Effect of Ginkgo Ketone Ester Drop Pills on Hemorheology and Serum Oxidative Stress in Patients with Unstable Angina

Liu Xiaoyuan①

Abstract

Objective: To explore the effect of Ginkgo Ketone Ester Drop Pills on hemorheology and serum oxidative stress of unstable angina (UA) of coronary heart disease. Methods: The 110 UA patients who were admitted to our hospital from Jan. 2018 to Aug. 2019 were selected. The patients were divided into the Control Group and the Ginkgo Group via a random number table, 55 patients in each group. The patients in Control Group received conventional medical treatment and the patients in the Ginkgo Group were treated with Ginkgo Ketone Ester Drop Pills in addition to the treatment given to the Control Group. The hemorheology, fibrinogen (FIB), Platelet Aggregation Rate (PAR), serum oxidative stress and incidences of adverse reactions between the two groups were compared. Results: Within 4 weeks of treatment, the high tangent value of whole blood, low tangent value of whole blood, plasma viscosity, FIB, PAR and ET-1 levels in both groups demonstrated a decreasing trend with levels of SOD and NOS showing an increasing trend ($P<0.05$). Following 2 weeks and 4 weeks of treatment, the high tangent value of whole blood, low tangent value of whole blood, plasma viscosity, FIB, PAR and ET-1 level in the Ginkgo Group were lower than those in the Control Group and the SOD and NOS levels in the Ginkgo Group were higher than those in the Control Group ($P<0.05$). There was no statistically significant difference between incidences of adverse reactions in two groups ($P>0.05$). Conclusion: The Ginkgo Ketone Ester Drop Pills could effectively improve the hemorheology and serum oxidative stress in UA patients, while did not increase the incidences of adverse reactions.

[Key words] Ginkgo Ketone Ester Drop Pills, Unstable Angina (UA), hemorheology and serum oxidative stress

The Unstable Angina (UA) is a common cardiovascular disease with coronary artery atherosclerosis as a pathological basis, and this disease could be induced by many factors, which could further result in occurrence of diseases such as malignant arrhythmia, acute myocardial infarction, heart failure and cardiac arrest, seriously threatening the life quality and life safety of patients [1-3]. Currently, although there is a more perfect guideline for treating this disease in clinical practice, related studies in recent years have found that traditional Chinese medicine preparations in combination with the conventional medication treatment protocols were helpful for more satisfactory clinical efficacy [4-5]. This study analyzed the effect of Ginkgo Ketone Ester Drop Pills on hemorheology and serum oxidative stress indicator of UA patients, and the outcomes were reported as follows.

① Guangdong Dongguan Qingxi Hospital, Dongguan City, Guangdong Province, 523660

Corresponding Author: Liu Xiaoyuan

1. Data and Methods

1.1 General Information

110 UA patients were selected in our hospital from Jan. 2018 to Aug. 2019. The Inclusion Criteria were in compliance with diagnostic criteria for UA as mentioned in *Consensus of Chinese Experts on Rehabilitation of Coronary Heart Disease and its Secondary Prevention* [6]; and the age was 18-75 years' old. The Exclusion Criteria: Patients diagnosed as acute myocardial infarction or Heart Function Level IV; patients suffering from hematological diseases or had a hemorrhagic tendency; patients

concurrently suffering from a malignant tumor or autoimmune disease; patients suffering from acute cerebrovascular disease or depressed level of consciousness; patients who were allergic to or could not tolerate the treatment drugs used in this study; patients concurrently suffering from digestive system disease. The patients were divided into the Control Group and the Ginkgo Group via a random number table, 55 patients in each group. All the patients and their family members were informed about this and they all agreed to sign the Informed Consent Form and this study was approved by the Ethics Committee of the hospital.

