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Clinical study

Association of lower leukocyte count before thrombolysis with early neurological improvement in acute ischemic stroke patients

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ABSTRACT

Early neurological improvement (ENI) after thrombolysis in acute ischemic stroke is associated with a favorable long-term outcome. With the goal to evaluate ENI, we aimed to investigate whether ENI bears a relationship with routine blood tests before thrombolysis. A total of 240 patients with confirmed early ischemic stroke and intravenous recombinant tissue plasminogen activator (rtPA) treatment were enrolled from two teaching hospitals, between June 2010 and March 2016. The primary endpoint was ENI that was defined as a decrease of National Institutes of Health Stroke Scale (NIHSS) scores ≥4 points or complete recovery in 24 h after thrombolysis. Patients underwent NIHSS score evaluation and head CT scan before and after 24 h of IV rtPA treatment. Blood samples for routine blood tests were drawn at admission before IV rtPA administration. Multivariate regression analysis was used to explore the relationship between test results and ENI. Of the results of routine blood tests, leukocyte count before thrombolysis was found to associated independently with ENI (adjusted odds ratio[$_{adj}$OR] = 0.894, P = 0.025, 95% CI = 0.810–0.986). Onset-to-treatment time (OTT; $_{adj}$OR = 0.993, P = 0.003, 95% CI = 0.988–0.997) and negative CT sign ($_{adj}$OR = 3.975, P < 0.001, 95% CI = 1.916–8.246) both were associated with ENI. The change of NIHSS score after 24 h of thrombolysis correlated with the leukocyte and neutrophil count, and neutrophil-to-lymphocyte ratio. A model that combined leukocyte count, positive CT sign, and OTT was generated to predict non-ENI (AUC = 0.717). Therefore, we determined that the leukocyte count was independently associated with ENI. Predicting non-ENI aid in selecting patients for mechanical thrombectomy after thrombolysis.

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1. Introduction

Mechanical thrombectomy has been recommended for acute ischemic stroke (AIS), however, intravenous administration of recombinant tissue plasminogen activator (rt-PA) is still the primary choice for AIS within 4.5 h of onset. About 28% patients show early neurology improvement (ENI) in the 24 h following thrombolysis [1]. ENI is a critical standard to assess the efficacy of rt-PA treatment since it predicts a better outcome at 3 months [2] and is highly associated with vessel recanalization [3].

ENI depends on various factors. Previous research has indicated that female sex, glucose levels <8 mmol/L, and absence of cortical involvement on the 24 h CT scan are associated with ENI [1]. The development of collaterals at admission was also found be independently associated with early neurologic improvement [4]. Non-cardioembolic origin [5] and mild to moderate stroke severity [6] were reported to be associated with major neurological improvement after intravenous rt-PA treatment.

Complete blood count is a common routine blood test. It has been noted that neutrophil count is independently associated with infarct volume [7], stroke severity [8] and death [9] after IV rt-PA treatment. A higher neutrophil count before thrombolysis for cerebral ischemia predicts symptomatic intracerebral hemorrhages [10]. However, the relationship of these blood tests to ENI is not clear. If the blood count could conduce to predict on the ENI and non-ENI, the benefit of transfer for endovascular thrombectomy

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for large vessel acute ischemic stroke will be improved. Therefore, we sought to determine the hypothesis that complete blood count tests are associated with ENI.

2. Methods

2.1. Study population

We designed a retrospective cohort analysis of consecutive patients with IV thrombolysis stroke treated between January 2009 and April 2016 at two medical centers (Nanfang Hospital of Southern Medical University and Guangzhou General Hospital of Guangzhou Military Command). No patient treated with endovascular therapy. The study was approved by the ethics committee of Nanfang Hospital.

2.2. Inclusion and exclusion criteria

The criteria for IV thrombolysis were as follows: (1) more than 18 years old; (2) less than 4.5 h after onset for anterior circulation and 6 h for posterior circulation; (3) no hemorrhage on brain CT scan before treatment; (4) diagnosis of AIS by experienced neurologists (W.X, S.W, L.Z, and Z.D). The exclusion criteria were as per AHA Guidelines 2010. All the patients received 0.9 mg/kg Alteplase (Boehringer Ingelheim Pharma, Germany) with 10% bolus, which was then maintained for 1 h. Blood collection for complete blood count analysis was completed before the bolus. Before treatment, and at the time point of 24 h after treatment, NIHSS scores were obtained by certified neurologists. CT scans were performed before and at 24 h after treatment. ENI was defined as a decrease of 4 or more points in the NIHSS score, or complete recovery. The neurological physical examination was done by two experienced neurologists Z.J and S.W separately.

