Change Trend of Plasma D-Dimer Level and Its Clinical Value in Patients with Acute Lower Limb Ischemia Treated by Catheter-Directed Thrombolysis

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Research Article

Keywords: Acute lower limb ischemia, Catheter-directed thrombolysis, D-dimer, Change trend

Posted Date: January 13th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-143092/v1>

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Abstract

To investigate the correlation between plasma D-dimer levels before and after catheter-directed thrombolysis (CDT) in acute lower limb ischemia (ALI) and lower limb arterial recanalization and the clinical value of the change trend of plasma D-dimer. A retrospective review of all patients who received CDT for the treatment of ALI between January 2013 and December 2019 was carried out. The change trend of plasma D-dimer of the patients during thrombolysis was statistically analyzed using repeated measures ANOVA. A total of 150 patients were included in the analysis. Among them, 3 days of CDT was ineffective in 41 cases, effective in 33 cases and markedly effective in 76 cases. The plasma D-dimer levels of the patients were significantly different between pre- and post-thrombolysis ($F = 23.856$, $P = 0.000$). There was an interaction effect between the measured time factors and thrombolysis efficacy ($F=13.991$, $P=0.000$). The change trends of plasma D-dimer levels in the three groups were statistically significant ($F = 3.246$, $P = 0.042$). The plasma D-dimer level changes regularly during CDT for ALI. We can predict the efficacy of CDT and guide adjustments of the therapeutic regimen according to the trend of D-dimer changes during thrombolysis to obtain better clinical effects.

Introduction

Acute lower limb ischemia (ALI) is caused by a reduction in arterial perfusion in the limb due to embolic migration or local thrombosis. In addition to the risk of limb damage or loss, it can cause life-threatening complications related to metabolic conditions triggered throughout the body. ALI should be treated urgently¹. Catheter-directed thrombolysis (CDT) has been used for the treatment of ALI for over 20 years²⁻⁴. Thrombolytic therapy can cause significant changes in plasma D-dimer⁵⁻⁷. D-dimer is a soluble fibrin degradation product that is the result of the orderly breakdown of thrombi by the fibrinolysis system. Its level is commonly used in the clinical diagnosis and treatment evaluation of venous thromboembolic (VTE)⁸. Thrombolytic efficacy can be evaluated by monitoring plasma D-dimer levels during CDT in patients with deep vein thrombosis⁹. Before and after thrombolysis, the changes in plasma D-dimer levels are also considered to be significantly correlated with coronary recanalization, which could be used to predict the thrombolysis efficacy after acute myocardial infarction^{6,7}.

The correlation between plasma D-dimer level and reperfusion has not yet been clarified in CDT applied for patients with ALI. Therefore, the purpose of this study was to investigate the correlation between the change trends of plasma D-dimer levels before and after CDT in ALI and lower limb arterial recanalization and whether the plasma D-dimer levels could predict the efficacy of thrombolysis.

Methods

Ethics and consent statement

This retrospective cohort study was approved by the Medical Ethics Committee of Ganzhou People's Hospital. All patients gave written informed consent with the approved guidelines. Written

informed consent was signed by the patients' direct relatives.

Study population

We retrospectively analyzed consecutive patients with ALI treated with CDT at Ganzhou People's Hospital from January 2013 to December 2019. Inclusion criteria: Patients receiving CDT intravascular treatment for ALI who were treated for at least 3 days. The exclusion criteria were as follows: (1) nonacute lower limb ischemia; (2) incomplete data; (3) patients receiving mechanical thromboembolism treatment; and (4) CDC duration shorter than 3 days.

The data of interest were collected through the electronic medical record system, focusing on plasma D-dimer levels during thrombolysis. In addition, according to the research needs, we collected the basic information of the eligible patients, including gender, age, alcohol consumption, smoking, degree of ischemia (Rutherford classification¹⁰), artery occlusion site, length of the thrombolytic catheter, and urokinase usage. Comorbidities of the patients were also collected, including hypertension, diabetes mellitus, atrial fibrillation, ischemic heart disease, cerebrovascular disease, renal insufficiency, chronic obstructive pulmonary disease, hyperlipidemia, and liver function.

