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 rheology 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 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 deoppilate 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 finalappraisal 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 X^2 test were applied with TheStatistic Software of The Capital Medical College Mathematics Faculty. All data were processed by IBM-PC.

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(cont'd)

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. Adiwl 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. ^{125}I-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.

General Information of the Patients
Table 1

	Hospital	No. of Patients			Age	Condition of the Illness			Dur. of Illness Bef.	Pretreatment
		Total	Male	Female		Mild	Moderate	Severe	Trtmt (# of Days)	Score
1	Beijing Xuanwu Hospital	210	126	84	61.51 ± 2.54	110	85	15	2.32 ± 2.54	17.16 ± 8.23
2	No. 2 Affiliated Hospital of Jiangxi Medical College	171	112	59	63.3 ± 9.13	89	73	9	3.61 ± 3.17	16.51 ± 7.11
3	Jiangxi People's Hospital	130	87	43	64.35 ± 9.83	105	20	5	26.72 ± 78.22	10.42 ± 7.50
4	Zhongshan Affiliated Hospital of Shanghai Medical College	50	27	23	66.49 ± 8.49	24	23	3	31.35 ± 37.59	15.51 ± 7.42
5	Affiliated Hospital of Tianjin Medical College	33	26	7	61.73 ± 9.38	10	17	6	26.72 ± 78.22	19.15 ± 11.36
6	Affiliated Hospital of West China Medical College	60	40	20	60.14 ± 7.78	28	27	5	6.10 ± 6.70	18.20 ± 9.15
7	Nanjing Brain Hospital	43	29	14	63.4 ± 8.78	33	7	3	13.74 ± 21.27	8.84 ± 9.75
8	Sichuan People's Hospital	50	39	11	66.2 ± 9.99	26	21	3	9.74 ± 23.76	16.2 ± 8.86
9	Affiliated Hospital of Chongqing Medical College	42	25	17	63.91 ± 9.29	29	12	1	6.21 ± 6.60	10.38 ± 8.77
10	No. 731 Hospital of Space Ministry	183	124	59	58.3 ± 9.52	120	44	19	7.23 ± 28.72	15.73 ± 8.89
11	No. 1 Handan Hospital	128	77	51	59.41 ± 8.67	95	31	2	2.72 ± 3.03	12.16 ± 7.35
12	Affiliated Hospital of Handan Second Medical School	97	53	44	62.00 ± 6.50	48	48	1	1.83 ± 2.17	16.67 ± 7.77
13	Handan Central Hospital	83	55	28	59.10 ± 8.26	46	33	4	3.33 ± 5.94	16.23 ± 8.14
14	Central Hospital of Handan Mineral Bureau	48	30	18	64.15 ± 5.28	28	20	0	1.50 ± 1.01	15.25 ± 7.13
15	An'yang People's Hospital	132	87	45	50.26 ± 8.07	80	42	10	2.97 ± 3.77	15.04 ± 9.87
16	Tangshan Workers' Hospital	100	64	36	61.31 ± 8.04	68	26	6	8.92 ± 10.15	13.54 ± 8.97
	Total	1560	1001	559	62.38 ± 8.13	939	529	92	9.93 ± 14.20	13.59 ± 8.20

