Effects of Keishi-bukuryo-gan on patients with cerebro-spinal vascular disease

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Abstract

The therapeutic effects of Keishi-bukuryo-gan on the chronic stage of cerebro-spinal vascular diseases were investigated in 9 patients : two cases of vertebrobasilar insufficiency, five cases of spinal vascular lesion, and two cases of multiple lacunar infarction. In 6 of 9 cases, some clinical signs and symptoms improved considerably following the administration of Keishi-bukuryo-gan for several weeks. In these 9 patients, the changes in blood flow volume after both short-term and long-term administration, of Keishi-bukuryo-gan were evaluated by using a video-microscope system. The changes in blood viscosity following the administration of this formula were also measured with a cone-plate rotational viscometer. The results obtained in this clinical study suggest that this formula possesses the potential to improve some concomitant signs and/or symptoms in about 67% patients with chronic cerebro-spinal vascular lesions, effects which may be brought about by improvement in microcirculation as well as in blood viscosity.

Key words Keishi-bukuryo-gan (Keisi-bukuryô-gan), microcirculation, blood viscosity, "oketsu" syndrome, cerebrovascular lesion, clinical study, Cinnamomi Cortex, Poria, Moutan Cortex, Persicae Semen, Paeoniae Radix.

Abbreviations FVe, blood flow rate ; FVo, blood flow volume ; Keishi-bukuryo-gan (Gui-Zhi-Fu-Ling-Wan), 桂枝茯苓丸 ; oketsu (Yu-Xue), 瘀血.

Introduction

In daily medical practice, one of the major problems is how to manage the complaints associated with cerebro-spinal vascular diseases, such as numbness, pain, dysesthesia, disturbance of urination, and spasticity of extremities. In some patients, adequate rehabilitation and/or medications successfully relieve such complaints. In a number of cases, however, their daily activities are restricted by these complaints in spite of vigorous medical efforts. Recently, we have tried to treat such patients with traditional Kampo medicine, and we have been able to achieve considerable results.

Keishi-bukuryo-gan (Gui-Zhi-Fu-Ling-Wan) is one of the most popular Kampo formulas for treating impaired blood flow.[1,2] We have already reported that this formula possesses the potential to improve microcirculation in normal subjects.[3] The present study was undertaken in an attempt to elucidate the effects of Keishi-bukuryo-gan on patients with cerebro-spinal vascular diseases both in terms of the clinical aspects as well as the microcirculation of bulbar conjunctiva and whole blood viscosity.

Subjects and Methods

Substances : Keishi-bukuryo-gan prepared by the hospital pharmacy of the Toyama Medical and Pharmaceutical University was used in this study. One six-gram pill consisted of 3.0 grams of honey and the following five medicinal plants : Cinnamomi Cortex 0.6 g, Poria 0.6 g, Moutan Cortex 0.6 g, Persicae Semen 0.6 g and Paeoniae Radix 0.6 g.

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Patients : Nine patients admitted to the Department of Japanese Oriental Medicine, Toyama Medical and Pharmaceutical University were evaluated in this study. All of them were judged as being in the indicative condition for Keishi-bukuryo-gan. The diagnosis, contraction period, and concomitant major signs and/or symptoms of each patient are listed in Table I.

Measurement of the blood flow volume in bulbar conjunctiva : By using a video-microscope system, both the blood flow rate and internal diameter of the microvessels were measured, and then the blood flow volume was calculated mathematically. The details of this procedure were described in our previous reports.[2,3]

Measurement of whole blood viscosity : Viscosities of whole blood were measured with a cone-plate rotational viscometer (Bio-rheolizer, Tokyo Keiki Co., Ltd., Tokyo). The measurements were carried out at a shear rate of 384.0 sec^{-1} (37℃) and a cone angle of 1°38′. For calibration of the viscometer, the standard oil solution JS10 (Showa Oil Co., Ltd., Tokyo, Lot No. 10) was employed. Each apparent blood viscosity was corrected to the values of 45% of hematocrit by using the following equation[4] :

$$\log_{10}\eta_{45} = \log_{10}\eta + 0.0113\ (45 - Ht)$$

Measurement of hematocrit : The value of hematocrit was measured by the capillary high speed centrifugation method using the centrifugal separator KH-120M (Kubota Co., Ltd., Tokyo) and a micro-capillary tube (75 mm length, ELMA Co., Ltd., Tokyo).

