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Observation on the Efficacy of Lumbrokinase in Treating Arteriovenous Fistula Thrombosis

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Ever since Brescia and Cimino invented arteriovenous fistula (AV fistula) in 1966, haemodialysis enters "the era of long-term dialysis", and the goal of long-term survival for uremic patients was finally realized. As a result, long-term haemodialysis is viewed as the "lifeline" for uremic patients on dialysis. AV fistula is the most commonly used access for long-term dialysis, with the advantages of prolonged usage and low infection rate. In clinical settings, however, for various factors some patients may develop fistula thrombosis, which leads to fistula stenosis,or even complete obstruction. This not only affects the effectiveness of dialysis, but may also cause some patients requiring fistula reconstruction or finding an alternative access, resulting in great suffering and financial burden to the patients. In this experiment, 42 cases of fistula thrombosis with incomplete obstruction in our dialysis centre (between January 2004 and June 2009) were treated with lumbrokinase or aspirin, and the efficacy in both group were analyzed and reported below.

1. MATERIALS AND METHODS

1.1 General Data: 28 male and 14 female, ranging between 23-78 years of age, all underwent hemodialysis 2-3 times weekly for 4.5 – 5 hours each time. Regular heparin was used as anticoagulant for all. Primary diagnoses: 21 with glomerulonephritis, 6 with diabetic nephropathy, 4 with polycystic kidney disease, 6 with hypertensive kidney disease, 2 with gouty nephropathy, 2 with obstructive nephropathy, and 1 with hepatitis B associated nephritis. Please refer to Table 1 for patient data comparison between groups.

Table 1 Comparison of Patients Data in the 2 Groups before Treatment ($\bar{x}\pm s$)

Group	Number of Cases	FBG (g/L)	WBC ($x10^9$/L)	Hb (g/L)	PLT ($x10^9$/L)	Hs-CRP (g/L)	Kt/V
A	26	3.4±0.5	5.2±2.1	91±17	142±56	3.32±1.53	1.27±0.22
B	16	3.4±0.4	5.2±2.2	89±15	147±68	3.28±1.60	1.25±0.19

Note: Fibrinogen (FBC), White blood cells (WBC), Hemoglobin (Hb), Platelet (PLT), High sensitivity C reactive protein (Hs-CRP), Indicator of dialysis adequacy: Kt/V

1.2 Conditions of Fistulae and Timing of Treatment: All fistulae were surgically created by end-to-end anastomosis of cephalic vein to radial artery and used when the fistulae were mature about 4-6 weeks after surgery. The onset of significant decrease in fistula flow rate was between 1 and 89 months after usage. Incomplete fistula thrombosis was

considered when dialysis could not be maintained even though flow rate was >200ml/min, significant decrease in fistula pulsation and murmur, decrease in blood flow on colour Doppler ultrasound examination, and formation of mural thrombus. All patients were treated within 3 days of fistula stenosis detection.

1.3 Grouping and Treatment Methods: 42 patients were randomly divided into 2 groups: ① Group A: 26 patients were treated with lumbrokinase, 600,000 U three times daily for 1 month; ② Group B: 16 patients were treated with aspirin, 0.1g everyday for 1 month.

1.4 Evaluation of Efficacy: patients were evaluated after 1 month of treatment with the following criteria: ① Treatment was considered effective if dialyzed blood flow is ≥ 200ml/min and dialysis could be maintained, fistula pulsation and murmur were strong or stronger, colour Doppler ultrasound re-examination showed good fistula blood flow, and mural thrombus was no longer apparent ② Treatment was considered ineffective if dialyzed blood flow was ≥ 200ml/min but could not be maintained, fistula pulsation and murmur were weak, no significant improvement in fistula blood flow and thrombus was still present on colour Doppler ultrasound re-examination.

1.5 Statistic Methods: All statistical data were processed by statistic software SPSSI 3.0. Data are presented as $\bar{x}\pm s$ and analyzed by t-test, while categorical data are analyzed by χ^2 -test.

2. RESULTS

2.1 Comparison of Efficacy for the 2 Groups: Pre-treatment data are showed in Table 1, which shows no significant difference in all parameters between the 2 groups. Table 2 shows the treatment was effective for 21 patients in Group A, with an efficacy rate of 81%; the treatment was ineffective in 5 patients because the dialysis requirement was not met. In Group B the treatment was effective in 7 patients, with an efficacy rate of 44%; the treatment was considered ineffective in 9 patients. The differences between both groups were statistically significant (χ^2 =4.56, P <0,05). In addition, the differences in FBG, Hb, Hr-CRP, Kt/V between the 2 groups after treatment were also statistically significant. Please refer to Table 3.