1.2 Methods

After enrollment into the study, all the patients were monitored with vital signs and intermittently provided with oxygen uptake, and the Control Group was given the conventional medical treatment, i.e. aspirin enteric-coated tablets (Manufacturer: Bayer HealthCare Manufacturing S.r.l, Approval Number: NMPA Approval Number J20171021, Specification: 100mg), 100mg, by oral, once per day; Simvastatin tablets (Manufacturer: Jingxin Pharmaceutical, Approval No.:NMPA Approval Number H20000009, Specification: 20mg), 20mg, by oral, once per day; Metoprolol Tartrate tablets (Manufacturer: AstraZeneca Pharmaceutical Co Ltd, Approval Number: NMPA Approval Number H32025391, Specification: 25 mg), 12.5 mg, twice per day, by oral; 250 ml of 0.9% Sodium Chloride Injectables+Nitroglycerin Injectables were given (Manufacturer: Guangzhou Baiyunshan Ming Xing Pharmaceutical Co., Ltd, Approval Number: NMPA Approval Number H44020569, Specification: 1 mL:5 mg) 20mg, Pumped In, Avoiding from Light, once per day, following 7 days of treatment, Replaced by the Isosorbide Mononitrate Sustained Release Tablets (Manufacturer: LEPU Pharmaceuticals, Approval Number: NMPA Approval Number H20066203, Specification: 40mg), 40mg, once per day, by oral; 100 ml of 0.9% Sodium Chloride Injectables+Coenzyme Complex for Injection (Manufacturer: SL Pharm, Approval Number: NMPA Approval Number H11020002, Specification: Coenzyme A 200 Units and Coenzyme I 0.2mg) 200 units, once per day, Infusion, following 7 days of treatment, it was replaced by Trimetazidine Hydrochloride tablets (Manufacturer: HuBei-Sihuan Pharmaceuticals Co., Ltd., Approval Number: NMPA Approval Number H20083596, Specification: 20mg) 20mg, 3 times per day, by oral. In addition to the treatment given in the Control Group, the patients in the Ginkgo Group was given Ginkgo Ketone Ester Drop Pills (Manufacturer: Beijing Handian Pharmaceutical Co.,Ltd, Approval Number: NMPA Approval Number Z20060461, Specification: Each pill contains 8mg of Ginkgo Ketone Ester), 5 pills, 3 times per day, by oral. The durations of treatment in both groups were 4 weeks.

1.3. Observation Indicators and Judgment Standards

For both groups, the fasting elbow venous blood was drawn separately upon enrollment, after 2 weeks and 4 weeks of treatment for testing on hemorheology, fibrinogen level (FIB), Platelet Aggregation Rate (PAR) and serum oxidative stress. (1) The hemorheological indicators in both groups were compared. The high tangent value of whole blood, low tangent value of whole blood and plasma viscosity were tested with a R-20 cone-plate viscometer. (2) The FIB and PAR were compared between the two groups. The FIB was tested by Clauss method; The PAR was tested by turbidimetry. (3) The serum oxidative stress indicators were compared between the two groups. The superoxide dismutase (SOD) level was tested with WST-1 method, and the NO synthetase (NOS) level was tested by photometry with dual-wavelength. The endothelin-1 (ET-1) level was tested with enhanced chemiluminescence immunoassay. (4) The incidences of adverse reactions were compared between the two groups during treatment, including bleeding symptom, stomach upset,, headache, head bloating,as well as liver and kidney damages.

1.4 Statistics Processes

The available data were statistically analyzed with SPSS 20.0 software, the measurement data were expressed with ($\bar{x} \pm s$), the comparison between groups was made by independent-samples t test, the comparison within one group was made by paired T test, the comparison among multiple time points was made by analysis of variance; The enumeration data was expressed with rate (%) and analyzed with X2 test, and $P<0.05$ was regarded as statistically significant.

2. Results

2.1 Comparison of General Data between the Two Groups

There were 31 males and 24 females in the Control Group at age in the range of 50-66 years' old with an average of 58.12±5.66 years' old; The duration of disease was 6-11 years with an average of 7.95±0.63 years; For NYHA Grading: 39 patients were in Level II and 16 patients were in Level III. In the Ginkgo Group, there were 33 males and 22 females at age in the range of 51-65 years' old with an average of 58.29±5.02 years' old; The duration of disease was 6-11 years with an average of 8.03±0.75 years; For NYHA Grading: 37 patients were in Level II and 18 patients were in Level III. The general data between the two groups were of no statistical significance,but.comparable with differences, (P>0.05)

2.2 Comparison of Hemorheological Indicators between the Two Groups

Upon enrollment, there was no statistically significant difference of high tangent value of whole blood, low tangent value of whole blood and plasma viscosity between the two groups (P>0.05). Within 4 weeks of treatment, the high tangent value of whole blood, low tangent value of whole blood and plasma viscosity in both groups presented a decreasing trend with differences of statistical significance (P<0.05). Following 2 weeks and 4 weeks of treatment, the high tangent value of whole blood, low tangent value of whole blood and plasma viscosity in the Ginkgo Group were statistically and significantly lower than those in the Control Group (P<0.05). See Table 1.

2.3 Comparison of FIB and PAR between the Two Groups

Upon enrollment, there was no statistically significant difference of FIB and PAR between the two groups (P>0.05). Within 4 weeks of treatment, the FIB and PAR in both groups demonstrated a decreasing trend with differences of statistical significance (P<0.05). Following 2 weeks and 4 weeks of treatment, the FIB and PAR in the Ginkgo Group were statistically and significantly lower than those in the Control Group (P<0.05). See Table 2.