Medication protocol in short-term study : Two or three days after admission to our department, an acute study of Keishi-bukuryo-gan administration was carried out in each patient. Following overnight fasting, from 9 : 00 a.m., blood pressure and heart rate were checked, and 10 ml of blood was taken from the cuvital vein in a plastic syringe with EDTA-2K (1.8 mg/ml) for measuring blood viscosity and hematocrit. Then the microcirculation of bulbar conjunctiva was evaluated with a video-microscope system.[2,3] After the video-recording, they were administered 6.0 grams of Keishi-bukuryo-gan with 200 ml of hot water (37℃). Following one hour of bed rest, blood pressure and heart rate were checked, blood samples were taken again, and then microcirculations of the bulbar conjunctiva were re-evaluated.

Medication protocol in the long-term study : Following the acute study, the patients were started on a constant regimen of Keishi-bukuryo-gan (six-grams, t.i.d.) lasting about five weeks, and changes in their signs and/or symptoms were

Table I Patient profiles.

Case No.	Sex	Age	Diagnosis	Contraction period	Signs and/or symptoms
1	Female	63	Vertebrobasilar insufficiency	10 months	recurrent vertigo** drop attack**
2	Male	45	Anterior spinal artery syndrome	3 months	Brown-Sequard syndrome at Th. 7th dysuria,** spastic paraparesis,* hypesthesia*
3	Male	49	Spinal intermittent claudication	1 year 8 months	intermittent claudication** with spastic paraparesis**
4	Male	62	Multiple lacunar infarction	4 years 9 months	pseudobulbar palsy Parkinsonism : speech,* gait*
5	Male	62	Vertebrobasilar insufficiency	2 months	Wallenberg syndrome : bulbar palsy,** cerebellar ataxia,* hypesthesia*
6	Male	67	Multiple lacunar infarction	3 years 2 months	right hemiparesis,** spastic gait,* dysesthesia in rt. upper extremities*
7	Female	48	Anterior spinal artery syndrome	2 years 1 month	spastic paraparesis, dysesthesia and pain in bil. lower extremities
8	Male	61	Spinal vascular insufficiency	1 year 5 months	dysesthesia in bil. lower extremities* weakness in bil. lower extremities
9	Male	63	Spinal vascular insufficiency	6 months	dysesthesia and pain in bil. lower extremities

Note : The chief complaints of each patient are underlined. * : Improved, ** : Markedly improved signs. Cases No. 1–6 are the response group, and cases No. 7–8 are the non-response group.

evaluated clinically. After that period, microcirculation, blood viscosity, blood pressure and pulse rate were re-evaluated at about 9 : 00 a.m. after overnight fasting. The pharmacodynamics of this formula has not been clarified yet, therefore in this study 9 : 00 a.m. was adopted as a standard time of the evaluation.

Results

Changes in blood flow rate and blood flow volume after the Keishi-bukuryo-gan administration

Figs. 1 and 2 comparatively show the changes in blood flow in the microcirculations of bulbar

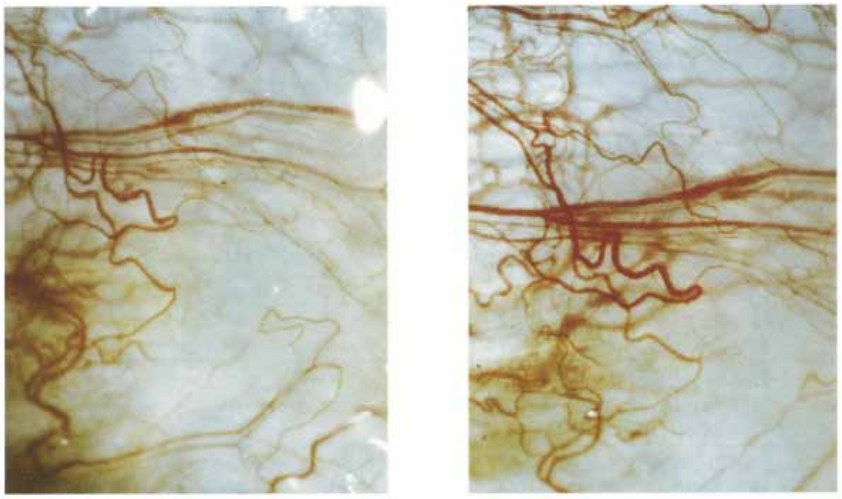

Fig. 1　Photomicrographs of the microvessels of bulbar conjunctiva showing increased blood flow after the oral administration of Keishi-bukuryo-gan.
Left : before, Right : after one hour of administration of the test drug. Case No. 3 in Table I (×30).

