Journal of Hainan Medical University

http://www.hnykdxxb.com

Relationship of serum S1P and HC−II levels with vasoactive substances and cytokines in patients with cerebral vascular restenosis after stent implantation

Yong Liu✉

Department of Neurology, Chongqing Three Gorges Central Hospital, Wanzhou District, Chongqing 404000, China

ARTICLE INFO

Article history:
Received 7 Jul 2016
Received in revised form 17 Jul 2016
Accepted 12 Jul 2016
Available online 24 Jul 2016

Keywords:
Cerebrovascular stent implantation
Sphingosine 1-phosphate
Heparin cofactor II
Vasoactive substances

ABSTRACT

Objective: To study the relationship of serum sphingosine 1-phosphate (S1P) and heparin cofactor II (HCII) levels with vasoactive substances and cytokines in patients with cerebral vascular restenosis after stent implantation. **Methods:** 52 patients who received cerebrovascular stent implantation and developed restenosis in our hospital between May 2012 and December 2015 were collected as observation group, and 40 healthy patients with cerebrovascular stent implantation who had re-examination in our hospital during the same period were selected as control group. ELISA method was used to detect serum S1P and HC-II levels as well as vasoactive substance and inflammatory factor contents. Spearman correlation analysis was used to evaluate the relationship of serum S1P and HC-II levels with vasoactive substances and inflammatory factors. Results: Serum S1P and HC-II levels of observation group were lower than those of control group (P<0.05); serum vasoactive substances endothelin (ET), angiotensin II (AngII) and thromboxane B_2 (TXB_2) contents of observation group were higher than those of control group while nitric oxide (NO) content was lower than that of control group (P<0.05); serum inflammatory factors hypersensitive C-reactive protein (hs-CRP), interleukin-1 (IL-1), IL-6, IL-8 and IL-11 contents of observation group were higher than those of control group (P<0.05). Serum S1P and HC-II levels in patients with cerebral vascular restenosis after stent implantation were directly correlated with vasoactive substance and inflammatory factor contents. **Conclusion:** Serum S1P and HC-II levels decrease in patients with cerebral vascular restenosis after stent implantation, and it is an important cause of cerebral vascular dysfunction and systemic inflammatory response.

1. Introduction

Cerebral infarction is a clinical common cerebrovascular disease, endovascular stent implantation has become a reliable treatment for patients with cerebral arterial stenosis, but cerebrovascular in-stent restenosis (ISR) directly affects the treatment effect and threatens patients' life safety[1,2]. The pathogenesis of ISR is not clear, and more scholars believe that it is closely related to excessive proliferation of endothelial cells, inflammation, etc. Sphingosine 1-phosphate (S1P) and heparin cofactor II (HCII) are the newly discovered factors that are closely associated with the ISR, S1P has endothelial protective effect, and HCII has anticoagulant activity, and they are considered as "anti-ISR factors" by many scholars[3,4]. At present, there is no clear theoretical support about the correlation of S1P and HCII with the occurrence and development of ISR. In the following study, the relationship of serum S1P and HC-II levels with vasoactive substances and cytokines in patients with cerebral vascular restenosis after stent implantation was analyzed.

2. Materials and methods

2.1. Clinical information

52 patients who received cerebrovascular stent implantation

✉Corresponding author: Yong Liu, Department of Neurology, Chongqing Three Gorges Central Hospital, Wanzhou District, Chongqing 404000, China.
Tel: 13594865480
Fund Project: Science and Technology Planning Project of Wanzhou District Chongqing (No: KJ20130108).

and developed restenosis in our hospital between May 2012 and December 2015 were collected as observation group, and 40 healthy patients with cerebrovascular stent implantation who had re-examination in our hospital during the same period were selected as control group. Observation group included 27 male cases and 25 female cases, they were 48–76 years old, and the body weight was 52–86 kg and (75.39±9.88) kg in average; control group included 22 male cases and 18 female cases, they were 46–74 years old, and the body weight was 50–84 kg and (73.17±9.45) kg in average. Two groups of patients were not statistically different in gender, age and weight distribution (P>0.05), the patients or families signed consent form, and the study was approved by the hospital ethics committee.

2.2. Inclusion and exclusion criteria

Inclusion criteria: (1) clearly clinically diagnosed by head magnetic resonance imaging (MRI); (2) without head injury events after cerebrovascular stent implantation; (3) participating in the whole research, and with complete clinical data. Exclusion criteria: (1) with basic blood coagulation disorder; (2) with severe heart, liver and kidney dysfunction; (3) with cerebrovascular malformation and other brain disorders; (4) with infectious diseases of other tissues and organs.

