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Role of CRP, Micro- ESR and CPIS in Diagnosis of Ventilator Associated Pneumonia in Neonates at a Tertiary Care Hospital in Rajasthan

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Abstract

Background: With increase in use of ventilator in NICU, Ventilator Associated Pneumonia has become a significant factor affecting the neonatal survival. Prevention with appropriate management of VAP requires early diagnosis.

Methods: Hospital based observational study conducted on all children below 1 month of age kept on mechanical ventilation for at least 48 hrs & admitted in Intramural NICU (patient directly admitted in NICU) and Extramural NICU (patients referred from other hospital) .

Results: Of 132 neonates who needed mechanical ventilation, 50(37.9%) developed VAP. Out of 50 cases who developed VAP, CRP was positive in 37 cases(52.1%) and 39 patients(81.2%) had CPIS $\geq$6. Sensitivity for CRP and CPIS was found to be 74% and 78% and specificity was 58.5% and 86.9% respectively while the positive predictive values were 52.1% and 81% and negative predictive values were 78.6% and 82% respectively. Significant risk factors associated with VAP were prematurity(OR=2.23), ventilation at early neonatal age(OR=2.5) and prolonged ventilation(OR=2.98).

Conclusion: VAP contributes significantly to hospital acquired infection among neonates. Both CPIS and CRP were useful in screening the cases of VAP in neonates. When used in conjuction the tests were able to predict VAP even better.

Keywords- CRP, Micro- ESR, Leucocyte count, CPIS

Introduction

Ventilator Associated Pneumonia is defined as pneumonia developing in a patient who has been on mechanical ventilation for at least 48 hours[1] provided that the pneumonia was neither present nor incubating at or before the time of intubation.

Incidence of VAP varies markedly worldwide. In neonatal population the incidence is highly influenced by gestational age and regional economic development with highest rates reported from developing countries. According to one study from India, the incidence was 30%[2] as against two studies from the west each reporting an incidence of 15.5%[8] and 16.6%[3].

The clinical pulmonary scoring system was developed by Pugin[4] and his associates incorporating six different clinical variables, to determine the likelihood that any given patient's clinical findings were the result of

pneumonia. It is an easy bedside test which does not require much skill or expertise nor does it involve any invasive procedures. It is very useful as an initial evaluation for suspected patients of VAP.

The accuracy of several biomarkers in the diagnosis and management of VAP have been continuously evaluated. These markers of inflammation show good relation with prediction of VAP[5]. Specific biomarkers of VAP allowing differentiation of pneumonia from colonization have been extensively studied in the adult population, but with unreliable results probably due to inconsistencies in the design of most of the studies[6]. The biochemical markers most frequently studied include CRP, procalcitonin and soluble triggering receptor expressed on myeloid cells(sTREM).

CRP is a well known marker of inflammation. Smith et al[7] used CRP as a useful sensitive marker of bacterial infection in cases of pneumonia. There was marked elevation of serum level of CRP within a few hours of infection. Alternative infectious sources, such as urinary tract, skin and soft-tissue infections, and device-related infections (i.e., central venous catheters) are common in hospitalized patients and should be ruled out before diagnosing VAP as these may also be cause for a raised CRP.

The search for an alternative, quick and less invasive diagnostic technique is still a big challenge. While under diagnosing may lead to delay in intervention and appropriate treatment, over diagnosing may in turn lead to unnecessary antibiotic therapy and complications related to therapy.

This study will be conducted to evaluate the utility of CPIS scoring system in combination with micro ESR and CRP as early bedside tools for prediction of VAP in suspected patients.

Materials and Methods

Study design: Hospital based observational study .

Study duration: 12 months (November 2017 to October 2018).

Study place: Department of Pediatrics and Microbiology, S.P.Medical College and P.B.M Hospital, Bikaner.

Study population: All children below 1 month of age kept on mechanical ventilation & admitted in Intramural NICU (patient directly admitted in NICU) and Extramural NICU (patients referred from other hospital) .

Sample size: The review of literature shows prevalence of VAP in India to be around 30%[13]. In our study we expected prevalence to be around 30%.With allowable error/precision of 0.08,the sample size was calculated to be 132, using the formula $4pq/d^2$ (where p=prevalence, q=1-p,d=allowable error).

Sampling Method: Convenience sampling

Inclusion criteria : Patients aged < 1 month , admitted in Intramural and Extramural NICU kept on mechanical ventilator for >48 hours.

Exclusion criteria: Patients already having pneumonia at the time of NICU admission and patients who developed pneumonia within the first 48 hours of mechanical ventilation. Patients with severe anemia , chromosomal, genetic or inborn errors of metabolism were excluded .