CDT procedure

The CDT procedure involves placing a multihole infusion catheter (Unifuse, AngioDynamics) into the thrombosis occlusion arterial segment of the lower limb under the guidance of digital subtraction angiography (DSA) and continuously pumping urokinase through the catheter. Urokinase is used at a dose of 30,000 to 50,000 U/h and then adjusted in accordance with the plasma fibrinogen levels. Thrombolysis will be stopped if the thrombus is completely dissolved or if the patient's plasma fibrin level is <1 g/L or complications of severe hemorrhage (such as bleeding at the puncture site or other sites) occur after thrombolysis.

Plasma D-dimer level monitoring

Blood samples to measure circulating levels of plasma D-dimer were collected from the peripheral blood on admission, and serial samples were then collected at 8, 16, 24, 32, 40, 48, 56, 64, and 72 h post-CDT. At least 10 repeated measurements of plasma D-dimer were performed in each case.

Grouping

For the purpose of this analysis, the patients were further divided into three subgroups depending on the immediate imaging results of the DSA images taken on the third day of CDT and limb distal arterial

Markedly effective group:

DSA images showed occluded segment unobstruction; pulsation of the dorsal foot artery and/or posterior tibial artery were palpable; and the lower extremity pain completely disappeared.

Effective group:

DSA images showed that the occluded segment was completely or partially unobstructed. The dorsal foot artery and/or posterior tibial artery pulses were not detectable, but the skin temperature of the lower extremity was warm, and the pain was relieved.

Ineffective group:

DSA images showed the occluded segment was still obstructed; the dorsal foot artery and/or posterior tibial artery pulses were not palpable; and the lower extremity pain did not improve.

Statistical analysis

SPSS software package version 24.0 (IBM, Armonk, NY, USA) was used for data management and statistical analysis. The continuous data of the three groups were described by means $\pm$ standard deviations (SDs), nonparametric data were expressed as medians (interquartile ranges), and categorical data were presented as percentages. The ordinal data of the three groups were analyzed by the Kruskal-Wallis test. Repeated measures ANOVA was used to analyze the change trends in the D-dimer levels among the three groups. All tests were two-sided with a significance level of 0.05.

Results

General data of the patients.

From January 2013 to December 2019, 325 patients with lower limb ischemia received CDT treatment in our hospital. Of them, 61 patients had non-ALI, 21 patients had incomplete information (no repeated measurement data of D-dimer), 35 patients underwent mechanical thrombus aspiration at the same time, and 58 patients continued thrombolysis for < 3 days (patients who had the thrombolytic catheter removed early because they had achieved good thrombolytic results or were unable to adhere to CDT due to complications such as severe bleeding), so the remaining 150 patients who met the inclusion criteria were included in the analysis (Fig. 1).

The average age was 76.1 (56–79) years, and 81 were males. The ischemic level of Rutherford IIb accounted for the highest proportion (92 cases, 61.3%). The most common site of occlusion was the

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CDT was ineffective in 41 cases (27.3%) and

effective in 33 cases and markedly effective in 76 cases, accounting for 73.7%. The patients were divided into three groups according to their outcome, and the baseline characteristics of the three groups are shown in Table 1. There were no statistically significant differences among the three groups for the degree of ischemia, occlusion site, type of thrombolytic catheter, or amount of urokinase.