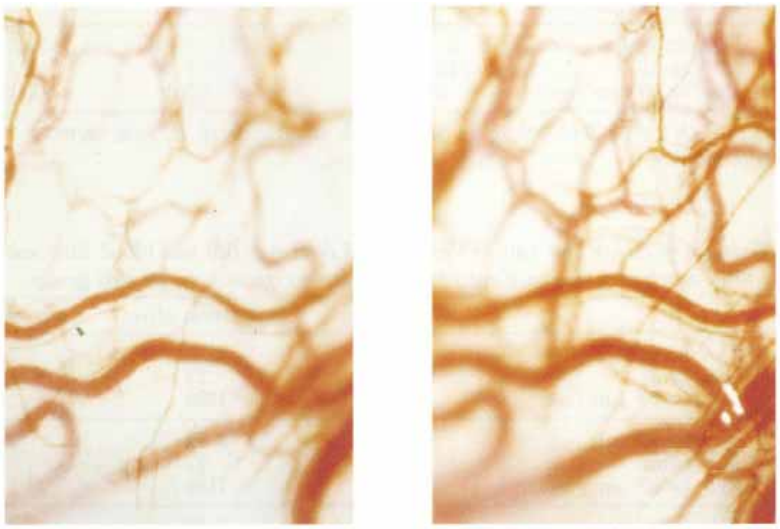

Fig. 2　Photomicrographs of the microvessels of bulbar conjunctiva from a TV monitor showing vasodilatation and increased blood flow in the capillary bed.
Left : before, Right : after one hour of administration of the test drug. Case No. 2 in Table I (×175).

conjunctiva before and after one hour of Keishi-bukuryo-gan administration.

Following about five weeks administration of Keishi-bukuryo-gan, 6 of 9 cases responded well to this drug and 3 cases did not show remarkable changes. The results obtained in each of the above in both the short-term and long-term studies are listed in Tables II and III, respectively. In the group which responded, the mean blood flow volume was seen to increase about 130% in both studies when compared with the pre-administration level. The group with no response, on the other hand, showed no remarkable changes in these parameters. Table IV shows the changes in blood pressure and heart rate in the group with response evaluated for each checkpoint, and indicates no significant changes between before and after the Keishi-bukuryo-gan administration.

Table II Changes in blood flow rate (FVe), internal diameter (Id) and blood flow volume (FVo) after administration of Keishi-bukuryo-gan in the responded group.

Case No.		Before	Short-term effect	Long-term effect
1	FVe (mm/sec)	3.20	4.40	4.18
	Id (μm)	19	19	19
	Fvo ($\times 10^3$ μm^3/sec)	907	1247	1185
2	FVe (mm/sec)	2.00	2.80	2.62
	Id (μm)	13	15	15
	Fvo ($\times 10^3$ μm^3/sec)	265	495	463
3	FVe (mm/sec)	2.20	2.67	2.80
	Id (μm)	19	19	19
	Fvo ($\times 10^3$ μm^3/sec)	623	757	793
4	FVe (mm/sec)	2.50	4.35	3.80
	Id (μm)	19	19	19
	Fvo ($\times 10^3$ μm^3/sec)	708	1233	1077
5	FVe (mm/sec)	2.73	3.00	3.20
	Id (μm)	15	15	15
	Fvo ($\times 10^3$ μm^3/sec)	482	530	565
6	FVe (mm/sec)	1.49	2.20	2.30
	Id (μm)	27	23	23
	Fvo ($\times 10^3$ μm^3/sec)	853	914	955
mean±S.D.	FVe (mm/sec)	2.35±0.54	3.24±9.84*	3.15±0.60**
	Id (μm)	18.3±4.38	18.3±2.75	18.3±2.75
	Fvo ($\times 10^3$ μm^3/sec)	640±219	863±301*	840±261**

Note : * : $p<0.05$, ** : $p<0.01$ before vs. short-term effect, before vs. long-term effect, respectively.

Table III Changes in blood flow rate (FVe), internal diameter (Id) and blood flow volume (FVo) after administration of Keishi-bukuryo-gan in the non-responded group.

Case No.		Before	Short-term effect	Long-term effect
7	FVe (mm/sec)	2.55	2.50	2.52
	Id (μm)	23	23	23
	Fvo ($\times 10^3$ μm^3/sec)	1059	1038	1046
8	FVe (mm/sec)	2.22	2.86	2.75
	Id (μm)	23	23	23
	Fvo ($\times 10^3$ μm^3/sec)	922	1188	1142
9	FVe (mm/sec)	2.20	2.37	2.28
	Id (μm)	16	14	15
	Fvo ($\times 10^3$ μm^3/sec)	442	365	403

Note : Cases No. 7–9 corresponds to those of Table I.

