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# Early changes in fibrinogen after administration of alteplase are associated with the short-term efficacy of thrombolysis

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**Abstract**

The authors aimed to determine whether early changes in fibrinogen were associated with the efficacy of intravenous thrombolysis at 24 hours after alteplase infusion. The authors retrospectively reviewed a consecutive series of 56 patients with acute ischemic stroke treated with alteplase in the clinical database. The fibrinogen levels were monitored at the first and fourth hours after alteplase infusion. Additionally, the National Institutes of Health Stroke Scale (NIHSS) scores were recorded to define the short-term efficacy of intravenous thrombolysis before and 24 hours after alteplase infusion. The patients were distributed into amelioration, deterioration, and inefficiency groups according the short-term efficacy of intravenous thrombolysis. One-way ANOVA and post hoc analysis were used to compare the differences in the clinical characteristics among these groups. The relationships among changes in the fibrinogen levels, other potential risk factors, and NIHSS scores were examined using logistic regression analysis. Fifty-two patients (mean age, 65.71 ± 11.04 years; male, 57.7%) were finally enrolled in the study. The median NIHSS of these patients was 11 (range, 2–23), and the mean time from symptom onset to thrombolysis was 187.17 ± 67.53 minutes. The frequency of hypertension in the deterioration group was significantly higher than that in the inefficiency group ($P = .01$). Changes in the fibrinogen level were more significant in the amelioration group than in the other groups ($P < .05$). Logistic regression analysis revealed that changes in the fibrinogen levels between the first and fourth hours were positively associated with the short-term efficacy of alteplase infusion (odds ratio, 3.98; 95% confidence interval, 1.56–10.16; $P = .004$). Early changes in fibrinogen levels may be a potential predictor for the short-term efficacy of alteplase treatment in acute ischemic stroke. Additionally, these changes may be helpful for determining the short-term efficacy of alteplase treatment and early therapeutic strategies in clinical practice.

**Abbreviations:** CT = computed tomography, CI = confidence interval, NIHSS = National Institutes of Health Stroke Scale, OR = odds ratio.

**Keywords:** acute ischemic stroke, alteplase, fibrinogen, short-term efficacy

## 1. Introduction

Acute ischemic stroke is mainly caused by arterial occlusion.[1] A previous study confirmed that early thrombolytic therapy with alteplase in patients with acute ischemic stroke can effectively improve their clinical outcome.[2] Since intravenous thrombolytic therapy with alteplase was approved in the United States in 1996,[3] it has been shown to improve the short-term outcome of patients with acute ischemic stroke.[4] However, the clinical factors associated with the short-term effect within 24 hours after alteplase infusion remain unclear. The initial 24 hours after thrombolysis therapy, in which patients have a higher risk of intracranial hemorrhage,[5] is critical for neurologic recovery, and it is necessary to identify the factors that influence the effects of in-hospital patient management with alteplase.[6]

Fibrinogen, a key determinant of blood viscosity, is an acute-phase protein.[2] It is involved in the process of platelet aggregation, primary hemostasis, and leukocyte–endothelial cell interactions.[2] Epidemiologic studies have indicated that hyperfibrinogenemia is an independent risk factor for both venous and arterial thrombosis.[7] Furthermore, the levels of fibrinogen after acute ischemic stroke are associated with a worse neurologic outcome[8] and efficacy for thrombolysis[7] because they independently and directly shorten the time to occlusion and increase thrombus resistance to thrombolysis.[7] Studies have indicated that dynamic changes in the level of coagulation and fibrinolytic activity markers, such as fibrinogen[9] and α2-antiplasmin,[10] are associated with the clinical outcome in patients treated with intravenous alteplase. However, previous studies have assessed only the changes in fibrinogen levels from baseline to 90 minutes, 3 or 24 hours after thrombolysis, which, to some extent, does not focus on the dynamic changes at the early stage after thrombolysis. We hypothesized that the early

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changes in the fibrinogen levels after administration of alteplase were associated with the short-term efficacy.

