Effects of Keishi-bukuryo-gan on erythrocyte aggregability in patients with multiple old lacunar infarction

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Abstract

Accelerated erythrocyte aggregation plays a role in the disturbance of microcirculation in cerebrovascular disease. Therefore, the improvement of accelerated erythrocyte aggregation is an important medical strategy for cerebrovascular disease.

In this study, the effects of Keishi-bukuryo-gan on erythrocyte aggregation as well as on fibrinogen concentration, one of its important determinants, were determined in 23 patients with multiple old lacunar infarction. Erythrocyte aggregability was evaluated by S10, an *in vitro* erythrocyte aggregability index, and the maximum diameter of the column of intravascular erythrocyte aggregation (DEA) was used as the *in vivo* erythrocyte aggregability index. Fibrinogen concentration was measured by the thrombin time method. The 23 patients were divided into three groups : 5 patients in the non-"oketsu" group, 10 patients in the mildly affected group, and 8 patients in the severely affected group, as determined by "Terasawa's oketsu score". The results from this study suggested that Keishi-bukuryo-gan had a pharmacologic action to reverse the acceleration of erythrocyte aggregation, and such action was especially distinct in the more severe "oketsu" (blood stagnation) state through the reduction of the fibrinogen level. Furthermore, a constant correlation between the "oketsu score" and erythrocyte aggregability was maintained after the improvement by the administration of Keishi-bukuryo-gan.

Key words "oketsu" syndrome, erythrocyte aggregation, Keishi-bukuryo-gan, multiple lacunar infarction, hemorheology.

Abbreviations DEA, maximum diameter of the column of intravascular erythrocyte aggregation ; IEA, intravascular erythrocyte aggregation ; Keishi-bukuryo-gan (Gui-Zhi-Fu-Ling-Wan), 桂枝茯苓丸 ; oketsu (Yu-Xue), 瘀血 ; S10, erythrocyte aggregation index.

Introduction

Erythrocyte aggregation, one of the hemorheologic factors, is the reversible adhesion of adjacent erythrocytes induced by the bridging of intercalated macromolecules (such as fibrinogen, immunoglobulins, *etc.*).[1] Erythrocyte aggregability is related to the pathogenesis of cerebrovascular diseases,[2-4] and accelerated erythrocyte aggregation causes the disturbance of cerebral blood flow.[5] Therefore, it is important to try to prevent erythrocyte hyperaggregability in order to ameliorate the microcirculatory disturbance in cerebrovascular disease.

Several studies have demonstrated that Keishi-bukuryo-gan, one of the Kampo prescriptions for improving the "oketsu" syndrome ("oketsu" improving drugs), exerts a pharmacological effect on decreasing blood viscosity[6] and increasing the

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conjunctival microcirculation, including the blood flow velocity and volume in the microvessels of conjunctiva, in patients with cerebro-spinal vascular disease.[7]

Recently, we reported that the severity of the "oketsu" state, defined by the diagnostic criteria presented by Terasawa *et al.*,[8] is correlated significantly with erythrocyte aggregability, and that the fibrinogen level is one of the important determinants of this condition in patients with multiple old lacunar infarction.[9] However, it was not clarified whether or not the significant correlation between the "oketsu" score and the erythrocyte aggregability was maintained even after improvement in the "oketsu" score was achieved by the use of the "oketsu" improving drug.

The present study was undertaken to elucidate the effects of Keishi-bukuryo-gan on both erythrocyte aggregability and plasma fibrinogen level in patients with multiple old lacunar infarction. Furthermore, it was investigated whether or not there is any fluctuation in erythrocyte aggregability while maintaining a constant correlation with the "oketsu score" after the administration of Keishi-bukuryo-gan.

Methods

Patients : The subjects were 23 male patients with multiple lacunar infarction, with a mean age of 66.7±10.3 (S.D.) years, who visited the Department of Japanese Oriental (Kampo) Medicine, Toyama Medical and Pharmaceutical University. Diagnosis was reached by neurological examination and magnetic resonance imaging. All patients were in the chronic phase and their signs or symptoms were fixed. Complications consisting of hypertension (9 patients), diabetes mellitus (5 patients), ischemic heart disease (5 patients) and hyperlipidemia (1 patient) were seen in 17 patients. Each complication was controlled by diet therapy and / or Western medicines. The Western medicines, which are listed in Table I, were not changed or stopped during this study.

