Correlation of Changes in Leukocytes Levels 24 Hours after Intravenous Thrombolysis With Prognosis in Patients With Acute Ischemic Stroke

Jie Chen, MD, Zengrui Zhang, MD, Luyun Chen, MD, Xiaowen Feng, MD, Wangwang Hu, MD, Wanqian Ge, MD, Xianmei Li, MD, Pingping Jin, MD, and Bei Shao, MD

Objective: Leukocytes play a crucial role in inflammation and immune response. This study aims to demonstrate the value of changes in leukocytes levels 24 hours after intravenous thrombolysis to predict prognosis in acute ischemic stroke (AIS). *Methods:* From Jan 2016 to Oct 2017, the patients who suffered AIS to our center within 4.5 hours of symptom onset were all treated with recombinant tissue-type plasminogen activator. Data from 213 AIS patients were analyzed. Patients were divided into 4 groups: persistent leukocytosis (PL), transient leukocytosis (TL), leukocytosis 24 hours (L24H) and no leukocytosis (NL). By comparison, the factors with statistically significant were selected in pairwise multiple comparisons. Good clinical outcome was defined as the Modified Rankin Scale score of 2 or lower. Multivariate logistic regression was used to assess the association of the indicators with clinical outcome. *Results:* By pairwise multiple comparisons, PL and L24H had higher baseline National Institutes of Health Stroke Scale (NIHSS) score than NL and were likely to lead poor clinical outcomes. TL had a better prognosis than L24H. As the results of multivariable analyses shown, PL and L24H were risk factors to poor functional outcomes (odds ratio [OR] = 2.668, 95% confidence interval [CI] = 1.139-6.249, $P = .024$; OR = 6.648, 95%CI = 2.048-21.584, $P = .002$). *Conclusion:* Persistent leukocytosis and leukocytosis 24 hours both had higher baseline NIHSS scores, more serious stroke and were more likely to lead to unfavorable outcome. Therefore, changes in leukocytes levels 24 hours after intravenous thrombolysis could be predicted the short-term functional outcome of AIS patients.
Key Words: Leukocytes levels—acute ischemic stroke—intravenous thrombolysis—prognosis—recombinant tissue-type plasminogen activator

Introduction

In 2005, stroke was discovered to be the leading cause of death in the third national survey on all death causes[1,2] and so far it was still the main cause of disability around the world.[3] The effectiveness and benefit of intravenous thrombolysis using recombinant tissue-type plasminogen activator within 4.5 hours of symptom onset for acute ischemic stroke (AIS) have been clearly proved.[4-7] Leukocytes, as well as C-reactive protein, are indicators of inflammation and immune response in our body and leukocytosis always associate with poor outcomes in AIS patients.[8] Stroke is known to produce an inflammatory response with leukocytosis in peripheral blood.[9] White blood cells (WBC) count increased has been shown to predict inhospital strokes indicating a close relationship between leukocytosis and stroke.[10-12] Previous studies have demonstrated that leukocytosis on admission has been correlated with initial stroke severity in AIS patients.[10,11] However, we found that some AIS patients who had normal Leukocytes on admission had

Leukocytosis after thrombolysis. This study aims to compare the characteristics and clinical outcome between 4 groups of different leukocytes levels and demonstrate the value of changes in leukocytes levels 24 hours after intravenous thrombolysis to predict prognosis in AIS.

Methods

Study Population

From Jan 2016 to Oct 2017, the patients who suffered AIS to our center within 4.5 hours of symptom onset were consecutively recruited. All patients who were diagnosed as AIS admitted to the stroke unit according to the World Health Organization Criteria.[13] NIHSS score were assessed by a specialist neurologist on admission. Emergency computed tomography (CT) was served to exclude cerebral hemorrhage and brain tumors. Emergency blood samples including white blood cells count were collected at admission.

