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The effects of lumbrokinase treatment in diabetes mellitus patients with microcirculation impairment

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[Abstract] Objective To study the clinical safety and efficacy of lumbrokinase in treating diabetic patients with microcirculation impairment. **Methods** Two hundred diabetes mellitus inpatients with microcirculatory impairment from our hospital were randomly divided into the treatment group and the control group. The control group was given Diamicron and the treatment group was given Diamicron plus lumbrokinase capsules, then treatment effects were assessed later. **Results** Microcirculation were improved significantly after treatment in both groups ($P < 0.05$). Compared with the control group, the microcirculation improvement in the treatment group was significantly better ($P < 0.05$). **Conclusions** The Diamicron plus lumbrokinase capsules can effectively treat microcirculatory impairment in diabetes mellitus without any major adverse reactions.

[Key Words] Diamicron; lumbrokinase; diabetes; microcirculation

Diabetes mellitus associated microcirculation impairment is commonly seen in clinical settings, and it is the pathological basis for developing other diabetic complications. If not diagnosed and treated early, microcirculatory impairment would often result in serious late-stage microvascular damages, leading to the eventual organ function failures. This author had used Diamicron plus lumbrokinase capsules treating diabetes mellitus associated microcirculatory impairment between January 2004 and December 2008, and the results were quite satisfactory. The research is reported below.

1. MATERIALS AND METHODS

1.1 General Information: Two hundred (200) diabetic patients with microcirculatory impairment were selected from our hospital inpatients from January 2004 to December 2008. All patients met the WHO 1999 diagnostic criteria for diabetes mellitus. Exclusion criteria include acute or chronic nephritis, urinary tract infections, lithiasis, vaginitis, fever, ketosis, heart failure, liver dysfunction, or a recent history of taking nephrotoxic drugs. Patients were randomly assigned into the control group and the treatment group with 100 patients in each. The treatment group had 5l males and 49 females with the average age being (58.56 ± 5.43) years; their duration of illness was 3-30 years with an average of (7.68 ± 2.34) years. The treatment group had 23 cases of type 1 diabetes and 77 cases of type 2 diabetes, with 56 patients also had dyslipidemia and 63 patients also had hypertension. The control group had 52 males and 48 females with the average age being (58.16 ± 5.50) years; their duration of illness was 2-25 years,

with an average of (7.62 4-2.294) years. The control group had 22 cases of type 1 diabetes and 78 cases of type 2 diabetes, with 57 patients also had dyslipidemia and 65 patients also had hypertension. The differences in the age, sex, and duration of illness between the groups were not statistically significant (P> 0.05).

1.2 Methods: All patients were given oral Diamicron (gliclazide) for blood sugar control at 80mg twice daily for 2-3 weeks. Then the dosage was adjusted based on blood and urinary sugar levels; the dose range was 80 to 240 mg per day. At the same time, the treatment group was also given oral lumbrokinase (Boluoke®) half an hour before a meal at 2 capsules 3 times daily for 3-4 weeks.

1.3 Monitoring Parameters: Nailfold microcirculation was measured, including nailfold loop morphology, loop blood flow pattern, loop surrounding, etc. In addition, hemorheology, routine blood tests, liver and kidney functions, and ECG were also monitored.

1.4 Statistical Methods: The parameters were expressed as the mean ± standard deviation ($\bar{x} \pm s$). The *t*-test was used to compare inter-group results. Data were analyzed using the SPSSl3.0 statistical analytic software, and P <0.05 for considered statistically significant.

2. RESULTS

2.1 Nailfold microcirculation parameters before and after treatment: The loop morphological score, loop blood flow pattern score, and the loop surrounding score were improved in both groups after treatment, and the differences were statistically significant (P <0.05). At the end of the study, the treatment group's loop morphological score, loop blood flow pattern score, and the loop surrounding score were reduced more than those of the control group, and the differences were also statistically significant (P <0.05). (See Table 1)

Table 1. Nailfold microcirculation indicators before and after treatment ($\bar{x} \pm s$)

Parameter	Control (n=100)		Treatment (n=100)	
	Before Tx	After Tx	Before Tx	After Tx
Loop Morphology Score	3.12 ± 0.50	2.95 ± 0.52*	3.25 ± 0.55	2.07 ± 0.56*Δ
Loop Blood Flow Pattern Score	2.15 ± 0.52	1.56 ± 0.56 *	2.23 ± 0.54	1.30 ± 0.57*Δ
Loop Surrounding Score	1.43 ± 0.45	1.28 ± 0.46 *	1.50 ± 0.45	0.90 ± 0.47*Δ