2.4 Comparison of Serum Oxidative Stress Indicators between the Two Groups

Upon enrollment, there was no statistically significant difference of SOD, NOS and ET-1 levels between the two groups (P>0.05). Within 4 weeks of treatment, the SOD and NOS levels in both groups showed a decreasing trend and the ET-1 levels showed an increasing trend with differences of statistical significance (P<0.05). Following 2 weeks and 4 weeks of treatment, the SOD and NOS levels in the Ginkgo Group were higher than those in the Control Group and the ET-1 level was lower than that in the Control Group with differences of statistical significance (P<0.05). See Table 3.

2.5 Comparison of Incidences of Adverse Reactions between the Two Groups

The incidences of adverse reactions were compared without statistical significance (X2=0.626, P=0.429). See Table 4.

Table 1, Comparison of Hemorheology Indicators between Groups [cP, $(\bar{x} \pm s)$]

Group	High Tangent Value of Whole Blood					Low Tangent Value of Whole Blood				
	Upon Enrollment	2 weeks of Treatment	4 weeks of Treatment	F value	P value	Upon Enrollment	2 weeks of Treatment	4 weeks of Treatment	F value	P value
Control Group (n=55)	5.86±1.12	5.39±0.92*	4.91±0.73#	7.125	0.005	19.79±2.73	16.22±1.92*	13.71±1.79#	9.368	0.000
Ginkgo Group (n=55)	5.81±0.98	5.03±0.89*	4.56±0.65#	8.2578	0.000	19.83±2.88	14.38±1.79*	10.04±1.69#	10.016	0.000

t value	0.249	2.085	2.655			-0.075	5.198	11.056		
P value	0.803	0.039	0.009			0.941	0.000	0.000		

Group	Table 1 (continue)				
	Plasma Viscosity				
	Upon Enrollment	2 weeks of Treatment	4 weeks of Treatment	F value	P value
Control Group (n=55)	6.83±1.39	4.51±0.86*	3.19±0.92#	8.697	0.000
Ginkgo Group (n=55)	6.79±1.29	3.22±0.81*	1.91±0.82#	10.002	0.000
t value	0.156	8.0979	7.702		
P value	0.875	0.000	0.000		

*P<0.05 comparing with those upon enrollment; # P<0.05 comparing with those following 2 weeks of treatment.

Table 2, Comparison of FIB and PAR between the Two Groups $(\bar{x} \pm s)$

Group	FIB %					PAR g/L				
	Upon Enrollment	2 weeks of Treatment	4 weeks of Treatment	F value	P value	Upon Enrollment	2 weeks of Treatment	4 weeks of Treatment	F value	P value
Control Group (n=55)	5.62±1.09	4.39±0.98*	3.61±0.79#	9.128	0.000	72.01±6.35	67.66±5.81*	60.11±4.13#	11.257	0.000
Ginkgo Group (n=55)	5.71±1.11	4.01±0.86*	3.11±0.65#	10.125	0.000	71.98±6.08	63.25±5.16*	55.08±3.91#	12.198	0.000
t value	-0.429	2.161	3.624			0.025	4.208	6.559		
P value	0.668	0.032	0.000			0.979	0.000	0.000		

*P<0.05 comparing with those upon enrollment; # P<0.05 comparing with those following 2 weeks of treatment.

Table 3, Comparison of Serum Oxidative Stress Indicators between the Two Groups $(\bar{x} \pm s)$

Group	SOD U/ml					NOS U/ml				
	Upon Enrollment	2 weeks of Treatment	4 weeks of Treatment	F value	P value	Upon Enrollment	2 weeks of Treatment	4 weeks of Treatment	F value	P value
Control Group (n=55)	81.12±5.03	108.75±6.26*	131.33±9.15#	12.896	0.000	20.33±3.02	27.52±3.88*	30.39±4.23#	10.878	0.000
Ginkgo Group (n=55)	80.89±5.11	125.59±7.01*	160.09±10.33#	15.198	0.000	20.27±3.21	30.05±4.11*	35.83±5.06#	13.257	0.000

t value	0.237	-13.288	-15.456			0.100	-3.319	-6.117		
P value	0.812	0.000	0.000			0.919	0.001	0.000		

Group	Table 3(continue)				
	ET-1 ng/L				
	Upon Enrollment	2 weeks of Treatment	4 weeks of Treatment	F value	P value
Control Group (n=55)	72.08±6.33	63.11±5.29*	58.27±4.25#	12.252	0.000
Ginkgo Group (n=55)	72.23±5.98	55.27±4.19*	49.32±3.97#	15.551	0.000
t value	-0.127	8.615	11.412		
P value	0.898	0.000	0.000		

*P<0.05 comparing with those upon enrollment; # P<0.05 comparing with those following 2 weeks of treatment.