Measurement of erythrocyte aggregability (in vitro) : *In vitro* erythrocyte aggregability was

Table I Characteristics of subjects.

	Non oketsu groups (N=5)	Mildly affected groups (N=10)	Severely affected groups (N=8)	p value	
Age (years)	59.8±8.56	67.6±9.35	70.0±11.3	0.084	a
Sex (M)	5 (100%)	10(100%)	8 (100%)	1.000	b
Duration (days)	718±836	1545±1531	2761±3377	0.230	a
Signs or symptoms	4 (80%)	7 (70%)	6 (75%)	0.914	b
Administration of each Western medicines					
Calcium antagonists	2 (40%)	4 (40%)	2 (25%)	0.772	b
ACE antagonists	1 (20%)	0 (0 %)	1 (13%)	0.386	b
Nitrates	0 (0 %)	3 (30%)	1 (13%)	0.318	b
Antiplatelet agents	1 (20%)	5 (50%)	1 (13%)	0.194	b
Complications					
Hypertension	1 (20%)	4 (40%)	4 (50%)	0.5576	b
Diebetes mellitus	1 (20%)	1 (10%)	2 (25%)	0.6955	b
Hyperlipidemia	1 (10%)	0 (0 %)	0 (0 %)	0.1523	b
Ischemic heart disease	0 (0 %)	4 (40%)	1 (13%)	0.1533	b

a : The values are expressed as means±standard deviation. Statistical analysis was done by the Kruskal-Wallis test.
b : The data are expressed as the number of patients (%). Statistical analysis was done by the chi-square test for independence.

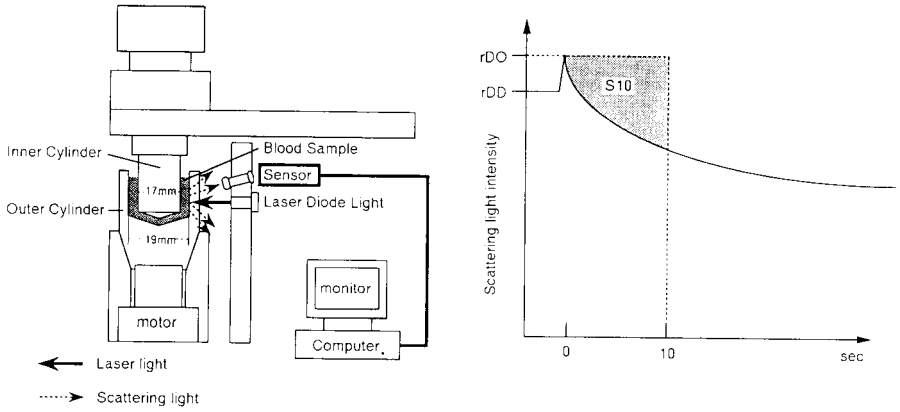

Fig. 1 Erythro-aggregometer (SEFAM™)

measured by using a SEFAM™ Erythro-aggregometer (SEFAM Co., Ltd., VANDOEUVER LES NANCY, FRANCE), a rotating viscometer with laser light backscattering (Fig. 1). Seven ml of blood was withdrawn from the cubital vein into a siliconized glass tube containing ethylene-diamine-tetra acetic acid-2 Na (1.5 mg/ml). After the hematocrit of which was adjusted to 40 % with autologous plasma at a stable temperature of 37°C, 1.4 ml of the whole blood sample was transfused into the space between the inner and outer cylinders. The blood sample was sheared for 10 seconds at a high shear rate (600 sec^{-1}). The erythrocytes deaggregated and became orientated to the flow.

The backscattering light level was defined as rDD. After the shear stress was discontinued abruptly, the erythrocytes became disoriented and a rapid increase in the backscattered light was recorded. The maximum light level was termed rDO (=1). The progressive decrease in the intensity of the backscattered light is said to be related to the formation of "rouleaux" and "rouleaux-networks." The light intensity curve was displayed on the monitor.

