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Effect of alprostadil combined with conventional therapy on serum markers in patients with acute cerebral infarction

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ABSTRACT

Objective: To study the effect of alprostadil combined with conventional therapy on serum markers in patients with acute cerebral infarction. **Methods:** Patients with acute cerebral infarction treated in our hospital from May 2012 to August 2014 were enrolled and randomly divided into two groups. Observation group received alprostadil combined with conventional therapy and control group received conventional treatment. Then serum markers of both groups were compared. **Results:** (1) contents of serum nerve function related molecules: serum NSE and S100β contents of observation group showed a decreasing trend, and BDNF and NGF contents showed an increasing trend; (2) contents of atherosclerosis related enzymes: serum GGT, iNOS and MPO contents of observation group showed a decreasing trend, and PON1 and PON2 contents showed an increasing trend; (3) platelet activation related molecules: serum PPARγ, CD62p, YKL-40, sCD40L and Fibulin-5 contents of observation group all showed a decreasing trend. **Conclusions:** Alprostadil combined with conventional treatment is helpful to alleviate neuronal damage and inhibit the processes of atherosclerosis and platelet activation; it's an ideal method for treating acute cerebral infarction.

1. Introduction

Acute cerebral infarction is the most common clinical cerebrovascular disease with higher incidence rate and disability rate. Infarction develops rapidly after the disease occurs, and can cause neurological damage in a short time. Thrombolytic therapy and interventional therapy are the optimal treatment of patients with cerebral infarction attack in 3–6 h, which can effectively restore the blood flow perfusion of cerebral vessels and reduce the hypoxic-ischemic damage of nerve cells. However, in clinical practice, the visiting time of most patients with cerebral infarction exceeds 6 h. They have missed the time window of thrombolytic or interventional therapy; for such patients, anticoagulation, neurotrophy and lowering blood lipid are conventional treatment methods. As the best treatment opportunity is missed, irreversible necrosis has happened to neuronal cells, and after treatment, varying degrees of neurological deficits are left behind. It has been a major concern of clinicians how to improve the treatment effect and nerve function of patients who have missed the opportunity of interventional or thrombolytic therapy. Alprostadil is a newly developed drug to treat cardiovascular and cerebrovascular diseases. It has the function of expanding vascular smooth muscle and inhibiting platelet activation[1]. In the following research, the effect of alprostadil combined with conventional therapy on serum markers in patients with acute cerebral infarction was analyzed.

2. Patients and methods

2.1. Enrolled patients

Patients were enrolled according to the following criteria: (1) patients with acute cerebral infarction treated in our hospital from

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May 2012 to August 2014; (2) being the first onset; (3) time of onset: 6–24 h; (4) diagnosed by imaging examination. Patients complicated with abnormal heart, liver and kidney function or complicated with mental illness were excluded. According to different treatment methods, they were randomly divided into two groups, each group with 45 cases. Control group received conventional anticoagulant, lipid-lowing.

2.2. Treatment methods

Control group received anticoagulant, lipid-lowing and other conventional drugs. Anticoagulant drugs were aspirin and clopidogrel, and lipid-lowering drug was simvastatin. Based on conventional therapy, observation group received intravenous injection of the mixture of 10 μg of alprostadil and 10 mL of normal saline, one time/d for continuous 7 d.

2.3. Evaluating methods of serum markers

On 1, 3, 5 and 7 d after treatment, peripheral blood of both groups was collected, let stand at room temperature and centrifuged to get serum. Detecting methods were as follows: (1) serum samples on 1, 3, 5 and 7 d after treatment were taken. ELISA kit was used to detect NSE, S100β, BDNF and NGF contents; (2) serum sample on 3 d after treatment was taken. RNA was extracted and PCR method was used to detect GGT, iNOS, MPO, PON1 and PON2 contents; (3) serum sample on 3 d after treatment was taken. ELISA kit was used to detect PPARγ, CD62p, YKL-40, sCD40L and Fibulin-5 contents.

2.4. Statistical methods

Detected data was input by SPSS19.0 software, differences between two groups by t test. Differences were considered to be statistically significant at a level of $P<0.05$.

3. Results

3.1. Contents of serum nerve function related molecules

Cerebral infarction will cause content changes of nerve function related molecules, among which BDNF and NGF are molecules with neurotrophic function, and the higher their contents are, the better the recovery of nerve function is; S100β and NSE are located in glial cells and neuronal cells, and the higher their contents are, the more serious the nerve function damage is. Contents of serum nerve function related molecules at various time points after treatment were detected and it was found out that serum NSE and S100β contents of observation group showed a decreasing trend; BDNF and NGF contents showed an increasing trend (Table 1).

