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Researching the Changes of Serum Procalcitonin Levels in Ventilator-Associated Pneumonia Patients

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Abstract

Background: Ventilator-Associated Pneumonia (VAP) is the most common hospital acquired infection in the intensive care unit with high mortality rate. The role of the clinical symptoms for the VAP diagnosis is limited. Procalcitonin (PCT), currently interested biomarkers, plays an important role in the diagnosis and the outcome of the ventilator-associated pneumonia patients.

Objective: To evaluate the changes of serum procalcitonin level for the diagnosis and the prognosis of the ventilator-associated pneumonia patients.

Materials and Methods: One hundred twenty two mechanical ventilated cases at Intensive Care Unit were divided into the VAP group (n=63) and the non-VAP group (n=59) depending on whether the patients developed VAP after 48 hour of endotracheal intubations and mechanical ventilation or not. The serum procalcitonin level, Clinical Pulmonary Infection Score (CPIS) described by Pugin et al. or Schurink et al. were determined at the following times: The starting of mechanical ventilation, the VAP onset, at days 3, 5, 7 after VAP.

Results: Serum procalcitonin level >0.5 ng/ml had a role at quite good VAP diagnosis with the Sensitivity (Se) 68.25% and the Specificity (Sp) 89.83%. When both Pugin's CPIS and procalcitonin were positive, the diagnostic efficiency were Se 59.58% and Sp 97.06%. When both Schurink's CPIS and procalcitonin were positive, the diagnostic efficiency were Se 51.99% and Sp 92.07%. Mortality rate was 5% at serum procalcitonin level <0.5 ng/ml but it was 75% at serum procalcitonin level ≥10 ng/ml.

Conclusions: Procalcitonin has both the diagnosis value in the ventilator- associated pneumonia patients and the prognostic value in their treatment outcome and the mortality rate. Serum procalcitonin concentration >0.5 ng/ml had a role at quite good VAP diagnosis with the sensitivity 68.25% and the specificity 89.83%. The higher serum procalcitonin level was associated with the higher mortality rate and the mortality rate was 75% at serum procalcitonin level ≥10 ng/ml in ventilator-associated pneumonia.

Key words

Procalcitonin; Ventilator-associated pneumonia

Introduction

American Thoracic Society in the guidelines for the management of adults with Hospital –acquired, Ventilator-associated, and Healthcare-associated Pneumonia in 2004 made the definition of Ventilator-Associated Pneumonia (VAP) that refers to pneumonia that arising more than 48-72 hours after endotracheal intubation [1]. Ventilator-Associated Pneumonia is the most common hospital acquired infection in the Intensive Care Unit (ICU).

The incidence of ventilator-associated pneumonia is 8-20% for patients in the intensive care unit and is 27% for the mechanical ventilated patients. The mortality rate varies from 24 to 50% and up to 76% [1]. The role of the clinical symptoms for the ventilator-associated pneumonia diagnosis is also limited. Recently, many authors have noticed the biomarkers. Currently interested biomarker is Procalcitonin (PCT).

Jia et al. [2] reported the optimal serum procalcitonin cut-off value for ventilator-associated pneumonia diagnosis on day 1 was 5 ng/mL with a sensitivity of 91% and a specificity of 71% after cardiac surgery. They concluded procalcitonin may be used as diagnostic marker for ventilator-associated pneumonia in patients following cardiac surgery [2].

Hakan et al. [3] found that the serum procalcitonin level on the day 3 of the pneumonia diagnosis >1 ng/ml was the strongest predictor of mortality in ventilator-associated pneumonia. Up to now any detailed study about the serum procalcitonin levels in the ventilator-associated pneumonia period and the relationship of the serum procalcitonin levels with clinical symptoms for the ventilator-associated pneumonia diagnosis and prognosis has not been carried out in Vietnam yet.

Therefore we made the research with the aim of evaluating the changes of serum procalcitonin level for the diagnosis and the prognosis of the ventilator-associated pneumonia patients at the intensive care unit in the hospital 103.