Clinical Response to Boluoke® (1560 cases total)
Table 2

	Hospitals	# of Patients	Basically Recovered	Significantly Improved	Improved	No Change	Significant Response Rate	Total Effective Rate
1	Beijing Xuanwu Hospital	**210**	28 (13.33%)	98 (46.67%)	44 (20.95%)	40 (19.05%)	126 (60%)	**170 (80.95%)**
2	No. 2 Affiliated Hospital of Jiangxi Medical College	**171**	64 (37.43%)	59 (34.50%)	37 (21.64%)	11 (6.43)	123 (71.93%)	**160 (93.57%)**
3	Jiangxi People's Hospital	**130**	17 (13.08%)	51 (39.23%)	42 (32.31%)	20 (15.38%)	68 (52.31%)	**110 (84.62%)**
4	Zhongshan Affiliated Hospital of Shanghai Medical College	**50**	2 (4.00%)	16 (32%)	25 (50%)	7 (14%)	18 (36%)	**43 (86%)**
5	Affiliated Hospital of Tianjin Medical College	**33**	4 (12.12%)	14 (42.42%)	10 (30.3%)	5 (15.15%)	18 (54.55%)	**28 (84.85%)**
6	Affiliated Hospital of W. China Medical College	**60**	8 (13.33%)	25 (41.67%)	15 (25%)	12 (20%)	33 (55%)	**48 (80%)**
7	Nanjing Brain Hospital	**43**	21 (48.84%)	12 (27.91%)	4 (9.3%)	6 (13.95%)	33 (76.74%)	**37 (86.05%)**
8	Sichuan People's Hospital	**50**	4 (8%)	34 (68%)	9 (18%)	3 (6%)	38 (76%)	**47 (94%)**
9	Affiliated Hospital of Chongqing Medical College	**42**	18 (42.86%)	13 (30.95%)	4 (9.52%)	7 (16.67%)	31 (73.81%)	**35 (83.33%)**
10	No. 731 Hospital of Space Ministry	**183**	87 (47.54%)	76 (41.53%)	7 (3.83%)	13 (7.1%)	163 (89.07%)	**170 (92.9%)**
11	No. 1 Handan Hospital	**128**	19 (14.84%)	73 (57.03%)	20 (15.63%)	16 (12.5%)	92 (71.88%)	**112 (87.5%)**
12	Affiliated Hospital of Handan 2nd Medical School	**97**	22 (22.68%)	44 (45.36%)	23 (23.71%)	8 (8.25%)	67 (69.07%)	**89 (91.75%)**
13	Handan Central Hospital	**83**	26 (31.33%)	41 (49.40%)	8 (9.64%)	8 (9.64%)	67 (80.72%)	**75 (90.36%)**
14	Central Hospital of Handan Mineral Bureau	**48**	11 (22.92%)	19 (39.58%)	11 (22.92%)	7 (14.58%)	30 (62.5%)	**41 (85.42%)**
15	An'yang People's Hospital	**132**	29 (21.97%)	71 (53.79%)	21 (15.91%)	11 (8.33%)	100 (75.76%)	**121 (91.67%)**
16	Tangshan Workers' Hospital	**100**	21 (21%)	48 (48%)	21 (21%)	10 (10%)	68 (68%)	**90 (90%)**
17	Total	**1560**	381 (24.42%)	694 (44.49%)	301 (19.29%)	184 (11.79%)	1075 (68.91%)	**1376 (88.21%)**

No. of patients that have deteriorated or died during the trial: 0% out of the 1560 cases

Fibrinogen and Euglobulin Lysis Time Changes
Table 3

	Hospital [§ P<0.05 , * P<0.01]	No. of Pts	Fibrinogen Level (mg/dl)		Euglobulin Lysis Time (Minute)	
			Before Treatment	**After Treatment**	Before Treatment	**After Treatment**
1	Beijing Xuanwu Hospital	**210**	355.86 +/- 55.98	**294.77 +/- 45.15 ***	196.89 +/- 70.24	**153.40 +/- 48.00***
2	Jiangxi People's Hospital	**130**	414.39 +/- 159.15	**356.50 +/- 103.88***	242.55 +/- 64.56	**207.85 +/- 56.54***
3	Zhongshan Affiliated Hospital of Shanghai Medical College	**50**	352.14 +/- 307.31	**208.38 +/- 138.14***	N/A	N/A
4	Affiliated Hospital of Chongqing Medical College	**42**	N/A	N/A	176. 15 +/- 40.58	**129.23 +/- 59.51§**
5	No. 731 Hospital of Space Ministry	**183**	448.47 +/- 124.91	**381.56 +/- 123.35***	194.16 +/- 71.80	**156.83 +/- 55.36***
6	No. 1 Handan Hospital	**128**	304.03 +/- 39.55	**295.78 +/- 34.35***	138.08 +/- 34.49	**119.06 +/- 24.40***
7	Affiliated Hospital of Handan Second Medical School	**97**	391.54 +/- 70.66	**311.71 +/- 61.34***	152.80 +/- 33.73	**130.30 +/- 23.81***
8	Handan Central Hospital	**83**	376.87 +/- 56.32	**323.48 +/- 58.91***	151.93 +/- 44.46	**131.37 +/- 32.95***
9	Central Hospital of Handan Mineral Bureau	**48**	358.75 +/- 82.42	**314.79 +/- 50.74***	165.81 +/- 33.99	**130.46 +/- 24.53***
10	An'yang People's Hospital	**132**	390.26 +/- 54.95	**334.25 +/- 39.67***	224.11 +/- 41.57	**214.95 +/- 42.04***
11	Tangshan Workers' Hospital	**100**	330.05 +/- 83.28	**269.88 +/- 58.89***	N/A	N/A

