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# Clinical research of Lumbrokinase in reversing carotid atherosclerotic plaques of patients with ischemic cerebrovascular disease

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**[ABSTRACT]** OBJECTIVE: To investigate the effect of lumbrokinase on plasminogen, hemorheology, blood lipid levels and carotid atherosclerotic plaque in patients with ischemic cerebrovascular disease. METHODS: Computer-generated random numbers to divide 60 ischemic cerebrovascular disease patients with carotid artery plaques and abnormal plasminogen levels into treatment group and control group, 30 patients in each group. Treatment group was given lumbrokinase with aspirin, atorvastatin; control group was given aspirin and atorvastatin. Conventional treatments were the same in both groups; treatment period was 6 months. Fibrinogen (FIB), hemorheology, blood lipids and carotid artery color Doppler ultrasound were examined before and after the treatment. RESULTS: After treatment, in the treatment group, the FIB, platelet aggregation, whole blood viscosity and carotid artery intima-media thickness and intimal plaque were lower compared with before treatment, the difference was statistically significant ($P < 0.05$ or $P < 0.01$); improvement level was higher than control group, the difference was statistically significant ($P < 0.05$ or $P < 0.01$). Comparison between before treatment and after treatment in both groups: the total cholesterol, triglyceride, low-density lipoprotein cholesterol were lower and high-density lipoprotein cholesterol were higher, the difference was statistically significant ($P < 0.01$); there was no significant difference in the above parameters ($P > 0.05$) within the two groups after treatment, but the treatment group had a greater reduction. During treatment, the treatment group had one case with skin itching and two cases with stomach discomfort. There were not any serious adverse reactions in the two groups. CONCLUSION: Lumbrokinase improved microcirculation, activated coagulation, dissolved fibrins, inhibited platelet aggregation and adjusted the role of blood lipids. It also had anti-lipid oxidation, protection of vascular endothelial and other properties. When used in combination with atorvastatin, it reduced atherosclerosis and plaque formation effectively.

**[Keywords]** ischemic cerebrovascular disease; lumbrokinase; hemodynamic; lipid; carotid atherosclerosis
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Carotid atherosclerotic plaque caused narrowing of carotid artery which is a dangerous factor in high blood pressure and cerebrovascular disease. An effective intervention to the present anemic cerebrovascular disease is a current research topic. To investigate the effectiveness of lumbrokinase in treating carotid atherosclerotic plaques in ischemic cerebrovascular disease, in Jan 12th, 2007, department of neurology in my hospital has proposed lumbrokinase and atorvastatin combination therapy, and results from color Doppler ultrasound imaging, intima-media thickness (IMT) and plaque examinations showed that treatment was effective.

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## 1 DATA AND METHOD

**1.1 General Information.** January to December 2007, there were 60 hospitalized patients in neurology department. The Fourth National Conference on Cerebrovascular Disease diagnosis standard was used as a diagnostic tool. Color Doppler ultrasound imaging and blood biochemical test were used to confirm patients had carotid artery atherosclerotic plaque formation, high blood viscosity and high blood lipid profile. Patients were randomly divided into treatment group and control group, 30 each. Treatment group: 18 males, 12 females; aged 58-86 years old, average (63.3±8.6) years

old; 19 with bilateral carotid artery plaque, 11 with unilateral; 22 with hyperlipidemia; 25 with hypertension; 19 with diabetes mellitus. Control group: 19 males, 12 females; age 59-85 years old, average (64.2±7.6) years old; 20 with bilateral carotid artery plaque, 10 with unilateral; 20 with hyperlipidemia; 21 with hypertension; 17 with diabetes mellitus. Both groups were statistically comparable in sex, age and clinical conditions (*P>0.05*).

**1.2 Method**

**1.2.1 Treatment Method.** Conventional treatment is the same in both groups, including citicoline 0.75g/d and XueShuanTong (Panaxnotoginsenosides) 300mg/d IV injection, aspirin tablets 100mg/d and atorvastatin 20mg/d. In addition to the conventional treatment method, the treatment group had additional use of lumbrokinase capsules (manufactured by Beijing Baiao Pharmaceutical Co. Ltd), two capsules each time and three times daily, before meal. Both groups' treatment period was six months.