3.2. Contents of atherosclerosis related enzymes

Atherosclerosis is the most important pathophysiological basis of the incidence of cerebral infarction and a variety of enzymes are involved in the process of atherosclerosis. GGT, iNOS and MPO have the function of promoting atherosclerosis; PON1 and PON2 have the function of inhibiting atherosclerosis. After treatment, contents of serum atherosclerosis related enzymes of both groups were detected and analyzed. Results showed that serum GGT, iNOS and MPO contents of observation group showed a decreasing trend; PON1 and PON2 contents showed an increasing trend (Figure 1).

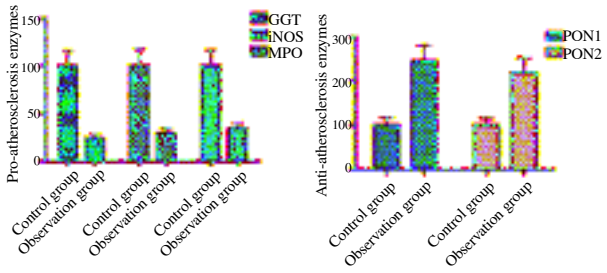

Figure 1. Contents of serum atherosclerosis related enzymes of both groups after treatment.

Serum GGT, iNOS and MPO contents of observation group were lower than those of control group; PON1 and PON2 contents were higher than those of control group. [a]: compared with control group at the same time point, there are differences, $P<0.05$.

Table 1

Comparison of the contents of serum nerve function related molecules at various time points after treatment between two groups (μg/L).

Group	Neurotrophy associated molecules		Nerve damage associated molecules	
	BDNF	NGF	S100β	NSE
Control group (n=45)				
1 d after treatment	4.02±0.55	118.34±15.62	0.88±0.09	27.76±3.45
3 d after treatment	3.75±0.49	103.48±13.19	1.38±0.18	38.52±5.51
5 d after treatment	4.31±0.60	122.39±19.39	1.14±0.14	27.41±3.05
7 d after treatment	4.78±0.62	131.48±18.76	0.49±0.06	15.67±2.15
Observation group (n=45)				
1 d after treatment	4.08±0.53	120.14±15.52	0.83±0.08	26.95±3.42
3 d after treatment	4.49±0.61[a]	126.75±14.48[a]	0.92±0.11[a]	28.94±3.95[a]
5 d after treatment	5.23±0.70[a]	140.19±17.87[a]	0.74±0.08[a]	17.76±2.42[a]
7 d after treatment	5.92±0.68[a]	158.69±20.25[a]	0.14±0.02[a]	9.30±1.03[a]

[a]: compared with control group at the same time point, there are differences, $P<0.05$.

3.3. Platelet activation related molecules

Exposure of underlying collagen in fibrous cap of atherosclerotic plaque and activation of platelet aggregation process are important links that cause the nature change of plaque and the incidence of cerebral infarction; transcription factor PPARγ and its downstream molecules CD62p, YKL-40, sCD40L and Fibulin-5 are involved in platelet activation process. Contents of serum platelet activation related molecules were detected and analyzed. Results showed that serum transcription factor PPARγ and its downstream molecules CD62p, YKL-40, sCD40L and Fibulin-5 contents all showed a decreasing trend (Table 2).

Table 2

Comparison of serum platelet activation related molecules between two groups.

Group	PPARγ (ng/L)	CD62p (ng/L)	YKL-40 (ng/L)	sCD40L (ng/L)	Fibulin-5 (μg/L)
Observation group	22.34±3.45	18.94±2.52	103.52±15.65	254.52±34.56	87.72±9.55
Control group	31.69±4.93	27.95±3.41	178.93±24.12	415.62±55.12	144.23±18.87
t	5.872	6.029	6.885	6.482	8.202
P	<0.05	<0.05	<0.05	<0.05	<0.05

4. Discussion

About 6 h after the incidence of acute cerebral infarction, patients have missed the best opportunity of thrombolytic or interventional therapy. Conventional anticoagulant, neurotrophic and blood lipid lowering treatment cannot completely reverse hypoxic-ischemic injury of brain tissue, and after treatment, different degrees of neurological dysfunction will remain. Alprostadil is a newly developed drug to treat cardiovascular and cerebrovascular diseases. Its active ingredient is prostaglandin E1, using lipid microsphere as a carrier and can target the drugs at damaged parts of blood vessels and prolong the time of drug action. The main pharmacological effect of prostaglandin E1 is increasing cAMP content, expanding vascular smooth muscle, reducing vascular resistance, and thus increasing blood supply of cerebral infarction lesion[2]; besides, the drug can also inhibit platelet activation and aggregation processes and enhance thrombolytic effect to a certain extent[3]. The incidence of cerebral infarction will cause neurologic damage and content change of related molecules. Neuron specific enolase (NSE) is located in neurons and neuroendocrine cells and has the function of maintaining cell membrane excitability[4]; S-100β protein is located in astrocytes and oligodendrocytes and has the function of regulating intracellular and extracellular signal transduction[5]. Cerebral infarction will cause damage of glial cells and neuronal cells as well as release of S-100β and NSE, which can on the one hand cross the blood-brain barrier into the blood circulation and become markers of damage degree, and on the other hand gather around the infarction lesion and delay the recovery of neural function. BDNF and NGF are neurotrophic factors existing in the central nervous system and have a promoting effect on nerve growth and development. Increasing BDNF and NGF contents is in favor of nerve function rehabilitation and reconstruction[6]. Contents of serum nerve function related molecules were detected and it was found out that 3, 5 and 7 d after treatment, serum NSE and S100β of observation group were lower; that BDNF and NGF contents were higher, which indicated that alprostadil treatment was helpful to alleviate neuronal cell damage and promote neuronal cell regeneration.