Materials and methods

This study was conducted at the intensive care unit in the hospital 103, Hanoi, Vietnam from Jan. 2009 to Dec. 2011. The study was approved of by Ethics and Research Committee of the hospital. All patients or their relatives provided their written informed consent before participating in the study. One hundred twenty two mechanical ventilated cases at the intensive care unit were divided into two groups: The VAP group included 63 VAP cases and the non-VAP group included 59 mechanical ventilated cases but non-VAP.

Selection criteria included all subjects undergone invasive mechanical ventilation with VAP or non VAP diagnosis. VAP diagnostic criteria defined according to American Thoracic Society [1]. Exclusion criteria included patients and their relatives refused to participate in the study, patients suffered from infection status before the intensive care unit admission or before 48 hours of mechanical ventilation as well as extra-pulmonary infection status e.g. urine infection, sepsis, or central venous inserted catheter-related infection ... during their treatment course in the intensive care unit, patients were performed endotracheal intubation or tracheostomy, and mechanical ventilation from other places, patients were diagnosed as lung cancer or thyroid diseases.

The study design was a longitudinal prospective described controlled study. The study variables included age, sex, Clinical Pulmonary Infection Score (CPIS) as described by Pugin et al. [4], clinical pulmonary infection score as described by Schurink et al. [5], VAP treatment outcomes, serum procalcitonin level.

VAP treatment outcomes were divided into very good (disappearing VAP symptoms and successfully ventilator weaning after seven-day treatment), good (disappearing VAP symptoms but changed antibiotics after seven-day treatment), failure (persistent VAP symptoms after 10-day treatment, unsuccessfully ventilator weaning or endotracheal tube extubation), and death.Serum procalcitonin level was determined by the method of the electrode chemi luminescence [6].

The study times included T_0 - the starting of mechanical ventilation, T_1 - the VAP onset, T_3 - day 3 after VAP, T_5 - day 5 after VAP, T_7 - day 7 after VAP.

Statistical analysis

Data were expressed as absolute numbers with percentages and as means with standard deviation. Comparisons were performed by t-test. Statistical analysis was performed with the EPI-INFO 2000 software. A probability value less than 0.05 was considered statistically significant.

Results

In the VAP group and the non-VAP group, mean age was 54.27±18.1 and 49.72±12.65, respectively while male rate was 82.54% and 74.58%, respectively (Table 1).

Characteristic	VAP group n (%)	Non-VAP group n (%)
Male sex	52 (82,54)	44 (74,58)
Age (years)[a]	54.27±18.1	49.72±12.65
[a]Values are means ± SD		

Table 1: Patient characteristics.

In the VAP group and the non-VAP group, serum procalcitonin level was 2.18 ng/ml and 0.43 ng/ml, respectively (Figure 1).

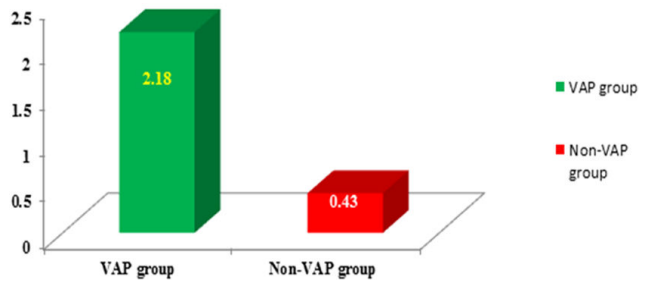

Figure 1: Mean value of serum procalcitonin level at the ventilator-associated pneumonia onset in two groups.

Se and Sp was 68.25% and 89.83%, respectively at serum procalcitonin level >0.5 ng/ml for VAP diagnosis (Table 2). Area under the Curve (AUC) was 0.78 for VAP diagnosis ability at very good level with 68.25% Se and 89.83% Sp at serum procalcitonin level ≥0.52 ng/ml (cut off point) (Figure 2).

