0.97	0.7
Albumin (g/dl)	2.6 (0.5)	3.1 (0.5)	- 2.92	0.02
Arterial blood gases [Mean (SD)]				
pH	7.4 (0.1)	7.4 (0.1)	1.73	0.08
$PaCO_2$ (mmHg)	51.1 (9.6)	43.8 (10.6)	2.68	0.009
PaO_2 (mmHg)	55.9 (13.9)	72.4 (30.3)	2.71	0.008
Blood culture [Frequency]				
Sterile	17 (53.1%)	20 (83.3%)	5.58	0.02
Klebsiella	5 (15.6%)	2 (8.3%)	0.17	0.7
S. aureus	4 (12.5%)	1 (4.1%)	0.37	0.5
Pseudomonas	3 (9.37%)	1 (4.1%)	0.05	0.8
E. coli	2 (6.2%)	0 (0%)	0.27	0.6
Candida	1 (3.1%)	0 (0%)	0.02	0.9

SD: Standard deviation

Table 4: Isolated organisms from Non-bronchoscopic bronchoalveolar lavage culture in Ventilator associated pneumonia -group

Organism		Frequency
Gram positive	*S. aureus*	5 (15.6%)
	Pneumococci	2 (6.2%)
Gram negative	*Klebsiella*	11 (34.3%)
	E. coli	4 (12.5%)
	Pseudomonas	7 (21.8%)
Fungi	*Candida*	3 (9.3%)

Discussion

Mechanical ventilation is an essential feature of modern NICU care. Unfortunately, mechanical ventilation is associated with a substantial risk of VAP[18]. Tracheal intubation is associated with a 3 to 21 fold risk to develop pneumonia. In addition, poor nutritional state and hypoalbuminemia also contribute to the development of VAP[19].

In this study, the mean gestational age of infants diagnosed with VAP was significantly lower than that of the non-VAP group (P=0.04). This result was in agreement with other studies that reported VAP rates significantly increase with decreasing gestational age[3,20]. Also, the mean birth weight of the VAP group was significantly lower than that of non-VAP group (P=0.01). This result was near to the results obtained by Stover et al[21] who reported in a cross sectional study that VAP rates were highest for the 1-1.5 kg birth weight categories.

In our series, patients with VAP showed significantly higher duration on mechanical ventilation. This result may be explained by the fact that prolonged duration of ventilation increases the risk of infection due to the exposure to humidifiers, neubilizers and ventilator circuits that are proven to be an important source and medium for microorganisms [22].

In this study, hypothermia, presence of auscultatory chest findings and mucopurulent ETT secretions characterized VAP group. Similar results were reported by other studies[5,23]. Chest radiographs were diagnostic in all cases clinically diagnosed as VAP which was in agreement with El-ward et al [24]. Regarding used drugs, we found that inotropes were significantly more used in VAP group in order to normalize their blood pressure. This is in agreement with Fischer et al[25].

In this study, enteral feeding is a significant risk factor for VAP as it increases the risk of stomach colonization with gram negative microorganisms and consequently leads to an increased rate of nosocomial pneumonia[26].

In the current study, we couldn't elicit any significant differences between VAP and non-VAP patients as regards the use of H_2 blockers. This result confirms what was reported by George et al[27]. On the other hand, Memish et al[26] reported in their study that to reduce the risk of nosocomial pneumonia, it is important to avoid unnecessary usage of antacids and H_2- antagonists.

In our study, invasive devices like umbilical vein catheterization and intercostal chest tubes are considered an important source of blood stream infection in ventilated babies. Similar results were obtained by Livingston[28].

In this study, there were significant differences between VAP and non-VAP groups regarding total leucocytic count and CRP titer. This is in agreement with Povoa et al[29]. Hypoalbuminemia which is considered as an indicator of poor nutritional status was significantly encountered in VAP group which may be due to favored hepatic production of acute phase proteins such as globulins, fibrinogen and haptaglobin[30].

In our study, VAP patients had a significantly higher mean PaCO2 and lower mean PaO2 than non-VAP patients. These results were the same obtained by Shaw [31].

In this study, the predominant microorganism associated with blood stream infection in VAP diagnosed group was *Klebsiella* (15.6%) while 53.1% of obtained blood cultures were sterile. This is in agreement with Berthelot et al [32].

The results of NB-BAL cultures reported in our study revealed that gram negative bacteria were isolated from the majority of VAP patients (68.6%), with *Klebsiella* organism predominating

the positive culture (34.3%). On the other hand, gram positive infection comprised 21.8% of the total cultures with *Staphylococcus aureus* predominating the positive cultures (15.6%) while *Candida* was positive in 9.3% of samples examined. Koksal et al [33] mentioned that *Acinobacter* was the most predominating causative agent whereas Petdachai [34] reported that *Pseudomonas* was the most common organism isolated.

There are several limitations in our study. There is no current gold standard for defining or diagnosis of VAP. Because tracheal aspirate was used as a means to identify organisms associated with VAP, we found some of our VAP patients (4 cases) had multiple organisms isolated and some were contaminated. Some of the VAP patients did not have purulent tracheal aspirate with no isolated organism, which suggests that some of these VAP episodes may represent colonization rather than true VAP.

Conclusion

The most important risk factors for developing VAP in our unit include prematurity, low birth weight, prolonged duration of mechanical ventilation, enteral feeding and invasive devices such as umbilical catheters. Gram negative microorganisms comprise the majority of cultures obtained by NB-BAL. So, we recommended strict training and supervision of infection control protocols, educated and expert nursing care, usage of disposable ventilator circuits, avoidance of un-necessary central venous catheters and other invasive procedures, closed suction and wide use of NB-BAL cultures for early diagnosis of VAP. Additional studies are necessary to develop interventions to prevent neonatal VAP.

Acknowledgment

Institute's ethical approval was obtained from the local research ethics committee.

Conflict of Interest: None

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