Lipid plaque in intima and atherosclerosis in artery are the pathophysiological basis of the incidence of cerebral infarction. Mechanisms involved in these processes are complicated. Studies have reported that a variety of enzymes are involved in the pathogenesis of atherosclerosis. According to the function, they can be divided into pro-atherosclerosis enzymes and anti-atherosclerosis enzymes. γ-glutamyltransferase (GGT), inducible nitric oxide synthase (iNOS) and myeloperoxidase (MPO) are currently known enzymes that can promote atherosclerosis process. Among them, the role of GGT is degrading in vivo antioxidant glutathione GSH and thus causing enhanced peroxidation. Oxidized low density lipoprotein LDL will form ox-LDL that settles in artery intima, injures endothelial function and activates platelet aggregation process[7]. Inducible nitric oxide synthase (iNOS) is an important enzyme that participates in NO synthesis. It is mainly expressed in monocytes-macrophages, neutrophils and neurons; after the incidence of cerebral infarction, hypoxia-ischemia, active oxygen free radicals and other factors will cause large synthesis of iNOS and mediate neuronal cell damage[8]. MPO is a class of ferroheme peroxidase produced by activated leukocytes. It can on the one hand confront the function of antioxidant, oxidatively modify LDL, increase the formation of foam cells and accelerate lipid deposition and atherosclerosis, and on the other hand enhance the function of metalloprotease, cause nature change in fibrous cap of atherosclerotic plaque and increase the vulnerability of the plate[9]. Paraoxonase (PON) is an enzyme with anti-atherosclerotic function. When connected with high density lipoprotein HDL, it can assist HDL in inhibiting lipid deposition and regulating lipid metabolism[10]; studies have shown that PON1 and PON2 have a clear anti-oxidation function and can inhibit ox-LDL generation and destroy ox-LDL structure[11]. After treatment, serum atherosclerosis related enzymes were analyzed and it was found out that serum GGT, iNOS and MPO contents of observation group were lower; that PON1 and PON2 contents were higher, which indicated that alprostadil treatment was

helpful to regulate the synthesis of atherosclerosis related enzymes and inhibit the incidence of atherosclerosis.

Recent studies have shown that exposure of underlying collagen in fibrous cap and activation of platelets are key pathological links that cause the nature change of arterial lipid plaque, and they are also key steps that cause thrombosis in cerebral vessels. PPAR-γ is a nuclear receptor that can play the activity of transcription factors and regulate the expression of multiple downstream genes. Studies have shown that PPAR-γ expression in hypoxic-ischemic brain tissue significantly increases and it can regulate a variety of platelet activation molecules at a transcriptional level[12]. CD62p is an adhesion molecule expressed on activated platelet surface. Generally speaking, its expression reaches a peak 10 min after platelet activation. It can mediate activated platelet adhesion to arterial intima and accelerate the process of thrombosis; besides, CD62p can also activate neutrophils and monocytes-macrophages and promote the infiltration of inflammatory cells in atherosclerotic plaque[13]. Chitinase protein 40 (YKL-40) is a newly discovered inflammatory cytokine. It is synthesized by activated macrophages, neutrophils and hypoxic-ischemic neurons[14]; soluble CD40 ligand (sCD40L) is a transmembrane glycoprotein of the TNF family. It is largely expressed in activated platelets and T-lymphocytes. In the development of cerebral infarction, expression of TKL-40 and sCD40L increases and they can promote the recruitment of inflammatory cells in atherosclerotic plaque and local thrombosis, thus accelerating platelet activation process. Fibulin-5 is a type of glycoprotein in extracellular matrix. It contains the RGD sequence that can be combined with integrins. Studies have shown that Fibulin-5 can be combined with integrin 5β1 through RGD, increase generation of active oxygen free radicals and cause the damage of vascular endothelial cells and the exposure of collagen in fibrous cap, thus activating platelet aggregation process[15]. Contents of platelet activation related molecules were analyzed and it was found out that serum PPARγ, CD62p, YKL-40, sCD40L and Fibulin-5 of observation group all showed a decreasing trend, which indicated that alprostadil treatment was helpful to inhibit platelet activation process.

Based on above discussions, it can be concluded that alprostadil combined with conventional treatment is helpful to alleviate neuronal damage and inhibit the processes of atherosclerosis and platelet activation; it's an ideal method for treating acute cerebral infarction.

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