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The value of monocyte volume index in predicting post-surgical bacterial infection.

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Abstract

Background: Previous studies have shown that the mean monocyte volume was significantly increased in postsurgical patients with bacterial infection. To further validate its potential clinical usefulness, we compare the monocyte volume index (MV-index), which is defined as ΔMMV × ΔMMV-SD, (where the changes in Mean Monocyte Volume (MMV) and its Standard Deviation (MMV-SD) before and after surgery called ΔMMV and ΔMMV-SD, respectively) with PCT in terms of diagnostic sensitivity and specificity for post-surgical bacterial infection.

Methods: Blood samples from 223 cardiac surgical patients without postsurgical infection, and 63 cardiac surgical patients complicated with postsurgical bacterial infection were studied.

Results: There are no statistically significant differences for WBC count and monocyte percentage prior to or after surgery between postsurgical non-infected and infected patients. However, the MV-index is significantly increased in postsurgical infected patients when compared with non-infected patients (P<0.05). Furthermore, the MV-index was correlated well with PCT on the second and third day after surgery. The receiver-operating characteristics analysis reveals the MV-index and PCT have the similar areas under curves (0.908, 0.910 on the second day and 0.955, 0.956 on the third day postsurgery, respectively).

Conclusion: MV-index shows comparable sensitivity and specificity to PCT for predicting postsurgical bacterial infection. It may be an effective postoperative infection indicator for clinical diagnosis.

Keywords: Cell population data, Monocyte, Bacterial infection.

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Introduction

Post-surgical infection is a serious medical problem that can delay recovery following surgery, increase hospital stays as well as medical care costs. Timely diagnosis of postoperative infection is critical for proper patient management. However, traditional parameters, such as White Blood Cell (WBC) counts or body temperature, may not be adequate to detect the infection because non-infectious leukocytosis and fever are common phenomena in post-surgical period. The systemic inflammatory response syndrome induced by surgical trauma is a well-known entity, with the resultant release of various inflammatory cytokines leading to fever and/or leukocytosis despite the absence of infection.

In recent years, Procalcitonin (PCT) has been proposed to be an ideal biomarker for systemic bacterial infection or sepsis. [1] PCT is the pro-hormone form of calcitonin and is produced by extra-thyroidal immune cells within 2-4 h of a bacterial insult and/or inflammatory response. Elevated PCT is seen in septic patients and concentrations correlate with severity of disease. Increasing PCT over time is associated with poor prognosis, while decreasing concentrations correlate to good prognosis and/or response to antibiotic therapy [2].

It has also been previously demonstrated that Cell Population Data (CPD), such as Mean Neutrophil Volume (MNV) and neutrophil volume distribution width, are significantly increased not only in septic patients with high WBC, but also in those with normal or low WBC counts as well as in the post-surgical patients complicated with bacterial infection [3-8]. The CPD are determined by modern coulter automated hematology analyzers with VCS technology, such as LH750 or DxH800 (Beckman Coulter, Brea, California). The VCS (volume, conductivity and light scatter) technology is able to generate the differential count based solely on the analysis of three parameters that are directly correlated to intrinsic biophysical properties of each WBC, using neither chemical reactions nor fluorescence. The volume or cell size is measured directly by impedance. The conductivity reflecting the internal cellular composition is measured by the conduction of radio frequency waves across the cells, and the laser light scatter gives direct information regarding cytoplasmic granularity and nuclear complexity.

Previous studies have shown that the mean monocyte volume was significantly increased in postsurgical patients with bacterial infection. To further validate its potential clinical usefulness, we investigate the clinical usefulness of monocyte CPD in post-surgical bacterial infection. We will compare the monocyte volume index (MV-index), which is defined as ΔMMV × ΔMMV-SD, (where the changes in mean monocyte volume (MMV) and its standard deviation (MMV-SD) before and after surgery called ΔMMV and ΔMMV-SD, respectively) with PCT in terms of diagnostic sensitivity and specificity for post-surgical bacterial infection. Then, we try to provide new and effective postoperative infection indicators for clinical diagnosis.

Materials and Methods

Study population

In this retrospective case-control study, peripheral blood specimens were drawn into dipotassium EDTA anticoagulant and serum separate clot activator in Vacutainer tubes (Becton Dickinson, Franklin Lakes, NJ, USA) and stored at room temperature. The subjects included 223 cardiac surgical patients (mean age: 50 y; M/F=1.1:1) without post-surgical infection, and 63 cardiac surgical patients (mean age: 51 y; M/F=1.1:1) with post-surgical infection confirmed by positive culture for bacteria at The Second Affiliated Hospital of Nantong University between April 2012 and August 2015. Prior to surgery, all patients had no fever (defined as maximum temperature ≤ 38.5°C), and their WBC counts and neutrophil (NE%) were within normal reference ranges. Blood samples were collected on the consecutive days after surgery. Ethical approval was obtained from the ethics committee of the First People's Hospital of Nantong (the approval number: 20120069).

Hematological data collection

Monocyte CPD, such as the MMV and MMV-SD were collected, which were generated during automated differential analysis by each individual cell passing through the aperture and were optically and electronically measured using the Coulter LH 750. The ΔMMV was calculated as: MMV after surgery-MMV before surgery, and ΔMMV-SD=MMV-SD after surgery-MMV-SD before surgery. Monocyte volume index (MV-index)=ΔMMV × ΔMMV-SD. All specimens were analysed within 2 h after collection. Daily quality controls were run according to the manufacturer’s instructions.

