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Risk Factors of Ventilation Associated Pneumonia in Critically Ill Neonates

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ABSTRACT

Background: ventilator associated pneumonia (VAP) is defined as nosocomial pneumonia in mechanically ventilated patients. It is considered to be the most important cause of infection-related death in intensive care unit and is thought to have a negative influence on patient's outcome. Because neonates have different anatomy, physiology and underlying diseases compared with older children and adults, specific studies of risk factors and outcomes for VAP in neonates are needed. Objective: study the characteristics and risk factors of VAP in critically-ill neonates. Material and method: Sixty consecutive neonates admitted to NICU, Zagazig University Hospital and two private hospitals with different diagnosis needed mechanical ventilation were included in the study. They were 34 neonates,(19 males and 15 females), with proven diagnosis of VAP and 26 neonates,(12 males and 14 females), who did not develop VAP and were served as control group. All studied neonates were subjected to history taking, clinical examination, routine investigations (CBC, CRP, ABG, blood culture and liver and kidney functions), and a daily chest X-ray as well as non-bronchoscopic alveolar lavage (NB-BAL) culture for VAP group only. Results: of 60 neonates who needed mechanical ventilation, 57.2% developed VAP. Prematurity, low birth weight and prolonged duration of mechanical ventilation were risk factors to develop VAP. Increased TLC and CRP and hypoalbuminemia were significantly presented in VAP-group. There were significant differences between VAP and non-VAP groups regarding hypothermia, mucopurulent ETT secretion, $PaCO_2$ and PaO_2. Microorganisms isolated in blood culture in VAP diagnosed group were *klebsiella* (15.7%), *S. aureus* (12.6%), *Pseudomonas* (9.38%), *E-coli* (6.3%), *Candida* (3.2%) while 53.2% of obtained blood cultures were sterile. In NB-BAL cultures obtained from VAP patients, 68.7% showed Gram negative infection, 21.9% showed Gram positive organisms and 9.4% revealed *Candida* infection. Conclusion: VAP occurred at a significant rate among mechanically ventilated newborn infants. The most important risk factors of VAP are prematurity, low birth weight, prolonged duration of mechanical ventilation, enteral nutrition and umbilical catheterization. Gram negative organisms comprised the majority of NB-BAL cultures.

Key words: Ventilator associated pneumonia - Non-bronchoscopic bronchoalveolar lavage.

Introduction

Ventilator associated pneumonia (VAP) is defined as nosocomial hospital acquired pneumonia occurring in patients on mechanical ventilation through an endotracheal or tracheostomy tube (Leone *et al.,* 2005). 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 late-onset pneumonia (Chastre and Fago, 2002). VAP accounts for up to 30% of nosocomial infections in NICU patients and complicates the course of 8 to 28% of patients on mechanical ventilation (Foglia *et al.,* 2007). The pathogenesis of VAP involves two processes; bacterial colonization of the aerodigestive tract then aspiration of contaminated secretions into the lower airways (Safdar *et al.,* 2005).

The etiologic agent of VAP may differ according to length of hospital stay, co-morbid conditions and exposition of anti microbials (Torres and Ewing, 2004). 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 (Shaw, 2005).

The diagnosis of VAP depends on the presence of new and/or persistent infiltrates in chest radiograph and two of the following(Torres and Ewing, 2004).

1. Temperature of >38.5° C or < 36.5° C
2. Leucopenia (WBCs ≤ 4000/mm^3) or leukocytosis (≥ 30.000 WBCs /mm^3)
3. Purulent tracheobronchial secretions

Use of a modified clinical pulmonary infection score (CPIS) has improved the diagnostic utility of clinical diagnosis (Niederman, 2005). The detection of the causative organism in VAP is imperative for guiding

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an appropriate therapy as there is strong evidence of the adverse effect of inadequate empirical treatment on outcome (Ioanas *et al.,* 2001).

Microbial investigation 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 (Carvalho *et al.,* 2005). Prevention remains the key for reducing VAP prevalence. Hand washing and the use of protective gowns and gloves remains the cornerstone in prevention of ICU acquired infections (Osmon and Kollef, 2010).

Treatment of suspected VAP is centered on an approach of initial empirical therapy with broad spectrum antibiotics followed by de-escalation to specific antimicrobial therapy once cultures are known or discontinuation of antibiotics if VAP is no longer suspected (Park, 2005).

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

Patients and Methods

This case control study was carried out in the neonatal intensive care unit of Zagazig University, Children's Hospital and two private hospitals, during the period between February and December, 2013 on 60 neonates who need mechanical ventilation for a period > 48 hrs because of different illnesses.

Patients were classified into 2 groups:

Group I :(VAP-group): included 34 neonates (19 males and 15 females) of ages ranged from 1 to 19 days (10.9 ± 5.3 days) who were clinically diagnosed with VAP according to clinical pulmonary infection score (Brenda and Fahy, 2009). Their weight ranged from 0.9 to 2.6 Kg (1.5 ± 0.87 kg), gestational ages ranged from 28 to 38 weeks (32.63 ± 3.3 weeks) and were on mechanical ventilation of duration ranged from 4 to 11 days (6.8 ± 1.67 days).