Table 4, Comparison of incidences of adverse reactions between groups during treatment, cases (%)

Group	Bleeding |Symptom	Stomach Upset	Headache and Head Bloating	Liver and Kidney Damages	Total
Control Group (n=55)	2（3.63）	3（5.45）	1（1.82）	1（1.82）	7（12.73）
Ginkgo Group (n=55)	3（5.45）	5（9.09）	1（1.82）	1（1.82）	10（18.18）

3. Discussion

With the change in the current life style and dietary habit, the clinical incidence of coronary heart disease shows an increasing trend year by year and many factors such as age, smoking, triglyceride and diabetes were important risk factors affecting this disease and could have a serious impact on the clinical prognoses of patients [7-8]. Although currently the clinical practice still did not thoroughly know the pathogenesis of coronary heart disease, the clinical observation results in current years showed that the hemorheology and oxidative stress played important roles in the occurrence and development of coronary heart disease. The hemorheology was an important factor for evaluating the condition of coronary heart disease and predicting its prognosis, while SOD was used to evaluate the myocardial damage of coronary heart disease, NOS could be used to evaluate vasomotor functions of coronary artery under coronary heart disease and ET-1 was used to predict prognosis of the coronary heart disease [9-12]. At present, both the Guidelines for Clinical Therapy and expert consensus have recommended the anti-platelet aggregation, improving the coronary blood flow, stabilizing the atherosclerotic plaque and reducing the oxygen consumption of myocardium as the conventional medication therapies for UA, while the clinical observation also showed that the treatment of UA with traditional Chinese preparations also achieved ideal efficacies [13-16].

With respect to traditional Chinese medicines, UA belongs to the category of “obstruction of qi or air in the chest”, of which, the major pathogeneses were “blood stasis in the heart vessels” and “Qi or air activity stasis” with “promoting qi or air circulation and removing obstruction in the collateral as well as promoting blood circulation to remove blood stasis” as main therapeutic principles, and the clinical observation also evidenced that the traditional Chinese preparation for “promoting qi or air circulation and removing the obstruction in the collateral as well as promoting blood circulation to remove blood stasis” in

combination with conventional medical treatment could improve to some extent the clinical treatment efficacy of UA patients [17]. This study used the Ginkgo Ketone Ester Drop Pills which could improve the treatment efficacy of coronary heart disease and observed changes to indicators of hemorheology and serum oxidative stress so as to explore the efficacy of Ginkgo Ketone Ester Drop Pills for UA.

This study results showed that within 4 weeks of treatment, the high tangent value of whole blood, low tangent value of whole blood, plasma viscosity, FIB, PAR and ET-1 levels in both groups showed a decreasing trend with levels of SOD and NOS showing an increasing trend ($P<0.05$). Following 2 weeks and 4 weeks of treatment, the high tangent value of whole blood, low tangent value of whole blood, plasma viscosity, FIB, PAR and ET-1 level in the Ginkgo Group were lower than those in the Control Group and the SOD and NOS levels in the Ginkgo Group were higher than those in the Control Group ($P<0.05$), which benefited the combination with Ginkgo Ketone Ester Drop Pills. And there was no statistically significant difference between incidences of adverse reactions in two groups ($P>0.05$). All those as mentioned above indicated that the Ginkgo Ketone Ester Drop Pills could effectively improve the hemorheology and serum oxidative stress in UA patients, while not increasing the incidence of adverse reactions, which suggested that the action mechanism of Ginkgo Ketone Ester Drop Pills in UA patients could be related to change in hemorheology and serum oxidative stress.

The Ginkgo Ketone Ester Drop Pill used in this study was extracted from ginkgo leaves and was a traditional Chinese preparation comprising of bilobalide and ginkgetin, which could play a role in “promoting blood circulation to remove blood stasis as well as activating meridians to stop pain”. The clinical pharmacology study results showed that both bilobalide and ginkgetin had a role in inhibiting platelet phosphodiesterase from promoting the blood circulation and anti-platelet aggregation and combination of both these ingredients could effectively expand coronary artery, improve arterial blood flow, repair ischemic injury of tissue and inhibit inflammatory stress response as well as eliminate free radicals, etc., and had ideal efficacies in treatment of many diseases such as coronary heart disease, hypertension and cerebral infarction [18-20].

Although this study showed that Ginkgo Ketone Ester Drop Pill could effectively improve hemorheology and serum oxidative stress of UA patients without an increased incidence of adverse reactions, UA usually needed long-term treatment due to its long course, and since the duration of this study was only 4 weeks, evaluation for long-term prognosis of patients following treatment was not feasible which required further observation.

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