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Effects of Keishi-bukuryo-gan and Trapidil on the microcirculation in patients with cerebro-spinal vascular disease

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Abstract

The therapeutic effects of Keishi-bukuryo-gan (KB) and Trapidil (TD) on microcirculation were investigated in 14 patients with cerebro-spinal vascular diseases through the short- and long-term administration of the two drugs. The conjunctival microcirculatory and rheological parameters, blood pressure, pulse rate and oketsu score were evaluated before and after each medication. The short-term trial showed that KB increased the internal diameter and flow rate in the conjuctival venules similar to TD. In the long-term trial the patients were divided into twe groups, and KB and TD were administered for four weeks in opposite order in the two groups (cross-over). KB increased the flow rate and improved intra-vascular erythrocyte aggregation in the microvessels, and also lowered whole blood viscosity significantly, but TD did not alter these parameters. In addition, improvement of neurological signs and symptoms was obtained in seven patients with KB.

This study indicated KB not only acts to lower blood viscosity and to increase the conjunctival microcirculation but also has a function to improve intra-vascular erythrocyte aggregation ; its mode of action on microcirculation was different from that of Trapidil, which is generally recognized as having the function to improve microcirculation.

Key words blood viscosity, conjunctival microcirculation, intra-vascular erythrocyte aggregation, Keishi-bukuryo-gan (Keisi-bukuryô-gan), Trapidil.

Abbreviations DEA, maximal diameter of the erythrocyte aggregation column ; IEA, intra-vascular erythrocyte aggregation ; KB, Keishi-bukuryo-gan (Gui-Zhi-Fu-Ling-Wan), 桂枝茯苓丸 ; oketsu (Yu-Xue), 瘀血 ; TD, Trapidil.

Introduction

We have previously reported that Keishi-bukuryo-gan (KB) has the effect of improving the symptoms of patients with cerebro-spinal vascular disorders, and demonstrated that KB decreases whole blood viscosity and increases conjunctival microcirculation.[1] However, a comparative study between KB and other medicines which also improve microcirculatory disorders has as yet not been performed.

Trapidil (TD), as well as KB, is a drug that has been used for patients with cerebro-spinal vascular disorder.[2] However, TD improves coronary and cerebral circulation,[3,4] and these effects have not been reported in KB. As far as previous reports are concerned, KB and TD have a similar effect on increasing conjunctival microcirculation,[5,6] improving red blood cell deformability,[7,8] decreasing thromboxane A_2 synthesis[9,10] and improving peripherel circulation.[11,12] The present study was undertaken to clarify differences in the effects of KB and TD on the microcirculation by both short- and long-term administration of the two drugs in patients with cerebro-spinal vascular disorders.

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Subjects and Methods

Subjects : The subjects were 14 patients (eight female, six male) with cerebro-spinal vascular disorders and their age was 66.5 ± 10.5 (Mean ± S.D.) years (Table I). Diagnosis was reached by neurological examination, brain computed tomography and magnetic resonance imaging. Their oketsu scores[13] were estimated as 44.5 ± 17.0 points. At the time of this study, their contraction period was 4.0 ± 3.2 (0.5-13) years and all patients were in a stable state. Twelve patients complained of symptoms of sensory disturbances and two of motor disturbances. Four patients had hemiparesis, but were able to walk without any assistance. Advised consent was obtained from all patients.

Thirteen patients had clinical complications. Four had diabetes mellitus, four had ischemic heart disease, four had hyperlipemia and three had hypertension. Blood biochemical examinations and abdominal echography prior to this study revealed no signs of liver and kidney ailments.

Substances : Keishi-bukuryo-gan prepared by the hospital pharmacy of the Toyama Medical Pharmaceutical University was used in this study.[1]

Measurement of conjunctival microcirculatory parameters : By using a video-microscope system,[14] blood flow rate and internal diameter of conjunctival postcapillary venules ranging within 20-30 μm were measured in this study. Because it is impossible to evaluate only microvessels with the same internal diameter, the average change (%) of blood flow rate and internal diameter in each patient were calculated before and after each medication. In addition, the maximal diameter of the erythrocyte aggregation column (DEA) was measured for the estimation of intra-vascular erythrocyte aggregation (IEA).

Measurement of rheological parameters (blood viscosity and hematocrit) : Viscosities of whole blood and plasma were measured with a cone-plate rotational viscometer (Bio-rheolizer, Tokyo Keiki Co., Ltd., Tokyo). The measurements

Table I Characteristics of patients.