The erythrocyte aggregation index (S10) was calculated from the relative area above the light intensity curve during the first 10 seconds after shear stress.[10]

Measurement of erythrocyte aggregability (in vivo) : The maximum diameter of the column of intravascular erythrocyte aggregation (DEA) was defined as the maximum diameter of the largest venule in which intravascular erythrocyte aggregation (IEA) in the pleural venule of the bulbar conjunctiva was observed by video-microscope system[11] (Fig. 2). In a previous investigation we showed that DEA served as a useful index for evaluating erythrocyte aggregability *in vivo*.[9]

Measurement of fibrinogen concentration : Plasma fibrinogen level was determined with a fibrometer (CA-5000, Toa medical electronic Co., Ltd., Japan) by a thrombin clotting method.[12]

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 (Hubei Prov., 湖北省 ; China) and the following five medical plants : Cinnamoni Cortex (桂枝), *Cinnamomum cassia* BLUME (Guangxi Prov., 広西省 ; China) 0.6 g, Poria (茯苓), *Poria cocos* WOLF, (North Korea) 0.6 g, Moutan Cortex (牡丹皮) *Paeonia moutan sicae* SIMS (Anhui Prov., 安徽省 ; China) 0.6 g, Persicae Semen (桃仁) *Purnus persicae* BATASCH (North Korea) 0.6 g and Paeoniae Radix (芍薬), *Paeonia lactiflora* PALL (North Korea) 0.6 g.[13]

Medication protocol : Keishi-bukuryo-gan (twelve grams per day) was administered to each

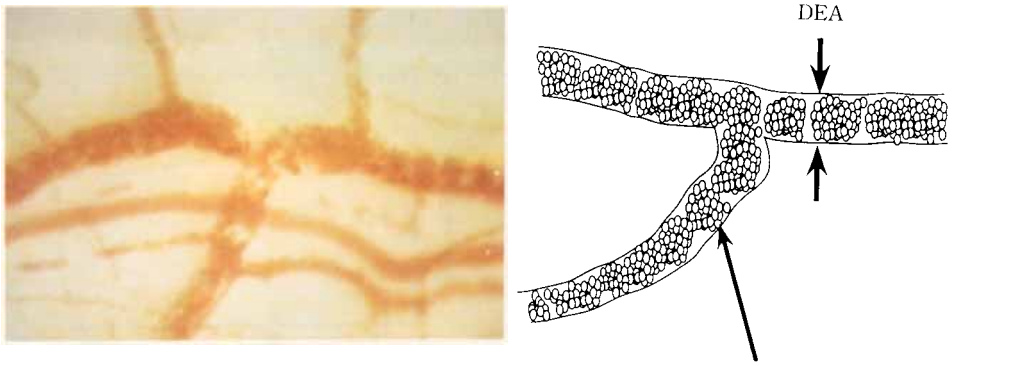

Fig. 2 Maximum diameter of the column of intravascular erythrocyte aggregation (DEA).

patient. The hemorheological parameters, including S10, DEA and fibrinogen level, were measured at about 9 : 00 a.m. after overnight fasting at 0 (before administration), 2 and 4 weeks after administration.

The oketsu score was determined by two specialists in Kampo medicine before measurement of the hemorheological parameters.

Statistical analysis : The results were presented as means ± S.D.. The significance of differences between the results obtained at 0 and 2 or 4 weeks after administration of Keishi-bukuryo-gan was assessed by two-tailed Wilcoxon signed-rank test, and the correlation between "oketsu" score and erythrocyte aggregability, or between the difference in "oketsu" score and the difference in the erythrocyte aggregation was used for Spearman's correlation coefficient. A two-sided probability level of 0.05 or less was considered to indicate statistical significance.

Results

Characteristics of patients

All patients were divided into three groups, a non-"oketsu" group (n=5), a mildly affected group (n=10) and a severely affected group (n=8), according to the diagnostic criteria presented by Terasawa *et al.*.[8] The three groups were similar with respect to baseline characteristics, including age, sex, duration, the existence of signs or symptoms, the respective use of Western medicines and the number of patients with complications (Table I).

