Journal of Hainan Medical University

http://www.jhmuweb.net/

Effect of probucol combined with atorvastatin adjuvant therapy on serum indexes of acute cerebral infarction patients during rehabilitation period

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ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
Acute cerebral infarction
Probucol
Atorvastatin

ABSTRACT

Objective: To analyze the effect of probucol combined with atorvastatin adjuvant therapy on serum indexes of acute cerebral infarction patients in rehabilitation period. **Methods:** A total of 102 patients with acute cerebral infarction were treated in our hospital from August 2011 to June 2015, were confirmed by magnetic resonance imaging and were randomly divided into observation group 51 cases and control group 51 cases according to the order of hospitalization. Control group received atorvastatin treatment alone, observation group received probucol combined with atorvastatin adjuvant therapy, and then differences in levels of serum CXCL16, HMGB1, CD40L and Fibulin-5, P-selectin, NPY, CGRP, visfatin and others, chemokines and inflammation-related factors, vascular endothelial cells and fibrinolytic function, etc were compared between two groups after treatment. **Results:** Serum CXCL16, HMGB1, CD40L and Fibulin-5 levels of observation group after treatment were lower than those of control group; serum P-selectin, NPY, visfatin, UCH-L1, sVCAM-1 and SAA levels of observation group after treatment were lower than those of control group while CGRP level was higher than that of control group; serum CCL-19, CCL-21, YKL-40, IL-33 and IL-18 values of observation group after treatment were lower than those of control group; serum vWF, PAI-1 and plasminogen levels of observation group after treatment were lower than those of control group while 6-K-PGF1 α and tPA levels were higher than those of control group. **Conclusions:** Probucol combined with atorvastatin adjuvant therapy for acute cerebral infarction patients in rehabilitation period can effectively optimize patients' general status and avoid re-infarction in recovery period, and it has positive clinical significance.

1. Introduction

Acute cerebral infarction is common in clinical practice and is one of the disabling and fatal diseases in patients, anticoagulation and thrombolysis are the main therapeutic principles for patients in acute period, and as for cerebral infarction patients in recovery period, the therapeutic interventions should be strengthened to avoid the secondary infarction or cerebral hemorrhage. Atorvastatin is typical statins and is the rate-limiting enzyme of cholesterol synthesis, and in recent years, its role in stabilizing atheromatous plaque has been recognized[1,2]. Given that atorvastatin regulates vascular endothelial function, enhance the endogenous NO release, enhance plaque stability, etc, it has been currently widely used in the secondary prevention of cerebral infarction. The intervention of inflammation and lipid level in recovery period of acute cerebral infarction is closely related to treatment outcome, and many studies have shown that the anti-inflammatory and lipid-adjusting treatment of cerebral infarction patients in recovery period has direct correlation with secondary cerebral infarction and cerebral hemorrhage. Probucol has lipid-adjusting and anti-lipid peroxidation effect, and can lower cholesterol synthesis, promote the decomposition of cholesterol,

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Fund project: Science and Technology Planning Project of Science and Technology Department of Shaanxi Province No: 2012JM4024.

inhibit intercellular adhesion factor levels, inhibit inflammatory factor expression, *etc*[3]. At present, some scholars recommend the combined use of probucol and atorvastatin in acute cerebral infarction patients in recovery period, embarking from the different mechanisms to increase lipid-adjusting and anti-inflammatory effects and optimize patient' outcome. In the research, the effect of probucol combined with atorvastatin adjuvant therapy on serum indexes of acute cerebral infarction patients in rehabilitation period was mainly analyzed, hereby reported as follows.

2. Materials and methods

2.1. Case information

A total of 102 patients with acute cerebral infarction were treated in our hospital from August 2011 to June 2015, were confirmed by magnetic resonance imaging and were excluded of the following: 1) those with severe heart, liver and kidney diseases; 2) those with malignant tumors of other organs; 3) those with stroke history in one recent year; 4) those with autoimmune diseases; 5) those with acute symptoms of infection after admission.

