Clinical Observations of Lumbrokinase Intervention in 60 Coronary Heart Disease Patients with Aspirin Resistance

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Clinical trials have shown that aspirin may reduce the incidence of thromboembolism in patients with cardiovascular, cerebrovascular and peripheral vascular disease by 23%[1]. However, thromboembolism still occurred in patients who were compliant with therapeutic dosage of aspirin. For those patients, increasing the dosage of aspirin did not achieve the therapeutic and preventive goals; instead it resulted in more adverse reactions. This is called "aspirin resistance, AR". In addition, platelet aggregation in these patients remains high while on aspirin, and AR intervention has become a central issue in the primary and secondary prevention of coronary heart disease. This study focused on lumbrokinase's influence on platelet aggregation in coronary heart disease (CHD) patients and its potential as an AR intervention.

1. SUBJECTS AND METHOD

1.1 Subjects   In 2006-2007 our cardiac care unit admitted 260 CHD patients with the age varying from 50-83 years old (average age was 68.03±13.50). All patients had taken 100mg/d of oral aspirin for more than one week. Using turbidimetry to measure platelet aggregation 60 AR patients were screened out for the study. All were determined to be free of hematological conditions such as hemorrhagic diseases, malignant tumors, active peptic ulcer and chronic obstructive pulmonary disease.

1.2 Intervention   All patients were stopped of aspirin administration for two weeks, then were randomly assigned into aspirin + lumbrokinase group and lumbrokinase group with 30 patients in each group. Aspirin + lumbrokinase group had 16 males and 14 females between 52-83 years of age (average age was 68.10±14.70). Each patient was given aspirin 100mg/d + lumbrokinase enteric capsules 600,000IU three times per day. Lumbrokinase only group had 13 males and 17 females between 53-82 years of age (average age was 62.31±17.61). They were given lumbrokinase enteric capsules 600,000IU, three times per day. Platelet aggregation was re-tested after one month.

1.3 Platelet aggregation test   5mL of venous blood was drawn and mixed with 3.8% sodium citrate anticoagulant. Within 30 minutes it was centrifuged at 800r/min for 5 minutes and platelet-rich plasma was isolated. It was further centrifuged at 3000r/min for 5 min and platelet-poor plasma was isolated. Employing turbidimetry, the test had to be completed within two hours of the blood draw using platelet aggregating function machine (model LBY2NJ2) made by Beijing Percil Group.

1.4 AR Standard[2]   Average platelet aggregating function $\geq 70\%$ when induced with 10mmol/L of adenosine diphosphate (ADP) and $\geq 20\%$ when induced with 0.5mmol/L of arachidonic acid (AA).

1.5 Statistical Methods   SPSS 13.0 software was used to perform paired t tests. Results were expressed by $\bar{x} \pm s$.

2. RESULTS

There was no significant difference between both groups in baseline ADP- and AA-induced platelet aggregations ($P>0.05$). There was a significant difference in ADP- and AA-induced platelet aggregation after intervention in both groups ($P<0.05$), and there was a significant difference in platelet aggregation between the two groups ($P<0.01$), as shown in table 1.

Table 1 Comparison of Plt aggregation before and after intervention ($\bar{x} \pm s$, n=30, %)

Group	ADP		AA	
	Baseline	After intervention	Baseline	After intervention
Aspirin + lumbrokinase	70.66 ± 6.79	60.28 ± 6.73[1)]	24.12 ± 6.51	12.24 ± 3.72[1)]
Lumbrokinase	71.02 ± 1.15	65.32 ± 7.11[1)2)]	24.38 ± 18.25	16.97 ± 8.67[1)2)]

Compared with baseline: 1) $P<0.05$
Compared with aspirin + lumbrokinase group: 2) $P<0.01$

3. DISCUSSION

Meta analysis of clinical trials shows that aspirin can decrease myocardial infarction and coronary heart disease mortality by 26% in patients whose estimated coronary artery incidence is less than 1%, by 20% in patients whose estimated coronary artery incidence is between 1%-3%, and by 35% in patients whose estimated coronary artery incidence is over 3% [3]. However, due to biochemical individuality some patients did not benefit from taking standard doses of aspirin because the platelet aggregating function was not impacted, namely aspirin resistance (AR). As a result, some patients were not protected and thromboembolism still occurred. A number of studies have shown that AR was an independent predictor in cardiovascular events [4,5], and it has become a new challenge for clinicians worldwide. A large number of foreign scholars, such as Helgason *et al* [6] and Gum *et al* [6], have conducted clinical trials and clinical observation specifically into AR mechanisms and its influencing factors, and have proposed various corresponding therapeutic strategies.

Lumbrokinase was a water-extract first isolated from Lumbricidae earthworms by Dr. Mihara in 1983. It has direct fibrinolytic and plasminogen activating effects, and has been used as an anticoagulant and an antithrombolytic in the treatment of cardiovascular, cerebrovascualar and peripheral vascular diseases. Our results indicated that lumbrokinase can inhibit platelet function and improve AR. Lumbrokinase can inhibit platelet activation and aggregation at multiple sites and through multiple mechanisms, which appear to be independent of cyclooxygenase-1 inhibition and have a synergistic anti-platelet effect when combined with aspirin. Therefore, lumbrokinase may be used in AR intervention and improve clinical prognosis of patients. Long term efficacy of the combined use of aspirin with lumbrokinase still needs to be validated through clinical studies with larger samples.

4. REFERENCES

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