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The effect of Keisi-bukuryô-gan on blood viscosity, platelet functions and blood coagulation in normal subjects

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Abstract

The effect of Keisi-bukuryô-gan on blood viscosity, platelet functions and thromboelastogram was investigated in ten healthy volunteers. Keisi-bukuryô-gan extract was administered orally for two weeks and then followed up for another two weeks. The values of whole blood viscosity decreased significantly at a high shear rate. Platelet aggregations induced by collagen and ADP were inhibited at two weeks after Keisi-bukuryô-gan administration. Thromboxane B_2 synthesis in the platelet was also suppressed after two weeks administration of Keisi-bukuryô-gan. There was no significant change in the thromboelastogram. The results obtained suggest that Keisi-bukuryô-gan has a salutary effect on the microcirculation through both a decrease of whole blood viscosity and the suppression of thromboxane synthesis.

Key words Keisi-bukuryô-gan, blood viscosity, platelet aggregation, thromboxane B_2, thromboelastography

Abbreviations ADP, adenosine-5′-diphosphate ; PPP, platelet poor plasma ; PRP, platelet rich plasma ; TXB_2, thromboxane B_2 ; MDA, malondialdehyde ; Keisi-bukuryô-gan (Gui-Zhi-Fu-Ling-Wan), 桂枝茯苓丸

Introduction

In the course of our investigations on the "oketsu" syndrome, we have reported that the value of blood viscosity in patients with this condition syndrome is significantly elevated when compared with normal subjects,[1] and also that thromboxane synthetic pathways are significantly accelerated.[2]

Keisi-bukuryô-gan (Gui-Zhi-Fu-Ling-Wan) is thought to be one of the most important prescriptions for improving the "oketsu" syndrome. In several pharmacological works, it has been demonstrated that Keisi-bukuryô-gan inhibits platelet aggregation induced by adenosine-5′ diphosphate (ADP) and collagen *in vitro*,[3] suppresses malondialdehyde (MDA) production in platelets and prevents the formation of hepatic vein thrombosis induced by endotoxine in hyperlipidemic rats.[4] However, the effects of the oral administration of Keisi-bukuryô-gan on human blood viscosity and human platelet functions have not been determined yet.

In the present paper, we attempted to estimate the effects of the oral administration of Keisi-bukuryô-gan on blood viscosity, platelet functions and blood coagulation in healthy subjects.

Materials and Methods

Substances : A granulated preparation of Keisi-bukuryô-gan extract (Tsumura Juntendo, Inc., Tokyo, lot no. 5231821) was used for this study. Seven and one half grams of this prescription contained 1.75 g of extract obtained from the following five crude drugs : Keishi (Cinnamomi Cortex) 3 g, Bukuryo (Hoelen) 3 g, Botanpi (Mou-

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tan Cortex) 3 g, Tohnin (Persicae Semen) 3 g and Shakuyaku (Paeoniae Radix) 3 g.

Protocol of medication : Ten healthy volunteers (5 males and 5 females) consisting of students of this university were investigated. Their age was 23.6 years (range 19—25). They had a mean body weight of 59.8 kg (range 52—70). By using Terasawa's diagnostic criteria of "oketsu" syndrome,[1] their "oketsu" scores were estimated to be 32.9±6.4 S.D. Consent was obtained from individuals. During the experimental period, the subjects ate a regular diet except for red fish meat, and were prohibited from taking alcoholic beverages and drugs which might affect platelet functions. There was a one-week observation period before starting the study. No abnormal findings were observed by conventional clinical and biochemical examinations. The subjects ingested 7.5 g of Keisi-bukuryô-gan extract t.i.d. for first two weeks. Blood samples were obtained from each subjects at the beginning of the medication, and then 1, 2, 3 and 4 weeks after the initiation of the medication in outpatients.

