Effects of Keishi-bukuryo-gan on the systemic hemodynamics in patients with old cerebral infarction

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Abstract

We determined the effect of Keishi-bukuryo-gan (KB) on the hemodynamics in 14 patients with old cerebral infarction. Diagnostic right-sided heart catheterization was performed after an overnight fast following discontinuation of all medication for at least 48 hours. Resting hemodynamic measurements by electronic integration were made of systemic and pulmonary arterial pressures, right atrial pressure and pulmonary wedge pressure. Cardiac output was determined by standard thermodilution technique. Values for pulmonary vascular resistance and systemic vascular resistance were calculated according to standard formulas. Following the establishment of hemodynamic values, nine patients were given 6.0 g of KB with 50 ml of water orally and five patients were given only water as a control. All hemodynamic parameters were remeasured every 15 min. up to 60 min. after the administration of the test drug or water. The parameters before the administration did not differ between the two groups. Following the administration of the test drug or water, these parameters showed no changes statistically. These results show that KB improved microcirculatory disturbances mainly directly through the micro-circulation rather than through changes in the systemic hemodynamics.

Key words Keishi-bukuryo-gan (Keisi-bukuryô-gan), hemodynamics, cardiac index, microcirculation.

Abbreviations Keishi-bukuryo-gan (Gui-Zhi-Fu-Ling-Wan), 桂枝茯苓丸 ; oketsu (Yu-Xue), 瘀血.

Introduction

Keishi-bukuryo-gan (KB) is one of the Kampo formulas for treating "oketsu" syndrome, which is closely correlated with abnormalities of the microcirculation.[1] The pharmacological effects of KB have been reported as follows ; improving Raynaud phenomenon in patients with collagen diseases,[2] lowering whole blood viscosity,[3,4] improving the symptoms of patients with cerebrospinal vascular disorders, and increasing conjunctival microcirculation.[4] However, it was not clear whether KB affects microcirculation itself, or whether this occurs under the influence of systemic hemodynamic changes. This study was undertaken to clarify the effect of KB on the systemic hemodynamics by using right-sided heart catheterization in patients with old cerebral infarction.

Subjects and Methods

Subjects : 14 patients (nine female, five male, ages 59.9±9.0 years) with old cerebral infarction referred to the hospital of Toyama Medical and Pharmaceutical University were enrolled in this study (Table I). Informed consent was obtained

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Table I Characteristics of patients.

Test drug	Case No.	Sex	Age	Foci of old infarction	Duration	Signs and/or symptoms	Complications	CTR	Oketsu-score
KB	1	M	65	BS	3 (y)	dysesthesia in right face, left hemi-hypesthesia	DM	41.7(%)	31
	2	M	70	CH	0.5	speech disturbance	HT, IHD	53.2	59
	3	M	70	CH, BG	7	dysesthesia in bilateral lower extremities	HT	47.0	41
	4	F	39	BG	1	dysesthesia in right lower extremity		41.0	62
	5	F	50	CH	4	dysesthesia in bilateral upper extremities		44.0	35
	6	F	59	BG	5	head heaviness		49.0	38
	7	F	63	CH, BG	2.5	dysesthesia in bilateral upper extremities	IHD	45.2	60
	8	F	65	CH	4	dysesthesia and hypesthesia in face	HT	56.5	61
	9	F	69	BG	4	head heaviness	IHD	55.7	33
Control	10	M	56	CH	0.33	weakness in right upper extremity	IHD	40.5	38
	11	M	67	CH	6	bulbar palsy (mild)	COPD	42.3	35
	12	F	52	CH	6	dysesthesia in bilateral lower extremities		42.6	44
	13	F	53	BG	4.5	left hemiparesis, spastic gait	HT, DM	44.7	51
	14	F	61	CH	0.5	dysesthesia in bilateral upper extremities	DM	45.6	46

BG : Basal ganglia, BS : Brain stem, CH : Gray matter of cerebral hemisphere, CTR : Cardio-thoracic ratio, DM : Diabetes Mellitus, HT : Hypertension, IHD : Ischemic heart disease.

from all patients. Diagnosis was reached by neurological examination, brain computed tomography and magnetic resonance imaging. At the time of this study, all patients were in a stable disease state and were free of severe anemia, arrhythmia, heart failure and unstable blood pressure.

Ten patients had complications other than the neurological disorder. Four patients had diabetes mellitus, three had ischemic heart disease, two had hypertension and one patient had chronic obstructive pulmonary disease. None of these complications were severe. Biochemistry examinations and abdominal echography prior to this study revealed no signs of liver and kidney ailments in these patients.