For the diagnosis of VAP Criteria of Centres for Disease Control and Prevention (CDC) was used[6].

Data Collection

As for the diagnosis have followed CDC guidelines and patients fulfilling clinical criteria will be subjected to the following:

a. Hemodynamic monitoring,
b. Laboratory investigations including total and differential white blood cell count.

c. Radiological evaluation for new pulmonary infiltrates through plain chest radiographs (posteroanterior view)
d. Assessment of serum CRP and Micro ESR after the patient had been on ventilator for at least 48 hrs.
e. Calculation of CPIS at the onset of suspected pneumonia .

After proper hand washing and wearing sterile gloves before suctioning, the endotracheal aspirate was collected from the endotracheal tube with the help of sterile Dele's mucous trap . BAL was obtained by non bronchoscopic blind with the help of a double lumen catheter. 2 ml of sterile noramal saline was injected and then aspirated through the catheter . The specimens collected were transported aseptically to the laboratory as soon as possible. Samples collected at night were stored at 4 degree centigrade overnight and sent to the laboratory next morning for culture. Samples were processed as per the standard methods. In case of Endotracheal aspirate culture, $>10^6$ cfu/ml was considered significant for the diagnosis of VAP. After achieving the growth, sensitivity was done as per CLSI(Clinical and Laboratory Standard Institute) guidelines.

CRP was measured using a CRP kit based on the principle of latex agglutination.. The kit used was of the brand "Recombigen", having a sensitivity of 6mg/L .At room temperature, one drop each of serum, positive control and negative control were placed separately on separate reaction circles on a glass slide, then one drop of CRP latex reagent was added to each circle. The slide was observed after mixing on a laboratory mixer for 2 minutes for visible agglutination and the same time compared with the positive and negative controls. For semiquantitative test the specimen was diluted using normal saline in increasing dilutions.CRP was measured twice, first on the day of intubation and again after 48hrs. Only cases which were negative on first test and became positive on day 3 were considered CRP positive with regards to VAP.

Micro ESR was measured bedside using heparinised micro capillary tube of length 90mm and internal diameter of 1mm. Blood was drawn by a heel prick and the capillary tube was filled up to at least half its length or more . Once sufficient blood was drawn, the bottom of the tube was sealed using soap and was allowed to stand by sticking it to a wall and leaving it undisturbed for 1 hour. At the end of 1 hr the fall in rbc column was measured using a measuring tape and recorded in millimetres. Micro ESR was measured twice, first on the day of ventilation and again after 48hrs of intubation. A value of more than 15mm was taken as positive regardless of the age of baby. Only cases which were negative on first test and became positive on day 3 were considered as positive Micro ESR with regards to VAP.

Data Analysis

To collect required information from eligible patients a pre-structured pre-tested Proforma was used. For data analysis Microsoft excel and statistical software SPSS were used and data was analyzed with the help of appropriate frequencies , figures , proportions, measures of central tendancy and appropriate statistical tests .

Results

Out of 132 ventilated neonates 57.6% had birth weight <2.5kg and 42.4% were >2.5kg. 47.72% were preterms and 52.28% were full term.

Out of 132 ventilated neonates , 37.9% (50) developed VAP.

Out of 50 VAP cases , the most common etiology was found to be gram negative organisms 62%and among them klebsiella was most common, followed by mixed flora at 28% . Gram positive organisms were seen in 6%.Fungal etiology was the least common at 4%.

Table 1. CRP (on day 3) in relation to VAP

CRP	VAP				Total	
	Yes		No			
	No.	%	No.	%	No.	%
Positive	37	52.1	34	47.9	71	53.8
Negative	13	21.3	48	78.7	61	46.2
Total	50		82		132	
χ^2	13.23					
P	0.002					

CRP was positive in 53.8% ventilated neonates on day 3. Out of these cases 52.1% had VAP. CRP was negative in 46.2% of ventilated neonates and only 21.3% neonates in this group had VAP. This difference was statistically significant with p=0.002.Sensitivity ,specificity, PPV and NPV of CRP was 74%, 58.54%, 52.11% and 78.69% respectively in diagnosing VAP in neonates.