Blood samples : For the determination of whole blood viscosity and plasma viscosity, 7 ml of blood was withdrawn from the cuvital vein into a siliconized glass tube containing ethylene-diamine-tetra-acetic acid-2Na (1.5 mg/ml). Each sample was divided into two parts, one for measuring whole blood viscosity and hematocrit, and the other for examining plasma viscosity. All samples were examined within one hour after sampling.

For the examination of platelet aggregation and thromboxane B_2 (TXB_2) formation, 10 ml of blood was collected into 3.8% (W/V) sodium citrate (9 : 1). After centrifugation at $150\times g$ for 12 min at 23℃, the supernatant was obtained ; this fluid was called platelet rich plasma (PRP). The precipitate was further centrifuged at $1100\times g$ for 15 min at 4℃, yielding another supernatant ; it was labeled platelet poor plasma (PPP). The number of platelets in PRP was determined with an automatic platelet counting apparatus (Celltac 4500, Nihon-Kohden Co., Ltd., Tokyo).

For thromboelastography, 2 ml of blood was withdrawn into a plastic syringe.

All samples were taken before supper (about 4 hours after lunch).

Measurement of viscosity : Viscosity of whole blood and plasma were measured by a cone-plate rotational viscometer (Bio-rheolizer, Tokyo Keiki Co., Ltd., Tokyo), as described in a previous paper.[1] The measurements were carried out at 37℃ and a cone angle of 1°37′. For calibration of the viscometer, the standard oil solution JS 10 (Syowa Oil Co., Ltd., Tokyo, lot no. 10) was employed. Measurement of whole blood viscosity was carried out at five different shear rates (19.2, 38.4, 76.8, 192.0, 384.0 sec^{-1}).

The values of whole blood viscosity (apparent viscosity) were corrected to a standard hematocrit value of 45% by using the following equation[1] :

$19.2\ sec^{-1}$; $\log_{10}\eta_{45}=\log_{10}\eta+0.0160\times(45-Ht)$
$76.8\ sec^{-1}$; $\log_{10}\eta_{45}=\log_{10}\eta+0.0111\times(45-Ht)$
$384.0\ sec^{-1}$; $\log_{10}\eta_{45}=\log_{10}\eta+0.0113\times(45-Ht)$

η : apparent viscosity (cp)
Ht : hematocrit (%)

Analysis using Casson's equation : In order to elucidate the rheometric characteristics of blood, we used Casson's equation, which is expressed as follows :

$$\sqrt{\tau}=\sqrt{\tau_f}+\sqrt{\eta_c}\times\sqrt{\dot{\gamma}}$$

τ : shear stress
η_c : Casson viscosity
$\dot{\gamma}$: shear rate
τ_f : Casson yield stress

The shear stress of each subject was calculated by using the blood viscosity values at five points of shear rate. Then by using the approximation method, both Casson viscosity and Casson yield stress were estimated. Further, they were corrected to a standard hematocrit value of 45% by using the following equations[1] :

$$\log_{10}\eta_{c45}=\log_{10}\eta_c+0.00936\times(45-Ht)$$
$$\tau_{f45}=0.00643\times(45-Ht)+\tau_f$$

Determination of platelet aggregation : The platelet count of PRP was adjusted to 3×10^5 per μl by adding autologous PPP. The aliquot of PRP (200 μl) was placed in a cuvette in an automatic

platelet aggregometer (NKK Hema-tracer I, Niko Bio-Science Inc., Tokyo), together with one of the platelet aggregation agents, collagen (Collagen reagent "HORM" from Hormon Chemie Co., Ltd., Munich, West Germany) or ADP (from Sigma Co., Ltd., St. Louis, MO., USA). The measurement of aggregability of each sample was estimated with the maximal aggregation. The threshold dose of aggregants was demonstrated with an observed value of 50% maximum aggregation at the beginning of the experimentation.