Correlation between "oketsu" score and erythrocyte aggregability (S10 or DEA)

Fig. 3 shows that the "oketsu" scores were correlated significantly with S10 at 0, 2 and 4 weeks after the administration of Keishi-bukuryo-gan (Rs=0.780, $p<0.001$; Rs=0.596, $p=0.0052$; and Rs=0.782, $p<0.001$, respectively ; n=23), and with the DEA at 0, 2 and 4 weeks post-administration (Rs=0.792, $p<0.001$; Rs=0.596, $p=0.0052$; Rs=0.801, $p<0.001$, respectively ; n=23). There was no significant difference in slope and intercept among the three regression lines in S10 or DEA (data not shown).

The differences in values ("oketsu" score, S10 or DEA) at 2 and 4 weeks were obtained by subtracting the value at 2 weeks (post-administration) from the value at 0 week and the value at 4 weeks from the value at 0 week, respectively. The difference in the "oketsu" score was significantly related to the difference in S10 at 2 and 4 weeks (Rs=0.696, $p=0.0011$ and Rs=0.807, $p<0.001$, respectively ; n=23), and to the difference in DEA at 2 and 4 weeks (Rs=0.586, $p=0.006$ and Rs=0.730, $p<0.001$, respectively ; n=23) (Fig. 4). There was no significant difference in slope and intercept between the two regression lines in S10 or DEA (data not shown).

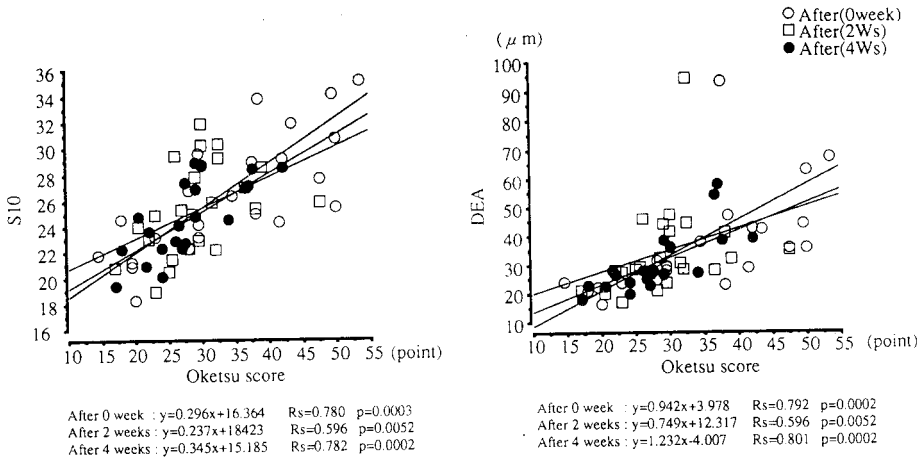

Fig. 3 Correlation between oketsu score and erythrocyte aggregability (S10 or DEA).

Oketsu score is correlated significantly with S10 (left) and DEA (right) at each time.

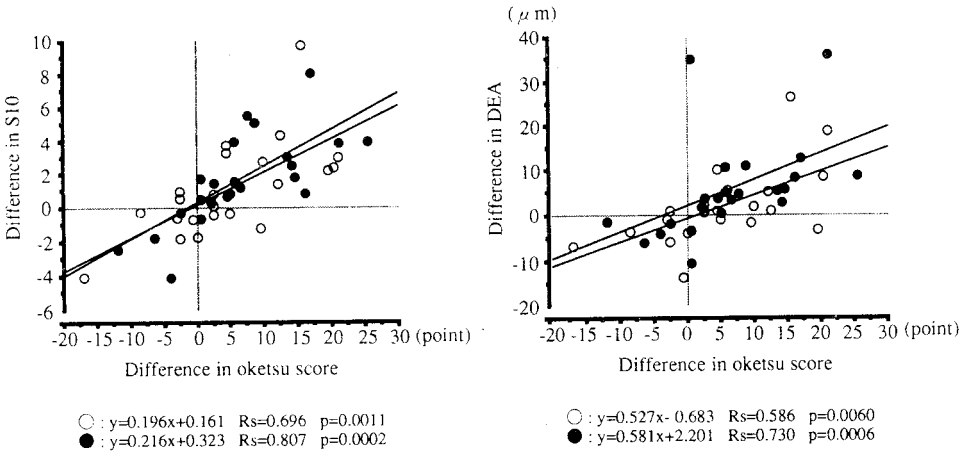

Fig. 4 Correlation between the difference in oketsu score and the difference in erythrocyte aggregability (S10 or DEA).