Table 2. Micro ESR (on day 3) in relation to VAP

Micro-ESR (mm)	VAP				Total	
	Yes		No			
	No.	%	No.	%	No.	%
>15	28	53.8	24	46.2	52	39.4
<15	22	27.5	58	72.5	80	60.6
Total	50		82		132	
χ^2	9.296					
p	0.002					

Micro ESR on day 3 was positive (>15mm) in 39.4% ventilated neonates. Out of these 53.8% had VAP .72.5% neonates with negative micro ESR(<15mm) did not have VAP.This difference was statistically significant with p=0.002 .Sensitivity , specificity, PPV and NPV of micro-ESR was 56%, 70.73%, 53.85% and 72.50% respectively in diagnosing VAP in neonates.

Table 3.Blood Culture in relation to VAP

Blood Culture	VAP				Total	
	Yes		No			
	No.	%	No.	%	No.	%
Positive	22	57.9	16	42.1	38	28.8
Negative	28	29.8	66	70.2	94	71.2
Total	50		82		132	
χ^2	9.085					
p	0.003					

Blood culture was positive in 28.8% ventilated neonates. 57.9% of these neonates had VAP while 70.2% ventilated neonates with negative blood culture did not have VAP. This difference was statistically significant with p=0.003. Sensitivity ,specificity, PPV and NPV of blood culture was 44%, 80.5%, 57.9% and 70.2% respectively in diagnosing VAP in neonates.

Table 4. Leucocytosis/leukopenia in realtion to VAP

Leucocytosis/ Leukopenia	VAP				Total	
	Yes		No			
	No.	%	No.	%	No.	%
Positive	45	50.6	44	49.4	89	67.4
Negative	5	11.6	38	88.4	43	32.6
Total	50		82		132	
χ^2	18.677					
p	<0.001					

67.4% ventilated neonates had abnormal leucocyte count. Out of these 50.6% had VAP. 88.4% ventilated neonates with normal leucocyte count did not have VAP. This difference was statistically significant with p<0.001. Abnormal leucocyte count had sensitivity ,specificity, PPV and NPV of 90%, 46%, 50.56% and 88.37% respectively in diagnosing VAP in neonates.

Table 5. BAL in relation to VAP

BAL	VAP				Total	
	Yes		No			
	No.	%	No.	%	No.	%
Positive	36	87.8	5	12.2	41	31.1
Sterile	14	15.4	77	84.6	91	68.9
Total	50		82		132	
χ^2	62.999					
P	<0.001					

In 31.1% ventilated neonates, BAL culture was positive. Out of these 87.8% cases had VAP. 84.6% cases with sterile BAL culture did not have VAP. This difference was statistically significant with p<0.001.Sensitivity ,specificity, PPV and NPV of positive BAL culture in ventilated neonates was 72%, 93.9%, 87.8% and 84.62% respectively in diagnosing VAP in neonates.

Table 6. CPIS in relation to VAP

CPIS	VAP				Total	
	Yes		No			
	No.	%	No.	%	No.	%
>6	39	81.2	9	18.8	48	36.4
<6	11	13.1	73	86.9	84	63.6
Total	50		82		132	
χ^2	60.298					
P	<0.001					

36.4% ventilated neonates had CPIS >6 . Out of these 81.2% cases had VAP.86.9% cases whose CPIS was negative (<6) did not have VAP. This difference was statistically significant with p<0.001.CPIS had sensitivity, specificity, PPV and NPV of 78%, 89%, 81.25% and 86.9% respectively in diagnosing VAP in neonates.

Table 7. CRP (on day 3) with CPIS in relation to VAP

CRP+CPIS	VAP				Total (n=132)	
	Yes		No			
	No.	%	No.	%	No.	%
All positive	29	76.3	9	23.7	38	28.8
All negative	3	5.8	48	94.1	51	71.2
χ^2	46.91					
P	<0.001					

In 28.8% ventilated neonates, both CRP and CPIS was positive. 76.3% of these cases had VAP .

VAP was not present in 94.1% neonates where both these tests were negative.

This difference was statistically significant with p<0.001. The sensitivity , specificity, PPV and NPV of combined CRP & CPIS was found to be 90.62%,84.21%,76.32%,94.12% respectively in diagnosing VAP in neonates.

Table 8. Micro ESR (on day 3) with CPIS relation to VAP

Micro ESR+CPIS	VAP				Total (n=132)	
	Yes		No			
	No.	%	No.	%	No.	%
All Positive	23	85.2	4	14.8	27	20.5
All Negative	6	10.2	53	89.8	59	44.7
χ^2	46.639					
P	<0.001					

Both micro ESR and CPIS was positive in 20.5% cases. Out of those 85.2% had VAP. VAP was not present in 89.8% cases where both these tests were negative. This difference was statistically significant with p<0.001. The

sensitivity , specificity, PPV and NPV of combined Micro-ESR & CPIS was found to be 79.3%, 92.9%, 85.19% and 89.83% respectively in diagnosing VAP in neonates.