Measurement of thromboxane B_2 formation[5] : TXB_2 formation was determined after collagen or ADP induced platelet aggregation. After 4 min of aggregation, 100 μl of the reaction mixture was transferred to a plastic tube containing 200 μl of 50 mM Tris HCl buffer (pH 7.5) with 1% gelatin. This tube was immediately dipped into liquid nitrogen for 10 sec and stored at −80℃ until the assay of TXB_2 by radioimmunoassay (TXB_2 [^{125}I] RIA KIT, New England Nuclear, Boston).

Thromboelastography[6] : In order to estimate the process of blood coagulation including fibrinolysis, we used thromboelastography (Thromboelastograph D, Hellige, Freiburg, West Germany). The thromboelastogram was evaluated by using the reaction time (r), the coagulation time (k), the clotting time (r+k), the maximum amplitude (ma) and the shear modulus (me).

Measurement of hematocrit and other parameters : The value of hematocrit (Ht) 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). Every sample was measured for total protein, albumin, total cholesterol, red blood cell count and total fibrinogen values.

Statistical evaluation : Statistical evaluation was performed by analysis of the paired Student's t-test between the results obtained before and after the ingestion of Keisi-bukuryô-gan extract.

Results

Changes in whole blood viscosity and plasma viscosity

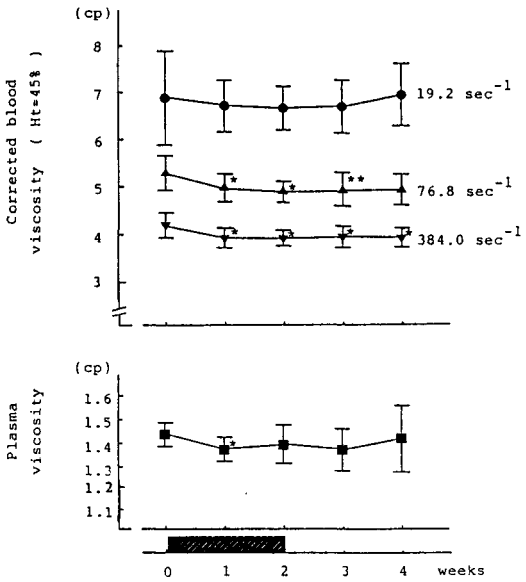

Fig. 1 Changes in blood viscosity and plasma viscosity during the experimental period.
The values of blood viscosity were corrected to a standard hematocrit values of 45% as described in "Materials and Methods." Plasma viscosity was measured at 384.0 sec^{-1}. Shaded parts indicate the administration period of Keisi-bukuryô-gan. Each value represents the mean±S.D. $*p<0.05$, $**p<0.01$.

The change of whole blood viscosity and plasma viscosity are shown in Fig. 1. The values of whole blood viscosity at 76.8 sec^{-1} and 384.0 sec^{-1} significantly decreased after Keisi-bukuryô-gan administration. The effects were seen to continue for a few weeks after the end of the administration. But those at low shear rate, 19.2 sec^{-1}, did not change. The value of plasma viscosity was seen to have decreased significantly at two weeks. On the other hand, there were no significant changes in Ht values throughout the experimental course (data not shown).

Changes in Casson viscosity and Casson yield stress

As shown in Table I, the values of Casson viscosity significantly decreased at one week ($p<0.05$) and at two weeks ($p<0.05$). There were no significant changes in Casson yield stress during the experiment.

Changes in platelet aggregability

Platelet aggregation induced by collagen,

Table I Effect of Keisi-bukuryô-gan extract on Casson viscosity and Casson yield stress in normal subjects.

	Casson viscosity[#1] (cp)	Casson yield stress[#1] (dyn/cm²)
before[#2]	3.55±0.26	0.132±0.032
1 week	3.32±0.18*	0.131±0.018
2 weeks[#3]	3.38±0.22*	0.115±0.028
3 weeks	3.38±0.21	0.124±0.029
4 weeks	3.32±0.17*	0.141±0.029

The values are expressed as mean±S.D. $*p<0.05$.
#1 corrected values at Ht 45%.
#2 before : at the beginning point of medication.
#3 2 weeks : at the complete point of medication.