Two groups received different adjuvant therapy in recovery period, and were randomly divided into observation group 51 cases and control group 51 cases according to the order of hospitalization. Control group included 27 male cases and 24 female cases, they were 42-70 years old and the average was (56.81±8.05) years; observation group included 26 male cases and 25 female cases, they were 44-71 years old, the average was (57.98±8.47) years. Differences in baseline information were not statistically significant between two groups (P>0.05).

2.2. Treatment methods

Both groups received probucol and atorvastatin treatment on the basis of conventional treatment in recovery period of acute cerebral infarction. Control group received atorvastatin treatment, which was as follows: atorvastatin 20 mg/time, 1 time/d. Observation group received probucol combined with atorvastatin treatment, which was as follows: oral administration of probucol 500 mg/time, 1 time/d. The usage and dosage of atorvastatin were the same as those of control group.

2.3. Observation indexes

After one course of treatment, 2 mL fasting peripheral venous blood was drawn from both groups in the morning to detect CXC chemokine ligand 16 (CXCL16), high mobility group box B1 (HMGB1), soluble CD40 ligand (CD40L), Fibulin-5, P-selectin, neuropeptide Y (NPY), calcitonin gene-related peptide (CGRP), visfatin, ubiquitin carboxy-terminal hydrolase-1 (UCH-L1), soluble vascular cell adhesion molecule-1 (sVCAM-1) and amyloid A (SAA). Chemokines and inflammation-related factors: chemokine 19 (CCL-19), chemokine 21 (CCL-21), YKL-40, interleukin-33 (IL-33) and interleukin-18 (IL-18). Vascular endothelial cells and fibrinolytic function: von Willebrand factor (vWF), 6-keto-prostaglandin F1 α (6-K-PGF1 α), tissue-type plasminogen activator (tPA), plasminogen activator inhibitor 1 (PAI-1) and plasminogen.

2.4L Statistical methods

Data obtained in the research was analyzed by SPSS 23.0 software, measurement data was in terms of Mean ± SD, comparison between two groups was performed by t test, and P<0.05 was set as the standard of statistical significanct differences.

3. Results

3.1. CXCL16, HMGB1, CD40L and Fibulin–5

Results showed that serum CXCL16, HMGB1, CD40L and Fibulin-5 levels of observation group after treatment were lower than those of control group (P<0.05), shown in Table 1.

Table 1
Comparison of serum CXCL16, HMGB1, CD40L and Fibulin-5 values between two groups after treatment

Groups	CXCL16 (ng/L)	HMGB1 (ng/L)	CD40L (ng/L)	Fibulin-5 (μg/L)
Observation	0.09±0.01	6.18±0.59	241.28±23.09	70.36±8.95
Control	0.23±0.02	11.57±1.07	376.55±30.76	91.52±8.03
t	5.182	7.394	13.209	8.394
P	<0.05	<0.05	<0.05	<0.05

3.2. P–selectin, NPY, CGRP, visfatin and so on

It showed that serum P-selectin, NPY, visfatin, UCH-L1, sVCAM-1 and SAA levels of observation group after treatment were lower than those of control group while CGRP level was higher than that of control group (P<0.05), shown in Table 2.

3.3. Chemokines and inflammation–related factors

It showed that serum CCL-19, CCL-21, YKL-40, IL-33 and IL-18 values of observation group after treatment were lower than those of control group (P<0.05), shown in Table 3.

3.4. Vascular endothelial cells and fibrinolytic function

The results showed that serum vWF, PAI-1 and plasminogen levels of observation group after treatment were lower than those of control group while 6-K-PGF1 α and tPA levels were higher than those of control group (P<0.05), shown in Table 4.

4. Discussion

The harm of acute cerebral infarction is great, and for patients that have passed the dangerous period and enter into the recovery period, anti-inflammatory and lipid-adjusting treatment should be strengthened in addition to conventional antiplatelet therapy. Both

Table 2

Comparison of serum P-selectin, NPY, CGRP, visfatin and so on between two groups after treatment.