Discussion

Ventilator Associated Pneumonia (VAP) is an important hospital acquired infection and a common problem encountered in intensive care units . Diagnosis is essential as it can direct the course of treatment and will help to reduce the burden of mortalily and morbidity contributed by it. There is no accepted gold standard .This has led to word wide debate as to the best method of diagnosis with so many studies showing conflicting and varying results. Most diagnostic techniques involve an invasive method like broncheoalveolar lavage, use of protected specimen brushing and lung biopsy. Such invasive methods are not always easy to perform and may delay diagnosis. It is for this reason and others that a diagnosis of VAP requires a combination of radiological, clinical,

and laboratory criteria[8] which is used as a reference standard. These is still a need to search for an easier, quicker and less invasive way to diagnose VAP. Many studies are have been done to compare the accuracy of the different methods but the results are still inconclusive. Lately, role of biomarkers have taken a centre stage in this quest . Keeping this in mind our study has focussed on the role of simple bedsides tests like Micro – ESR , CRP and CPIS in the early detection of VAP.

In our study the incidence of VAP was 37.9% . When we take only the neonatal population into account, the incidence is highly influenced by gestational age and regional economic development[9]. Afjeh et al reported an incidence of 17.3% , the study was conducted in Iran[10]. Incidence of 28.5% was reported by Apisarnthanarak et al in a prospective cohort study of LBW infants in the NICU[11].

The most common etiology of VAP in our study was gram negative micro-organisms which was found in 62% of all VAP cases. Most common bacterial isolate from ETA of VAP patient was Klebsiella spp by Tripathi et al[2] while Apisarnthanarak et al reported isolation of multiple organisms from tracheal aspirates (TA)[11].

In our present study VAP was found in 52.1% positive CRP on day 3 ($p=0.002$) and 50.6% of abnormal leucocyte count($p<0.001$). In a study conducted by P. Povoa to evaluate response of CRP, temperature and white cell count in the clinical resolution of VAP, he found that the increase in CRP value in non survivors was much greater than that of the survivors of VAP[12]. Lisboa et al. investigated the correlation on days 1 and 4 between quantitative tracheal aspirate and CRP concentrations in 68 patients with VAP. They observed a good correlation between the bacterial load and CRP concentrations[13].

In our study 57.9% positive blood culture was found in VAP ($p=0.003$) . The rate of positive blood cultures in VAP ranges from 8 to 20%[14] . Apisarntharak showed that bloodstream infection before VAP (adjusted odds ratio: 3.5) was an independent risk factor for VAP after adjustment for the duration of endotracheal intubation[11]. In another study on 162 patients with suspected VAP, Luna *et a*,showed that the sensitivity of blood cultures in 90 patients with VAP confirmed by BAL was only 26% and, in many cases, the bacteria isolated in the blood cultures probably had an extrapulmonary source. Blood cultures were also positive in 5 of 72 patients without VAP (6.9%)[15].

53.8% positive Micro-ESR ($p=0.002$) was found in VAP patients in our study. Not much studies have been done to link micro-ESR to VAP but as we already know that they

are good markers of sepsis[16], it is understood well ahead what their likey relationship with VAP could be as is seen in our study which shows a good co-relation .

A prospective study was undertaken by Waliullah SM in Dhaka Shishu Hospital to evaluate the role of simple hematological test for early diagnosis of neonatal sepsis, Micro-ESR, CRP, I/T ratio and platelet count had moderately high sensitivity and specificity[17].

CPIS is a very good predictor of VAP. Even in our study it had a good specificity of 89%. VAP occurred in 81.2% neonates with CPIS >6 while only 13.1% with CPIS <6 had VAP ($p<0.001$) . Pugin[4], the person who developed CPIS also stated that a CPIS >6 was associated with high likelihood of pneumonia (sensitivity 93%,specificity 100%) . Fabregas et al[18] attempted to check the accuracy of the CPIS by using the presence of both histological and positive microbiologic evidence of pneumonia in patients receiving mechanical ventilation . CPIS >6 as was considered a predictor of VAP. When CPIS was combined with CRP , 76.3% of neonates with both tests positive had VAP ($p<0.001$) and sensitivity was improved to 90.62%. When it was combined it Micro-ESR , 85.2% of neonates with both tests positive had VAP ($p<0.001$) and improved specificity to 92.9%.

Conclusion

Simple bedside tests like CRP, Micro- ESR, abnormal Leucocyte count, and CPIS were fairly predictive of VAP in neonates.

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