No.	Age	Sex	Diagnosis	Duration	Signs and/or symptoms
Keishi-bukuryo-gan→Trapidil					
1	73	M	MLI	4.0 (y)	dysesthesia* and hypesthesia in face.
2	70	M	MLI	0.5	speech disturbance.* left hemiparesis.
3	65	M	CI	3.0	dysesthesia in right face and in left leg.* hypalgesia.
4	83	F	MLI	13.0	dysesthesia in bil. lower extremities.
5	63	F	MLI	2.5	dysesthesia in bil. lower extremities.
6	63	F	VBI	5.0	head heaviness. vertigo.
7	40	F	ASA	2.5	dysesthesia and hypesthesia in left lower extremity.
Traidil→Keishi-bukuryo-gan					
8	83	M	MLI	5.0	swallowing disturbance.*
9	69	M	MLI	7.0	head heaviness. tinnitus.
10	68	M	MLI	1.1	hypogeusia.* right hemiparesis.
11	69	F	MLI	4.0	head heaviness.*
12	69	F	VBI	3.0	head heaviness. vertigo.
13	65	F	MLI	5.0	head heaviness.*
14	61	F	MLI	0.5	dysesthesia in bil. lower extremities.

Note. * : Improved signs during the long-term administration of Keishi-bukuryo-gan.
Abbreviations. ASA : Anterior spinal artery syndrome, CI : Cerebral infarction,
MLI : Multiple lacunar infarction, VBI : Vertebrobasilar insufficiency.

were carried out at a shear rate of 384 sec^{-1} (37°C) and a cone angle of 1° 34′. The values of hematocrit were measured by the capillary high speed centrifugation method using the centrifugal separator KH 120 M (Kubota Co., Ltd., Tokyo) and a micro-capillary tube (75 mm length, ELMA Co., Ltd., Tokyo).

Medication protocol in short-term trial : After overnight fasting, patients visited our department at 9 : 00 am. After 30 minutes of bed rest, their microcirculation was evaluated. Then they were administered 6.0 g of KB with 50 ml of hot water (37°C) or 200 mg of TD with the same amount of hot water. After one hour of bed rest, their microcirculation was re-evaluated. Blood pressure, pulse rate and the rheological parameters were evaluated both before and after each medication.

Medication protocol in long-term trial : Following the short-term trial, the patients were started on a constant regimen of KB or TD. Following the administration of one drug for four weeks, the other drug was administered for the second four-week period (in a cross-over manner). Before and after each long-term medication, the parameters were measured and changes in their signs and symptoms were evaluated clinically.

Patients were divided into two groups ; seven of them were administered 6.0 g of KB and 300 mg/day of TD in this order (KB→TD group), and the others followed the reverse order (TD → KB group). Their grouping was decided on the basis that there would be no appreciable differences in age and sex between the two groups. The measurements of the microcirculatory and rheological parameters, blood pressure, pulse rate and oketsu score were evaluated before and after the long-term administration (24 hours after the last administration) of each drug. Other drugs which these patients had been taking up to one month prior to the start of this study were continued through to the end of the study.

Statistical analysis : The Student's t-test was used for these parameters between before and after each medication. The level of statistical significance was defined as $p<0.05$.

Results

Because there were no differences between any of the parameters before the administration of the first and second drug between the "KB→TD" and "TD→KB" groups, and there were no differences in any of the parameters before each medication, the following parameters in the 14 patients before and after each medication were analyzed, regardless of the order of administration.

Changes in conjunctival microcirculatory parameters (Fig. 1)

In the short-term trial the internal diameter in the conjunctival microcirculation increased significantly by oral administration of TD and KB, respectively. Blood flow rate increased significantly by both drugs. DEA showed no changes.

In the long-term trial, however, there were no changes in the internal diameter by either drug. The blood flow rate increased significantly by KB, but stayed unchanged by TD. KB caused DEA to decrease significantly, but TD had no such effect.

Changes in rheological parameters (Fig. 2)

In the short-term trial, hematocrit, whole blood viscosity and plasma viscosity did not change by KB and TD, except a slight decrease of whole blood viscosity by TD. In the long-term trial, hematocrit and whole blood viscosity decreased significantly by KB, but remained unchanged by TD. Plasma viscosity showed no change with either medication.

Changes in other parameters

In the short-term trial by TD, systolic blood pressure decreased significantly from 141.3±6.8 (Mean ± S.E.) mmHg to 128.4 ± 5.8 mmHg, but diastolic blood pressure and pulse rate remained unchanged. There were no changes in blood pressure and pulse rate by KB. In the long-term trial, blood pressure and pulse rate showed no changes.