2.3. Statistical analyses

SPSS 19.0 statistical software was used to analyze clinical data. Kolmogorov-Smirnov test was adopted to test the normality of continuous variables. We compared groups utilising the chi-square test with Yates correction or Fisher exact test for categorical variables and *t*-test or the Mann–Whitney *U* test for continuous variables. We evaluated the correlations between continuous variables with the Spearman test. A two-sided P value of <0.05 was regarded as statistically significant.

We used the following steps according to a predetermined statistical analysis approach:

- Compared baseline characteristics between patients with and without ENI
- Compared whole blood test results between patients with and without ENI
- Compared outcomes among the 4 patient groups based on quartiles of the leukocyte count
- Continuous leukocyte count was transformed into categorical variable through dividing by 10^9/L. (0–0.99 × 10^9/L = 1, 1–1.99 × 10^9/L = 2, and so on). Similarly, OTT time was transformed into categorical variable through dividing by 60 min. Stepwise forward conditional logistic regression analyses were done with clinical outcome (classified as 1 for ENI and 2 for non-ENI). The independent variables included of leukocyte count in categorical, a positive CT sign, OTT in categorical, PLT count, blood glucose, triglyceride were added into binary logistic regression. Correlations between independent variables were checked for possible collinearity between variables (defined as rho = 0.6); adjusted odds ratios (adjORs) and 95% confidence intervals (CIs) were based on the logistic regression analyses.
- Used receiver operating characteristic curves to determine the predictive values of the area under the curve and 95% CI, for the regression equation; for the biological value that better predicts outcome, we also determined the cutoff points that better distinguish early clinical outcome; we considered the point at which the sum of specificity and sensitivity was the highest; we considered an area under the curve value of 0.70 or higher as indicating an acceptable discrimination.

3. Results

3.1. Main baseline characteristics

Out of 258 patients who received IV rt-PA treatment, we recruited 240 patients who met the inclusion criteria for this study, after exclusion of 12 patients owing to the absence of NIHSS score at 24 h, 5 patients with stroke mimics, 1 patient with over 6 h time window for posterior circulation stroke (Fig. 1). The baseline characteristics of the study population are described in Table 1. ENI was noted in 86 (35.7%) patients. The baseline of NIHSS before thrombolysis was 9.0 (9.0,17.0) in the ENI and 11.0 (6.0,18.0) in the non-ENI groups; there was no significant difference between the two groups (P = 0.456). After 24 h of rt-PA treatment, the NIHSS improved to 4.0 (2.0,8.0) in the ENI and 11.0 (6.0,17.0) in the non-ENI groups.

3.2. Multiple blood tests and clinic characters were an unadjusted association with ENI

Whole blood test and clinical characteristics of the ENI and non-ENI groups are detailed in Table 1. We found that diabetes mellitus, onset-to-sample time, OTT, negative CT sign before thrombolysis, blood glucose levels, leukocyte and neutrophil counts, neutrophil-to-lymphocyte ratio (NLR), eosinophil and platelet counts, and triglyceride levels showed unadjusted associations with ENI (P < 0.05).

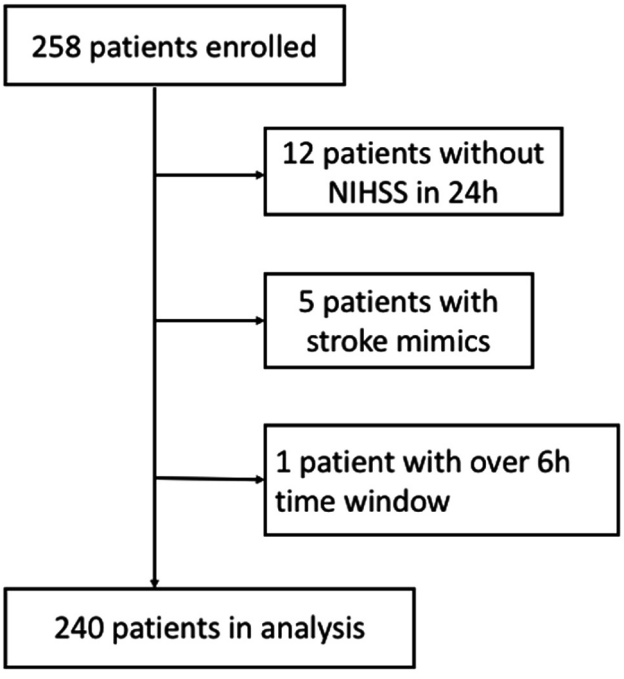

Fig. 1. The flowchart of patient inclusion.

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