

Platelet and Cholesterol Responses Caused by Oral Administration of Ginseng Extract in 66% Hepatectomized Rats

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Summary. Platelet counts and serum cholesterol levels in the blood were examined after oral administration of ginseng extract (GE) to 66% hepatectomized rats. A significant decrease in the platelet count (PC) and adhesiveness (PA) was obtained 3 days after hepatectomy when GE 125 mg/kg/day was administered, and the PA reduction was dose dependent in the range of 0-250 mg/kg/day. The serum concentration of total cholesterol was also decreased by the GE administration, but food intake was unaffected. Serum parameters indicating liver and kidney functions were unchanged after GE administration except for lipid metabolic parameters.

Because enhanced PC and PA in the presence of hypercholesterolemia are apt to lead to thromboembolism after major abdominal surgery, these results suggest that orally administered GE is capable of preventing the thromboembolic tendency associated with major hepatic surgery.

Key words—major abdominal surgery, hepatic resection, ginseng delivery, platelet, cholesterol, postoperative complications.

INTRODUCTION

Thromboembolism after major abdominal surgery is a significant problem for both surgeon and patient.¹⁻³⁾ The mechanisms of postoperative thromboembolism are considered to be multifactorial: circulating platelets are implicated in mural thrombus formation, and platelets become hyperreactive in the presence of hypercholesterolemia.⁴⁻⁶⁾ Recently it was

found that cholesterol concentration at the time of 66% hepatectomy in rats could be reduced by oral administration of ginseng extract (GE, an oriental medicine made from the roots of panax ginseng C.A. Meyer).^{7,8)} In connection with this, either a lipophilic fraction or saponins from panax ginseng has been shown to regulate the levels of platelet activating factors such as 5-hydroxytryptamine, cGMP, cAMP, and thromboxane A₂, in addition to inhibiting the aggregation of human and rat platelets induced by thrombin, collagen, or surgical injury *in vivo*.⁹⁻¹³⁾ These findings imply that GE moderates the postoperative thromboembolic tendency. However, in platelet thrombus formation, the platelet aggregation process is initiated by platelet adhesion,⁹⁻¹⁵⁾ and the effect of GE on this adhesion has not yet been evaluated.

This study was designed to investigate whether orally administered GE influences rat platelet and cholesterol under conditions of a 66% hepatectomy simulating major abdominal surgery.

MATERIALS AND METHODS

Forty-two male Wistar rats (Charles River Japan Inc., Tsukuba) were used. They were housed in the laboratory animal facility of Niigata University. The animals were reared separately and allowed free access to laboratory chow (Oriental MF, Oriental Co., Tokyo) and tap water. The room temperature was controlled to 24±1°C with 12 h/12 h light/dark cycles (lighting from 07:00 to 19:00 h). Estimates of individual body weight, food and water intake and surgery were made between 10:00 and 12:00.

The animals were divided into two groups: ginseng extract (GE)-treated (n=24) and saline-treated groups (n=18). The dose of GE was 125 or 250 mg/

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kg/day; this dose was effective in reducing the serum cholesterol concentration.^{7,8)}

when the animals attained a weight of about 180 g (at 5.6–5.8 weeks of age), hepatectomy was performed under ketamine hydrochloride (35 mg/kg, i. p.) anesthesia by the method previously described.¹⁶⁾ In brief, the median and left lateral lobes of the liver, constituting two-thirds of the total liver mass, were removed. The abdominal wall was closed in layers. After surgery, the animals were returned to their cages and allowed access to food and water.

Blood for determination of the platelet count (PC) and adhesiveness (PA) was taken from the abdominal aorta, and the PA was estimated by Hellem's method¹⁷⁾: native blood was forced through a glass bead column, and PC before and after passing the column was taken from blood with EDTA added; then the percentage of retained platelets defined as PA was calculated.

Blood for chemical analysis was obtained from the aorta, cooled immediately with iced water, and centrifuged at 2,200 rpm for 20 min. Then the separated serum was stored at -20 °C until measurement of the following parameters with an autoanalyzer (Hitachi-736, Hitachi, Tokyo)^{16,18)}: albumin (Alb, Bromcrezol green method), glutamic pyruvic transaminase (GPT, Ultraviolet method), alkaline phosphatase (Alp, Bessey-Lowry method), total bilirubin (TB, Azobilirubin method), blood urea nitrogen (BUN, Urease ultraviolet method) and total cholesterol (TC, Cholesterol oxidase colorimetric method).