## 2. Patients and methods

### 2.1. Patients

We retrospectively reviewed our database of consecutive patients with acute ischemic stroke admitted to our stroke care unit and administered alteplase from April 2012 to June 2016. We enrolled patients using the following inclusion criteria: patients had a definite diagnosis of acute ischemic stroke confirmed by brain computed tomography (CT) or magnetic resonance imaging; all patients were given intravenous alteplase; and patients underwent a brain CT scan before alteplase infusion and a follow-up CT scan 24 hours after alteplase infusion. We excluded patients whose clinical data lacked integrity. We collected the following data for each patient: demographics (age and sex); history of hypertension, atrial fibrillation, diabetes mellitus, and hypercholesterolemia; the time from symptom onset to alteplase infusion; National Institutes of Health Stroke Scale (NIHSS) scores before alteplase infusion and 24 hours after alteplase infusion; blood pressure before alteplase infusion and 24 hours after alteplase infusion; and the level of fibrinogen at the first (1st) hour and fourth (4th) hour after alteplase infusion. According to the previous literature,[10] amelioration was defined as a decrease of 4 or more points in the NIHSS score at the 24th hour after alteplase infusion. We defined deterioration as a higher NIHSS score at the 24th hour than at baseline, and inefficiency was defined as an NIHSS score decrease of <3 points. Therefore, patients were assigned to an amelioration group, deterioration group, and inefficiency group according to the NIHSS changes. And the research was approved by the Ethics Committee of Sun Yat-sen University.

### 2.2. Statistical analyses

All statistical analyses were performed with the IBM SPSS Statistics for Windows software (Version 22.0, IBM Corp., Armonk, NY). Continuous variables with a normal distribution are presented as the mean and standard deviation. Categorical variables are summarized as the median and range or percentage. One-way ANOVA or a Chi-squared test with Bonferroni post hoc analysis was used to detect differences between groups. The variation in the fibrinogen level between the 4th hour and the 1st hour after alteplase infusion, which was divided by the fibrinogen level on the 1st hour after alteplase infusion, was defined as the change in the fibrinogen level. Before logistic analysis, the changes in the fibrinogen level were transformed into rank data, in which −100% was scored as 9 and 100% was scored as 0, with a 20% interval as described in Table 1 and Figure 1. In model 1, ranked changes in the fibrinogen level were the only factor indicated in univariate logistic regression to have a potential effect on the short-term efficacy of alteplase infusion (defined as a decrease of 4 or more points in the NIHSS score at 24 hours after alteplase infusion). In model 2, the ranked changes in the fibrinogen level, NIHSS score before alteplase infusion, blood pressure before alteplase infusion, and time from symptom onset to alteplase infusion were included in the multivariate logistic analysis (forward likelihood, 0.05 in, 0.10 out) as factors that could have a potential effect on the short-term efficacy of alteplase infusion. The odds ratio (OR) and 95% confidence interval (CI) were obtained. The results were considered statistically significant when the $P$ value was <.05.

**Table 1**

**Logistic regression of fibrinogen changes and efficiency of thrombolysis.**

| | Odds ratio | Odds ratio 95% Confidence intervals | *P* value |
|---|---|---|---|
| Model 1 | | | |
| Fbg changes | 3.01 | 1.34–6.73 | .007 |
| Model 2 | | | |
| Fbg changes | 3.98 | 1.56–10.16 | .004 |
| Onset to thrombolysis | 1.02 | 1.00–1.03 | .029 |

Fbg, fibrinogen.
$P < .05$ indicates statistical significance.

## 3. Results

Fifty-six patients in our database met the inclusion criteria. Four patients were excluded for missing data on the fibrinogen level at the 1st hour and 4th hour after alteplase infusion (n = 3) and the intravenous thrombolysis bridged endovascular interventions (n = 1). Fifty-two patients (mean age, 65.71 ± 11.04 years; male, 57.7%) were finally enrolled in our study. The median NIHSS score of these patients was 11 (range, 2–23), and the mean time from symptom onset to thrombolysis was 187.17 ± 67.53 minutes.