The oketsu score stayed unchanged by TD, but decreased significantly by KB (Fig. 3).

Changes in neurological signs and symptoms during the short and long-term trials

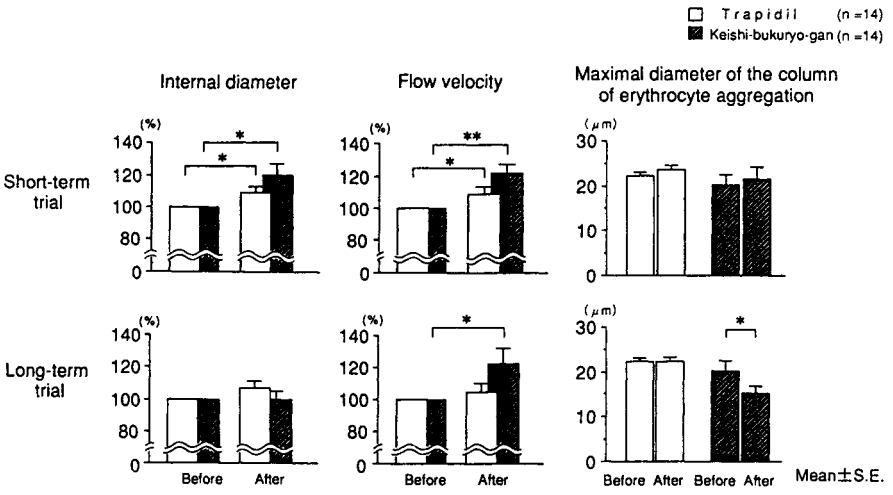

Fig. 1 Changes in the conjunctival microcirculatory parameters after administration of Trapidil and Keishi-bukuryo-gan.

Open columns and hatched columns express the mean ± S.E. of the patients. ** : $p<0.01$, * : $p<0.05$, before vs. after each medication.

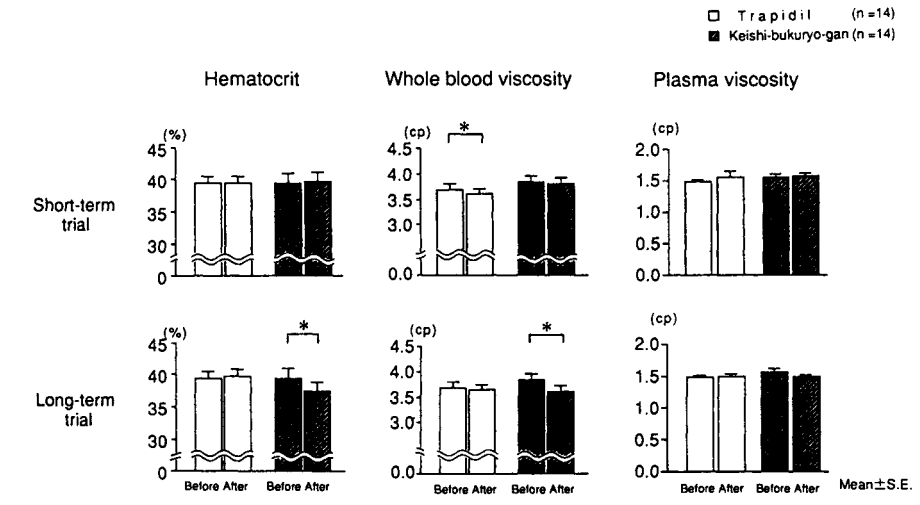

Fig. 2 Changes in the rheological parameters after administration of Trapidil and Keishi-bukuryo-gan.

Open columns and hatched columns express the mean±S.E. of the patients. * : $p<0.05$, before vs. after each medication.

Improvements of neurological signs and symptoms were obtained in three of seven patients in the "KB→TD" group and in four of seven patients in the "TD→KB" group by the administration of KB. The details of changes in these symptoms were as follows. The duration of dysesthesia in case 1 (Table I) decreased from all day to a few times a day. Case 3, who could not sleep because of severe dysesthesia at night, came to be able to sleep without any sleeping drug. Speech disturbance in case 2 due to motor aphasia improved, and he was able to answer our questions more promptly. The time required to drink a glass of water in case 8 shortened from about 40 seconds to about 20 seconds. Case 10, who had hypogeusia, was able to distinguish a salty taste. Head heaviness in cases 11 and 13 decreased from all day to a few times a day and improved in severity.