Difference in each value (oketsu score, S10 or DEA) is obtained by subtracting the value at 2 weeks (○) or 4 weeks (●) from the value at 0 week after the administration of Keishi-bukuryo-gan.

Change in "oketsu" score after administration of Keishi-bukuryo-gan

The mean (±S.D.) "oketsu" score in all patients decreased from 34.1±11.8 points at 0 week to 29.3±6.7 points at 2 weeks ($p<0.05$) and to 27.8 ±6.4 points at 4 weeks after the administration of Keishi-bukuruo-gan ($p<0.005$). The changes in the "oketsu" score post-administration in each group (non-"oketsu" group, mildly affected group and severely affected group) are shown in Fig. 5. The mean "oketsu" score decreased from 47.2± 4.4 points at 0 week to 34.1±6.9 points at 2 weeks

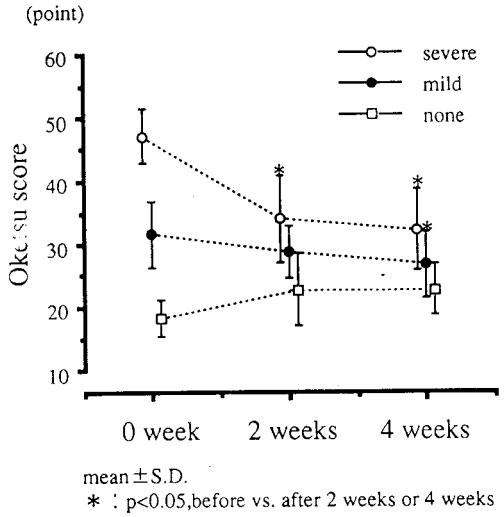

Fig. 5 Change of oketsu score in each group after administration of Keishi-bukuryo-gan.

($p < 0.05$) and to 32.3±6.5 points at 4 weeks ($p < 0.05$) in the severely affected group, and from 31.6±5.2 points at 0 week to 28.7±4.1 points at 2 weeks (p=0.15) and to 26.8±5.2 points at 4 weeks ($p < 0.01$) in the mildly affected group. There was no significant change in the mean oketsu score after administration of Keishi-bukuryo-gan in the non-oketsu group (18.3±2.3 points at 0 week, 22.8±5.4 points at 2 weeks and 22.8±4.0 points at 4 weeks).

Change in erythrocyte aggregability (S10 or DEA) after administration of Keishi-bukuryo-gan

The mean (±S.D.) S10 in all patients decreased from 26.5±4.6 at 0 week to 25.4±3.6 at 2 weeks (p=0.08) and to 24.8±3.0 at 4 weeks ($p < 0.001$) after the administration of Keishi-bukuryo-gan. The mean DEA in all patients decreased from 36±18 at 0 week to 34±16 at 2 weeks (no significance) and to 30±10 at 4 weeks ($p < 0.01$).

To investigate whether or not differences in the degree of severity of the "oketsu" state caused differences in the effect of Keishi-bukuryo-gan on erythrocyte aggregability (S10 or DEA), the aggregability at 2 weeks or 4 weeks was compared with that at 0 week in each group (Fig. 6). The mean S10 decreased from 29.8±3.9 at 0 week to 27.3±3.0 at 2 weeks ($p < 0.05$) and to 26.3±2.5 at 4 weeks ($p < 0.05$) post-administration in the severely affected group, and from 26.4±3.6 at 0 week to 28.7±4.1 at 2 weeks (p=0.139) and to 24.6±3.3 at 4 weeks ($p < 0.05$) in the mildly affected group. There was no significant change in mean S10 in the non-"oketsu" group (21.4±2.3 at 0 week, 22.5 ±2.7 at 2 weeks and 22.7±2.1 at 4 weeks).

