• BRIEF REPORTS •

Abnormal function of platelets and role of angelica sinensis in patients with ulcerative colitis

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Abstract

AIM: To explore the abnormal function of platelets and the role of angelica sinensis injection (ASI) in patients with ulcerative colitis (UC).

METHODS: In 39 patients with active UC, 25 patients with remissive UC and 30 healthy people, α-granule membrane protein (GMP-140) and thromboxane B_2 (TXB_2) were detected by means of ELISA, 6-keto-PGF_{1a} was detected by radioimmunoassay, platelet count (PC) and 1 min platelet aggregation rate (1 min PAR) were detected by blood automatic tester and platelet aggregation tester respectively, and von Willebrand factor related antigen (vWF:Ag) was detected by the means of monoclonal -ELISA. The 64 patients with UC were divided into two therapy groups. After routine treatment and angelica sinensis injection (ASI) + routine treatment respectively for 3 weeks, all these parameters were also detected.

RESULTS: The PC, 1 min PAR and levels of GMP-140, TXB_2, and vWF:Ag in active UC were significanrly higher than those in remissive UC and normal controls ($P<0.05$-0.01).Meanwhile, 1 min PAR and levels of GMP-140, TXB_2, and vWF:Ag in remissive UC were still significantly higher than those in normal controls ($P<0.05$). Furthermore, 6-keto-PGF_{1a} level in active and remissive UC was remarkably lower than that in normal control ($P<0.05$-0.01). These parameters except 6-keto-PGF_{1a} were significantly improved after the treatment in ASI therapy group ($P<0.05$-0.01), whereas they all were little changed in routine therapy group ($P>0.05$).

CONCLUSION: Platelets can be significantly activated in UC, which might be related with vascular endothelium injury and imbalance between TXB_2 and 6-keto-PGF_{1a} in blood. ASI can significantly inhibit platelet activation, relieve vascular endothelial cell injury, and improve microcirculation in UC.

INTRODUCTION

Although the pathogenesis of ulcerative colitis (UC) still remains unknown, clinical observations have found that increased platelet number and platelet activation are notable characteristics of UC[1-6]. Reseaches revealed that the extract of platelets from patients with UC could induce intense inflammatory reaction for a few hours after they were injected into the skin of healthy people while the extracts of neutrophils and basophils had no such effect, suggesting that platelet was an important inflammatory cell, and could directly cause inflammation response[7,8]. Moreover, recent investigations indicated that the high blood coagulative state in patients with UC was closely related with the abnormal function of platelets, which resulted in high a probability of microvascular thrombosis and microcirculation dysfunction, main causative factors for UC[9,10]. More and more studies suggested that the role of platelets might represent a previously unrecognized component of UC pathogenesis and that antiplatelet drugs may provide new therapeutic possibilities in the management of UC[7,8,11-19].

The principal ingredient of ASI is sodium ferulate (SF), possesses various pharmacological effects on platelet function and blood circulation including regulating activity of platelets, inhibiting aggregation and liberation of platelets, improving microcirculation and decreasing consistency of blood[20-25]. Moreover, ASI almost has no toxicity[20]. So we presume that ASI might contribute to the treatment of UC. The aim of this study was to further explore the abnormal function of platelets and their mechanism in 64 patients with UC. At the same time, changes of the parameters related to platelet activation as well as clinical symptoms were observed before and after the treatment with ASI to investigate the effects of ASI on the abnormal function of platelets.

