

The Effect of Lumbrokinase on the Fibrinogen Increase Following Percutaneous Coronary Intervention

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[ABSTRACT] OBJECTIVE: To investigate the effect of lumbrokinase on the fibrinogen increase following percutaneous coronary intervention (PCI). METHOD: 65 PCI candidate patients were randomly divided into 2 groups: control group (n = 27) and lumbrokinase group (n = 38). Standard therapy was given to the control group since 1 week pre-PCI, and in the lumbrokinase group, additional lumbrokinase was administered. Fibrinogen concentration was measured in both groups at baseline, 1 day pre-PCI, 1 day post-PCI and 1 week post-PCI, respectively. RESULTS: In control group, the level of fibrinogen at 1 week post-PCI was higher than that of baseline level (4.83 ± 1.06 vs $3.86 \pm 0.73\text{g}^*\text{L}^{-1}$, $P < 0.01$), and the difference was also statistically significant if compared with that of lumbrokinase group at the same period (4.83 ± 1.06 vs $4.16 \pm 0.87\text{g}^*\text{L}^{-1}$, $P < 0.05$). In lumbrokinase group, there was no statistically difference of fibrinogen concentration between baseline level and that of 1 week post-PCI (4.16 ± 0.87 vs $3.98 \pm 0.58\text{g}^*\text{L}^{-1}$, $P > 0.05$). CONCLUSION: PCI can result in fibrinogen increase; pre-intervention lumbrokinase administration is beneficial to prevent such an unfavorable reaction.

[KEY WORDS] lumbrokinase; percutaneous coronary intervention; fibrinogen

Fibrinogen (Fg) is a component of the coagulation cascade, and is reported to be intimately associated with restenosis and complications after percutaneous coronary intervention^[1, 2]. On the other hand, percutaneous coronary intervention (PCI), itself could cause plasma Fg to rise^[3, 4]. Currently, there are only few clinical effective treatments for Fg-related blood diseases. This study investigates the influences of lumbrokinase on post-PCI elevation of Fg.

MATERIAL AND METHOD

1. SUBJECTS

65 subjects with coronary angiographic confirmation of pathological changes and scheduled dates for PCI were chosen for the study. The average age was (61 ± 9.5) years, with 47 males and 18 females. Sixteen patients had stable angina pectoris, 37 patients had acute coronary syndrome (ACS) including unstable angina pectoris (UAP) and acute myocardial infarction. Elimination standard: ① Hemorrhage and hemorrhage tendency; ② Allergies; ③ History of Post-PTCA restenosis or had received thrombolytic therapy within 2 weeks; ④ Diabetics with poor blood sugar control; ⑤ Severe kidney, liver or hematological impairment. Patients randomly divided into lumbrokinase treatment group (38 patients) and control group (27 patients).

2. INTERVENTION

Treatment started one week prior to PCI till one week post-PCI. Control group used conventional aspirin treatment (HuNan Nam Kwong Pharmaceutical Co., Ltd, lot no. 20030510) 150-300mg, qd. Heparin may be used during procedure if necessary, but no urokinase nor batroxobin was used. Lumbrokinase group received Baiao Lumbrokinase (Beijing Baiao Pharmaceutical Co. Ltd, lot #20030804, 0.23g/capsule), two capsules tid, in addition to the above conventional treatment.

3. BLOOD SAMPLES AND PLASMA Fg LEVEL EXAMINATION

Blood samples were drawn to evaluate plasma Fg levels (used Japan Sysmex Company's CA-1500 automatic hemagglutination analysis device, PT-algorithm) one week prior to treatment, one day prior to treatment, one day after treatment and one week after treatment.

4. STATISTICAL METHODS

SPSS software was used and results were expressed by $\bar{x} \pm s$. Analysis of variance was used to compare the difference between pre-treatment and post-treatment. If there were any significant differences, Student-Newman-kouls was used to analyze the results. Paired *t* test was used for comparison of lumbrokinase group and control group.

RESULTS

Results for both groups' plasma Fg one week pre-PCI, one day pre-PCI, one day post-PCI and one week post-PCI are shown in table 1.

Table 1, Comparison of plasma Fg level before and after PCI in 2 groups, $\bar{x} \pm s$, $g \cdot L^{-1}$

Group	<i>n</i>	One week prior	One day prior	One day after	One week after
Treatment	38	3.98 ± 0.58	3.93 ± 0.76	4.12 ± 0.98	4.16 ± 0.87
Control	27	3.86 ± 0.73	3.87 ± 1.02	4.09 ± 0.86	4.83 ± 1.06 ^{ab}

a: compared with one week prior, $P < 0.05$; b: compared with control group, $P < 0.01$

Prior to treatment, there was no significant difference in plasma Fg level between both groups. One day post-treatment, plasma Fg level had increased in both groups, but non-significantly. One week post-treatment, plasma Fg level in control group had increased substantially and the difference was statistically significant when compared with baseline ($P < 0.01$). The between-group difference in the one week post-PCI Fg level was also significant ($P < 0.05$). The one week post-PCI plasma Fg level in lumbrokinase group had increased mildly, and the difference from the baseline was not statistically significant.

