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Post-thrombolysis haemostasis changes after rt-PA treatment in acute cerebral infarct. Correlations with cardioembolic aetiology and outcome

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ABSTRACT

Background: Little is known, in man, in the post-thrombolytic molecular dynamics of haemostasis, particularly the effect of rt-PA on antifibrinolytic components such as alpha2 anti-plasmin and Factor XIII.
Aims and hypothesis: The purpose of this study was to systematically determine changes in coagulation and fibrinolytic parameters after thrombolysis with rt-PA during 24 h. We also aimed to correlate these parameters with different acute ischemic stroke subtypes and global outcome.
Methods: Eighty consecutive patients with cerebral infarcts treated with rt-PA had their plasma levels of fibrinogen, plasminogen, alpha2-antiplasmin, Factor XIII, fibrin(ogen) degradation products (FDP) and D-Dimers measured at baseline (h0), 2 (h2) and 24 h (h24) after initiation of thrombolysis. Correlations between the variations of these components were statistically studied, using the Spearman rank test or the Pearson test. These haemostatic parameters were also compared with cardioembolic and non cardioembolic patients, as well as between poor and favourable outcome patients.
Results: Between h0 and h2, a decrease in fibrinogen, plasminogen, alpha2-antiplasmin, and factor XIII was observed, while an increase in FDP and D-Dimers took place. These values returned to the initial levels at h24. At 2 h, the decrease in fibrinogen was significantly correlated with that of plasminogen (0.48, $p = 0.01$), alpha2-antiplasmin (0.48, $p = 0.004$), and factor XIII (0.44, $p = 0.01$); the decrease in plasminogen was significantly correlated with those of antifibrinolytic components, factor XIII (0.47, $p = 0.02$) and alpha2-antiplasmin ($r = 0.77$, $p < 0.001$). These variations were independent of NIHSS. Cardioembolic infarcts showed a statistically significant greater h0–h2 decrease in plasminogen ($p = 0.04$) and an h0–h2 increase in FDP ($p = 0.02$). Poor outcome was linked to low plasminogen values at 2 and 24 h.
Conclusions: Supposed to be fibrin-specific, rt-PA induces a decrease in circulating fibrinogen, significantly linked to a decrease in plasminogen. A collateral increase in antifibrinolytic agents such as factor XIII and alpha2-antiplasmin is also observed. At 2 h, a significant decrease in plasminogen and a significant increase in fibrin(ogen) degradation products (FDP) are observed in cardioembolic infarcts, and appear as early independent predictors of this aetiology. A low plasminogen value at 2 h is potentially predictive of poor prognosis at 3 months.

1. Introduction

Intravenous recombinant tissue plasminogen activator (tPA) administered within 4.5 h of symptom onset has been proven to be an effective therapy for acute ischemic stroke [1,2]. Clinical failure of thrombolysis has been shown to be related to absent or partial recanalization, and to reocclusion, i.e. to phenomena possibly related to haemostatic events [1,3–5]. Thus, knowledge of biological haemostatic events, which may predict final outcome and/or haemorrhagic complications of thrombolysis, is of importance.

Data on the baseline values of haemostatic agents in stroke are numerous and may provide indications as to post-thrombolytic clinical outcome [6–16]. Inversely, data on the dynamics of the thrombolytic process, with assays at predetermined post-thrombolytic times, are scarce [17–20]. An early post-thrombolytic coagulopathy, with high FDP (Fibrinogen Degradation Products) values at 2 h, has been shown to be related to parenchymatous hematomas [20]. Thus, a modulation of the haemostasis cascade could be an option to improve the efficacy and/or safety of thrombolytic therapy. Systematic studies are needed to observe these molecular changes.

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2. Aims and hypothesis

The purpose of this study was to systematically evaluate, at predetermined times, changes in several coagulation and fibrinolytic parameters after rt-PA thrombolysis. Correlations among variations of these factors were studied. Moreover, we explored the potential predictive values of these haemostasis data in terms of cardioembolic aetiology and global poor outcome. Specific correlations between haemostatic changes and parenchymal haematomas have been taken into account in a brother study.

3. Materials and methods

3.1. Patient population and design

Patients were included consecutively with their consent in an already mentioned protocol [21], which involved a dose of 0.8 mg/kg of rt-PA. They were eligible for rt-PA therapy if they were 18 to 81 years of age and had received a clinical diagnosis of acute ischemic infarct in the carotid or vertebrobasilar territory. A cerebral computed tomography (CT) scan was performed to exclude patients who had an intracranial haemorrhage. Despite pre-thrombolytic stroke MRIs often having been performed, no MRI criteria, either related to size of the DWI and PWI lesions, or to the existence of a mismatch area, was taken into account for inclusions or exclusions. Treatments with intravenous heparin, oral anticoagulants, aspirin, clopidogrel, dextrans, low molecular heparin, and subcutaneous heparin were strictly prohibited during the first 24 h after administration of the study drug. Institutional approval of the study was obtained.