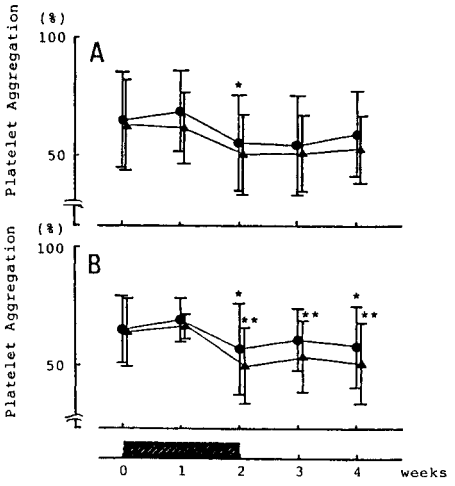

Fig. 2 Changes in platelet aggregation during the experimental period.
(A) ; Platelet aggregation induced by collagen (● ; 1 μg/ml) or ADP (▲ ; 3 μM). (B) ; Platelet aggregation induced by a threshold dose of collagen (●) or ADP (▲). Each value represents the mean±S.D. $*p<0.05$, $**p<0.01$.

ADP, or threshold doses of aggregants during the experimental period is shown in Fig. 2. Both platelet aggregation induced by collagen (1 μg/ml) and ADP (3.0 μM) decreased at two and at three weeks. The effects of Keisi-bukuryô-gan were seen to last for at least two weeks after the end of the administration.

Platelet aggregation induced by threshold doses of collagen and ADP decreased significantly after oral administration.

There were no significant changes in platelet count in any of the subjects during the experiment (data not shown).

Thromboxane B_2 formation

TXB_2 formation induced by threshold doses of collagen and ADP was significantly suppressed after two weeks administration of Keisi-bukuryô-gan (Table II). The suppression was also

Table II Effect of Keisi-bukuryô-gan extract on thromboxane B_2 formation.

	Threshold dose	
	collagen	ADP
before[#1]	56.0±51.9 (ng/ml)	65.1±22.2 (ng/ml)
1 week	57.0±27.5	66.0±18.0
2 weeks[#2]	27.1±25.4*	33.4±16.0*
3 weeks	43.0±27.8	52.2±29.6
4 weeks	40.6±27.0	62.5±19.6

The values are expressed as mean±S.D. $*p<0.05$.
#1 before : at the beginning point of medication.
#2 2 weeks : at the complete point of medication.

Table III Effect of Keisi-bukuryô-gan extract on thromboelastogram.

	r (min)	k (min)	r+k (min)	ma (mm)	me (%)
before#1	12.0±3.00	6.2±1.41	17.2±4.03	46±6.5	92±22.4
1 week	12.0±1.75	5.9±1.39	18.0±2.94	49±3.7	95±14.0
2 weeks#2	12.5±3.14	5.7±1.52	17.8±4.25	47±7.7	94±27.2
3 weeks	12.3±1.31	5.6±0.77	17.9±1.95	46±4.8	87±16.4
4 weeks	12.4±1.66	6.1±1.32	18.4±2.68	47±3.5	90±12.6

The values are expressed as mean±S.D. r : reaction time, k : coagulation time, r+k : clotting time, ma : maximum amplitude, me : shear modulus.
#1 before : at the beginning point of medication.
#2 2 weeks : at the complete point of medication.

Table VI Effect of Keisi-bukuryô-gan extract on red blood cell count, total protein, albumin, total cholesterol and total fibrinogen.