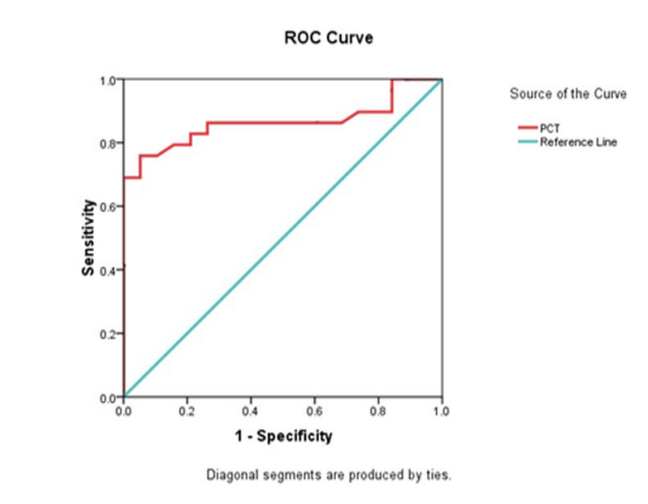

Figure 2: Area under the curve (AUC) of serum procalcitonin level in the VAP group.

PCT (ng/ml)	VAP group		Non-VAP group	
	Number of patients	Percentage	Number of patients	Percentage
≤ 0.5	20	31.75	53	89.83
>0.5	43	68.25	6	10.17

Table 2: Serum procalcitonin level change at the ventilator-associated pneumonia onset in two groups.

When both procalcitonin and Pugin's CPIS were positive, Se and Sp were 59.58% and 97.06%, respectively. When both procalcitonin and Schurink's CPIS were positive, Se and Sp were 51.99% and 92.07%, respectively. When procalcitonin or Pugin's CPIS was positive, Se and Sp were 95.96% and 63.94%, respectively. When procalcitonin or Schurink's CPIS was positive, Se and Sp were 92.44% and 19.78%, respectively (Table 3). The very good treatment outcome patients had the low serum procalcitonin level (1.08±0.94 ng/ml) at the ventilator-associated pneumonia onset and till the seventh day the serum procalcitonin level was below 0.5 ng/ml (0.35±0.08 ng/ml).

Diagnostic methods	Sensitivity (%)	Specificity (%)
Pugin's CPIS	87.3	71.18
Schurink's CPIS	76.19	22.03
PCT	68.25	89.83
PCT and Pugin's CPIS were positive	59.58	97.06
PCT and Schurink's CPIS were positive	51.99	92.07
PCT or Pugin's CPIS was positive	95.96	63.94
PCT or Schurink's CPIS was positive	92.44	19.78*
*P<0.05		

Table 3: The ventilator-associated pneumonia diagnostic value of the combination of serum procalcitonin level with Pugin's CPIS or Schurink's CPIS.

The patient who died after 7 days of the ventilator-associated pneumonia treatment had the high serum procalcitonin level (3.23±1.68 ng/ml) at the ventilator-associated pneumonia onset and reduction of serum procalcitonin levels within 7 days was not significant (2.87±0.91 ng/ml) (Table 4). Mortality rate was 5% and 75% at serum procalcitonin level <0.5 ng/mL and ≥10 ng/ml, respectively (Table 5).

Serum procalcitonin levels (ng/ml)	Treatment outcomes			
	Very good	Good	Failure	Death
T1	1.08±0.94	1.34±0.63	2.57±1.07	3.23±1.68
T3	1.03±0.17	1.28±0.33	1.71±0.81	3.05±1.34
T5	0.66±0.16	0.91±0.25	1.48±0.72	2.95±0.87
T7	0.35±0.08	0.58±0.24	1.19±0.41	2.87±0.91

Table 4: Serum procalcitonin level change with treatment outcomes in the VAP group.

PCT level (ng/ml)	Survivor		Non-survivor		Mortality rate at different PCT levels (%)
	Number of patients	Percentage	Number of patients	Percentage	
<0.5	19	30.15	1	1.58*	5
0.5 - <2	21	33.33	6	9.52	22.22
2 - <10	7	11.11	5	7.93	41.67
≥ 10	1	1.58	3	4.76*	75
* p<0.05					

Table 5: Relationship between serum procalcitonin levels at the ventilator-associated pneumonia onset and survivor and non-survivor rates in the VAP group.