MATERIALS AND METHODS

Patients and grouping

A total of 64 patients with UC were recruited from Renmin Hospital of Wuhan University and Zhongnan Hospital of Wuhan University between January, 2000 and March, 2003. The diagnosis of UC was established according to the criteria reported in the literature[15]. According to the evaluating criteria of Jones standards for UC phase[26], 39 cases were evaluated as active UC (16 males, 23 females, aged 29 to 65, mean age 46.3 years, average disease course 10.6 months), 25 cases were evaluated as remissive UC (11 males, 14 females, mean age 43.6 years, average disease course 18.8 months). Thirty healthy volunteers without administration of antiplatelet medicine in recent 1 month (19 males, 11 females, mean age 42.8 years) were also enrolled in the study as normal control group. All the patients and healthy volunteers had no smoking history and administration of antiplatelet medicine. The 64 patients were randomly divided into routine therapy group and ASI therapy group according to the age. Among the 33 cases in routine therapy group and the 31 cases in ASI therapy group, 31 cases and 30 cases completed the experiment respectively. All groups showed comparable characteristics in sex and age.

Measurement of observed parameters

Venous blood samples 2 ml from the 64 patients without breakfast in the morning were obtained 24 hours after admission. At the same time, 2 ml blood sample was obtained from the 30 healthy volunteers under the same conditons. After mixed with 5% EDTA-Na$_2$ (v/v), an anticoagulant, the blood samples were quickly centrifuged at 3 000×g for 5 min. After separated from plasma, the blood samples were stored at -40℃ until detection for α-granule membrane protein (GMP-140), thromboxane B$_2$ (TXB$_2$), 6-keto-prostaglandin F$_{1a}$ (6-keto-PGF$_{1a}$) and von Willebrand factor related antigen (vWF:Ag). GMP-140 and TXB$_2$ were detected by using the ELISA kits, 6-keto-PGF$_{1a}$ was detected by the radioimmunoassay kit, and vWF:Ag was detected by the monoclonal-ELISA kit following the manufacturer's instructions. All the above detection kits were purchased from Institute of Thrombosis and Coagulation, Medical College of Suzhou University in China. At the same time, platelet count (PC) and 1 min platelet aggregation rate (1 min PAR) were measursed by a blood automatic tester (Beckman Co. USA) and a platelet aggregation rate tester (Wuxi Second Electronic Apparatus Factory) respectively using another venous blood sample obtained from all the subjects under the same conditon. After the treatments for 3 weeks, venous blood samples from 64 patients were obtained again and all the observed parameters were detected for the second time.

Treatment

After admission, the 33 patients in routine therapy group received routine treatment for 3 weeks including having semifluid diet, correctting the disorder of liquid and electrolyte and 2 g/day Etiasa, modified-release microgranules in sachets produced by Laboratoires Ethypharm, 2-3 times a day. Based on the above routine treatment, 40 ml ASI produced by Pharmaceutical Factory of Zhongnan Hospital of Wuhan University was added to 250 ml 10% glucose iv. drop once a day for 3 weeks for the 31 patients in ASI therapy group.

Statistical analysis

Experimental results were expressed as mean±SD. Statistical differences between groups were determined by ANOVA followed by Student's *t* test. A *P* value less than 0.05 was considered statistically significant.

RESULTS

Change of all observed parameters in patients with UC

Compared with normal group, 1 min PAR and levels of GMP-140, TXB$_2$, and vWF:Ag in UC group and in remissive UC group and active UC group were all significantly increased while 6-keto-PGF$_{1a}$ level was remarkably decreased (*P*<0.05-0.01). Meantime, PC in active UC group was obviously higher than that in normal group (*P*<0.01), whereas there was no significant difference in PC between remissive group and normal group (*P*>0.05). Furthermore, PC, 1 min PAR and levels of GMP-140, TXB$_2$, and vWF:Ag in active UC group were also significantly elevated compared with remissive group (*P*<0.05), while 6-keto-PGF$_{1a}$ was little changed (*P*>0.05) (Table 1).

Effects of ASI on abnormal function of platelets in patients with UC

After the treatment for 3 weeks, all observed parameters had no obvious changes compared with those before the treatment in the routine therapy group (*P*>0.05), whereas the elevated PC, 1 min PAR and levels of PC, GMP-140, TXB$_2$, and vWF: Ag were significantly decreased in the ASI therapy group compared with those before the treatment (*P*<0.05-0.01), while 6-keto-PGF$_{1a}$ level was still little changed (*P*>0.05) (Table 2).