Groups	P-selectin (μg/L)	NPY (pg/mL)	CGRP (pg/mL)	Visfatin (μg/L)	UCH-L1 (μg/L)	sVCAM-1 (μg/L)	SAA (mg/L)
Observation	6.13±0.54	142.37±13.59	224.84±23.57	24.37±2.05	0.12±0.01	712.38±69.75	25.47±2.19
Control	9.47±0.86	267.48±24.95	153.29±13.26	51.28±5.84	0.24±0.03	977.01±103.27	40.23±4.18
t	7.823	12.394	13.209	8.394	5.093	15.384	9.834
P	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05

Table 4

Comparison of serum vascular endothelial cells and fibrinolytic function between two groups after treatment.

Groups	vWF (μg/L)	6-K-PGF1 α (ng/L)	tPA (kIU/L)	PAI-1 (kIU/L)	Plasminogen (mg/L)
Observation	104.29±12.76	21.27±2.68	1.98±0.14	8.23±0.85	213.27±24.84
Control	119.65±21.84	17.34±1.95	1.34±0.12	9.11±0.95	261.48±30.52
t	8.394	7.832	5.823	5.282	7.293
P	<0.05	<0.05	<0.05	<0.05	<0.05

abnormal lipid level and inflammatory cascade reaction are involved in the occurrence and development process of acute cerebral infarction, the above reaction is weakened in recovery period, but the probability of re-infarction, cerebral hemorrhage and other adverse events sharply rises in those with improper intervention[4]. Both probucol and atorvastatin are lipid-adjusting drugs with much clinical application, and atorvastatin adjusts lipid, stabilizes atheromatous plaque, enhances NO function, expand blood vessels, and so on; probucol, in addition to adjusting lipid, is with anti-oxidative stress, anti-inflammation and other roles, and many scholars recommend the combined application of the above two drugs in patients with recovery period of cerebral infarction, embarking from different mechanisms to optimize the state of patients' systemic lipid, inflammation, oxidative stress and other aspects[5]. In the research, patients with acute cerebral infarction were selected as the research subjects, and probucol and atorvastatin were respectively applied to the patients to observe the effect of different treatment combinations on patients' general condition.

CXCL16 can regulate cell adhesion and promote cell proliferation, it has been confirmed as one of the main precipitating factors causing atherosclerosis, and it is also of great significance in cerebrovascular diseases. Study shows that serum CXCL16 levels increase significantly in cerebral infarction patients, which may be because that it causes plaque instability and damage after atherosclerosis and forms cerebral infarction[6]. Brain tissue with different extent of ischemia can produce more HMGB1, effectively activate microglia and macrophages, show positive feedback effect of HMGB1 and participate in cell movement and inflammatory cascade reaction. Soluble CD40L mainly comes from platelets or activated T cells, is massively expressed in the acute phase of cerebral infarction, and can effectively promote vascular adhesion factor expression and accelerate vascular endothelial cell adhesion and vascular dysfunction[7]. Elevated Fibulin-5 level can strengthen endothelial cell adhesion and activate extracellular matrix viscosity. Fibulin-5 combination with integrin can improve endothelial cell and extracellular matrix adhesion and resist local shear force. Above research results showed that serum CXCL16, HMGB1, CD40L and Fibulin-5 levels of observation group were lower after treatment, and application of probucol combined with atorvastatin treatment in recovery period of cerebral infarction could effectively stabilize infarction-related factor levels.