Discussion

In the present study, there was no significant difference between two groups in terms of age, sex (p>0.05) (Table 1). The mean serum procalcitonin level at the ventilator-associated pneumonia onset in the VAP group was significantly higher the non-VAP group (p<0.05) (Figure 1). Because patients of two groups suffered from infection status before the intensive care unit admission as well as extra-pulmonary infection status e.g. urine infection, sepsis, or central venous inserted catheter-related infection ... during their treatment course in the intensive care unit were excluded from the study. Therefore, the serum procalcitonin level in the VAP group was higher than in the non-VAP group due to lung infection but wasn't any associated complication. Christ-Crain M et al. reported that serum procalcitonin level >0.5 ng/ml was considered as lung infection [7]. In the our study, the serum procalcitonin level just before starting of the mechanical ventilation wasn't measured because the serum procalcitonin level at that time may be less meaning due to serum procalcitonin level increases in infection status whereas patients suffering from infection status before the mechanical ventilation were excluded from the study. Liao et al. studied 49 suspected episodes of ventilator-associated pneumonia in 31 cases and found that serum procalcitonin levels were 0.68 mcg/L and 0.18 mcg/L, respectively in patients with and without ventilator-associated pneumonia on the suspicion day [8]. In the present study, the sensitivity and the specificity of serum procalcitonin value for the ventilator-associated pneumonia diagnosis were 68.25% and 89.83%, respectively (Table 2). The Area under the curve (AUC) was 0.78 for a quite good diagnostic value and the cutoff point was 0.52 ng/ml (Figure 2). The results of our study are similar to those of Zhou et al. [9], Luyt et al. [10]. The two authors took serum procalcitonin value over 0.5 ng/mL at the time of the ventilator-associated pneumonia diagnosis. Luyt et al. studied on 73 ventilator-associated pneumonia cases in intensive care unit and also reported that serum procalcitonin level >0.5 ng/ml on the first day of ventilator-associated pneumonia had 41% sensitivity and 85% specificity [10]. Zhou et al. studied 61 ventilator-associated pneumonia cases in intensive care unit and found serum procalcitonin level >0.5 ng/ml had 74.1% sensitivity and 80% specificity [9]. Furthermore, Zhou et al. concluded serum procalcitonin level may help to make early ventilator-associated pneumonia diagnosis through serum procalcitonin level progressive monitoring [9]. In our study, when

combination of serum procalcitonin level with Pugin's CPIS, if both positive methods increased the accuracy of the ventilator-associated pneumonia diagnosis (due to increasing in the specificity). If there was an only positive method, this combination increased the sensitivity of the ventilator-associated pneumonia diagnosis (Table 3). Pelosi P et al. investigated the role of the clinical pulmonary infection score, serum procalcitonin level in 58 cases with severe brain injury receiving mechanical ventilation in the detection of the cases with early ventilator-associated pneumonia. Clinical pulmonary infection score had value for ventilator-associated pneumonia diagnosis with 97% sensitivity and 80% specificity. Procalcitonin increased the specificity of clinical pulmonary infection score to 100%. The author concluded that procalcitonin may be a useful marker to predict which patients subsequently have early ventilator-associated pneumonia [11]. Ramirez P et al. made sequential measurement of serum procalcitonin level and the calculation of the simplified clinical pulmonary infection score in 44 patients mechanically ventilated for >48 hours with neither active infection for the duration or suspicion of ventilator-associated pneumonia. He found clinical pulmonary infection score ≥6 had 78% sensitivity and 80% specificity. A clinical pulmonary infection score ≥6 combined with serum procalcitonin levels ≥2.99 ng/ml resulted in 100% specificity [12]. According to the guideline of American Thoracic Society [1], there were 63 VAP cases in our study but only 43 VAP cases (68.25%) in the VAP group had serum procalcitonin level >0.5 ng/ml and 20 VAP cases (31.75%) in the VAP group had serum procalcitonin level ≤0.5 ng/ml (Table 2). Therefore, if VAP diagnosis was only based on serum procalcitonin level >0.5 ng/ml, 20 cases (31.75%) in the VAP group were missed out the VAP diagnosis. Then, combination of procalcitonin with some clinical scores for VAP diagnosis e.g. Pugin's CPIS or Schurink's CPIS ... made more acute VAP diagnosis. In the present study, the combination of procalcitonin with Schurink's CPIS increased the diagnostic value of Schurink's CPIS. Furthermore, when procalcitonin, Pugin's CPIS, and Schrink's CPIS were all positive, the sensitivity and the specificity were not significant between the two combined methods ($p > 0.05$) but when there was only one of two positive methods, the specificity of combination of procalcitonin with Pugin's CPIS was significantly higher than combination of procalcitonin with Schurink's CPIS ($p<0.05$) (Table 3). On the contrary, Liao et al. reported combination of procalcitonin with Schurink's CPIS had similar value to combination of procalcitonin with Pugin's CPIS for ventilator-associated pneumonia diagnosis [8]. In the our study, when procalcitonin or Pugin's CPIS was positive, Se increased up 95.96% as compared with Se was 68.25% and 87.3%, if the only diagnostic method of procalcitonin or Pugin's CPIS was applied, respectively. However, both procalcitonin and Pugin's CPIS were positive, Sp increased up 97.06% as compared with Sp was 89.83% and 71.18%, if the only diagnostic method of procalcitonin or Pugin's CPIS was applied, respectively (Table 3). Therefore, serum procalcitonin level should be combined with Pugin's CPIS to make acute ventilator-associated pneumonia diagnosis.