Table 2. Comparison of Efficacy between the Two Groups after Treatment.

Group	Number of Cases	Effective		Ineffective	
		Number of Cases	%	Number of Cases	%
A	26	21	81	5	19
B	16	7	44	9	56

Table 3. Comparison of Post-Treatment Parameters between the Groups ($\bar{x}$±s)

Group	Number of Cases	FBG (g/L)	Hb(g/L)	Hr-CRP (g/L)	Kt/V
A	26	3.1±0.4	94±14	2.4±1.2	1.29±0.11
B	16	3.4±0.5	83±12	3.8±1.4	1.19 ±0.08
t value		2.24	2.46	3.47	3.11
p value		<0.05	<0.05	<0.01	<0.01

2.2 Adverse Effects of Medication: 2 patients experienced mild epigastric burning sensation and discomfort after taking aspirin. The symptoms improved after anti-acid regimen was added, and patients were able to continue and tolerate aspirin treatment. Lumbrokinase was tolerated well by patients. No hemorrhage in skin, mucus and digestive tract was noticed in either group.

3. DISCUSSION

At present the clinical guidelines of International and American Societies of Nephrology both recommend arteriovenous fistula as the preferred treatment option for patients without cardiac insufficiency or blood vessel limitation. With the advancement in dialysis technology, ecomonics, and the society in general, the survival time for dialysis patients has been prolonged. As a result, how to prevent the loss of effective dialysis access has becomes much more important. AV fistula thrombosis caused by increased blood viscosity, dehydration secondary to over-dialysis, compression on fistula, hypotension, and poor technique in accessing the fistula are all leading causes of fistula stenosis and/or obstruction. Hai-Bo Yang and Han-Min Wang had satisfactory results using urokinase and low-molecular weight heparin combination to treat complete obstruction of AV fistula. For patients with incomplete fistula obstruction secondary to thrombosis, while the effectiveness of urokinase was excellent, the risk of systemic hemorrhage would also be increased with repeated dosing due to urokinase's lack of specificity for fibrin protein. Some dialysis centers chose to use aspirin and dipyridamole instead with minimal side effects, but the effectiveness in thrombus resolution was less than ideal. Today, the treatment for thrombosis includes surgical removal, Fogarty catheter thrombectomy, and thrombolytic therapy, with varied success rates in the literature. A relatively new treatment technique for AV fistula thrombosis is high velocity pulse with jet-acceleration and suction (高速脈衝式噴射加速加回吸). However, the procedure is complicated and costly, and the recurrence rate is high. Lumbrokinase is an extract from earthworms, and the medicinal use of earthworms was already recorded in the traditional medical textbook *Compendium of Materia Medica* (本草綱目) as early as 1596. In 1879, the French discovered that the digestive secretions of earthworms can degrade fibrin. Since 1970s scientists in China, Japan and Korea have studied the enzymatic components, physical properties and clinical applications of earthworm extracts. In 1979, Pak discovered that earthworm extract contains hydrolases that can degrade casein, gelatin, and albumin. In

1983, Mihara and others isolated a crude extract with fibrinolytic activity from *Lumbricus rubellus*, and named it lumbrokinase. Ever since, earthworm fibrinolytic enzymes (EFE), serine endoprotease, phospholipid kinase from earthworms have also been isolated. Of all, EFE has a stronger fibrinolytic activity and is suitable for the prevention of thrombosis and thromboembolic diseases; it is thus the main active component of lumbrokinase. The anti-thrombotic effect of EFE is by direct and indirect (via plasminogen activation) hydrolysis of fibrin, and simultaneously lowering plasma fibrinogen level. It has the advantages of strong thrombolytic effect and low/minimal side effects (such as hemorrhage). At present, lumbrokinase has been widely used in the treatment of cerebrovascular thrombosis and coronary heart disease, and the effectiveness has been excellent. However, the use of lumbrokinase in improving AV fistula function of uremic patients on dialysis has not been reported. Our research shows that lumbrokinase can significantly improve the blood blow of AV fistula patient with partial obstruction secondary to thrombosis, and maintain the adequacy of dialysis. In addition, as an oral format lumbrokinase possesses the advantages of convenient dosing and minimal side effects. Since oral medications take longer to exert their effectiveness and lumbrokinase injectables are not yet available, urokinase may be a more appropriate choice for patients with a complete obstruction of AV fistula. For patients with partial obstruction of the AV fistula, lumbrokinase not only can dissolve the thrombus that is already formed via its stronger fibrinolytic effect, but it can also prevent thrombosis recurrence by lowering fibrinogen level in the blood. Therefore, lumbrokinase is safe and highly efficacious for treating patients with an incomplete thrombosis of AV fistula.

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