2.3. Serum S1P and HC–II levels

Immediately after admission, 1.5–2.0 mL of cubital venous blood was extracted from two groups of patients, with anti-coagulated with sodium citrate (Shandong Wego Group Medical Polymer Products Co., LTD., approved by H20013323), let stand for 15 min at room temperature and centrifuged in a low-speed centrifuge (Changsha Pingfan Instrument Co., LTD., model TDL-10) to get supernatant and freeze it at -20 ℃for test. ELISA method was used to detect S1P and HCII.

2.4. Vasoactive substances and inflammatory factors

Immediately after admission, peripheral blood serum was obtained from two groups of patients in the same way, and ELISA method was used to detect vasoactive substances endothelin (ET), nitric oxide (NO), angiotensin II (AngII), thromboxane B_2 (TXB_2), hypersensitive C-reactive protein (hs-CRP), interleukin-1 (IL-1), interleukin-6 (IL-6), interleukin-8 (IL-8) and interleukin-11 (IL-11).

2.5. Statistical analysis

The data obtained in the study was organized and input in software SPSS15.0 by specially-assigned person, measurement data was in terms of $\bar{x}\pm s$, comparison between two groups was by t test, correlation was by Spearman correlation analysis and $P<0.05$ indicated statistical significance in differences.

3. Results

3.1. Serum S1P and HC–II levels

Comparison of serum S1P and HC-II levels between two groups of patients was as follows: serum S1P level of observation group was (92.17±9.84) ng/mL, and HC-II level was (0.64±0.07) ng/mL, serum S1P level of control group was (118.65±13.58) ng/mL and HC-II level was (0.92±0.09) ng/mL. Serum S1P and HC-II levels of observation group were lower than those of control group, and differences between groups were statistically significant ($P<0.05$), shown in Table 1.

Table 1

Comparison of serum S1P and HC-II levels (ng/mL, $\bar{x}\pm s$).

Groups	n	S1P	HCII
Observation group	52	92.17±9.84	0.64±0.07
Control group	40	118.65±13.58	0.92±0.09
t		6.392	5.758
P		<0.05	<0.05

3.2. Vasoactive substances

Comparison of serum vasoactive substances ET, NO, AngII and TXB_2 contents between two groups of patients was as follows: serum vasoactive substances ET, AngII and TXB_2 contents of observation group were significantly higher than those of control group while NO content was significantly lower than that of control group. Differences in serum vasoactive substances ET, NO, AngII and TXB_2 contents were statistically significant between two groups of patients ($P<0.05$), shown in Table 2. Pearson correlation analysis showed that serum S1P and HC-II levels were negatively correlated with vasoactive substances ET, AngII and TXB_2 contents, and positively correlated with No content.

3.3. Inflammatory factors

Comparison of serum inflammatory factors hs-CRP, IL-1, IL-6,

Table 2

Serum vasoactive substance contents ($\bar{x}\pm s$).

Groups	n	ET (ng/L)	NO (nmol/L)	AngII (ng/mL)	TXB_2 (ng/L)
Observation group	52	92.46±9.05	1.63±0.21	64.29±7.24	198.36±27.54
Control group	40	66.38±7.17	2.75±0.29	38.77±4.52	101.57±12.63
t		9.384	5.273	11.283	14.385
P		<0.05	<0.05	<0.05	<0.05

IL-8 and IL-11 contents between two groups of patients was as follows: serum inflammatory factors hs-CRP, IL-1, IL-6, IL-8 and IL-11 contents of observation group were higher than those of control group. Differences in serum inflammatory factors hs-CRP, IL-1, IL-6, IL-8 and IL-11 contents were statistically significant between two groups of patients (P<0.05), shown in Table 3. Pearson correlation analysis showed that serum S1P and HC-II levels were negatively correlated with hs-CRP, IL-1, IL-6, IL-8 and IL-11 contents.

