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Pentraxin 3 as an early marker in diagnosis of ventilator associated pneumonia

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ABSTRACT

Objective: To assess the role of pentraxin 3 (PTX3) in early diagnosis of ventilator associated pneumonia (VAP).
Background: The early diagnosis of VAP remains a challenge because the clinical signs and symptoms lack sensitivity and specificity and microbiological analysis and identification of organisms may take 48–72 h.
Methods: This prospective randomized study was conducted on forty patients diagnosed with VAP by clinical pulmonary infection score (CPIS) admitted in the intensive care unit (ICU) of Menoufia University Hospitals. We measured the level of PTX 3 in serum and bronchoalveolar lavage (BAL) and the level of CRP within 24 h from intubation and mechanical ventilation then after the onset of VAP diagnosed by CPIS > 6.
Results: VAP was diagnosed in 31 patients; 30 had BAL PTX 3 level ≥6 ng/ml with 96.7% sensitivity, 100% specificity,100% positive predictive value and 90% negative predictive value for pneumonia confirmed by Area under the receiver operating characteristic curve (AUC^{ROC}) analysis (AUC^{ROC} = 0.966, SE = .006, 95% CI = 0.985–1, P < .0001) and 27 had serum PTX 3 level ≥6 ng/ml with 87% sensitivity, 88.8% specificity, 96.4% positive predictive value and 66.6% negative predictive value for pneumonia confirmed by (AUC^{ROC}) analysis (AUC^{ROC} = 0.842, SE = .104, 95% CI = .639–1, p = .002) and 24 had CRP level ≥12 mg/l with 77.4% sensitivity, 33.3% specificity, 80% positive predictive value and 30% negative predictive value for pneumonia confirmed by (AUC^{ROC}) analysis (AUC^{ROC} = 0.590, SE = .1, 95% CI = .39–.79, p = .418).
Conclusion: BAL PTX3 level ≥6 ng/ml is discriminative for microbiologically confirmed VAP, serum PTX3 is also sensitive but less than BAL PTX3.

Introduction

VAP is defined as pneumonia that occurs more than 48 h after endotracheal intubation and the initiation of mechanical ventilation. The definite VAP diagnosis is challenging for ICU members. The CDC guidelines postulated that the clinical VAP diagnosis is made on the basis of the presence of leucocytosis, fever, purulent lung secretions, and new pulmonary infiltrates on chest X-rays [1]. Bacterial culture of bronchoalveolar lavage is a good standard for diagnosis of VAP, but it usually needs two to three days for the results to be obtained [2]. Gram stain can give rapid results but it is usually non-specific [3].

Biomarkers may help in improving accuracy and speed of VAP diagnosis. PTX3 is a mediator of acute inflammation that is produced at sites of infection and inflammation and can be measured in few hours. In the lungs; leucocytes, endothelial cells and epithelial cells may produce PTX3 when stimulated [4–6].

Abbreviations: PTX3, Pentraxin 3; VAP, Ventilator associated pneumonia; CPIS, Clinical pulmonary infection score; ICU, Intensive care unit; BAL, Bronchoalveolar lavage; AUC^{ROC}, Area under the receiver operating characteristic curve; CI, Confidence index; CRP, C reactive protien; MV, Mechanical ventilation; PaO2/FiO2, The ratio of partial pressure of arterial oxygen to the fraction of inspired oxygen; CBC, Complete blood count; CFU, Colony forming unit; ELISA, Enzyme-Linked Immunosorbent Assay; TLC, Total leucocytic count; HTN, Hypertension; CKD, Chronic kidney disease; HCV, Hepatitis C virus; SD, Standard deviation; PPV, Positive predictive value; NPV, Negative predictive value.

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Patients and methods

Forty critically ill adult patients intubated and mechanically ventilated were enrolled in this prospective randomized study through their admission to the ICU Department at Menoufia University Hospitals after obtaining the approval of the local ethical committee and after a written informed consent from all patient's relatives. The patients having pneumonia at the time of admission to the ICU and/or chronic respiratory disease as chronic obstructive pulmonary disease, interstitial lung disease, etc were excluded from the study. Demographic data including gender and age were collected. Also, the general characters of the patients including his initial diagnosis, indication and period of mechanical ventilation and comorbidities were recorded. APACH II score was evaluated within 24 h of admission in the ICU.

During the first 24 h of intubation and mechanical ventilation (MV) and then after 48 h after the appearance of any evidence of VAP (by using the CPIS >6 for VAP diagnosis or fever >38.2 °C, purulent endotracheal secretions, newly developed lung infiltrates and leucocytosis >12,000/mm − 3), data were collected from every patient which included temperature measurement, heart rate, respiratory rate, blood pressure, oxygen saturation, central venous pressure, urine output monitoring continuously and the ratio of partial pressure of arterial oxygen to the fraction of inspired oxygen (PaO2/FiO2). Plain chest X-ray was done during the first day of intubation and MV then follow up for the occurrence of new lung infiltrates. Other radiological investigations were requested if needed.