GE (Tsumura & Co., Tokyo) dissolved in saline was used. GE 125 or 250 mg/kg was orally given once a day (10:00–12:00 h). This agent was given from 3 days before hepatectomy, and continued until the rats were sacrificed. The volume of each administration was 0.1 ml. Saline was given as the control. A test solution was first confirmed as swallowed when it was dropped on the tongue.

Data were ANOVA analyzed, and specific values were evaluated by Duncan's multiple range test: $p < 0.05$ was defined as significant.

RESULTS

PC and PA enhanced by hepatectomy were significantly decreased by GE 125 mg/kg/day administration 3 days after hepatectomy. There was no dose dependency in the PC reduction, while the PA reduction was dose dependent in the range of 0–250 mg/kg/day (Figs. 1 and 2).

Food intake was unchanged, but water intake was decreased during GE administration (Table 1).

Although hepatectomy failed to change the serum TC concentration, it was decreased significantly by GE administration 3 days after hepatectomy, and the TC decrease tended to be dose dependent (Fig. 3). Serum chemical parameters related to liver and kidney function were unchanged except for cholesterol (Table 2).

Table 1 Food and water intake during GE administration

	Saline	GE (250 mg/kg/day)
Food intake (g)	117.0±3.8	120.3±3.2
Water intake (ml)	168.1±10.7	189.1±8.4 ^a

These values were obtained during the period from 3 days before to 3 days after hepatectomy. Values are the mean±SEM (n=6).

^a $p < 0.01$ vs saline.

Table 2 Serum chemical scores after GE administration

	Saline	GE (250 mg/kg/day)
Alb (g/dl)	1.7±0.1	1.7±0.1
GPT (U/L)	45.2±5.1	44.1±3.5
Alp (U/L)	1113±105	1148±127
TB (mg/dl)	0.1±0.0	0.1±0.0
BUN (mg/dl)	12.8±0.3	12.9±0.4
TC (mg/dl)	64.3±2.0	54.1±1.8 ^a

These values were obtained 3 days after hepatectomy. Values are the mean±SEM (n=6). ^a $p < 0.01$ vs saline.

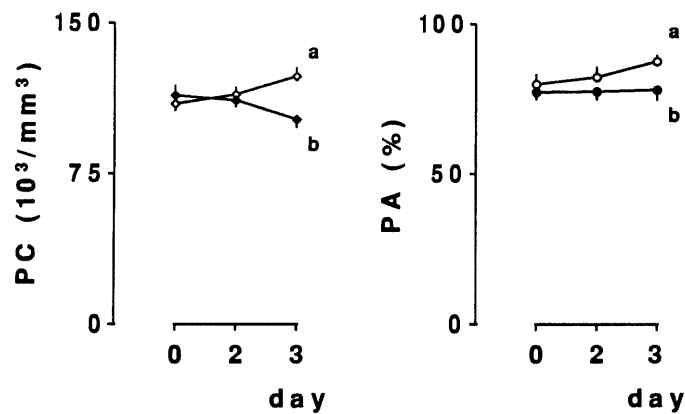


Fig. 1. Time courses for PC and PA after GE administration. GE (◆-●, 125 mg/kg/day) or saline (○-◇) was given orally. Day 0 is the day of hepatectomy. Values are the mean \pm SEM (n=6). ^a $p < 0.01$ vs saline (day 0). ^b $p < 0.01$ vs saline (day 3).

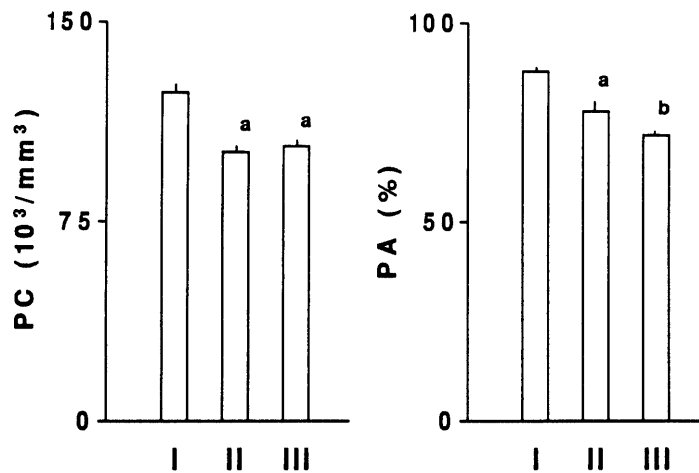


Fig. 2. Changes in PC and PA after GE administration. Two different doses of GE (II, 125 mg/kg/day; III, 250 mg/kg/day) and saline (I) were given orally, and values 3 days after hepatectomy were taken. Values are the mean \pm SEM (n=6). ^a $p < 0.01$ vs I. ^b $p < 0.05$ vs II.