**1.2.2 Laboratory Examination.** On the first day and after six months, perform a blood test on fibrinogen (FIB), hemorheology, blood lipids and other indicators.

**1.2.3 Carotid Artery Ultrasound** During the six months, all patients had a carotid ultrasound examination before and after treatment and use the GEVID7 colored Doppler supersonic diagnostic equipment manufactured by General Electric (USA) for examination. Patients lay on the back with the head tilted backward and the neck fully exposed. Scan started from the carotid artery, moving slowly towards the common carotid artery bifurcation, internal carotid artery, and external carotid artery, reaching the highest possible carotid position before patients were instructed to rotate the head 90 degrees. Then the neck was scanned horizontally along the arterial route to see if internal carotid arterial imtima is intact, whether there is thickening, plaque position, size and echo characteristics. Finally the thickest spot was recorded as the intima-media thickness of the carotid artery. According to modified Crouse scoring system, IMT>1.2mm was considered as the presence of an atherosclerotic plaque.

**1.3 Statistical Method** All data are using the SPSS 10.0 statistical method to analyze. Measurement data represented by $\bar{x}\pm s$, use *t test* for two groups' mean, *P< 0.05* as statistically significant.

## 2. RESULT

**2.1 FIB & hemorheology changes of the two groups before and after treatment.** Hemorheology and FIB decreased (*P<0.05* or *P<0.01*) in the two groups before and after treatment; degree of improvement in indicators of the treatment group was more obvious than the control group; it was statistically significant (*P<0.05* or *P<0.01*), see table 1.

**2.2 Blood lipid changes of the two groups before and after treatments.** After treatment, two groups' total cholesterol, triglyceride, low density lipoprotein decreased compared to before treatment; high density lipoprotein raised compared with before treatment. Improvement in the treatment group was more effective than control group, there was a significant difference (*P<0.01*); comparison of the treatment group and the control group, there was no significant difference, (*P>0.05*), see table 1.

Table 1 Two groups' plasminogen, hemodynamic and lipid changes before and after treatment ($\bar{X}\pm s$)

| Group | n | Plasminogen (mg/L) | Platelet aggregation (%) | High-shear whole blood (mPa*s) | Hematocrit (%) | Total cholesterol (mmol/L) | Triglyceride (mmol/L) | LDL (mmol/L) | HDL (mmol/L) |
|---|---|---|---|---|---|---|---|---|---|
| Control | 30 | | | | | | | | |
| Before treatment | | 6.00±1.80 | 42.20±3.70 | 5.93±0.56 | 37.90±3.20 | 6.86±0.60 | 1.83±0.43 | 4.38±0.48 | 1.38±0.31 |
| After treatment | | 5.10±1.10[a] | 41.00±2.00[a] | 4.81±0.60[b] | 36.10±3.10[b] | 4.89±0.55[b] | 1.64±0.36[b] | 2.43±0.51[b] | 1.77±0.41[b] |
| Treatment | 30 | | | | | | | | |
| Before treatment | | 6.10±1.70 | 43.20±3.80 | 5.92±0.58 | 38.50±3.40 | 6.89±0.56 | 1.91±0.39 | 4.28±0.46 | 1.42±0.33 |
| After treatment | | 3.10±0.60[ac] | 35.80±2.3[ad] | 3.93±0.51[bd] | 34.80±2.50[bc] | 4.53±0.52[b] | 1.47±0.28[b] | 2.28±0.50[b] | 2.07±0.34[b] |

Note: compared with before treatment, [a] *P <0.05*, [b] *P<0.01*;
compared with control group after treatment, [c] *P<0.05*, [d] *P<0.01*.