The patients who underwent thrombolysis were all chosen by 2015AHA/ASA Statement: Inclusion and Exclusion Criteria for AIS.[14] Intravenous recombinant tissue-type plasminogen activator (Boehringer, Ingelheim amRhein, Germany) (from .9 mg/kg to a maximum of 90 mg) was used with 10% of the total as a bolus and the rest 90% over 1 hour. No patient was delivered antithrombotic agents within 24 hours after thrombolysis.[15] CT was served for AIS patients after thrombolysis 24 hours or whose symptoms had suddenly deteriorated. Blood samples especially white blood cells count were collected within 24 hours after thrombolysis. Patients would be excluded who has an increase in inflammation indicators except leukocytes or any image exams and laboratory tests suggest infection. Exclusion criteria: (1) the high oral temperature ($\geq 38°C$), (2) C-reactive protein ≥ 20 mg/L, (3) coughing with thick sputum and the chest CT suggest lung infection, (4) urinary urgency and dysuria and the urine routines suggest urinary tract infection, (5) the antibiotics were already used, and (6) other rare infections, such as rectal perianal abscess.

Some baseline characteristics were collected as follows: age, sex, smoking, hypertension, diabetes, hyperlipidemia, cardiac disease, onset to treatment (OTT) time, baseline NIHSS score, systolic blood pressure (SBP) before thrombolysis, diastolic blood pressure (DBP) before thrombolysis, and stroke subtypes. Hypertension was defined as high blood pressure (SBP greater than or equal to 140 mmHg or DBP greater than or equal to 90 mmHg) or the taking of antihypertensive agents. Diabetes was diagnosed by a high fasting plasma glucose level (higher than or equal to 7.0 mmol/L) or the taking of hypoglycemic agents. Hyperlipidemia was defined by a high level of serum total cholesterol (>5.6 mmol/L), Triglycerides (>1.7 mmol/L), low-density lipoprotein cholesterol (>3.4 mmol/L), High-density lipoprotein (<.9 mmol/L) or treatment with antihyperlipidemic agents after a diagnosis of hyperlipidemia. Cardiac disease was defined as atrial fibrillation, coronary atherosclerotic heart disease or valvular heart disease, either in the past or during this stroke, or when there was a history of pacemaker implantation and cardiac surgery.

The patients were divided into 4 groups: persistent leukocytosis, transient leukocytosis, leukocytosis 24 hours, and no leukocytosis. Persistent leukocytosis (PL), defined as the patients whose leukocytes was greater than or equal to 9.5×10^9/L on admission and the indicator was also greater than or equal to 9.5×10^9/L after intravenous thrombolysis within 24 hours. Transient leukocytosis (TL), diagnosed by a high level leukocytes levels on admission (greater than or equal to 9.5×10^9/L), but a low level leukocytes levels after thrombolysis within 24 hours (less than 9.5×10^9/L). Leukocytosis 24 hours (L24H), defined by a low level leukocytes on admission (less than 9.5×10^9/L), but a high level leukocytes after thrombolysis within 24 hours (greater than or equal to 9.5×10^9/L). No leukocytosis (NL), defined as the patients whose leukocytes were persistent less than 9.5×10^9/L within 24 hours from admission to thrombolysis finished.

In this prospective study, only anonymized data previously acquired, as part of the patient workup or for service evaluation purposes, were used. The study proposal was reviewed locally and further ethical review was not deemed necessary.

Statistics

Continuous variables were expressed as the mean value ± standard deviation or medians with interquartile ranges according to the normality of data distribution. Baseline characteristics were analyzed with ANOVA, Kruskal-Wallis test and Chi-square test. Multiple samples between each other were compared by LSD-t test and Kruskal-Wallis test followed by all pairwise multiple comparisons. Variables that differed significantly with a P value less than .10 were selected as covariates for multivariable logistic regression analysis. Good clinical outcome was defined as mRS score of 2 or lower in the multivariable analysis. Statistical significance was set at a P value < .05.

All statistical analyses were performed using SPSS version 19.0 (SPSS Inc, Chicago, IL).

Results

Baseline characteristics of all study patients were shown in Table 1. Of the 213 patients screened, 45 (21.1%) patients had persistent leukocytosis, 25 (11.7%) had transient leukocytosis, 28 (13.1%) had leukocytosis 24 hours, and 115 (54.0%) had no leukocytosis. By comparison, 4 groups were similar in sex, hypertension, hyperlipidemia, cardiac disease, diabetes, SBP before thrombolysis, DBP before thrombolysis, and stroke subtypes. Although the rate of smoking in the PL group seems to be higher than those in the other groups, the result was calculated with a P value > .05, showing that smoking also did not have statistical difference among the groups. We observed statistical significance with