Coagulation and Fibrinolysis Study after Local Thrombolysis of a Cerebral Artery with Urokinase

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Abstract

Coagulation and fibrinolysis factors were studied in six patients after local thrombolysis with urokinase (720,000 IU). Transient abnormalities, such as prolonged prothrombin time, decreased plasminogen and α_2 -antiplasmin activities, decreased fibrinogen, and increased fibrin degradation products were seen on the day after thrombolysis, but tended to return to the normal range on the 4th day except for one patient who suffered from disseminated intravascular coagulation. Antithrombin III activity did not change so much. Therefore, the dosage of urokinase should be as low as possible to prevent fluctuations in the coagulation and fibrinolysis system.

Key words: local thrombolysis, cerebral artery, urokinase, α_2 -antiplasmin, antithrombin III, plasminogen

Introduction

Local thrombolysis therapy with plasminogen activators such as tissue-type plasminogen activator (t-PA) or urokinase has recently achieved good clinical results in patients with atherothromboembolic occlusion of cerebral arteries.^{1-5,8,16,18,19,23,31,33,34} However, no thorough hematological study of the effect on coagulation and fibrinolysis factors has been done,^{25,27} although this seems to be necessary for the prevention of complications such as cerebral hemorrhage or disseminated intravascular coagulation (DIC).

We report our study of the effect of local thrombolysis with urokinase on coagulation and fibrinolysis factors in six patients.

Patients and Materials

This study included three males and three females aged 56 to 74 years old (mean 66 yrs) (Table 1). The patients showed multiple neurological signs such as

deterioration of consciousness, hemiparesis, and aphasia. Computed tomography (CT) revealed no obvious cerebral infarction on admission. Superselective catheterization was achieved with a Tracker-18 (Target Co., Fremont, Cal., U.S.A.). The local thrombolysis used a total of 720,000 IU urokinase. Urokinase solution (6000 IU/ml physiological saline) was infused through the Tracker catheter for 10 minutes to the sites distal and proximal to the obstruction. After thrombolysis, 80 mg of an antagonist to thromboxane A₂ synthetase, ozagrel sodium (Xanbon; Kissei Co., Matsumoto, Nagano) was continuously infused. No heparin was given.

Coagulation and fibrinolysis factor examination was performed before thrombolysis, and on the next and 4th days after thrombolysis. Case 2 was the only patient who showed clinical signs of DIC. Long-term follow-up was continued for about 2 months. The activities of plasminogen, α_2 -antiplasmin, and antithrombin III were measured by the segregation of p-nitro-aniline from synthesized substrate (normal range 70-130%). Prothrombin time (PT), thrombo test, and activated partial thromboplastin time (APTT) were measured by the coagulation method. Fibrin degradation products (FDP) and fibrinogen

Table 1 Summary of patients

Case No.	Age	Sex	Occluded artery	Time to recanalization (hrs)	Urokinase infusion ($\times 10^4$ IU)	Result		
						Hemorrhage*	Reocclusion	Symptom
1	56	M	MCA (M ₁)	4	72	+	—	no change
2	73	F	MCA (M ₁)	5	72	+	—	no change (DIC [#])
3	74	M	MCA (M ₁)	4	72	—	—	improved
4	62	M	MCA (M ₂)	7	72	—	—	no change
5	60	F	ICA (C ₄)	5	72	+	—	improved
6	70	F	BA	2	72	—	—	no change

*CT showed cerebral hemorrhage (hemorrhagic transformation) on the next day. [#]Decreased platelet count, prolonged PT, and increased FDP were seen on the 14th day after thrombolysis. This suggests that DIC might have occurred in this patient. BA: basilar artery, ICA: internal carotid artery, MCA: middle cerebral artery.

Table 2 Coagulation and fibrinolysis studies after local thrombolysis with urokinase

	Pre-thrombolysis (n = 4)	The day after thrombolysis (n = 6)	Four days after thrombolysis (n = 6)
PT (% , normal range 70–130)	94.84 $\pm$ 9.72	73.7 $\pm$ 10.849*	82.317 $\pm$ 11.92*
Thrombo test (% , normal range 70–130)	99 $\pm$ 26.442	54.025 $\pm$ 13.961	93.86 $\pm$ 34.734
Plasminogen (% , normal range 70–130)	83 $\pm$ 13.441	61.167 $\pm$ 12.156*	82.167 $\pm$ 20.673 [#]
α_2 -Antiplasmin (% , normal range 70–130)	98.5 $\pm$ 11.619	51 $\pm$ 11.849*	92.167 $\pm$ 12.09 [#]
Antithrombin III (% , normal range 70–130)	97.75 $\pm$ 16.235	96 $\pm$ 12.247	105.833 $\pm$ 23.051
APTT (ratio of coagulation time)	0.947 $\pm$ 0.231	0.944 $\pm$ 0.106	1.012 $\pm$ 0.186
FDP (μ g/ml)	3.867 $\pm$ 2.454	16.25 $\pm$ 8.797*	10.52 $\pm$ 14.611
Fibrinogen (mg/dl)	265.8 $\pm$ 45.63	199.35 $\pm$ 68.002	338.567 $\pm$ 120.929 [#]

Values are mean $\pm$ SD. Asterisk or sharp means significant difference ($p < 0.05$) compared to pre-thrombolysis or the day after thrombolysis, respectively.

were measured by the latex agglutination and thrombin-time methods. Statistical analysis used the paired t-test. $p < 0.05$ was considered to be significant. The correlation between serum α_2 -antiplasmin and antithrombin III activities was examined with the simple regression method.