3.2. Clinical assessment

NIHSS scores at entry, onset of treatment times (OTT) and mRankin score at 3 months were considered. A systematic etiological screening was performed, including transthoracic and transesophagal echocardiographies, carotid Doppler and electrocardiography. Episodic atrial fibrillation recorded during the hospital stay was taken into account. The cardioembolic causes included all established major and minor causes of cardioembolism. For etiologies, patients were classified into six categories: isolated cardioembolic, large artery atherothrombotic, mixed cause (cardioembolic and atherothrombotic), small artery thrombosis, dissection, and undetermined. Prethrombolytic histories of vitamin K antagonists (INR < 1.7) and anti-platelet agents were also registered.

3.3. Haemostasis studies

Haemostasis was evaluated before treatment, and at 2 and 24 h after the initiation of thrombolysis. Blood cell count was performed on EDTA samples with an ADVIA 120 counter (Siemens Healthcare Diagnostics, Saint Denis, France). For coagulation evaluation, blood was collected in 5 mL evacuated tubes containing 0.5 mL sodium citrate 0.109 M (Vacutainer®, Becton Dickinson, Meylan, France) and further centrifuged.

Activated partial thromboplastin time (aPTT), INR, D-Dimers, fibrin(ogen) degradation products (FDP) and fibrinogen were determined on fresh plasma. Plasma was otherwise stored in aliquots at −80 °C. APTT, INR and fibrinogen were photooptically measured using an ACL-Top® coagulometer (IL, France). FDP were measured semiquantitatively by an antibody-coated latex particle agglutination assay (FDP PLASMA®, Diagnostica Stago). D-Dimers were measured by an Enzyme Linked Fluorescent Assay (VIDAS D-Dimer Exclusion®, Biomérieux, Marcy-l'Etoile, France). Alpha2-antiplasmin, factor XIII (Berichrom α2-Antiplasmin® and Berichrom F XIII®, Siemens Healthcare Diagnostics), and plasminogen (Coamatic® plasminogen, Chromogenix, Milano, Italy) activities were measured with chromogenic assays.

3.4. Statistical analysis

Descriptive values of coagulation, haemostatic and post-thrombolytic parameters were studied as median, mean, standard deviation (SD), minimum and maximum values, unless explicitly noted otherwise. In all calculations, the changes in these parameters between baseline and 2 h were defined as the ratios (h2–h0): h2. The hypothesis of normal distribution for each variable was tested using the Kolomogorov–Smirnov test. Comparisons of the parameters between h0 and h2 (p1), h2 and h24 (p2), and h0 and h24 (p3) were performed using a Student test for matched pair, while the comparison between the 3 periods (p4) was performed with the mixed model for repeated measures.

The correlations among coagulation parameters and changes were tested using the Spearman rank test when the hypothesis of normality was not verified and the Pearson test when it was.

In the comparison studies, patients with incomplete haemostatic data or doubtful clinical data were excluded.

Concerning the comparison of infarct subtypes, a univariate comparison of means was performed using the parametric Student test when the hypothesis of normal distribution was verified and the non-parametric Wilcoxon test when it was not. Patients with isolated cardioembolic cause were compared with patients having non isolated cardioembolic cause. Variables with a p value less than 0.05 were then included in a multivariate logistic regression. Odds ratios were first adjusted for age and sex and were presented with their 95% confidence intervals. An additional adjustment on baseline NIHSS was performed. Patients with aspirin were compared with patients without aspirin.

A univariate comparison of haemostasis dynamics was done between poor outcome patients (mRS 2–6) and favourable outcome patients (mRS 0.1) without taking into account post-thrombolytic haemorrhages, which will be studied and presented in a brother article. Multivariate logistic regressions adjusted on age, sex, NIHSS, and final

Table 1
Median values (Q1–Q3) of the hemostatic parameters measured before thrombolysis (h0), at 2 h (h2) and 24 h (h24) after thrombolysis. Student test was used for paired comparison: p1 between h0 and h2; p2 between h2 and h24; and p3 between h0 and h24. Comparison between the 3 periods (p4) was performed with the mixed model for repeated measures.

Haemostasis parameter	h0	h2	h24	p1 h0–h2	p2 h2–h24	p3 h0–h24	p4
Fibrinogen (g/L)	3.4 (2.9–4.1)	2.7 (2.4–3.2)	3.1 (2.6–3.6)	<0.0001	<0.0001	<0.0001	<0.0001
Plasminogen (%)	102 (113.0–93)	60.5 (56–68.5)	84 (76–91)	<0.0001	<0.0001	<0.0001	<0.0001
α2-antiplasmin (%)	108.5 (101–116)	31 (21–46)	81 (69–88)	<0.0001	<0.0001	<0.0001	<0.0001
Factor XIII (%)	103.5 (96–117.5)	100.5 (121–87)	100 (117–82)	0.05	0.007	0.0001	0.0004
FDP (mg/L)	5 (5–5)	20 (5–20)	5 (5–10)	<0.0001	<0.0001	0.06	<0.0001
D-Dimers (mg/L)	0.8 (0.4–1.2)	4 (2.3–4)	1.3 (0.9–3.3)	<0.0001	<0.0001	<0.0001	<0.0001

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