Blood Viscosity, Plasma Viscosity, Platelet Aggregation before and after Treatment
Table 4

	Hospital (*P<0.01, § P<0.05)	# of Pts	Whole Blood Viscosity		Plasma Viscosity		PAgT	
			Pretrtmt	After Trtmt	Pretrtmt	After Trtmt	Pretrtmt	After Trtmt
1	Beijing Xuanwu Hospital	**210**	5.60 +/- 0.59	5.18 +/- 0.54*	1.83 +/- 0.12	1.72 +/- 0.09*	67.08 +/- 17.52	46.20 +/- 14.00
2	Zhongshan Affiliated Hospital of Shanghai Medical College	**50**	7.28 +/- 1.64	6.48 +/- 1.47*	1.71 +/- 0.15	1.56 +/- 0.22*	N/A	N/A
3	Nanjing Brain Hospital	**43**	7.68 +/- 2.39	6.98 +/- 1.85 §	1.90 +/- 0.80	1.85 +/- 0.58 §	N/A	N/A
4	No. 721 Hospital of Space Ministry	**183**	9.35 +/- 2.51	8.30 +/- 1.72*	1.77 +/- 0.21	11.67 +/- 0.12*	61.14 +/- 18.12	51.70 +/- 18.89
5	No. 1 Handan Hospital	**128**	8.95 +/- 1.13	8.15 +/- 0.77*	1.81 +/- 0.11	1.70 +/- 0.08*	67.89 +/- 6.72	63.63 +/- 8.65
6	Central Hospital of Handan Mineral Bureau	**48**	6.77 +/- 0.87	6.20 +/- 0.72*	1.85 +/- 0.12	1.66 +/- 0.11*	71.25 +/- 11.33	65.06 +/- 4.75
7	Affiliated Hospital of Handan Secondary Medical School	**97**	7.02 +/- 1.27	6.02 +/- 1.21*	1.83 +/- 0.12	1.70 +/- 0.10*	70.01 +/- 7.00	64.98 +/- 5.78
8	Handan Central Hospital	**83**	7.80 +/- 1.65	6.92 +/- 1.45*	1.87 +/- 0.12	1.72 +/- 0.13*	67.11 +/- 9.59	61.28 +/- 5.2
9	An'yang People's Hospital	**132**	8.27 +/- 1.73	8.19 +/- 1.26*	1.70 +/- 0.11	1.57 +/- 0.15*	57.49 +/- 22.18	47.58 +/- 22.1
#	Tangshan Workers' Hospital	**100**	4.42 +/- 0.56	4.03 +/- 0.41*	1.69 +/- 0.14	1.00 +/- 0.09*	73.08 +/- 13.39	60.10 +/- 10.

Adverse Reaction Rates (out of 1560 cases)
Table 5

Symptoms	No. of Cases	Percentage
Skin Itching	**9**	**0.58%**
Skin Rash	**3**	**0.19%**
Nausea	**18**	**1.15%**
Out of 1,560 cases: Total Cases of Adverse Reactions	**30**	**1.92%**