Table 2 summarizes the demographic characteristics and clinical features among these 3 groups. The frequency of hypertension among these groups was significantly different ($P = .006$). The post hoc analysis showed that the frequency of hypertension of the deterioration group was significantly higher than that of the inefficiency group ($P = .01$). The change in the fibrinogen level was more significant in the amelioration group than in the other groups according to post hoc analysis ($P < .05$). The frequency of hemorrhagic transformation in the deterioration group was higher than that in the other groups, but the difference was not statistically significant ($P = .08$). In addition, enlargement of infarction on CT from baseline to the 24th hour after thrombolysis was observed in 5 of 52 patients, but it was not

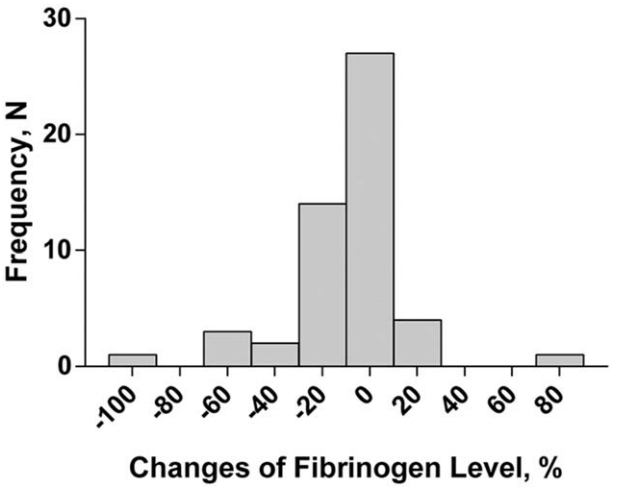


**Figure 1.** Changes of fibrinogen level between 1st and 4th hour after thrombolysis. The abscissa axis indicates the changes in the fibrinogen level from −100% to 100%. The vertical axis indicates the numbers of patients with each fibrinogen level changes.

**Table 2**

**Clinical characteristics of included patients.**

| | All (n=52) | Amelioration (n=5) | Deterioration (n=15) | Inefficiency (n=32) | *P* value |
|---|---|---|---|---|---|
| Age, y | 65.71±11.04 | 58.40±11.59 | 69.80±9.84 | 64.94±11.05 | .109 |
| Sex, male, (%) | 30 (57.7) | 5 (100) | 7 (46.7) | 18 (56.3) | .131 |
| Onset to thrombolysis, mean±SD, min | 187.17±67.53 | 209±210 | 173.33±61.37 | 190.25±185.00 | .553 |
| Hypertension, n (%) | 33 (63.5) | 5 (100) | 13 (86.7) | 15 (46.9) | .006* |
| Atrial fibrillation, n (%) | 18 (34.6) | 0 (0) | 6 (40) | 12 (37.5) | .228 |
| Diabetes mellitus, n (%) | 13 (25) | 2 (40) | 4 (26.7) | 7 (21.9) | .786 |
| Hyperlipidemia, n (%) | 22 (42.3) | 2 (40) | 3 (20) | 17 (53.1) | .086 |
| NIHSS before thrombolysis, median (range) | 11, 2–23 | 10, 7–13 | 13, 5–18 | 10, 2-23 | .264 |
| NIHSS after thrombolysis, median (range) | 10, 1–23 | 2, 1–5 | 16, 12-19 | 8, 1-23 | .001* |
| Fbg level in 1st hour after thrombolysis, mean±SD, g/L | 2.17±0.83 | 2.88±0.46 | 2.09±1.05 | 2.09±0.73 | .134 |
| Fbg level in 4th hour after thrombolysis, mean±SD, g/L | 1.83±0.66 | 1.75±0.64 | 1.66±0.89 | 1.91±0.53 | .481 |
| Change of Fbg level, median, range | −0.07, −0.96 to 0.78 | −0.32, −0.63 to 0.22 | −0.02, −0.96 to 0.27 | −0.07, −0.36 to 0.78 | .009* |
| Systolic BP before thrombolysis, mean±SD, mm Hg | 149.19±18.08 | 164.40±9.81 | 152.33±17.68 | 145.34±18.09 | .063 |
| Diastolic BP before thrombolysis, mean±SD, mm Hg | 81.77±11.28 | 89.80±7.26 | 83.60±7.41 | 79.66±12.69 | .132 |
| Systolic BP after thrombolysis, mean±SD, mm Hg | 151.67±23.98 | 162.20±11.28 | 150.33±23.17 | 150.66±25.84 | .595 |
| Diastolic BP after thrombolysis, mean±SD, mm Hg | 83.79±17.26 | 92.20±8.04 | 78.53±15.39 | 84.94±18.67 | .261 |
| Hemorrhagic transformation, n (%) | 8 (15.4) | 0 (0) | 5 (33.3) | 3 (9.4) | .080 |
| Enlargement of infarction, n (%) | 5 (9.6) | 0(0) | 1(6.7) | 4(12.5) | .610 |

BP=blood pressure, Fbg=fibrinogen.