Analysis of variance of repeated measures data of plasma D-dimer levels in the 3 groups

The plasma D-dimer levels of the three groups with different thrombolytic efficacies are shown in Table 2. The plasma D-dimer levels were significantly different pre- and post-thrombolysis ($F = 23.856$, $P = 0.000$). The same was true in each group, with F values of 42.452, 58.01, and 124.12, respectively, $P = 0.000$. No difference was found in plasma D-dimer levels among the three groups before thrombolysis ($\chi^2 = 2.656$, $P = 0.265$) (Kruskal-Wallis test). There was an interaction effect between the measured time factors and the thrombolysis results ($F = 13.991$, $P = 0.000$). The change trends of plasma D-dimer levels in the three groups were statistically significant ($F = 3.246$, $P = 0.042$). The trend chart (Fig. 2) showed that the plasma D-dimer level in all three groups increased at the beginning and then decreased after thrombolysis. The d-dimer level in the markedly effective group increased rapidly at the beginning of thrombolysis, reached its peak 16 hours later, and then decreased quickly to the preoperative level. The d-dimer of the ineffective and effective groups increased slowly after beginning thrombolysis, peaked 24 hours later, and then slowly declined. In the ineffective group, the plasma D-dimer level increased again 48 hours after beginning thrombolysis and had another peak.

Discussion

This study indicated that the relationship between the change trend of plasma D-dimer levels before and after CDT treatment and thrombolytic outcomes for ALI. By analyzing the plasma D-dimer change trends, we can predict the reperfusion of ischemic lower limbs after thrombolytic therapy and know the results of CDT in a timely manner. This has rarely been reported in previous studies.

ALI is caused by a sudden interruption of the main blood perfusion of the lower limb for various reasons, and it usually requires immediate revascularization. CDT has become one of the most commonly used methods for the treatment of ALI^{11,12}. After thrombolytic therapy, the vascular stenosis, occlusion and other lesions can be treated simultaneously with interventional therapy, which improves the short-term and long-term patency rate of such occlusive lesions and reduces the need for open surgery in most of these patients⁴.

D-dimer is the degradation product of cross-linked fibrin, and its plasma level reflects the formation and degradation of fibrin. D-dimer is considered a useful biomarker because of its potential to identify individuals in a high coagulation state. D-dimer is often associated with thrombi, and its elevation should be used in the diagnosis of VTE^{8,16,17}. If the plasma

D-dimer test is negative, the diagnosis of acute VTE can be ruled out; if the plasma D-dimer test is positive, the diagnosis of VTE can be confirmed by the symptoms and an ultrasound examination⁸. There have also been many relevant studies in some cardiovascular diseases, such as atrial fibrillation¹⁸⁻²⁰, coronary heart disease^{13,21,22}, stroke^{23,24} and aortic dissection²⁵⁻²⁷, and D-dimer can even be used as a predictor of the diagnosis and prognosis of such diseases²⁸⁻³¹.

D-dimer levels are lower in the circulation in healthy individuals and higher in the presence of thrombi⁸. During the CDT process, the fibrin in the thrombus degrades, and D-dimer is produced. These dissolved substances are continuously released into the blood, causing the plasma D-dimer content to change constantly^{9,32,33}. The D-dimer level increases continuously during thrombolysis and is positively correlated with the degree of thrombolysis⁵. D-dimer has a half-life of approximately 8 hours until it is cleared by the kidney and reticuloendothelial system³⁴. In the later stage of thrombolysis, with the gradual opening of the occluded vessels, the thrombus load in the vessels decreases, and the D-dimer content in the blood decreases continuously until it returns to the prethrombolysis level. Monitoring the changes in plasma D-dimer content pre- and posttreatment is also often used to evaluate the therapeutic effect^{7,32,33,35}. Davies, J. et al. analyzed systemic inflammatory response syndrome following catheter-directed thrombolysis of acute iliofemoral deep venous thrombosis and found that plasma D-dimer increased from 1465 ng/ml to 182,835 ng/ml after 48 hours of thrombolysis and then decreased to the prethrombolysis level 36 hours later. As a result of this presentation, thrombus occlusion of the iliofemoral vein had restored patency after CDT treatment⁹. Cakar, M. A. et al. analyzed D-dimer levels pre- and post-thrombolysis in 186 patients with acute coronary syndrome treated with intravenous tissue-type plasminogen activator (100 mg) or streptokinase (1,500,000 U) and found that D-dimer levels were markedly high after thrombolytic therapy versus before (155 mg/dl, 362 mg/dl, $P < 0.005$)⁶.