In the present study, the patient who died after 7 days of the ventilator-associated pneumonia treatment had the high serum procalcitonin levels at the ventilator-associated pneumonia onset and the seventh day after the ventilator-associated pneumonia (Table 4). In the VAP group, the higher serum procalcitonin level was associated with the higher mortality rate (Table 5). Twenty cases at serum procalcitonin level ≤0.5 ng/ml in the VAP group only had one mortality case with the lowest mortality rate (5%) at different procalcitonin levels whereas 43 cases at serum procalcitonin level >0.5 ng/ml in the VAP group had 14 mortality cases with the mortality rate from 22.22% to 75%. Moreover, serum procalcitonin level ≥10 ng/ml had the highest mortality rate (75%) at different procalcitonin levels in the VAP group (Table 5). Therefore, serum procalcitonin level can effectively be used as prognosis purpose in ventilator-associated pneumonia. Bloos et al. studied on 175 cases including 57 cases with Community Acquired Pneumonia (CAP), 61 cases with Ventilator-Associated Pneumonia (VAP) and 57 cases with Hospital Acquired Pneumonia (HAP). Initial serum procalcitonin levels were higher in community acquired pneumonia than ventilator-associated pneumonia patients but not significantly different to hospital acquired pneumonia. The 28-day intensive care unit mortality rate for all patients was 18.3% with a median intensive care unit length of stay of 16 days. Serum procalcitonin levels were higher in non-survivors than in survivors. The authors concluded procalcitonin appears to be a prognostic marker of morbidity and mortality comparable to the Acute Physiology and Chronic Health Evaluation II (APACHE II) score [13]. Luyt et al. studied 63 ventilator-associated pneumonia cases in which 38 ventilator-associated pneumonia cases had unfavorable outcomes. Serum procalcitonin levels decreased during the clinical course of ventilator-associated pneumonia but were significantly higher from the first day to the seventh day in cases with unfavorable outcomes. Multivariate analyses retained serum procalcitonin levels on days 1, 3, and 7 as strong predictors of unfavorable outcome. Based on these data, the author concluded that procalcitonin could be a prognostic marker of outcome during ventilator-associated pneumonia [14].

Conclusion

Procalcitonin has the diagnosis value in the ventilator-associated pneumonia patients. Serum procalcitonin level >0.5 ng/ml had a role at quite good ventilator-associated pneumonia diagnosis (the area under the curve 0.78) with the sensitivity 68.25% and the specificity 89.83%. Furthermore, procalcitonin has also prognostic value in treatment outcome and mortality rate in the ventilator-associated pneumonia patients. Mortality rate was 75% at serum procalcitonin level ≥10 ng/ml in the ventilator-associated pneumonia, and the higher serum procalcitonin level was associated with the higher mortality rate.

Limitations

Our study had a limitation that serum procalcitonin level was assessed only on T_1, T_3, T_5, and T_7 with reference to the time of the ventilator-associated pneumonia diagnosis. We suggest that determining the variable either daily or more frequently would be more useful.

Conflict of Interest Statement

None of the authors has a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

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