Changes in blood viscosity after the Keishi-bukuryo-gan administration

In both acute and chronic studies on the group which responded both the apparent and corrected blood viscosities in each patient decreased significantly (Table V). The changes in blood viscosity in the acute and chronic studies exhibited a different appearance, *i.e.*, the values of blood viscosity decreased more prominently in the cases of the chronic study, except the corrected

Table Ⅳ Changes in blood pressure (BP) and heart rate (HR) after administration of Keishi-bukuryo-gan in the responded group.

Case No.		Before	Short-term effect	Long-term effect
1	BP (mmHg)	138/78	130/74	128/74
	HR (beats/min)	74	72	68
2	BP (mmHg)	136/80	130/70	132/68
	HR (beats/min)	75	70	64
3	BP (mmHg)	140/82	132/76	134/74
	HR (beats/min)	62	60	60
4	BP (mmHg)	150/88	148/84	140/80
	HR (beats/min)	70	70	68
5	BP (mmHg)	146/84	140/80	140/78
	HR (beats/min)	66	64	65
6	BP (mmHg)	154/90	148/84	140/80
	HR (beats/min)	72	68	64
mean±S.D.	BP_S (mmHg)	144.0±6.5	138.0±7.8**	135.7±4.7**
	BP_D (mmHg)	83.7±4.2	78.0±5.2**	75.7±4.2**
	HR (beats/min)	70.0±4.6	67.3±4.1*	64.8±2.7*

Note : BP : systolic/diastolic, BP_S ; systolic pressure, BP_D ; diastolic pressure.
* ; $p<0.05$, ** ; $p<0.01$ before vs. short-term effect, before vs. long-term effect.

Table Ⅴ Changes in blood viscosity after administration of Keishi-bukuryo-gan in the responded group.

Case No.		Before	Short-term effect	Long-term effect
1	Apparent viscosity	3.78 cp	3.42 cp	2.79 cp
	Hematocrit	44.0%	44.0%	39.0%
	Corrected viscosity	3.69 cp	3.55 cp	3.30 cp
2	Apparent viscosity	3.34 cp	3.11 cp	2.99 cp
	Hematocrit	40.5%	41.0%	35.0%
	Corrected viscosity	3.61 cp	3.41 cp	3.38 cp
3	Apparent viscosity	3.63 cp	3.21 cp	3.13 cp
	Hematocrit	48.0%	47.5%	46.0%
	Corrected viscosity	3.41 cp	3.06 cp	3.00 cp
4	Apparent viscosity	3.16 cp	3.06 cp	2.78 cp
	Hematocrit	35.5%	35.0%	34.0%
	Corrected viscosity	3.94 cp	3.45 cp	3.15 cp
5	Apparent viscosity	3.96 cp	3.49 cp	3.10 cp
	Hematocrit	48.5%	46.0%	40.5%
	Corrected viscosity	3.76 cp	3.31 cp	3.35 cp
6	Apparent viscosity	3.43 cp	3.20 cp	3.04 cp
	Hematocrit	39.0%	38.5%	38.0%
	Corrected viscosity	4.00 cp	3.85 cp	3.50 cp
mean±S.D.	Apparent viscosity	3.55±0.27	3.25±0.16**	2.97±0.14**
	Hematocrit	45.6±4.72	42.0±4.33	38.8±3.93*
	Corrected viscosity	3.74±0.20	3.44±0.24*	3.23±0.19**

Note : * ; $p<0.05$, ** ; $p<0.01$ before vs. short-term effect, before vs. long-term effect.

Table VI Changes in blood viscosity after administration of Keishi-bukuryo-gan in the non-responded group.

Case No.		Before	Short-term effect	Long-term effect
7	Apparent viscosity	2.89 cp	3.20 cp	2.98 cp
	Hematocrit	35.5%	36.5%	36.0%
	Corrected viscosity	3.03 cp	3.58 cp	3.61 cp
8	Apparent viscosity	3.96 cp	3.76 cp	3.89 cp
	Hematocrit	44.0%	45.0%	44.8%
	Corrected viscosity	4.05 cp	3.77 cp	3.91 cp
9	Apparent viscosity	4.00 cp	3.84 cp	3.92 cp
	Hematocrit	48.0%	47.0%	47.6%
	Corrected viscosity	3.75 cp	3.61 cp	3.70 cp

Note : Cases No. 7–9 corresponds to those of Table I.

one, of case No. 5. Table V also shows that the hematocrit values did not change in the acute study, but decreased significantly following long-term administration of this formula. On the other hand, the group with no response showed no significant changes both in blood viscosity and hematocrit values (Table VI).