Electrocardiography was done for all included patients and echocardiography when needed to diagnose and exclude any cardiac conditions that might cause pulmonary infiltrates. Arterial blood gas analysis and complete blood count (CBC), sodium, potassium, kidney function tests, liver function tests were done for all cases. C-reactive protein (CRP) was measured by the semi-quantitative method at the onset of intubation and after the onset of VAP.

Flexible bronchoscopy was performed for quantitative bacterial culture and antibiotic sensitivity and the growths were expressed as a number of colony forming units (CFU)/ml. The threshold applied to quantitative cultures for the diagnosis of VAP was 10^4 CFU/ml. Also, assessment of alveolar PTX3 in the bronchoalveolar lavage (BAL) fluid was done and serum PTX3 was measured in all cases. Serum and BAL samples were centrifuged and then stored at −80 °C until analysis by using *the Assay-Max Human pentraxin3 ELISA (Enzyme-Linked Immunosorbent Assay) kit.*

Results

This prospective randomized study enrolled forty critically ill adult patients intubated and mechanically ventilated. There was no significant correlation between the level of PTX3 and general characters of patient (P > .05) (Table 1). There was no significant affection of CPIS score and other parameters as TLC, temperature and Po2/FiO2 ratio on the level of PTX3 (P > .05) (Table 2).

The levels of PTX3 in BAL and serum were significantly higher in the presence of pneumonia with p-value < .0001 compared to CRP which was not significantly effective with p-value > .05 (Table 3). The level of BAL PTX3 was highly specific and sensitive in the early diagnosis of VAP more than the level of serum PTX3 and CRP (Table 4).

Discussion

Our results showed that pneumonia was diagnosed in 31 patients; 30 of them had BAL PTX3 level ≥6 ng/ml, 27 of them had serum PTX3 level ≥6 ng/ml and 24 of them had serum CRP l evel ≥12 mg/l. According to our study, A cut-off value of PTX3 le vels ≥6 ng/ml in BAL fluid serum (identified by Youden index) was associated with 96.7% sensitivity, 100% specificity, 100% positive predictive value (PPV) and 90% negative predictive value (NPV) for culture-positive pneumonia and diagnostic accuracy of PTX3 levels in BAL fluid in early diagnosis of VAP was confirmed by Area under the receiver operating characteristic curve (AUC^{ROC}) analysis that showed that the levels after 48 h of intubation predicted pneumonia (AUC^{ROC} = 0.966, SE = 0.006, 95% CI = 0.985 to 1, P < .0001).

According to our study, a cutoff value of serum PTX3 levels ≥6 ng/ml in serum (identified by Youden index) was associated with 87% sensitivity, 88.8% specificity, 96.4% positive predictive value and 66.6% negative predictive value for culture-positive pneumonia and diagnostic accuracy of PTX3 levels in the serum in early diagnosis of VAP was confirmed by AUC^{ROC} analysis that showed

Table 1
General characters of the studied patients (n = 40).

General characters of patients	Patients with BAL PTX3 <6 (*n* = 10, 25%)	Patients with BAL PTX3 ≥6 (*n* = 30, 75%)	Test of significance	P- value
Age, *mean (SD)*	45 (±9.17)	45.8 (9.5)	Mann-Whitney *U* test	.82
Gender, *n (%)*				
Male	5 (50)	25 (83.3)	Fisher exact test	.085
Female	5 (50)	5 (16.7)		
History, *n (%)*				
Hypertension (HTN)	0 (0)	2 (6.7)	Pearson Chi- Square test	.329
Chronic kidney disease (CKD)	0 (0)	1 (3.3)		
HTN and CKD	1 (10)	2 (6.7)		
Diabetes	2 (20)	4 (13.3)		
HCV	2 (20)	1 (33.3)		
Pregnancy	0 (0)	1 (33.3)		
Atrial fibrillation	2 (20)	3 (60)		
Free	3 (30)	16 (53.3)		
Cause of admission, *n (%)*				
Burn	1 (10)	1 (3.3)	Pearson Chi- Square test	.957
Trauma	2 (20)	9 (30)		
Cerebrovascular disease	5 (50)	13 (43.3)		
Electricity	0 (0)	1 (3.3)		
Toxicology	1 (10)	2 (6.7)		
Postoperative	1 (10)	4 (13.3)		
Onset of VAP, *Mean (±SD)*	5 (±1.3)	6.2 (±1.9)	T-Test	.329
APACHE, *Median (Range)*	10 (8−20)	14.5 (4−20)	Mann-Whitney *U* test	.315