Substances : Keishi-bukuryo-gan prepared by the hospital pharmacy of the Toyama Medical Pharmaceutical University was used in this study. Six grams of Keishi-bukuryo-gan pills consisted of 3.0 g of honey (*Apis indica* RADOSZKOWSKI, China) and the following five medicinal plants : Cinnamomi Cortex (*Cinnamomum cassia* BLUME, China) 0.6 g, Poria (*Poria cocos* WOLF, North Korea) 0.6 g, Moutan Cortex (*Paeonia moutan* SIMS, China) 0.6 g, Persicae Semen (*Prunus persicae* BATASCH, North Korea) 0.6 g and Paeoniae Radix (*Paeonia lactiflora* PALL, North Korea) 0.6 g.

Protocol : Diagnostic right-sided heart catheterization using a balloon flow-directed catheter (Swan-Ganz catheter) was performed by insertion into the right inguinal vein after an overnight fast, and treatment with all medications was discontinued for at least 48 hours prior to the study. Resting hemodynamic measurements were made of systemic and pulmonary arterial pressures, right atrial pressure and pulmonary wedge pressure, with mean pressures determined by electronic integration. Cardiac output was determined by standard thermodilution technique. Arterial and venous blood gases and plasma atrial natriuretic peptide (in the right atrial blood) were measured. Values for total peripheral resistance and pulmonary arteriolar resistance were calculated according to standard formulas.

Following the establishement of hemodynamic values, nine patients (six female, three male) were given 6.0 g of KB with 50 ml of water orally and five patients (three female, two male) were given only water as a control. Measurement of all hemodynamic parameters was repeated and all calculations were re-measured every 15 min. up to 60 min. after the administration of KB. Arterial and venous blood gases and plasma atrial natriuretic peptide were re-measured 60 min. after the medication.

Statistical analysis : The means and SDs were computed for all of the variables measured. A test for equal variance for the parameters in the two groups was performed before the administration of the medication. A two-way analysis of

variance was employed to determine the changes of all parameters in the KB group and the control group. The level of statistical significance was defined as $p<0.05$.

Results

Patient characteristics

Sex population between the two groups had no difference. Age in the control group was 57.8 ±10.3 years and 61.1±10.4 years in the KB group, duration was 3.4±2.9 years in the control and 3.4 ±2.0 years in the KB, the cardio-thoracic ratio was 43.1±2.0 % in the control and 48.1±5.8 % in the KB, and Oketsu scores[5] were 42.8±6.4 points in the control and 46.7±13.4 % in the KB. Thus, these parameters concerning patient characteristics indicated no siginificant differences between the two groups. A comparison of the foci of old cerebral infarction in both groups seemed to indicate that the control group consisted of more cases with old infarction in the gray matter of the cerebral hemisphere and the KB group consisted of more cases with the basal ganglia affected, but there was no significant difference between the two. A comparison of the complications also failed to show any significant differences between the two groups.

Results of the medication trial

(a) Data before the medication (Table II)

There was no difference in systolic and diastolic blood pressure and heart rate between the two groups. The values of central venous pressure, mean pulmonary pressure and pulmonary wedge pressure were within normal range. The average value of the cardiac index was slightly low, and the total peripheral resistance was slightly high. These parameters showed no statistically significant differences between the two groups.

(b) Data after the medication

After administration the mean blood pressure in the control group was not changed, but decreased by five mmHg for 30 min. in the KB group, only to recover to the pre-administration level after that (Fig. 1a). The heart rate in both groups were not changed (Fig. 1b). Central venous pressure, mean pulmonary artery pressure and pulmonary capillary wedge pressure remained unchanged (Fig. 2a-c). The cardiac index decreased slightly and gradually (by about 0.3 L/min./m² at 60 min.), but otherwise the cardiac index in the KB group stayed at the same level (Fig. 3a). The total peripheral resistance in

Table II Hemodynamic parameters before administration of Keishi-bukuryo-gan (KB).

	Control	KB	
Systolic blood pressure	127.2±20.4	144.9±25.8	(mmHg)
Diastolic blood pressure	75.6±18.2	80.1±18.1	
Mean blood bressure	92.8±18.6	101.7±20.0	
Heart rate	65.6±9.9	62.0±10.9	(beats/min.)
Central venous pressure	3.0±1.9	2.8±1.7	(mmHg)
Mean pulmonary artery pressure	10.6±0.9	10.8±2.0	
Pulmonary capillary wedge pressure	5.0±0	4.4±1.9	
Cardiac output	4.22±1.15	4.09±0.80	(l/min.)
Cardiac index	2.82±0.61	2.79±0.64	(l/min./m²)
Stroke index	43.2±9.5	45.2±7.2	(ml/m²
Total peripheral resistance	2696±938	2973±983	(dyne·sec·cm⁻⁵·m²)
PaO_2	84.0±9.5	85.0±9.2	(torr)
$PaCO_2$	41.0±4.6	41.2±1.9	
$P\bar{v}O_2$	43.0±7.7	45.3±6.2	
$P\bar{v}CO_2$	44.0±4.9	43.4±3.0	
Atrial natriuretic peptide	42.2±13.0	33.5±12.3	(pg/m)