Improvement of signs and symptoms

The signs and / or symptoms improved by the Keishi-bukuryo-gan administration are indicated by asterisks in Table I. As shown in the Table, recurrent vertigo, drop attack and bulbar palsy associated with vertebrobasilar insufficiency (cases 1 and 5) improved remarkably by this formula. Dysuria, intermittent claudication and spastic paraparesis with the spinal vascular lesion (cases 2 and 3) also showed notable improvement. In cases of multiple lacunar infarction (cases 4 and 6), Parkinsonian symptoms and hemiparesis decreased in severity following the Keishi-bukuryo-gan administration of about five weeks.

Discussion

There has been no report which revealed the effects of Keishi-bukuryo-gan on the vascular lesion of the central nervous system. Previous reports dealing with vascular disorders of the brain were mainly focused on anticoagulant therapy[5,6] and inhibitory agents for platelet aggregation.[7] Recently, the significance of microcirculation in the central nervous system was emphasized by several authors.[8-10] However, no concrete therapeutic procedure for improving microcirculation of the central nervous system has been established.

In the present study we revealed that in about 67% of cases, Keishi-bukuryo-gan possesses the potential to improve the clinical signs and/or symptoms associated with cerebro-spinal vascular lesions by both increasing the blood flow volume of the microvessels and lowering the blood viscosity.

Concerning the pharmacological effects of the medicinal plants contained in Keishi-bukuryo-gan on the cardiovascular system and blood cells, Wan *et al.*[11] revealed that the methanol extracts of both Persicae Semen and Moutan Cortex relax the isolated aortic strips precontracted with noradrenaline. Harada *et al.*[12] reported that cinnamaldehyde derived from Cinnamomi Cortex increases the peripheral blood flow. Paeonol, a main component of Moutan Cortex, inhibits platelet aggregation.[13] Taken together, these studies suggest that Keishi-bukuryo-gan may have some effects on the microcirculation.

Oda *et al.*[14] reported that Keishi-bukuryo-gan improves the deformability of erythrocytes in the aged rat. Further, we have reported that this formula decreases both whole blood and plasma viscosities, and inhibits platelet aggregation induced by exogenous aggregants such as collagen and adenosine-diphosphoric acid in healthy volunteers.[15] The present study indicated that in the group which responded, a long-term administration of this formula decreases both hematocrit values and corrected viscosities. Corrected viscosity represents the characteristics of blood without the influence of hematocrit values.

Therefore, it appears that this formula improves microcirculation by a decrease in hematocrit, a decrease in plasma viscosity, and an improvement in the deformability of red blood cells.

Through this investigation it has become apparent that Keishi-bukuryo-gan has a salutary effect on some signs and/or symptoms associated with vascular lesions in the central nervous system, and that this may be a result of improved blood flow volume in the microcirculation due to lowered blood viscosity, at least as far as the group with response to this formula are concerned. The results also suggested that the group with no response for long-term administration of this formula showed impaired pharmacological responses to the short-term study of this drug, therefore the short-term study may provide information to predict a subject who may respond to this formula.

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和文抄録

脳・脊髄血管障害慢性期の諸種神経症状に対する桂枝茯苓丸の治療効果を9症例において検討した。症例の内訳は椎骨脳底動脈不全症2例，脊髄血管障害5例，多発性小窩性脳梗塞2例であった。桂枝茯苓丸の投与により約5週後に67%の症例において臨床症状の何らかの改善が得られた。これら9症例について桂枝茯苓丸の眼球結膜微小循環動態に対する効果を本剤の単回投与試験ならびに長期投与（5週間）試験により評価した。血流動態は顕微鏡ビデオ装置を用いて観察した。またこの際の全血粘度の変化を円錐平板型粘度計を用いて測定した。臨床症状の改善の得られた6症例ではいずれも血液粘度の低下と毛細血管床における血流量の有意の増加が観察され，他方無効例では血流の改善はみられなかった。本研究により桂枝茯苓丸は脳・脊髄血管障害に伴う神経症状を改善する作用を有し，この効果が微小循環改善作用によるものであることが示唆された。

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