* $P<.05$ indicates statistical significance.

statistically significant in a comparison among these groups ($P=.610$). No significant differences were observed in the other clinical characteristics in a comparison among these groups. In model 2, ranked changes in the fibrinogen level were independently associated with an improvement in the NIHSS score at the 24th hour after thrombolysis (OR, 3.98; 95% CI, 1.56–10.16; $P=.004$). This translated into a reduction of 20% in the fibrinogen level and was associated with a 3.84-fold increase in the likelihood of amelioration. Therefore, early changes in the fibrinogen level after intravenous thrombolysis onset may predict the short-term efficacy of thrombolysis.

## 4. Discussion

The clinical factors associated with the short-term efficacy 24 hours after alteplase therapy were determined in this retrospective study. We found that the short-term efficacy was affected by the early changes in the fibrinogen levels from the 1st hour to the 4th hour after alteplase administration. To the best of our knowledge, this is the first study to analyze the effect of these changes on the short-term efficacy of intravenous thrombolysis.

The goal of intravenous thrombolysis with alteplase is to achieve recanalization and restore blood flow to the ischemic brain tissue.[11] Recanalization has been reported to be associated with clinical outcomes.[12] Therefore, we used the NIHSS score at the 24th hour after thrombolysis to assess the short-term efficacy of intravenous thrombolysis. In this situation, recording of the NIHSS score is straightforward and easily implemented. Our data suggested that the fibrinogen levels in the inefficiency and deterioration groups were lower than that in the amelioration group ($P<.05$; Table 2). However, after identifying potential confounders, we demonstrated that the early changes in the fibrinogen levels from the 1st hour to the 4th hour after the administration of alteplase were significantly related to the short-term efficacy of alteplase infusion by logistic regression analysis, after adjusting for potential factors (including hypertension, atrial fibrillation, diabetes mellitus, and the time from symptom onset to thrombolysis) that are known to be associated with the efficacy of thrombolysis. However, one point to consider is that the changes in the fibrinogen level from the 1st hour to the 4th hour after the administration of alteplase, instead of the fibrinogen levels at the 1st and 4th hours after thrombolysis, were significantly different among these groups. Our data were not consistent with the results reported by Joan Martí Fàbregas et al,[9] which showed that the likelihood of recanalization was not associated with the changes in the fibrinogen levels. Several reasons may account for the contradictory results. First, the timing of fibrinogen level monitoring was different. Samples were obtained at the 1st hour and 4th hour after alteplase infusion in our study, while fibrinogen levels were monitored before and 90 minutes after alteplase infusion in the former study. Because the dynamic changes in fibrinogen levels began at the 2nd hour after alteplase infusion and the level remained low until the 24th hour,[2] our research design may be better to explore the relationship between changes in the fibrinogen levels and the short-term efficacy after alteplase therapy. Second, the patients in the 2 studies were different. The former study enrolled patients with proximal or distal middle cerebral artery occlusion before infusion, whereas our study included patients with all types of brain infarction. Third, the methods to determine the intravenous thrombolysis efficacy were dissimilar. The former study evaluated the venous thrombolysis effect by time-of-flight magnetic resonance angiography or reconstructed CT angiography, while we used the NIHSS score instead. Other factors, such as the sample sizes and race, may contribute to the contradiction.

According to our findings, changes in the fibrinogen levels are independently associated with the short-term efficacy of alteplase infusion 24 hours after thrombolysis. Our results revealed that each 20% reduction in the fibrinogen levels was associated with a 3.84-fold increase in the likelihood of amelioration. Collen et al[13] showed that the extent of fibrinogen breakdown was very important during intravenous alteplase infusions in patients with acute myocardial infarction. Moreover, a previous study showed that an insufficient reduction in the levels of fibrinogen after thrombolysis was associated with a poor effect of thrombolysis in ischemic heart disease.[14] However, excessive reduction may be

related to a poor outcome because it has been demonstrated to be a significant risk factor for bleeding.[15] Post-thrombolysis symptomatic intracerebral hemorrhages were significantly associated with excessive reduction in the fibrinogen levels (the levels were reduced >25% or the level was <2 g/L after thrombolysis).[16] In our study, hemorrhagic transformation was more frequent in the deterioration group than the other groups, but the difference was not statistically significant. In the 5 patients with hemorrhagic transformation in the deterioration group, the changes in the fibrinogen levels were not evident (median, 3.0%; range, −96% to 27%), and the fibrinogen level was reduced by >25% in only 1 patient. This can be explained by the different timing of fibrinogen level monitoring between the studies. In contrast to our study, Vandelli et al[16] monitored the fibrinogen levels before and 2 hours after thrombolysis. Further studies are needed to identify the safe cut-off point for early changes in fibrinogen levels from the 1st hour to the 4th hour after the administration of alteplase.

