Phase III Clinical Trial Summary of Boluoke Capsule in Treating Ischemic Cerebrovascular Disease

Cerebral infarct is one of the most commonly seen cerebrovascular diseases; it has an abrupt onset, a high morbidity and affects people's psychosomatic health mostly. Up to date, no oral medicine with the effect of tissue-typed plasminogen activator (t-PA) has been found, though there are many drugs for treatment of cerebral infarct. Boluoke capsule is a multi-component pure-natural medicine extracted from earthworms, and includes at least two kinds of enzymes: plasminogen activator and plasmin.

Since 1990, affiliated Xuanwu Hospital of Capital Medical College, Jiangxi Provincial People's Hospital and No.2 Affiliated Hospital of Jiangxi Medical College have studied the clinical manifestations and the blood rheologic changes in 453 patients with ischemic cerebrovascular disease by randomized double-blinded method. The results indicated that the total effective rate is 93.73% and the significant response rate is 73.60%. Organized by Chinese Medical Society, a collaborative group of 16 hospitals has performed a phase III clinical trial of Boluoke (lumbrokinase) capsule in treating ischemic cerebrovascular disease from June 1992 to December 1993. Totally, 1560 patients were studied according to "the censorship and approval regulations of new drugs "to further verify the clinical efficacy and investigate the adverse effects. The total effective rate is 88.21% and the significant response rate is 68.91 %. Several hospitals also studied the changes in blood rheology. These results all showed that Boluoke capsule is a promising new anti-thrombotic agent with a definite efficacy and no obvious toxic/adverse effects, worthy of extensive applications.

Patients and Methods

1) Case selection: All cases in our trial were diagnosed according to the Diagnostic Criteria of the Second National Symposium on Cerebrovascular Diseases (China). They all had various degrees of hemiplegia and infarct foci shown on CT scan. The clinical efficacy of 1560 patients was investigated according to the unified therapy protocol. There were 1001 males and 559 females; the mean age was 52.38 +/- 8.13. The majority of patients took Boluoke capsule within one month from the onset (see Table 1).

2) Administration method: Two Boluoke capsules were taken orally half an hour before meal each time, three times a day for 21 days. During this period, other drugs that can dilate cerebral vessels, affect blood rheology and deoppliate the blood vessels were prohibited.

3) Appraisal of the clinical efficacy: The clinical neural deficit before and after the administration was scored by “The score criteria of clinical nervous function deficiency degree in patients with stroke” passed by the Second National Symposium on Cerebrovascular Diseases. Score 0-15 was defined mild; score 16-30 moderate and score 31-45 severe.” Beijing score criteria of clinical efficacy in patients with stroke was adopted in the final appraisal of efficacy (score declined more than 90% was defined basically recovered; score declined from 46% to 89% significantly improved, score declined from 18% to 45% improved; score declined less than 18% or increased less than 18% no changed and deficiency score increased more than 18% deteriorated). Some hospitals also studied the changes in fibrinogen and euglobulin lysis time. The blood was sampled at 8:00-8:30AM and the sampled site was ante-cubital vein.

4) Data processing: t-test and X² test were applied with TheStatistic Software of The Capital Medical College Mathematics Faculty. All data were processed by IBM-PC.
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Results
The results indicated that the total effective rate was 88.21 %, and the significant response rate was 68.91 % (see Table 2). The results of those hospitals performed fibrinogen and euglobulin lysis time tests showed that fibrinogen and euglobulin lysis time were significantly reduced and the blood rheology was significantly changed after using Boluoke capsule (see Table 3 and Table 4). The adverse effects were very rare (see Table 5).

Discussion
Using earthworms as medicine was recorded in the Chinese traditional medicine masterpiece entitled Ben Cao Gang Mu (The Catalog of Herbal Medicine). It was deemed that the earthworm has the nature of warding off “wind” and unblocking the body’s meridians and channels, and can be used to treat hemiplegia or pain syndromes due to “evil” blockages. In the 1983’s international symposium of thrombosis and hemostasis, a Japanese scholar reported that the extract of earthworms had the effect of thrombolysis and denominated it “Lumbrokinase”. In 1986, Korea Drugs Administration Bureau approved the manufacture of Lumbrokinase. Since then this enzyme has come into the market of many countries abroad and has been applied extensively. The trade name of Lumbrokinase in Hong Kong is “the Hart of Dragon”. Boluoke capsule is a multi-component enzyme preparation and has the analogous component of t-PA, which can lyse the thrombi in vivo. There are at least two mechanisms: one is that Boluoke has the effect of plaminogen activator and the other is that it has special affinity to fibrin and thus degrades fibrin rapidly.

Because Boluoke capsule is an enzyme preparation, it is best taken half an hour before meals in order to reduce the effect of gastric acid. The low gastric volume and gastric acid enables the enzyme to be transported to intestinal tract as soon as possible.

In recent years, with further study on bioengineering technology, how large molecules such as protein penetrates the biomembrane has been extensively investigated. Fifteen years ago, Dr. Adiw in US suggested that protein could be absorbed in vivo as peptides. In 1989, a Japanese professor verified this point by experiment. Many studies have found the general phenomena of trans-membrane transportation of protein and have elucidated theoretically that protein and enzyme can be transported transmembranely to all parts of the body and exert their normal physiological functions. Biophysics Institute of Chinese Academy of Sciences has made animal models to verify the thrombolysis effect of Boluoke. 125I-Labelled fibrinogen was intermingled when the thrombi were formed on the rabbit model for acute pulmonary artery embolism. Then Boluoke was given via duodenum and radioactive intensity was measured at the time of half-an hour, 1 hour, 2 hours and 5 hours post-administration. The result demonstrated that the radioactivity significantly increased 3 hours and 5 hours after administration, which means the effect of thrombolysis was significant 4-8 hours after administration. A Japanese professor also reported that the replicated venous thrombi of Beagle dog were dissolved overtly after oral administration of Lumbrokinase.