The mean DEA decreased from 45±13 μm at

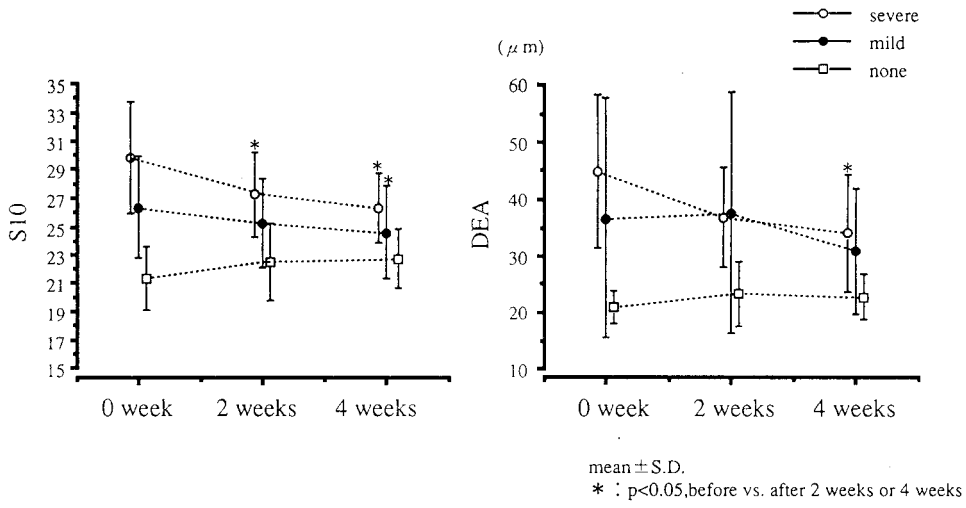

Fig. 6 Change of erythrocyte aggregability (S10 or DEA) in each group after administration of Keishi-bukuryo-gan.

0 week to 37±9 μm at 2 weeks (p=0.07) and to 34 ±10 μm ($p<0.05$) at 4 weeks after the administration in the severely affected group, and changed from 37±21 μm at 0 week to 38±21 μm (p=0.88) at 2 weeks and to 31±11 μm (p=0.09) at 4 weeks in the mildly affected group. There was no significant change in mean DEA after the use of Keishi-bukuryo-gan in the non-oketsu group (21±3 at 0 week, 23±6 at 2 weeks and 23±4 at 4 weeks).

Change in fibrinogen concentration after administration of Keishi-bukuryo-gan

Fig. 7 shows the change of fibrinogen concentration in each group. Similar to the change in "oketsu" score or S10, the mean (±S.D.) fibrinogen level decreased from 445.1±136.4 mg/dl at 0 week to 332.6±31.8 mg/dl ($p<0.05$) at 2 weeks and to 331.5±50.7 mg/dl ($p<0.05$) at 4 weeks after the administration of Keishi-bukuryo-gan in the severely affected group, and from 326.1±101.3 mg/dl to 307.6±78.1 mg/dl (p=0.44) at 2 weeks and to 273.8±65.7 mg/dl (p=0.17) at 4 weeks in the mildly affected group. The fibrinogen level in the non-"oketsu" group did not change significantly (233.2 ±52.9 mg/dl at 0 week, 239.0±46.1 mg/dl at 2 weeks and 268.8±22.6 mg/dl at 4 weeks).

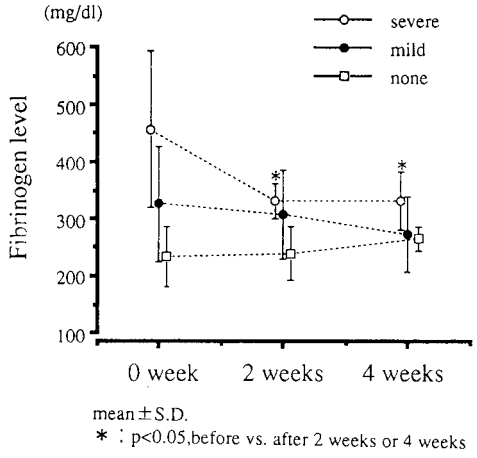

Fig. 7 Change of fibrinogen level in each group after administration of Keishi-bukuryo-gan.