As reported in previous studies,[17] our study demonstrated that acute ischemic stroke with hypertension exhibited a relatively high incidence of hemorrhagic transformation, which is the most severe complication of intravenous thrombolysis. In our study, 6 of the 8 patients with hemorrhagic transformation (75%, data not shown) also had hypertension. Our study showed no significant differences among groups regarding other relevant risk factors, such as age, time from symptom onset to thrombolysis, atrial fibrillation, and diabetes mellitus, reported in prior studies (Table 2). Cardioembolism has been linked to a high frequency of hemorrhagic transformation.[18] Consistent with previous research, our result revealed that 3 of the 18 patients with cardioembolism (data not shown) also had hemorrhagic transformation. Compared with the other groups, no patient in the amelioration group had cardioembolism. We speculate that cardioembolism may be associated with the short-term efficacy of thrombolysis. But the frequency of cardioembolism among these groups was not significantly different ($P = .228$). Further studies are required for confirmation.

Our results revealed that each reduction of 20% in the fibrinogen level was associated with a 3.84-fold increase in the likelihood of amelioration. Fibrinogen may be a rapid, simple, and accurate biomarker of success for intravenous thrombolysis. Compared to the other studies using neuroimaging methods, such as CT or transcranial Doppler ultrasonography, to assess the effect of intravenous thrombolysis with alteplase, monitoring the fibrinogen level is easier to apply in routine clinical practice. It may be beneficial to assess the fibrinogen levels every hour after the administration of alteplase in all patients with acute ischemic stroke. An appropriate fibrinogen-depleting therapy during the early phase (4 hours) after intravenous thrombolysis may be a useful supplemental therapy, http://links.lww.com/MD/C178. Because the early change in the fibrinogen level from the 1st hour to 4th hour after intravenous thrombolysis is a potential predictor for short-term efficacy of intravenous thrombolysis, it may be helpful to determine the timing to bridge endovascular interventions.

Our findings support the hypothesis that the early changes in the fibrinogen levels after intravenous thrombolysis administration of alteplase are associated with the short-term efficacy of thrombolysis. It should be noted that our study focused on the short-term rather than the long-term outcome. Because the short- and long-term outcomes are not entirely equivalent,[12] whether the early changes in the fibrinogen levels can affect the long-term outcomes requires further confirmation.

Certain limitations should be considered prior to interpreting our research results. One limitation is the small sample size. Because our hospital is a regional tertiary referral center, most patients with stroke might receive a preliminary treatment and miss the window of intravenous thrombolysis before admission. Another potential limitation is that we prospectively collected the stroke registry data from our stroke care unit alone, which might introduce selection bias. Some severe patients with stroke may immediately undergo surgical treatments or be transferred to the intensive care unit within 24 hours after admission. Due to the diverse severity of stroke in patients, we did not monitor the fibrinogen levels every hour after intravenous thrombolysis in all patients. As a result, we cannot compare the fibrinogen levels at the 1st hour and other time points.

In conclusion, the findings from the present study show that the measurement of early changes in the fibrinogen level from the 1st hour to the 4th hour after alteplase treatment provide useful information for evaluating the short-term efficacy from a practical point of view. Further confirmatory prospective studies with a large sample size are required to confirm our results.

## Author contributions

**Conceptualization:** W. Xian, H. Yang.
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**Investigation:** T. Lu.
**Methodology:** T. Lu, J. Liang.
**Project administration:** H. Yang.
**Software:** T. Lu.
**Supervision:** H. Yang.
**Validation:** T. Lu
**Visualization:** T. Lu.
**Writing – original draft:** T. Lu.
**Writing – review & editing:** T. Lu, W. Xian, J. Liang, H. Yang, B. Weng.

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