4. Discussion

S1P is the intermediate of sphingomyelin metabolism, it is combined with cell surface receptor to exert extensive biological effects, and it has been confirmed that it's directly involved in endothelial protection and adhesion molecule expression suppression[5]. More than 65% of S1P in plasma exists in the form of lipoprotein, and it is found in the study about myocardial infarction rats that exogenous S1P application can reduce 20%–40% of the infarction area, and increase the blood perfusion in ischemic local area through Gi/MARK signaling pathway. HC-II belongs to anticoagulant factors, it is a member of the serine protease inhibitor family, study has confirmed that the HC-II application can greatly increase the anticoagulation system activity, and plasma HC-II consumption is regulated by the self-stabilization system of the body[6]. The occurrence of cerebral vascular restenosis after stent implantation is associated with both vascular endothelial injury and coagulation system dysfunction, so some scholars speculate that S1P and HC-II contents in circulating blood can accurately predict the illness in patients with cerebral vascular restenosis after stent implantation, but related research is less. In the study, serum S1P and HC-II contents were compared between two groups of patients at first, and it was found that compared with control group, serum S1P and HC-II contents of observation group were lower (P<0.05), confirming that S1P and HC-II are involved in the occurrence of cerebral vascular restenosis after stent implantation, but their effect on the disease progression remains to be further analyzed below.

Cerebrovascular dysfunction is one of the core causes of cerebral infarction and restenosis after stent implantation, cerebral vessels and coronary arteries are extremely sensitive to ET, studies have shown that the ET receptor content in the cerebral infarction area is several times of that in normal parts, and it increases the calcium ion concentration in vascular endothelial cells to exert vasoconstrictive effect[7,8]. NO is the vesodilatory substance corresponding to ET, and can also protect brain cells[9]. AngII is the vaso-excitor material with the most extensive effects in the body, and it can also exert pro-inflammatory effect and induce the massive expression of inflammatory factors and adhesion molecules[10]. TXB_2 is one type of prostaglandins, it has the dual roles of platelet aggregation and vasoconstriction, and the elevated TXB_2 level can increase the risk of thrombosis, and is one of the independent risk factors for restenosis after stent implantation in patients with cerebral infarction[11]. In the study, serum contents of above vasoactive substances were detected, and it was found that compared with control group, the observation group were with higher serum ET, AngII and TXB_2 levels, and lower NO level (P<0.05), the results are consistent with the physiological roles of these factors, it confirms that there are highly expressed vaso-excitor materials and lowly expressed vesodilatory materials in patients with cerebral vascular restenosis after stent implantation, and it is one of the main causes of restenosis.

Inflammation is the important mechanism that causes restenosis after stent implantation, the damaged cerebral vascular intima is rough, and it activates platelet system and then releases adhesion molecules and inflammatory mediators, which lead to inflammation cell chemotaxis and gathering largely in endometrial lesions[12,13]. hsCRP can reflect the overall intensity of inflammation, IL-1, IL-6 and IL-8 are the most important pro-inflammatory factors, and they can be released and then positively feed back on mononuclear macrophages, induce them to massively release inflammatory mediators, and aggravate cerebral vascular endothelial injury and local thrombosis[14]. IL-11 can stimulate macrophage growth, its function is similar to that of IL-6, and it has been confirmed by clinical research that it is highly expressed in the circulating blood of patients with restenosis after coronary PCI[15]. In the study, the contents of the above inflammatory factors were detected, and it was found that compared with control group, the observation group were with higher serum hs-CRP, IL-1, IL 6, IL-8 and IL-11 contents (P<0.05), confirming that there is obvious inflammation in patients with cerebral vascular restenosis after stent implantation.

S1P and HC-II are closely related to vascular endothelial injury, hypercoagulable state and systemic inflammatory response, and it is still not clear at present about the specific mechanisms for lowly expressed S1P and HC-II in serum of patients with cerebral vascular restenosis after stent implantation to affect the disease occurrence and development[16]. In the study, Spearman correlation analysis was used to determine the correlation of serum S1P and HC-II levels with vasoactive substance and between inflammatory

Table 3

Serum inflammatory factor contents ($\bar{x}\pm s$).

Groups	n	hs-CRP (mg/L)	IL-1 (pg/mL)	IL-6 (ng/mL)	IL-8 (pg/mL)	IL-11 (ng/mL)
Observation group	52	15.48±1.79	315.38±34.79	17.09±2.53	154.38±16.71	15.48±1.94
Control group	40	9.17±0.98	197.66±25.43	8.65±0.91	89.67±9.34	7.53±0.86
t		7.393	15.462	9.382	11.027	8.495
P		<0.05	<0.05	<0.05	<0.05	<0.05

cytokine contents, and it was found that serum S1P and HC-II levels in patients with cerebral vascular restenosis after stent implantation were directly correlated with vasoactive substance and inflammatory factor contents. It shows that the lowly expressed S1P and HC-II are involved in the occurrence of cerebral vascular restenosis after stent implantation through influencing the vaso-excitor/vesodilatory material balance, increasing the pro-inflammatory factor secretion and other mechanisms.