DISCUSSION

Recent investigations indicate that platelets not only involve the increased incidence of systemic thromboembolism and a procoagulant blood state in UC but exhibit several proinflammatory properties including release of inflammatory and coagulant mediators such as platelet activated factor, thromboxane, thrombocytin (5-HT), platelet factor 4, platelet beta-thromboglobulin, platelet –derived growth factors, and recruitment, chemotaxis and modulation of the activity of other inflammatory cells[7-12, 27-31]. Moreover, platelet activation in UC might be responsible for the secondary activation of polymorphonuclear leukocytes (PMN) and increased the production of reactive oxygen species by PMN, which could account for the increase in PMN-mediated tissue injury associated with UC[32]. In addition, Danese and his coworkers found that activated platelets in UC expressed enhanced levels of CD40 ligand and interacted with CD40-positive human intestinal microvascular endothelial cells, which could produce

Table 1 Changes of all observed parameters in patients with UC 24 h after admission (mean±SD)

Group	n	PC(×10^9/L)	GMP-140 (ug/L)	TXB$_2$ (ng/L)	6-keto-PGF$_{1a}$ (ng/L)	1 min PAR (%)	VWF:Ag (%)
Normal control	30	158.2±32.5	41.4±10.2	68.4±26.4	18.3±6.8	38.6±14.2	103.6±23.7
Patients with UC	64	189.8±68.3[a]	52.1±17.8[b]	98.8±55.4[b]	12.9±8.2[b]	58.2±21.5[b]	143.6±52.7[b]
Remissive UC	25	173.7±36.4[c]	48.4±11.4[ac]	87.4±32.7[ac]	14.5±6.0[a]	47.8±16.5[ad]	127.9±46.1[ac]
Active UC	39	201.8±48.6[b]	54.9±13.2[b]	115.5±46.8[b]	11.3±6.4[b]	65.5±19.2[b]	154.5±48.9[b]

[a]*P*<0.05, [b]*P*<0.01 *vs* normal control, [c]*P*<0.05, [d]*P*<0.01, *vs* active UC group.

Table 2 Effects of ASI on abnormal function of platelet in patients with UC (mean±SD)

Group	n	PC(×10^9/L)	GMP-140 (ng/L)	TXB$_2$ (ng/L)	6-keto-PGF$_{1a}$ (ng/L)	1 min PAR (%)	VWF:Ag (%)
Routine therapy							
Before therapy	33	188.6±38.5	52.3±15.2	96.9±38.1	13.9±5.3	59.4±14.7	149.1±48.0
After therapy	31	179.3±36.2[c]	48.8±13.7[c]	87.7±28.6[c]	16.2±5.7[c]	53.1±15.6[c]	137.3±48.2[c]
ASI therapy							
Before therapy	31	193.9±41.4	51.1±13.8	99.3±33.1	12.7±5.3	56.8±17.2	139.5±50.2
After therapy	30	171.3±37.8[a]	37.0±10.9[b]	70.2±25.9[b]	16.4±6.2[c]	45.3±14.4[b]	102.4±24.7[b]

[a]*P*<0.05, [b]*P*<0.01, [c]*P*>0.05 *vs* before therapy group.

proinflammatory mediators, up-regulate cell adhesion molecule expression and secrete chemokines such as IL-8, a very important proinflammatory interleukin in UC. Meantime, the expression of functional IL-1R and IL-8R on the surface membrane of platelets in UC was found to be significantly increased[33,34].