Discussion

"Oketsu" syndrome is one of the pathophysiological concepts of the Japanese Oriental medicine and is defined as the circulatory insufficiency of "ketsu" (blood).

Several studies have demonstrated that the "oketsu" syndrome is concerned with the disturbance of microcirculation, including blood viscosity,[14] blood flow in microvessels of bulbar conjunctiva[15] and platelet function.[16] Previously we reported that the acceleration of erythrocyte aggregation contributes to the severity of the "oketsu" state in patients with multiple old lacunar infarction.[9] However, it is unknown whether erythrocyte aggregability may be lowered if the "oketsu" state in the patient is improved by administering "oketsu"-improving drugs.

In the present study, we examined the relation beween the change of erythrocyte aggregation and that of "oketsu" score by administering Keishi-bukuryo-gan, a representative "oketsu"-improving drug, to patients with multiple old lacunar infarction. The results showed that a significant correlation between the "oketsu" score and erythrocyte aggregability was maintained at each time point (at 0, 2 or 4 weeks) after the administration of Keishi-bukuryo-gan, and that there was no significant difference in the slopes or intercepts of the regression lines among the three time points. Furthermore, the difference in "oketsu" score correlated significantly with the difference in erythrocyte aggregability at 2 and 4 weeks post-administration, and the slopes and intercepts of the two regression lines were similar.

These findings indicate that the constant correlation between the "oketsu" score and erythrocyte aggregability was kept not only before giving the "oketsu"-improving drug but also when the "oketsu" score changed after its use, and that erythrocyte aggregability closely participates in the pathogenesis of the "oketsu" syndrome in patients with multiple old lacunar infarction.

Keishi-bukuryo-gan is known as one of the most popular Kampo formulas for treating the

"oketsu" syndrome. In previous studies, we reported that Keishi-bukuryo-gan has the pharmacologic effects of lowering blood viscosity and increasing the microcirculatory flow rate.[6,7] Thus, as erythrocyte aggregation is understood to be one of the most important determinants of whole blood viscosity, it is inferred that Keishi-bukuryo-gan is effective in improving erythrocyte aggregation.

In the present study it was suggested that Keishi-bukuryo-gan has the pharmacologic activity to work against accelerated erythrocyte aggregation and to lower the fibrinogen level. When comparing the efficacy of Keishi-bukuryo-gan on erythrocyte aggregability and the fibrinogen level among the three groups, the response of the severely affected group was stronger than that of the mildly affected group, with the non-"oketsu" group showing no effect.

In this study the neurological deficits in patients with multiple lacunar infarction did not improve when erythrocyte aggregation and the fibrinogen level were lowered by the administration of Keishi-bukuryo-gan. Ernst *et al.* suggested that erythrocyte aggregation is one of the risk factors for ischemic strokes.[2] Further, Wilhelmsen *et al.* demonstrated that the fibrinogen level plays an important role in the develoment of strokes.[17] For these reasons, patients with "oketsu" syndrome may be a high-risk group for strokes, and the use of Keishi-bukuryo-gan may possibly reduce their occurence.

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和文抄録

赤血球集合は脳血管障害における微小循環障害に影響を与えている。したがって，亢進した赤血球集合を改善させることは，脳血管障害を治療するうえで重要である。

今回，我々は multiple old lacunar infarction の患者23例を対象に，赤血球集合およびその重要な影響因子であるフィブリノーゲン濃度に対する桂枝茯苓丸の影響について検討した。赤血球集合能については，*in vitro* の指標として S10 を，*in vivo* の指標として血管内赤血球集合柱の最大内径（DEA）を用いた。また，フィブリノーゲン濃度については，トロンビン時間法を用いて測定した。対象23例を寺澤の瘀血スコアにもとづき非瘀血群5例，軽度瘀血群10例，重度瘀血群8例に群分けし比較検討した。その結果，桂枝茯苓丸は赤血球集合能の亢進を改善し，その効果は，より重度の瘀血状態で顕著であった。また，赤血球集合能の改善はフィブリノーゲン濃度の低下を介していることが示唆された。さらに桂枝茯苓丸の投与によって瘀血スコアが変化しても，瘀血スコアと赤血球集合能との相関は一定に維持されることが示された。

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