To sum up, it is concluded as follows: serum S1P and HC-II levels decrease in patients with cerebral vascular restenosis after stent implantation, and they regulate the vasoactive substance and inflammatory factor contents to participate in the disease occurrence and development.

References

[1] Lin QW, Zhu XL, Zhang C, et al. Predictive value of serum STIM1 and Adropin contents in cardiovascular events and restenosis after PCI operation. *J Hainan Med Univ* 2016; **22**(3): 233-236.

[2] Sasao H, Fujiwara H, Horiuchi N, et al. Comparison of long-term clinical outcomes after drug-eluting stent implantation in patients with coronary artery disease with and without prior cerebral infarction. *Ann Vasc Dis* 2015; **8**(2): 79-86.

[3] Yang HY, Jing XD, XiongY, et al. The predictive values of sphingosine-1-phosphate and adiponectin in patients with in-stent restenosis. *Chongqing Med* 2015; **44**(1): 40-43.

[4] Seo KD, Lee KY, Kim BM, et al. Delayed cerebral infarction due to stent folding deformation following carotid artery stenting. *Korean J Radiol* 2014; **15**(6): 858-861.

[5] Qu ZS, Zhang QD, Li L. Impact of low-dose urokinase in peritoneal dialysis on serum oxidative stress, nitric oxide andendothelin in cerebral infarction complicated with uremia. *Int J Clin Exp Med* 2015; **8**(1): 1333-1341.

[6] Liu CH, Liu Y. Effect of probucol combined with rosuvastatin on extracranial cerebral vascular restenosis after stent implantation. *Shandong Med J* 2016; **56**(42): 51-54.

[7] Qu ZS, Zhang QD, Li L. Impact of low-dose urokinase in peritoneal dialysis on serum oxidative stress, nitric oxide and endothelin in cerebral infarction complicated with uremia. *Int J Clin Exp Med* 2015; **8**(1): 1333-1341.

[8] Hu H, Huang Y, Jiang L, et al. Relationship between eNOS gene polymorphism and cerebral infarction of young and middle-aged Chinese Han population. *Bratisl Lek Listy* 2014; **115**(11): 708-711.

[9] Zhang Q, Li YX, Shang XM, et al. Effect of Shenshao oral liquid on serum vasoactive substances and cytokines after coronary intervention. *Chin J Gerontol* 2015; 35(6): 1487-1490.

[10]Meng YC, Ding ZY, Wang HQ, et al. Effect of microRNA-155 on angiogenesis after cerebral infarction of rats through AT1R/VEGFR2 pathway. *Asian Pac J Trop Med* 2015; **8**(10): 829-835.

[11]Dai J, Lv SZ, Song XT, et al. The mechanism, prevention and treatment progress of stent restenosis. *Chin J Geriatr Heart Brain Vessel Dis* 2014; **16**(3): 322-325.

[12]Xu R, Yin X, Xu W, et al. Assessment of carotid plaque neovascularization by contrast-enhanced ultrasound and high sensitivity C-reactive protein test in patients with acute cerebral infarction: a comparative study. *Neurol Sci* 2016; **37**(7): 1107-1112.

[13]Meng W, Li BZ, Wang YH, et al. Yiqihuoxuejieduhuajie method intervention on restenosis after coronary stenting and inflammatory factors. *Chin Arch Trad Chin Med* 2016; **34**(1): 142-145.

[14]Jiang Y, Lian YJ. Effects of Danhong injection on hemodynamics and the inflammation-related NF-κB signaling pathway in patients with acute cerebral infarction. *Genet Mol Res* 2015; **14**(4): 16929-16937.

[15]Zhu Y, Yang H, Diao Z, et al. Reduced serum level of interleukin-10 is associated with cerebral infarction: a case-control and meta-analysis study. Mol Neurobiol 2016; **53**(4): 2698-2704.

[16]Dai BB, Jin XH, Lei L. Plasma antithrombin-III and heparin cofactor II level change in patients with systemic lupus erythematosus and rheumatoid arthritis and the significance. *Heilongjiang Med J* 2016; **29**(1): 161-164.