Group II: (non-VAP group): included 26 neonates (12 males and 14 females) of ages ranging from 1 to 18 days (8.4 ± 2 days) who did not develop VAP. Their weight ranged from 2.0 to 3.0 Kg (2.65 ± 0.38 kg), gestational ages ranged from 33 to 38 weeks (35.7 ± 1.66 weeks) and were on mechanical of ventilation of duration ranged from 3 to 6 days (4.7 ± 1.1 days).

Ethical approval was obtained from the local research ethics committee and 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 (Ballard *et al.,* 1991) and clinical evidence of sepsis and pneumonia (e.g. lethargy, temperature instability, decreased peripheral perfusion and ausculatory chest findings).
3- Routine laboratory investigations including complete blood count (CBC), according to Malik *et al.* (2011), C-reactive protein (positive test above 6 mg/L) (Jaye and Waites, 1997), kidney and liver functions, blood culture (Buttery, 2002) and arterial blood gases monitoring.
4- Chest X-ray done daily after mechanical ventilation to look for a new persistent or progressive lung infiltrates.
5- Non-bronchoscopic bronchoalveolar lavage culture (Arora *et al.,* 2002)

Sample collection of NB-BAL

An end hole suction catheter size 8 F was used for ETT of size 3.5mm, wherease 6 F 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 catheters was then advanced immediately into ETT until 1cm beyond the tube tip and suction back the sterile water from the lower airways.

Sample examination

The obtained samples were examined microscopically for micro-organisms and then centrifuged and the pellet was inoculated into blood, chocolate and Mac- Conkey 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 (X^2). Data were carried out with the Statistical Package for Social Sciences (SPSS), version 16 software. P-values less than 0.05 were considered statistically significant.

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Results:

Table 1 showed significant differences between VAP and non-VAP groups regarding gestational age and weight. Duration on mechanical ventilation was highly statistically significantly longer in VAP patients compared to non-VAP. Mean while, there were non-significant differences regarding gender, mode of delivery and indication of NICU admission.

Analysis of clinical and radiological characteristics revealed that hypothermia, mucopurulent secretions from ETT and presence of infiltration in CXR 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).

Table 3 presented the laboratory data of 34 patients with VAP versus 26 non VAP. 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 18 patients with VAP (53.2%) and 21 of non-VAP group (83.3%).

The most prevalent organism isolated from NB-BAL fluid in VAP patients was *klebsiella* (34.4%) while *pneumococci* were the least one (Table 4).

Table 1: Demographic characteristics of the studied groups

Variables	VAP- group (n=34)	Non-VAP group (n=26)	P
GA (weeks)	32.63 ± 3.3	35.7 ± 1.7	0.04*
Weight (kg)	1.5 ± 0.87	2.65 ± 0.38	0.01*
Sex Male Female	 19 (56.25%) 15 (43.75%)	 12 (45.8%) 14 (54.2%)	0.75
Duration on MV (days)	6.8 ± 1.67	4.7 ± 1.1	0.001**
Diagnosis at time of admission			
RDS	13 (35.9)	11 (41.7)	0.83
Congenital pneumonia	9 (28.1)	9 (33.3)	
MAS	8 (21.9)	3 (12.5)	
HIE	4 (12.5)	3 (12.5)	
Mode of delivery			
NVD	20 (59.4)	14 (54.1)	0.48
CS	14 (40.4)	12 (45.8)	

GA: gestational age MV: mechanical ventilation RDS: respiratory distress syndrome MAS: meconium aspiration pneumonia
HIE: hypoxic ischemic encephalopathy NVD: normal vaginal delivery CS: cesarean section: significant **: highly significant*

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

	VAP-group (n=34)		Non-VAP group (n=26)		P
	No	%	No	%	
Clinical findings:					
Temperature: Hypothermia (< 36.5°) Hyperthermia (> 38.5°)	 18 7	 56.2 15.6	 8 5	 29.1 16.6	0.04*
Auscultatory chest finding	12	31.2	7	29.1	0.46
Mucopurulent ETT secretions	24	75.0	3	12.5	0.001**
Radiological finding	34	100	0	0.0	0.001**
Medications:					
Inotrops (Vasopressors)	28	87.5	12	50	0.02*
Antacids (H2-blockers)	27	84.3	15	62.5	0.06
Surfactant	7	21.9	4	16.6	0.88
Feeding:					
Enteral	17	53.1	6	25.0	0.03*
Total parenteral nutrition	10	20.8	7	29.1	0.23
Invasive maneuvers:					
Chest tubes	9	25.0	3	8.3	0.001**
UVC	25	75.0	7	25	0.001**

*ETT: endotracheal tube UVC: umbilical vein catheterization *: significant **: highly significant*