	RBC ($\times 10^4$)	TP (g/dl)	Alb (g/dl)	Cho (mg/dl)	Fib (mg/dl)
before#1	449±45	7.2±0.2	5.1±0.26	171±20	196±39
1 week	432±51	7.1±0.2	5.0±0.22	164±17	205±36
2 weeks#2	449±41	7.6±0.3**	5.3±0.20**	175±21	214±27
3 weeks	446±51	7.3±0.4	5.1±0.27	165±22	204±27
4 weeks	435±46	7.2±0.3	5.1±0.19	168±23	188±32

The values are expressed as mean±S.D. **$p<0.01$. RBC : red blood cell count, TP : total protein, Alb : albumin, Cho : total cholesterol, Fib : total fibrinogen.
#1 before : at the beginning point of medication.
#2 2 weeks : at the complete point of medication.

observed both at three and four weeks, although not significantly.

Changes in parameters of the thromboelastogram

There were no significant changes in r, k, r + k, ma and me values during the experiment (Table III).

Changes in parameters of blood chemistry and hematological examinations

The values of total protein and serum albumin significantly increased at two weeks ; however, no significant changes were observed in the other parameters (Table IV).

Discusion

We have previously reported that the "oketsu" syndrome was closely related to hyperviscosity of blood and accelerated MDA production in platelets.[1,2] In this paper, we have investigated the effects of oral administration of Keisi-bukuryô-gan on blood viscosity, platelet functions and blood coagulation.

Keisi-bukuryô-gan was first described in Chinese medicinal classics "Chin-Kuei-Yao-Lueh"[7] (金匱要略, 200 A.D.) and is known as one of the most important "Kampoh" prescriptions used as a remedy for the "oketsu" syndrome. This prescription contains Moutan Cortex, Persicae Semen and Paeoniae Radix, which are all thought to improve the "oketsu" syndrome. In our daily practice of Kampoh medicine, we sometimes prescribe Keisi-bukuryô-gan for the patients with Raynaud syndrome[8] or with a hyperviscosity condition, *i.e.*, intermittent claudication[9] and coronary heart disease.[10]

Blood is considered to be a non-Newtonian fluid, and so its apparent viscosity is significantly affected by hematocrit. In order to eliminate this influence of hematocrit, a mathematical method was employed and the apparent values of viscosity were corrected. As shown in Fig. 1, Keisi-bukuryô-gan has the effect of reducing

whole blood viscosity at 76.8 sec^{-1} and at 384 sec^{-1} in healthy volunteers. On the other hand, in order to elucidate the rheometric characteristics of blood, we used Casson's equation. The shear stress of each subject at each time was calculated by using the blood viscosity values at five points of shear rate, *i.e.*, 19.2, 38.4, 76.8, 192.0, and 384.0 sec^{-1}. Then, by using the approximation method, both Casson viscosity and Casson yield stress were estimated. These values are not affected by the shear rate, so they are thought to be reliable parameters for estimating the features of blood flow. The results obtained from each subject showed a good correlation with Casson's equation. The results further indicate that the changes of the rheometric characteristics of blood can be explained by two values, Casson viscosity and Casson yield stress. As shown in Table I, significant decreases in Casson viscosity were observed after the oral administration of Keisi-bukuryô-gan. These results suggested that Keisi-bukuryô-gan has the potential to improve peripheral microcirculation by reducing the blood viscosity.

Isogai[11] has pointed out five significant factors which may affect blood flow : hematocrit, erythrocyte aggregation, erythrocyte deformability, internal erythrocyte viscosity and plasma viscosity. The mechanisms by which the values of whole blood viscosity and Casson viscosity were decreased have yet to be been demonstrated. It is well known that erythrocyte agregation is related to blood viscosity at a low shear rate and Casson yield stress.[12] However, these parameters did not change in this experiment, and also the values of hematocrit and plasma viscosity did not change so remarkably. Therefore the mechanisms may be at least partially related to changes in erythrocyte deformability and/or internal erythrocyte viscosity. In fact, Oda *et al.*[13] have reported that Keisi-bukuryô-gan increased erythrocyte deformability in rats. Further investigations are called for to resolve this issue.

With respect to platelet functions, the platelet aggregation induced by external aggregants was not changed after one week of administration ; however, the aggregation was then seen to be suppressed at two weeks, and this effect remained even after the end of the administration (Fig. 2).