DISCUSSIONS

Plasma Fg is a glycoprotein synthesized from the liver. When it loses fibrinopeptide A and B, it turns into fibrin. Epidemiology research demonstrated that the occurrence, development and prognosis of atherosclerosis (AS) are closely related to plasma Fg level. Fg is an acute phase protein, and during PCI injuries to the coronary intima and media would cause inflammation and may activate white blood cells causing it to release Interleukin-6. This stimulates the liver cells to synthesize and to secrete Fg, which results in an increase in plasma Fg levels^[3]. The result of this study showed that plasma Fg level increased significantly one week post-PCI, which concurs with available literature^[4]. Montalescot, *et al*^[5] had suggested that plasma Fg elevation is a strong predictor of restenosis after PTCA. Many studies have also confirmed that the increase in plasma Fg level is closely related to post-PCI adverse cardiovascular events.^[1,2,6] The mechanism of how plasma Fg increase leads to post-PTCA restenosis or cardiovascular

complications is unclear. It may be related to the formation of fibrin, platelet aggregation, inflammation response, and/or muscular smooth muscle cell proliferation^[7]. Kawasaki, *et al*^[8] used carotid ligation model in mice to demonstrate that fibrinogen reduction could minimize the formation of neointima, suggesting the presence of fibrinogen is crucial to the development of neointima. To date, there has been limited clinical research on the prevention of post-PCI plasma Fg rise.

Lumbrokinase is a proteolytic enzyme extracted from earthworm, with a molecular weight of $(21-65) \times 10^3$. It contains multiple enzymes and has properties similar to tissue plasminogen activator (t-PA); it is categorized as a plasminogen activator and a fibrinolytic agent^[9]. Fan, *et al*^[10] demonstrated certain components of lumbrokinase may be absorbed as a whole protein into the bloodstream from the intestines. Animal and clinical studies have proven that it could decrease fibrin and fibrinogen levels and is effective in treating coronary heart diseases^[11]. This study used lumbrokinase as an intervention for pre-PCI surgery patients and results showed that it decreased the post-PCI plasma Fg rise, which may be clinically significant in the prevention of post-PCI restenosis and complications. Still, long term efficacy of lumbrokinase needs to be validated through long-term follow-up and further clinical studies.

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REFERENCE

1. Germing A, von Dryander S, Machraoui A, *et al*. Hyperfibrinogenemia increases the risk of cardiac events after coronary artery stenting [J]. *Heart Vessels* 2000; 15(6): 263-267.
2. Otsuka M, Hayashi Y, Ueda H, *et al*. Predictive value of preprocedural fibrinogen concerning coronary stenting [J]. *Atherosclerosis* 2002;164(2): 371-378.
3. Fu, Mingde. Fibrinogen and cardiovascular disease. [J]. *Advances in Cardiovascular Disease* 1994;15(4):197-201.
4. Ge, Zhiping, Guo, Jingxuan. PTCA/STENT patients Fibrinogen and Antithrombin - III changes [J]. *Chinese Journal of Cardiovascular Medicine* 2002;7(3):166-167.
5. Montalescot G, Ankri A, Vicant E, *et al*. Fibrinogen after coronary angioplasty as a risk factor for restenosis [J]. *Circulation* 1995;92(1): 31-38.
6. Rahel BM, Visseren FL, Suttorp MJ, *et al*. Preprocedural serum levels of acute-phase reactants and prognosis after percutaneous coronary intervention [J]. *Cardiovasc Res* 2003;60 (1): 136-140.
7. Schillinger M, Exner M, Mlekusch W, *et al*. Fibrinogen predicts restenosis after endovascular treatment of the iliac arteries [J]. *Thromb Haemost* 2002;87 (6): 959-965.
8. Kawasaki T, Dewerchin M, Lijinin HR, *et al*. Mouse carotid artery ligation induces platelet-leukocyte-dependent luminal fibrin, required for neointima development [J]. *Circ Res* 2001;88 (2): 159-166.

9. Cheng, Aizheng, Wang, Xinde, Xu, Zhongbao, *et al.* Lumbrakinase multi-center, double-blind, placebo-controlled treatment of ischemic cerebrovascular disease laboratory results [J]. *Chinese Journal of New Drugs* 2002;11 (1): 82-84.
10. Fan Q, Wu C, Li L, *et al.* Some features of intestinal absorption of intact fibrinolytic enzyme III – 1 from *Lumbricus rubellus* [J]. *Biochim Biophys Acta* 2001;1526(3): 286-292.
11. Wang, Changshu, Gu, Tongyuan, Li, Ming, *et al.* The impact and significance of lumbrakinase vasoactive substances in patients with coronary heart disease [J]. *Chinese Journal of Clinical Pharmacy* 2002;11 (3): 147-150.