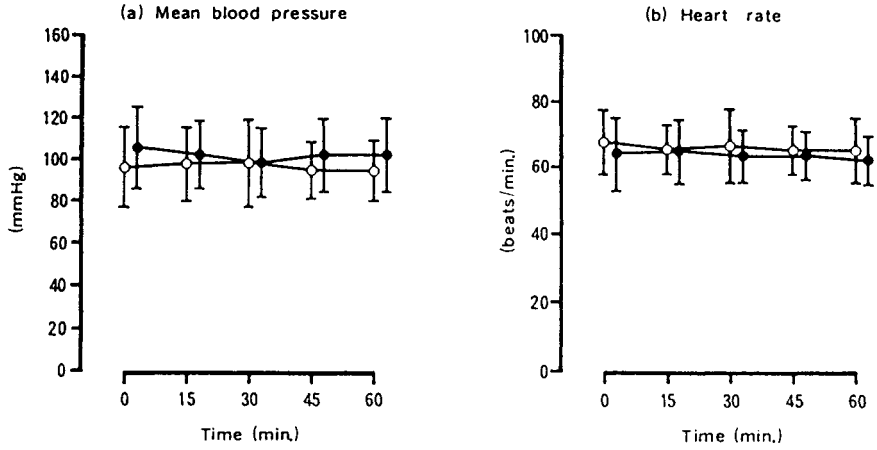

Fig. 1 Changes in blood pressure (a) and heart rate (b) in the control group (○, n=5) and the KB group (●, n=9).

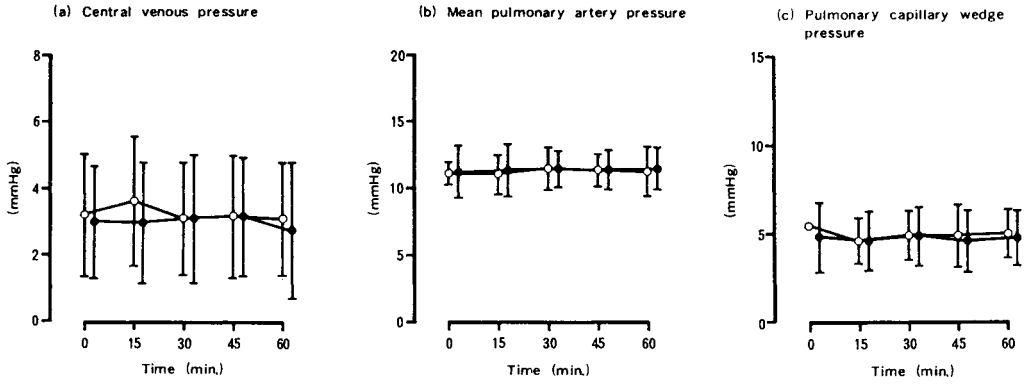

Fig. 2 Changes in the intra-cardiac pressure (a−c) in the control group (○, n=5) and the KB group (●, n=9).

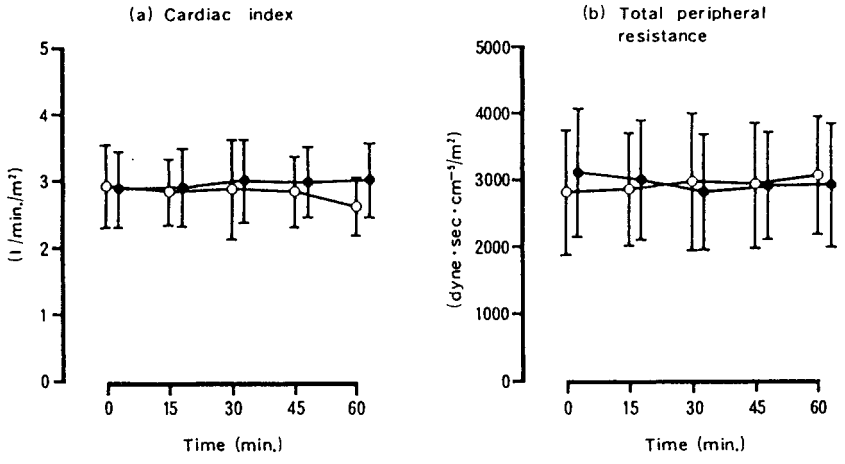

Fig. 3 Changes in cardiac index (a) and total peripheral resistance (b) in the control group (○, n=5) and the KB group (●, n=9).