Table 3: Laboratory investigations in studied groups

Variable	VAP-group (n=34)	Non-VAP group (n=26)	P
TLC($\times 10^3$ c/mm^3)	19.2 ± 7.8	10.55 ± 10.4	0.001**
HB (g/dl)	9.73 ± 2.96	8.66 ± 2.14	0.11
platelets ($\times 10^3$/cmm)	138.7 ± 61.2	175.7 ± 89.4	0.06
CRP (mg/L)	54.5 ± 40.57	28.0 ± 41.92	0.03*
Urea (mg/dL)	33.4 ± 13.2	34.4 ± 8.3	0.74
Creatinine (mg/dl)	0.67 ± 0.26	0.55 ± 0.21	0.07
AST (U/L)	19.4 ± 12.5	15.3 ± 6.1	0.13
ALT (U/L)	35.9 ± 11.1	33.3 ± 8.4	0.66
Albumin (g/dL)	2.60 ± 0.53	3.06 ± 0.49	0.02*
ABG:			
PH	7.37 ± 0.13	7.42 ± 0.09	0.08
$PaCO_2$ (mmHg)	51.1± 9.6	43.8 ± 10.6	0.009*
PaO_2 (mmHg)	55.9± 139	72.4 ± 30.3	0.008*
HCO_3 (mmol/l)	29.4 ± 5.2	27.2 ± 4.5	0.1
Blood culture :			
Sterile	18 (53.1%)	21 (83.3%)	0.018*
Klebsiella	6 (15.6%)	3 (8.3%)	0.68
S. aureus	4 (12.5%)	1 (4.1%)	0.54
Pseudomonas	3 (9.37%)	1 (4.1%)	0.82
E-coli	2 (6.2%)	0 (0%)	0.6
Candida	1 (3.1%)	0 (0%)	0.88

*TLC: total leucocytic count HB: hemoglobin CRP: C-reactive protein AST: aspartate transaminase ALT: alanine transaminase ABG: arterial blood gases *: significant **: highly significant*

Table 4.Isolated organisms from NB-BAL culture in VAP-group

	No.	%
Gram positive:		
S. aureus	5	15.6%
Pneumocci	2	6.2%
Gram negative:		
Klebsiella	12	34.3%
E-coli	4	12.5%
Pseudomonas	8	21.8%
Fungi:		
Candida	3	9.3%

NB-BAL: Non-bronchoscopic bronchoalveolar lavage

Discussion

Mechanical ventilation is an essential feature of modern NICU care. Unfortunately, mechanical ventilation is associated with a substantial risk of VAP (Aly *et al.,* 2008). Tracheal intubation is associated with a 3 to 21 folds risk to develop pneumonia. In addition, poor nutritional state and hypoalbuminemia also contributes to the development of VAP (Shalini *et al.,* 2010).

In this study, the mean gestational age of neonates diagnosed with VAP was significantly lower than that of the non-VAP group (P=0.04). This result was in agreement with other studies who reported that VAP rates had significantly increased with decreasing the gestational age (Foglia *et al.,* 2007 and Chastre 2005). 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.,* (2001) who reported in a cross sectional study that VAP rates were highest for the 1-1.5 kg birth weight categories.

Our neonates with VAP showed significantly longer duration on mechanical ventilation. This result may be explained by prolonged duration of ventilation increases the risk of infection due to the exposure to humidifiers, neubilizers and ventilator circuits that were proven to be an important source and media for microorganisms (Apisarnthanarak *et al.,* 2003).

In this study, hypothermia, presence of auscultatory chest findings and mucopurulent ETT secretions characterized VAP group. Similar results were reported by other studies (Torres and Ewing; 2004 and Erbay *et al.,* 2004). Chest radiographs were diagnostic in all cases clinically diagnosed as VAP which was in agreement with El ward *et al.* (2002). Regarding used drugs, we found that inotropes were significantly frequently used in VAP group in order to normalize their blood pressure. This is in agreement with Fischer *et al*. (2009). In this study, enteral feeding is a significant risk factor for VAP as it increases the risk of stomach colonization and consequently leads to an increased rate of nosocomial pneumonia (Memish *et al.,* 2008).

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.* (1998). On the other

hand, Memish *et al.* (2008) 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, (2000). 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.* (2005). 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 (Alp *et al.,* 2004)

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, (2006). 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.* (2001).

The results of NB-BAL cultures reported in our study revealed that gram negative bacteria was 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 culture (15.6%) while *Candida* was positive in 9.3% of samples examined. Koksal *et al.* (2006) mentioned that *Acinobacter* was the most predominating causative agent whereas Petdachai, (2004) reported that *Pseudomonas* was the most common organism isolated.

Conclusion:

The most important risk factors for developing VAP in our study 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, usage of disposable ventilator circuits, avoidance of un-necessary central venous catheters and other invasive procedures and wide use of NB-BAL cultures for early diagnosis of VAP.

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