Results

Plasminogen and α_2 -antiplasmin activities decreased significantly on the day after thrombolysis, but these abnormalities returned to the normal range on the 4th day (Table 2). PT was prolonged and FDP increased significantly on the day after thrombolysis, and recovery of both on the 4th day was incomplete. The thrombo test showed the same tendency as the PT, although the change was not significant. Fibrinogen also decreased on the day after thrombolysis, and had increased over the pre-thrombolysis level on the 4th day, but not significantly. Antithrombin III activity and APTT did not change so much.

α_2 -Antiplasmin activity showed a significant positive correlation with antithrombin III activity before

(regression coefficient = 0.983, $p = 0.017$) and on the 4th day after the thrombolysis (regression coefficient = 0.959, $p = 0.003$), but no correlation was observed on the day after thrombolysis (Fig. 1).

In Case 2, hemorrhagic transformation was seen in the basal ganglia on the day after thrombolysis and hemorrhage from the bladder occurred on the 4th day. Decreased platelet count, prolonged PT, and increased FDP were also prominent. Nafamostat mesilate was infused for the treatment of DIC (Fig. 2).

Discussion

Although the average plasma half-life of urokinase is only 9–12 minutes, a large amount of plasminogen is converted to plasmin in this short period.^{21,26,29,32)} The plasmin generated can degrade fibrinogen and factors V and VIII besides fibrin and elongate the coagulation time for several days.^{15,21)} Furthermore, plasmin is very quickly inactivated by α_2 -antiplasmin, which forms a complex with plasmin and antagonizes its protease or esterase activity, so α_2 -antiplasmin is also consumed.³⁰⁾ Our results also

Fig. 1 Relationship between α_2 -antiplasmin activity and antithrombin III activity. Numbers show the case numbers. $\bullet$: pre-thrombolysis, $\times$: the day after thrombolysis, $\circ$: 4 days after thrombolysis.

showed the consumption of these coagulation factors, plasminogen and α_2 -antiplasmin, with increased FDP on the day after thrombolysis. The consumption of these coagulation factors elongated the coagulation time, as manifested by the PT and thrombo test, but not reflected in the APTT. Of these changes, those of α_2 -antiplasmin, FDP, and fibrinogen were almost the same as those previously reported.²⁸⁾ Ozagrel sodium is reported to increase α_2 -antiplasmin activity and FDP and to decrease fibrinogen, so our results may have been influenced by this agent.¹⁴⁾

α_2 -Antiplasmin and antithrombin III belong to the same serine protease inhibitor family and are thought to have important competitive functions.^{6,9,24)} It is notable that α_2 -antiplasmin activity decreased prominently despite the absence of any remarkable change of antithrombin III activity on the day after thrombolysis. α_2 -Antiplasmin activity showed a strong positive correlation with antithrombin III activity before and on the 4th day after thrombolysis, suggesting that the patient is in a hyperfibrinolytic condition compared with coagulation and may easily suffer a cerebral hemorrhage.

The safe and effective dose of urokinase is very difficult to determine. The recanalization rate with focal urokinase increases dose-dependently up to 960,000 IU.¹²⁾ However, the increase of FDP and decreases of α_2 -antiplasmin activity and fibrinogen occur even with a small amount of urokinase (<480,000 IU).²⁸⁾ These changes are also dose-dependent, so the dosage of urokinase should be as low as possible to prevent fluctuations in the coagulation

Fig. 2 Follow-up study of coagulation and fibrinolysis after local thrombolysis with urokinase in Case 2. $\bullet$: fibrinogen, $\blacktriangle$: FDP, $\times$: platelet, $\blacksquare$: α_2 -antiplasmin, $\diamond$: plasminogen, $\circ$: APTT, $\triangle$: PT, $\square$: thrombo test.

and fibrinolysis system. Any instability in this system might cause DIC. The combination of decreased platelet count, prolonged PT, and increased FDP suggested that DIC happened 2 weeks after thrombolysis in Case 2.

t-PA has a high affinity for fibrin, and only the binary complex formed by t-PA and fibrin has a high affinity for plasminogen.^{7,11,26,30,32)} Therefore, activation of plasminogen to plasmin by t-PA and degrada-

tion of fibrin by the plasmin proceed mainly on the fibrin surface without significant plasmin generation in the plasma.^{7,26,30,32)} In contrast, urokinase does not have selectivity for fibrin and can generate more plasmin in the plasma than t-PA.²¹⁾ Accordingly, t-PA is thought to be relatively safe, although even t-PA can disturb the coagulation-fibrinolysis system and cause cerebral hemorrhage and DIC due to its unspecific binding.^{1,10,13,15,17,19,20,22,29)}

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