P-selectin regulates inflammatory mediators, mediates neutrophil aggregation and infiltration around the injured nerve cells, increases cerebral blood flow change as well as stimulates the release of inflammatory mediators, accelerates the blood-brain barrier damage and aggravates cerebral edema. NPY belongs to neuroactive peptides and is closely associated with vasomotor function, and elevated NPY levels can accelerate the occurrence of cerebral infarction[8]. CGRP is a neuropeptide containing many amino acid residues and has strong diastolic effect on blood vessels of brain, and declined CGRP level is one of the causes of cerebral infarction. Visfatin is derived from fat cells, and is closely related to lipid levels. Visfatin is also a kind of proinflammatory factor that can induce high expression of serum interleukin-6, *etc*, activate vascular endothelial cell surface thromboplastin, promote prothrombin conversion into thrombin and fibrinogen deposition in the vessel wall, and worsen the condition of patients with acute cerebral infarction[9,10]. UCH-L1 was first found in the brain tissue, is one of brain tissue proteins with rich content and is highly specifically distributed in neurons. UCH-L1 has been regarded as the marker of the nervous system, is with small molecular weight, and is easy to cross through the blood-brain barrier and enter into the circulating blood after cerebral infarction. sVCAM-1 is distributed in vascular endothelial cells, participates in the vascular adhesion process of white blood cells through combination with ligand, and also participates in white blood cell permeability and migration to the outside of the vessels. Amyloid A (SAA) is an acute phase protein produced by the liver cells, and can promote the expression of IL-1, IL-18, IL-23 and other inflammatory factors, and further promote macrophage adhesion and medial smooth muscle cell migration[11]. When inflammation occurs in patients with cerebral infarction, the serum level of SAA rises rapidly in a short time and declines rapidly in recovery period of disease, so the SAA can effectively reflect the degree of acute cerebral infarction, and is more sensitive than C-reactive protein. Above research results showed that serum P-selectin, NPY, visfatin, UCH-L1, sVCAM-1 and SAA values of observation group after treatment were lower while CGRP value was higher, indicating that probucol combined with atorvastatin could restore cerebrovascular systolic and diastolic balance and promote patients' recovery.

CCL-19 and CCL-21 have common receptor CCR7, and have been proven to be closely associated with cardiovascular disease. In patients with myocardial infarction and cerebral infarction, CCL-19 and CCL-21 levels rise significantly. YKL-40 is a newly discovered inflammatory factor secreted by damaged or activated neutrophils

and macrophages, and a study shows that it plays an important role in tissue necrosis and inflammation[12]. IL-33 is a cytokine of IL-1 family that is mainly involved in immune function regulation and inflammatory response. IL-33 can adjust Th2 cell-mediated immune response and regulate Th1/Th2 cellular immune response balance. IL-18 is involved in the occurrence and development of acute cerebral infarction, it is an important pro-inflammatory factor, and elevated IL-18 level is an independent risk factor for prediction of acute cerebral infarction[13]. In above research, serum CCL-19, CCL-21, YKL-40, IL-33 and IL-18 values of observation group were lower after treatment, indicating that probucol combined with atorvastatin had significant anti-inflammatory effect and reduced the secondary damage to patients' blood vessels caused by local accumulation of inflammatory factors.

vWF is macromolecule glycoprotein synthesized by vascular endothelium, is massively released into bloodstream after nerve cell damage and can accelerate blood platelet adhesion. Increased vWF content and activity is a sign of vascular endothelial damage, and can start the blood coagulation function and induce thrombosis[14]. 6-K-PGF1 α is an index of hypercoagulability and prostacyclin metabolism and 6-K-PGF1 α levels drop in patients with acute phase of cerebral infarction, indicating that patients have severe vascular endothelial damage. Fibrinolytic enzyme is mainly produced by liver and vascular endothelium, and plasminogen is activated by tPA and converted into fibrinolytic enzyme, which plays the role of thrombolysis, and meanwhile, is specifically combined with fibrin clot and strengthens fibrinolytic effect. Under normal circumstances, tPA and PAI-1 are in dynamic equilibrium and protect vascular integrity, patency, and so on, and imbalance expression can cause thrombus or hemorrhagic events. Patients with acute cerebral infarction are accompanied by abnormal function of blood coagulation and anticoagulation system, and determination of tPA, PAI-1, plasminogen and so on can be indirectly evaluate fibrinolytic system function and vascular endothelial function[15]. Above research results showed that serum vWF, PAI-1 and plasminogen values of observation group after treatment were lower while 6-K-PGF1 α and tPA values were higher, indicating that probucol combined with atorvastatin was of positive significance in restoring patients' anticoagulation and blood coagulation system balance as well as accelerating complete recanalization of infarction vessels and avoiding re-infarction of lesion blood vessels.

To sum up, it is concluded that probucol combined with atorvastatin adjuvant therapy for acute cerebral infarction patients in rehabilitation period can effectively optimize patients' general status and avoid re-infarction in recovery period, and it's worth popularization and application in clinical practice in the future.

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