* vs. pre-Tx, *P*< 0.05; Δ vs. control, *P*< 0.05

2.2 Hemorheology parameters before and after treatment: The low-shear viscosity, high-shear viscosity, ESR, and ESR K value were improved after treatment in both groups, and the differences were statistically significant (P <O.05). At the end of the study, the treatment group's low-shear viscosity, high-shear viscosity, ESR, and ESR K value were reduced more than those of the control group, and the differences were also statistically significant (P <0.05). (See Table 2)

Table 2. Hemorheology parameters before and after treatment ($\bar{x} \pm s$)

Parameter	Control (n=100)		Treatment (n=100)	
	Before Tx	After Tx	Before Tx	After Tx
Low-Shear Viscosity (3/s)	15.40 ± 3.20	13.41 ± 3.24*	15.45 ± 3.25	11.45 ± 3.30*Δ
High-Shear Viscosity (200/s)	6.66 ± 2.20	5.68 ± 2.23 *	6.32 ± 2.21	4.41 ± 2.22*Δ
Plasma Viscosity (mPa·s)	2.02 ± 1.88	1.52 ± 1.90	2.04 ± 1.89	2.78 ± 1.87
RBC Aggregation Index	3.50 ± 2.10	3.46 ± 2.08	3.61 ± 2.15	3.51 ± 2.20
ESR (mm/h)	21.30 ± 4.69	16.57 ± 4.72*	20.95 ± 4.12	15.02 ± 4.36*Δ
Hematocrit (L/L)	0.48 ± 0.04	0.47 ± 0.03	0.48 ± 0.03	0.45 ± 0.04*Δ
ESR K value	98.20 ± 6.30	76.81 ± 6.24*	95.43 ± 6.48	64.23 ± 6.33*Δ

* vs. pre-Tx, $P< 0.05$; Δ vs. control, $P< 0.05$

2.3 Adverse Reactions: There were no serious adverse reactions reported in both groups. Routine blood tests, liver and kidney functions, and ECG monitoring did not show any abnormalities either.

3. DISCUSSION

Microcirculation changes are intimately associated with the initiation, progression and complications of many illnesses, and can be very helpful in determining the prognosis of those conditions. Microcirculation impairment includes three aspects: hemodynamic abnormalities, microvascular pathologies, and changes in hemorheology. Generally hemodynamic abnormalities are the early manifestation of microcirculatory impairment and the associated complications are often preclinical. As disease progresses, microvascular damages and changes in hemorheology become obvious; at this stage most complications would show typical pathological changes and clinical presentations. In the late stage, microvasculature is seriously damage and organ failure ensues. As disease progresses, most diabetic patients would develop microcirculatory impairment, which leads to the development and progression of various chronic complications; diabetic nephropathy and retinopathy are the classic examples. Currently there are many treatment options for the early treatment and prevention of diabetes associated microcirculatory impairment. Among those options, lumbrokinase has been referred to as the king of thrombolysis because it inhibits platelet aggregating function and has been widely used in clinical practice.

Our research showed that the loop morphological score, loop blood flow pattern score, and the loop surrounding score were improved in both groups after treatment. However, the parameters in the treatment group were reduced more than those of the control group, and the differences were statistically significant ($P < 0.05$). The low-shear viscosity, high-shear viscosity, ESR, and ESR K value were improved after treatment in both groups. Again, the parameters in the treatment group were reduced more than those of the control group, and the differences were statistically significant ($P < 0.05$). These results indicated that lumbrokinase was effective in improving the microcirculation and hemorheology in diabetic patients with microcirculatory impairment.

Long-term poor glycemic control in diabetic patients can cause elevated glycosylated hemoglobin, increased red blood cell aggregation, decreased membrane fluidity and membrane composition changes, leading to reduced red blood cell deformability. This will result in microvascular stagnation, increased resistance to blood flow, microvascular blockage, reduced blood flow, and microcirculatory hypoperfusion. Diabetic patients often have increased plasma macroglobulin, which inhibits plasmin activity and promotes hypercoagulability. Furthermore, hyperglycemia-induced low-inositol, high-sorbitol, and hyperosmolar tissue state can impair vascular endothelial cell proliferation and affect endothelial repair. Therefore, increased erythrocyte aggregation, increased platelet adhesion, elevated fibrinogen, microvascular endothelial damage, and microcirculatory impairment are the major factors for diabetic microangiopathy. Whereas, lumbrokinase precisely can break down fibrin, lower lipids, enhance plasmin activity, reduce platelet aggregation, reducing vascular resistance, and improve microcirculation. Thus it is especially suited for treating microcirculatory impairment and improving microangiopathy in diabetes. In addition, through the monitoring of routine blood tests, urinalysis, liver function, and kidney function, lumbrokinase has been found to be safe, reliable, and without toxic side-effects.

In short, the positive effects of lumbrokinase in treating diabetic microcirculatory impairment have been confirmed. Lumbrokinase can significantly improve patient's hemorheology and microcirculation without any major adverse reactions; it is worthy of further clinical research and broader clinical applications.

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