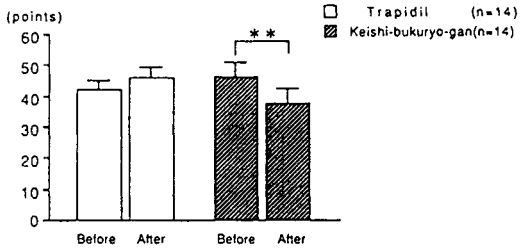

Fig. 3 Changes in oketsu score after administration of Trapidil and Keishi-bukuryo-gan.
Open columns and hatched columns express the mean ± S.E. of the patients. **: $p < 0.01$, before vs. after each medication.

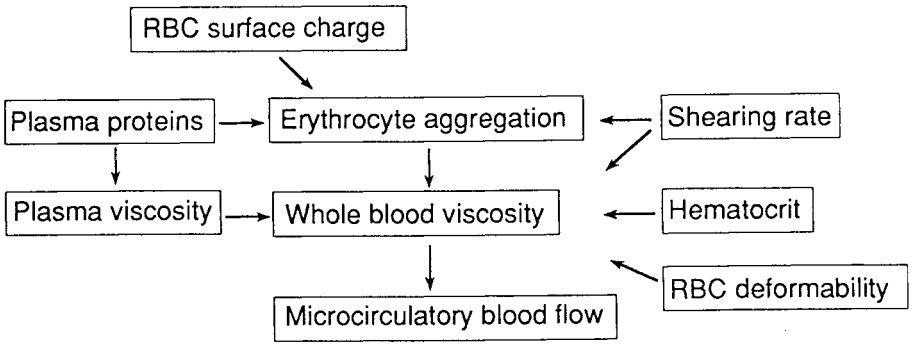

Fig. 4 The relationship of the microcirculatory factors influencing blood viscosity.

There were no improvements by TD. Mild general malaise in two, headache in one, dizziness in one and worsening of head-heaviness in one patient were recognized during the TD administration. There were no side effects by KB.

Discussion

It has been studied mainly *in vitro* that IEA increases blood viscosity and disturbs the microcirculatory blood flow[15] (Fig. 4). However, there have been no clinical studies based on following IEA *in vivo* with a constant administration regimen. This may perhaps be due to the difficulty of evaluating the degree of IEA, because it is greatly influenced by the local condition of the blood flow. Isogai[16] classified its degree into four grades (non, mild, intermediate and severe) by the internal diameter of the conjunctival microvessels of patients with diabetes mellitus. In patients with the severe grade, he found that the values of the erythrocyte sedimentation rate were low, and plasma viscosity and fibrinogen were high. While considering this classification, we measured DEA as a parameter for estimating IEA. Decreases of DEA meant that IEA changed and appeared in narrower microvessels, not in wider ones, suggesting improvement in IEA.

The short-term trial in this study showed that KB increased the conjunctival microcirculation in patients with cerebro-spinal vascular dis-

eases, and this effect was similar to that of TD. We considered this effect to be due to relaxation of the smooth muscle of venules and arterioles by Cinnamomi Cortex, one of the ingredients of KB.[17]

However, the long-term trial showed differences between the two drugs. Administration of KB increased the microcirclatory flow rate, lowered DEA, hematocrit, whole blood viscosity and oketsu score, and improved symptoms in seven of 14 patients without any side effect. These effects were not recognized with TD. Then, we considered the improvement in microcirculation by the long-term administration of KB to likely be the result of the improvement in IEA and decrease in whole blood viscosity.

This study revealed that KB not only has the effect of lowering blood viscosity and increasing the conjunctival microcirculation which we had reported previously,[1,6] but also exerts an action to improve IEA. Moreover, the modes of the action on microcirculation were different from those of Trapidil, a drug which has already become generally established for its ability to improve microcirculation.

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和文抄録

脳脊髄血管障害患者14例を対象として桂枝茯苓丸(KB)とTrapidil (TD)による急性および長期投与試験を行なった。長期投与においては対象を2群にわけて，投与順序を群間で変えて，それぞれ4週間クロスオーバーして投与した。投与前後で，眼球結膜微小血管の血管内径・血流速度と赤血球集合柱最大径，ヘマトクリット値，全血粘度，血漿粘度，血圧，脈拍数を測定した。両薬剤の急性投与ではともに眼球結膜微小血管の血流増加効果がみられたが，長期投与ではKBにより血流速度の増加，赤血球集合の改善，ヘマトクリット値と全血粘度の低下とともに7例で症状の改善を認めたが，TDにはこれらの効果はみられなかった。

本研究により，桂枝茯苓丸の微小循環改善作用は同じく微小循環改善剤とされるTDとは異なった機序で効果を発現していることが示唆された。

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