PCT determination

PCT was measured using the electro-chemiluminescent immunoassay on the Cobas e601 instrument (Roche Diagnostics, Mannheim, Germany) according to the manufacturer’s recommendations. The assay has a measuring range from 0.02 to 100 ng/ml. Imprecision varied between 2.7% and 3.9% at concentrations of 0.72~55.4 ng/ml. The reference range was up to 0.046 ng/ml.

Statistical analysis

All analyses, including Receiver-Operating Characteristics (ROC), were performed using the Statistical Package for the Social Science (SPSS) software, version 13.0 (SPSS, Chicago, IL, USA). Comparison between two means was performed by the Student t test. Correlations were determined using Spearman’s rank correlation coefficients. Results were expressed as the mean ± Standard Deviation (SD). A P-value less than 0.05 was considered significant.

Results

MV-index and PCT in post-surgical infection

WBC count, NE% and MO% were within normal reference ranges for all patients prior to surgery. Although WBC count and NE% were both increased and MO% was decreased after surgery as expected, no statistical differences were seen between post-surgical non-infected and infected patients (P>0.05). The MV-index also did not show significant difference on the first day after surgery (Table 1). However, the MV-index in infected patients was significantly increased when compared with non-infected patients on the second and third day after surgery (the second: t=14.15, P=0.000; the third: t=28.77, P=0.000; Table 1). The PCT in infected patients was also significantly increased when compared with non-infected patients on the second and third day (the second: t=12.54, P=0.000; the third: t=16.74, P=0.000; Table 1). The MV-index was correlated well with PCT on the second and third day after surgery (r=0.826 and r=0.871, P<0.01).

Table 1. *The results of all markers after surgery.*

Item	Non-infected patients (n=223)			Infected patients (n=63)		
	First day	Second day	Third day	First day	Second day	Third day
MO%	3.04 ± 0.46	2.06 ± 0.52	1.96 ± 0.55	3.14 ± 0.43	1.90 ± 0.51	1.85 ± 0.54
MV-index	24.34 ± 5.75	36.77 ± 10.59	52.34 ± 13.16	24.21 ± 5.11	61.92 ± 17.59	123.97 ± 27.84
PCT (ng/ml)	0.12 ± 0.03	0.22 ± 0.06	0.15 ± 0.10	0.12 ± 0.04	1.02 ± 0.95	1.33 ± 1.04

P<0.05, compared with non-infected patients; P<0.05, compared with the first day in infected patients.

Determination of sensitivity and specificity for predicting post-surgical infection

The sensitivity and the specificity of the MV-index and PCT for predicting post-surgical bacterial infection were next evaluated. The ROC curve analyses showed that the MV-index and PCT had the similar Areas Under the Curves (AUC) of 0.908 and 0.910 on the second day, and 0.955 and 0.956 on the third day, respectively after surgery. Using the cut-off points of ≥ 56.33 for MV-index and ≥ 0.416 for PCT, the sensitivities of 86.84% and 86.79% and specificities of 90.37% and 91.05% were achieved, respectively (Table 2). These results suggested that MV-index is comparable to PCT as a sensitive marker to predict post-surgical bacterial infections.

Table 2. *Sensitivity and specificity of various parameters in predicting postsurgical infection on the second day after surgery.*

Test result variable (s)	The second day				The third day			
	Area under the curve	Cut-off value	Sensitivity (%)	Specificity (%)	Area under the curve	Cut-off value	Sensitivity (%)	Specificity (%)
MV-index	0.908	≥ 56.33	86.84	90.37	0.955	≥ 67.52	89.39	93.15
PCT(ng/ml)	0.910	≥ 0.416	86.79	91.05	0.956	≥ 0.383	91.15	92.87

Discussion

The presence of fever and leukocytosis has traditionally been utilized as the diagnostic marker of infection. However, several recent studies suggested that fever and leukocytosis are poor predictors for diagnosing post-surgical infection [9-11]. Other commonly used laboratory tests include blood culture for bacterial microorganisms, CRP level and erythrocyte sedimentation rate, but the diagnostic value of these parameters also vary greatly. Although microscopic evaluation of a peripheral blood smear can also detect the morphologic changes of reactive neutrophils, such as the presence of toxic granulation, toxic vacuolization, and Dohle bodies in the cytoplasm, it is labor intensive, time-consuming, and requires manual examination by a trained medical technologist. In addition, the results are subjective, because they depend on human interpretation, and only 100 or 200 cells are evaluated in a typical microscopic manual differential count, leading to imprecision and lack of confidence of the test results among clinicians [12,13]. Determination of serum PCT levels [2,14,15] and CD64 expression on peripheral blood leukocytes [16,17] has recently been shown to improve diagnostic sensitivity and specificity for bacterial infection. These tests, however, require high technical support and are relatively expensive. Therefore, there is a clear need for a new and more cost-effective marker for acute bacterial infection.

It had been verified that MMV is significantly increased in post-surgical infected patients when compared with non-infected patients [18]. In the present study, we further demonstrate that MV-index shows comparable sensitivity and specificity to PCT, which has been proposed to be an ideal biomarker for systemic bacterial infection or sepsis [1]. However, the clinical application of MV-index offers several additional advantages. The parameter is generated during automated differential analysis without additional specimen requirements. It is quantitative, more objective, and more accurate than manual differential counts because over 8000 leukocytes are simultaneously evaluated. In addition, the MV-index determined by the Coulter LH750 offer more robust turnaround time and are more cost-effective. Therefore, the potential clinical application of MV-index for post-surgical infection merits further exploration in a larger prospective study.

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