DISCUSSION

Data from this study showed that GE corrects the quantity and quality of platelets under hepatectomy simulating major abdominal surgery; enhanced PC and PA caused by 66% hepatectomy were reduced by oral administration of GE. This is partially consistent with the view that Panax ginseng inhibits platelet aggregation or coagulation in animals in the absence of hepatectomy.^{12,15} Although platelet aggregation follows platelet adhesion in platelet thrombus formation,⁹⁻¹⁵ GE exhibits an action relevant to this adhesion.

The PA response may be peculiar to GE because there was dose dependency, even though it is difficult to explain the mechanism. At least, however, the PA response could not simply be ascribed to the PC response showing no dose dependency. GE may alter the quantity and quality of platelet differentially. Further study on this point is required.

Thromboembolism after major surgery is initiated and promoted by several factors, and enhanced PC, PA and hypercholesterolemia play key roles.⁴⁻⁶ In this study, cholesterolemia associated with hepatectomy was also suppressed by GE. This is in keeping with previous reports indicating that ginseng reduces the blood cholesterol concentration^{7,8,19,20} by

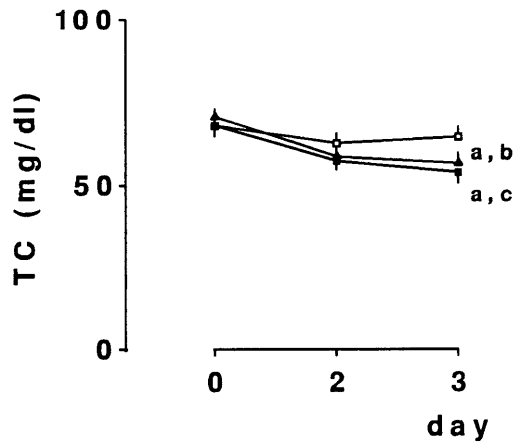


Fig. 3. Time courses for TC concentrations after oral GE administration. Two different doses of GE (▲, 125 mg/kg/day; ■, 250 mg/kg/day) and saline (□) were given. Day 0 is the day of hepatectomy. Values are the mean \pm SEM (n=6). ^a $p < 0.01$ vs saline (day 0). ^b $p < 0.05$ vs saline (day 3). ^c $P < 0.01$ vs saline (day 3).

inhibiting cholesterol acyltransferase.²¹⁾ Considering this finding together with the result showing that GE reduces PC and PA after major hepatic resection, it is possible to postulate that GE effects the regression of postoperative thromboembolic formation.

Dietary cholesterol has been shown to modify liver lipid metabolism,²²⁾ and GE has been shown to change food intake,²³⁾ but the dose of GE used in this study did not affect consumption (Table 1). It is believed that cholesterol in the food is not involved in the cholesterol response observed.

Although GE has been found to improve GPT and Alp liver functional parameters,²⁴⁾ these concentrations were unchanged after GE administration (Table 2). It appears that the dose of GE utilized was too small to have any effect.

In the clinical field, low-molecular-weight heparin, which has a longer half-life in the blood, has been used to prevent thromboembolism after major surgery, and the agent is administered intravenously.²⁵⁻²⁸⁾ On the other hand, GE was administered orally and its action lasted for a day. It is likely that GE has an advantage as an oral medicine.

As mentioned above, GE works to depress the thromboembolic tendency associated with hepatectomy simulating major abdominal surgery.^{27,28)} Clinical application of GE for hepatic resection is awaited. However, since GE comprises many different constituents,²⁹⁾ those specific constituents of GE producing such an action should also be identified.

These observations lead us to the conclusion that GE may be applicable in the prevention of thromboembolic tendency evoked by major abdominal surgery.

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