For the convenience of analysis, we grouped our patients according to the results of thrombolysis. The change trends of D-dimer in the three groups during thrombolysis are shown in Fig. 2. During thrombolytic therapy, the lower limb arteries of patients whose plasma D-dimer level rose rapidly, reached its peak, and then rapidly dropped to the preoperative level obtained complete recanalization. The lower limb arteries of patients whose plasma D-dimer level rose slowly, then reached its peak slowly or had two peaks, and then dropped slowly to the preoperative level might achieve partial recanalization or remain occluded.

Accordingly, we believe that after CDT treatment of ALI, if the plasma D-dimer levels show a significant increase within a short period of time and then a rapid decline without a rebound, this suggests that the thrombolytic therapy was effective. If the plasma D-dimer continues to rise slowly and decline slowly, this suggests that the thrombolytic catheter may not be in sufficient contact with the thrombus or the thrombolytic drug dose is insufficient, which requires appropriate adjustments. If the D-dimer exhibits multiple peaks, this may be due to the presence of a new thrombus, unobstructed vascular outflow tract or occlusion of the artery by the old thrombus, which should be solved by combining CDT with other

third day, we confirmed the reasons for the

ineffective treatment of CDT for the patients in this study, and then corresponding measures were taken, such as adjusting the location of the thrombolytic catheter, increasing the time and amount of the thrombolytic agent, or combining the CDT with percutaneous transluminal angiography (PTA)/stent implantation. These additional measures improved the blood supply of the ischemic limbs, avoiding gangrene. As a result, the limb salvage rate of patients with ALI was improved.

Several limitations of this analysis should be acknowledged. In this study, patients with CDT thrombolysis for 1–2 days were excluded because these patients did not have 3 days of complete D-dimer data, which reduced the sample size of our study. In addition, the grouping in this study was based on the recovery of the lower limb blood supply of patients on the third day of CDT. In fact, patients with a poor CDT response were still receiving treatment after 3 days, such as continued CDT treatment or a combination of other treatments, so the final clinical results for all of the patients were not provided in this study. In addition, CDT therapy for non-ALI is also widely used in clinical practice^{36,37}, but the lesions in these patients are not mainly thrombotic and often require PTA and/or stent implantation, so they were excluded from this study. Therefore, a multicenter, prospective, randomized controlled study may be the best way to further understand the trends and clinical significance of plasma D-dimer changes during CDT in patients with ALI.

Conclusion

In conclusion, the plasma D-dimer level changes regularly during CDT for ALI. Occluded arteries may be recanalized in patients whose D-dimer appears to rise rapidly during CDT, peaks, and then rapidly declines to pretreatment levels. Therefore, we can predict the results of CDT and guide adjustment of the therapeutic regimen according to the trends of D-dimer changes during thrombolysis to obtain better clinical effects and allow more ischemic limbs to be salvaged.

Declarations

Author Contributions

Y.F.L. conceptualized and designed the study. X.C.L., G.F.Z., and H.L.X. performed and supervised data collection. X.C.L. and G.F.Z. contributed in data analysis. X.C.L. and G.F.Z. prepared the first draft of the paper. All the authors contributed in revision of the manuscript. All the authors have read and approved the final manuscript.

Additional Information

Supplementary information accompanies this paper at

Competing Interests:

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The author(s) declare no competing interests.

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Tables

Due to technical limitations, tables are only available as a download in the Supplemental Files section.

Figures

Figure 1

Patient Flowchart

Figure 2

The cumulative rate of ulcer healing

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Table1.Baselinecharacteristicsofthepatients.docx](#)
- [Table2.AnalysisofvarianceofrepeatedmeasuredataofplasmaDdimerlevels.docx](#)