In order to elucidate the mechanism of the anti-aggregatory effect of Keisi-bukuryô-gan we investigated the thromboxane formation. Thromboxane A_2 (TXA_2) is the most important arachidonic acid metabolite because of its potent aggregatory effect on platelets. As shown in Table II, the values of TXB_2, a stable metabolite of TXA_2, were suppressed at two weeks by Keisi-bukuryô-gan administration. Accordingly, the reduction of platelet aggregation by the oral administration of Keisi-bukuryô-gan might be ascribed to a decrease in thromboxane formation.

The results obtained in this study are essentially the same as those of our preceding papers using Tôki-syakuyaku-san,[14] one of the anti-"oketsu" drugs, and Keisi-bukuryô-gan.[2] But, in those studies, we measured the changes of platelet agregation and MDA production with only one week of administration.

In the present experiment it was noted that blood viscosity and platelet functions were affected by normal clinical doses of Keisi-bukuryô-gan extract. The effects appeared one to two weeks after the start of administration and lasted at least one week after it was ceased.

Tani *et al.*[15] reported that Keisi-bukuryô-gan decreased the blood viscosity in rats. Hirai *et al.*[5] revealed that Moutan Cortex and its main component, paeonol, inhibit platelet aggregation *in vivo* and *in vitro*. In addition, Takenaga *et al.*[16] reported that cinnamic aldehyde, a main component of Cinnamomi Cortex, reduced platelet aggregation *in vitro*. Both Moutan Cortex and Cinnamomi Cortex are ingredients of Keisi-bukuryô-gan. Keisi-bukuryô-gan has been reported to have not only anti-fibrinolysis or anti-coagulation activity, but also anti-platelet aggregation activity *in vitro*.[3] The results obtained in the present study *in vivo* are in agreement with these reports.

We applied thromboelastography in order to study the effects of this prescription on blood coagulation and fibrinolysis. As shown in Table III, the values of r, k, r+k, ma and me did not change appreciably, and in fact, all remained

within normal limits. Although it has been reported that the thromboelastogram revealed a statistically significant negative correlation with the "oketsu" syndrome,[17] the present data suggested that Keisi-bukuryô-gan might have no effects on blood coagulation in normal subject. In addition, significant changes in the values of hematocrit, total cholesterol, red blood cell counts and total fibrinogen were not observed. There were no recognizable subjective complaints such as anorexia, general malaise, diarrhea or headache and no elevation of transaminases during the experimental period.

In conclusion, our present paper demonstrated that Keisi-bukuryô-gan possesses the potential to improve peripheral microcirculation by reducing blood viscosity and platelet aggregation. This reduction of platelet aggregation might be due to the inhibition of TXA_2 formation. These results, at least in part, reflect the well known medical concepts about the properties of this prescription in traditional Japanese-Oriental (Kampoh) medicine.

Research into Kampoh prescriptions requires a clear understanding of the relationship between "SHO" (indicative conformation of the prescription) and the medication that has to be administered for each "SHO." The results presented in this paper were obtained during a four-week observation period of healthy subjects, so it must be considered necessary that any further research of the clinical effects of Keisi-bukuryô-gan be performed in conjunction with a reliance upon the concept of "SHO."

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和文抄録

桂枝茯苓丸の血液粘度，血小板凝集能，トロンボエラストグラムに対する作用を，健常人10人について検討した。実験は，桂枝茯苓丸エキス7.5gを2週間経口投与し，その後2週間まで，1週間ごとに測定した。ヘマトクリット45%に補正した全血粘度は，投与1週間後で高ずり速度において，有意に低下した。血小板凝集能とトロンボキサンB_2の生成は，投与2週間後で抑制された。トロンボエラストグラムは変化がなかった。以上，全血粘度の低下およびトロンボキサンB_2生成の抑制を介して，桂枝茯苓丸は微小循環を改善する可能性のあることが示唆された。

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