**2.3 Comparison of intima-media thickness (IMT) and intimal plaque within the two groups** Comparison of before and after treatment in the two groups: IMT and intimal plaque were smaller, there was significant difference (*P<0.01*); after treatment, comparison between the two groups: there was significant different (*P<0.01*), see table 2.

Table 2 IMT & intimal plaque in the two groups, before and after treatment (mm, $\bar{X}\pm s$)

| Group | n | IMT | Intimal plaque |
|---|---|---|---|
| Control Group | 30 | | |
| Before treatment | | 1.18±0.08 | 1.49±0.18 |
| After treatment | | 0.94±0.07[a] | 1.11±0.15[a] |
| Treatment Group | 30 | | |
| Before treatment | | 1.19±0.08 | 1.49±0.19 |
| After treatment | | 0.79±0.06[ab] | 0.95±0.15[ab] |

Note: compared with before treatment, [a]*P<0.01*;
compared with control group after treatment, [b]*P<0.01*; "IMT" intima-media thickness.

**2.4 Adverse Reaction** Treatment group: one week after the treatment, there was one case with skin itchiness and rash; subject treated with antihistamine and symptoms disappeared. Two patients had stomach burning feelings; when treatment dosage amount reduced, symptoms disappeared in five days. Other adverse reactions included weakness, nausea, abdominal distension, stomached, maldigestion and others. During treatment period, there was not any bleeding in both groups.

## 3. DISCUSSION

Patients with acute cerebral infarction taken lumbrokinase within 3-6hr have effective treatment results. The use of snake venom proteases within 3 hrs of acute cerebral infarction has similar effects; this proved that early intervention in blood coagulation and fibrinolytic system of acute cerebral infarction can effective cure acute cerebral infarction and ischemic cerebrovascular disease [1,3]. Proteolylic enzymes are extracted from *Eisenia foetida* to make lumbrokinase with a molecular weight of 16000-

45000 and contains fibrinolysin and plasminogen activator [4]. The anti-thrombus function mechanisms: ①Has special fibrin affinities which can directly hydrolyze fibrinogen and produce soluble fibrinogen degradation product; hence, it helps to reduce fibrinogen content. ② Activates plasminogen into plasmin, activates fibrinoloytic system and enhances endogenous fibrinolysis. ③ Reduces platelet aggregation and improves hemorheology [5].

Results from this clinical research compared with before treatment showed that a reduction in both FIB and hemodynamics (platelet aggregation, blood viscosity) in both groups. There was a significant difference between the treatment group and the control group. This proved that lumbrokinase has more effective results and is a more effective intervention for cerebral infarction. It has some degrees of improvement in blood viscosity and fibrinogen abnormalities. This can strongly proved that lumbrokinase has anticoagulate and hydrolysis effects which can effectively treat cerebral infarction and other ischemic cerebrovascular diseases.

Atherosclerosis is a chronic, progressive and multi-artery disease involving the imtima, often affecting large-size and medium-size arteries. Clinically coronary and cerebral arterial plaques have the most impact on patient morbidity and mortality. Hence, prevention of atherosclerosis and plaque formation has a high clinical relevance. Using the colored Doppler to examine carotid artery IMT allows us to check for cerebral arthrosclerosis and coronary artery disease; if diagnose early, it helps to monitor plaque formation and treatment progression or plaque disappearance estimations [6]. This clinical research demonstrated that after treatment, patients of the two groups had reduction in IMT and plaque, the difference was significant; improvement in treatment group was better than control group; two groups' difference had significance. This proved that lumbrokinase with atorvastatin improve arteriosclerosis condition and reduce plaque formation; combination of these two drugs can balance blood lipids, have anti-arteriosclerosis effect, aid in disappearance of plaque, thus, reduce heart and brain blood damages.

Clinical studies have proven that lumbrokinase is safe and plays an influential role in the reduction of atherosclerotic plaque. It can effectively treat and prevent cerebrovascular disease. As far as long term care of treating atherosclerotic plaques and blood lipid balances, this study did not have enough representative number of participants. Hence, it needs to be further assessed.

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