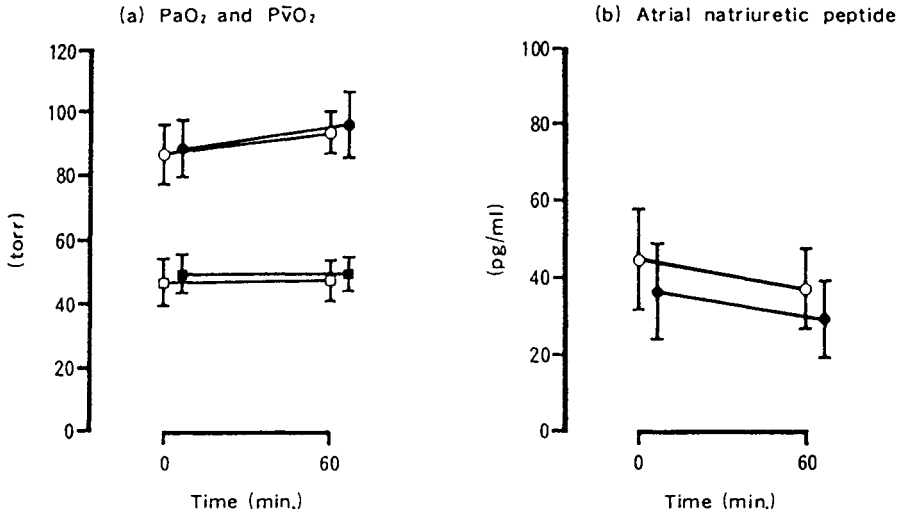

Fig. 4 Changes in arterial and venous oxygen pressure (a) and plasma atrial natriuretic peptide (b) in the control group (○, except □ in PvO_2, n=5) and the KB group (●, except ■ in PvO_2, n=9).

the control group increased slightly (by 200 dyne·sec·cm^{-5}·m^2) during the 60 min. duration, while the resistance in the KB group decreased slightly, to be 300 dyne·sec·cm^{-5}·m^2 down at 30 min. (Fig. 3b). Cardiac index and total peripheral resistance in both groups showed no significant difference.

PaO_2 in both groups increased after the medication and PvO_2 did not change (Fig. 4a). Plasma atrial natriuretic peptide decreased after the medication similarly in both groups (Fig. 4b). PaO_2, PvO_2 and atrial natriuretic peptide showed no significant differences between the two groups.

Discussion

Some papers have reported on the relationship between blood viscosity and cardiac index. Iwatani[5] reported a high coincidence between cardiac indexes by using the ear-oximeter dye-dilution method and blood viscosities of patients with anamia. Fowler *et al.*[6] was able to decrease average blood viscosities in dogs to 60% and increase cardiac indexes by almost 100% by administration of dextran, and determined that the changes in blood viscosity altered the cardiac output.

We have already reported that Keishi-bukuryo-gan has the ability to decrease whole blood viscosity in normal subjects and patients with cerebro-vascular disease[3,4,8] and we proposed the possibility that this formula may increase cardiac index. Alhough we reported that this formula had no effect on blood preessure and cardiac index using the ear-oximeter dye-dilution method in our previous study,[9] this study evoked some difficulties. The possibility that the ear-oximeter dye-dilution method might be less accurate than the thermodilution method, action on the intra-cardiac pressure was unknown, and the subjects in the previous study were not patients but normal volunteers. To resolve these problems, we performed the present study by using a Swan-Ganz catheter in patients with diseases which we usually treat with KB.

In this study the cardiac index, the heart rate and the intra-cardiac pressure were not changed after the administration of KB under monitoring with the right heart catheterization, either. These results indicate that this formula has no effect either on the heart or on large vessels in normal subjects and patients with old cerebral infarction. In our previous studies, we have revealed that KB increases blood flow volume in

the bular conjunctiva. Therefore it is suggested by the present study that the site of action of this formula can be considered to be in the peripheral circulation, especially in the microcirculation.

和文抄録

桂枝茯苓丸の大循環系に及ぼす影響を陳旧性脳梗塞を有する14例を対象として検討した。9例には自家性桂枝茯苓丸6gを水50mlの水と共に投与し，5例には水のみを投与した。最低48時間の薬剤中止後，右大腿静脈よりスワンガンツカテーテルを挿入後，血圧，心拍数，中心静脈圧，肺動脈圧，肺動脈楔入圧，心係数，総末梢血管抵抗を負荷前，負荷後15分，30分，45分，60分において測定した。負荷前の各循環諸量に本方剤投与群とコントロール群で差はなかった。試験薬剤負荷後，これら諸量に明らかな変化は認められなかった。本方剤が作用する部位は，末梢循環系，特に微小循環系にあることが，今回の検討により示唆された。

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