GMP-140, a membrane glycoprotein, is mainly located in α-granule membrane of normal platelets. Only when platelets were activated and the granule were releasod, GMP-140 was expessed on the platelets surface and released into blood. Therefore, GMP-140 was commonly considered as the specific marker of platelet activation[4,35]. Furthermore, investigations have proven that GMP-140 could aggravate inflammatory response in UC by adhesion of leukocytes, facilitate diapedesis and induce proinflammatory cytokine production from monocytes such as MCP-1, IL-8[35]. At the same time, TXB_2 in blood and PRA have been found to be classic markers of platelet activation[4,5,12]. In our study, 1 min PAR and levels of GMP-140 and TXB_2 in blood of patients with UC were significantly increased compared with those in normal controls. Meatime, these parameters in patients with active UC were much higher than those in patients with remissive UC. These results suggested that platelets in circulation were obviously activated in UC and degree of the platelet activation was parallel to the severity of UC. Our study also indicated that the number of activated platelets in active UC was remarkably increased compared with those in remissive UC and normal controls. So, numerous activated platelets took part in the inflammatory response.

Our study revealed the mechanisms underlying the activation of platelet in UC might be as follows: The intestine mucosal vascular endothelial cells might be damaged and the collagen was exposed, thus activating the platelets in circulation because vWF:Ag, a macromoleculear glycoprotein mainly synthesized by vascular endothelial cell, was significantly increased in patients with UC in this study, which could sensitively reflect the injury of vascular endothelium. The parallel change between vWF:Ag and GMP-140 in this study also supported the hypothesis. Thromboxane $A_2 (TXA_2)$, a strong vasoconstrictor, can intensely promote aggregation and activation of platelets while the effect of prostaglandin $I_2 (PGI_2)$, a vasodilationor, on platelet is just on the contrary. In normal situation, TXA_2 and PGI_2 are in dynamic balance and their stable metabolites are TXB_2 and 6-keto-PGF_{1a}. In our study, significantly increased TXB_2 and remarkably decreased 6-keto-PGF_{1a} in patients with UC showed the obvious imbalance between TXA_2 and PGI_2, thus promoting platelet activation as well as resulting in dyfunction of microcirculation. The above results demonstrated that inhibition of platelet activation and improvement of microcirculation shuld be involved in the treatment for UC.

Numerous investigations have demonstrated that SF, a ASI' s principal ingredient, is not only a inhibitor of TXA_2 synthetase and cyclooxygenase-2, a crucial synthetase for arachidonic acid (AA) metabolism, but depresses the activity of phospholipase A_2, thus preventing the release of AA from phospholipid of cell membrane and effectly reducing the production of AA metabolites including TXA_2 and PGE_2[36-40]. Meantime, SF could compensativly promote the synthesis of 6-keto-PGF_{1a} during AA metabolism[41]. As a result, ASI could partly correct the imbalance between TXA_2 and 6-keto-PGF_{1a} in UC. Moreover, SF could directly inhibit 5-HT liberation and MDA synthesis from platelets[7,41]. In addition, SF could reduce the content of fibrinogen in blood, increase the charges on cell membrance, thus inhibiting the cell aggregation, lowering the blood consistency. SF could prolong plasma prothrombin time (PPT) and reduce the weight and length of thrombus, thus ameliorating microcirculation[20].

In our study, PC, 1 min PAR, and levels of GMP-140, TXB_2, and vWF:Ag were significantly decreased after 3 weeks treatment while 6-keto-PGF_{1a} level was little changed compared with those before treatment in the ASI group. At the same time, there was no significant difference in all observed parameters before and after the treatment in the routine therapy group. Furthermore, clinical symptoms such as abdomen pain, diarrhea, occult blood, fever in the patients of ASI group were relieved and controlled more quickly than those in the patients of routine therapy group. The above results suggested that ASI remarkably inhibited the activation of platelets, attenuated the injury of vascular endothelial cells as well as improved the microcirculation in patients with UC, thus contributing to relieve the inflammatory response in UC. The protective effect of ASI on vascular endothelial cell might be related with SF' s strong anti-oxidation property[2,3,20,42-44].

In summary, the results of this study have shown that ASI can significantly inhibit platelet activation, relieve vascular endothelial cell injury in UC. ASI in combination with the well-established drugs may contribute to an optimal treatment for UC.

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