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Original Article

Study on correlation analysis of hyper-sensitive C-reactive protein and re-stenosis after internal carotid artery stent implantation

Shuaitao Shi*, Zhidong Zhang*, Kewei Zhang, Kai Liang, Xiaoyang Fu, Weixiao Li, Guoquan Wang, Shuiting Zhai

*Department of Vascular and Endovascular Surgery, Henan Province People's Hospital, Zhengzhou, 450000, China. *Co-first authors.*

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Abstract: Objective: To study the changes in serum level of hyper-sensitive C-reactive protein (hs-CRP) in patients restenosis after internal carotid artery stent implantation (CAS) and its clinical value. Methods: The clinical data of 57 patients, who were readmitted to review stent condition by angiography after CAS, were retrospectively analyzed in this study. The rate of restenosis was measured using cerebral angiography. The patients were divided into restenosis group and non-restenosis group according to the criteria of stent restenosis. Venous blood was drawn at different time point (7 days, 3 months and 6 months) after CAS to measure hs-CRP level, and the results were analyzed by statistical method. Results: All the 57 patients, who underwent carotid artery stenting, were reviewed by cerebral angiography, among them, 11 cases (19.3%) had stent restenosis, including 5 patients (8.8%) with stenosis > 50% and 6 cases (10.5%) with stenosis of 30%-50%; 46 cases didn't have stent restenosis. Difference in preoperative hs-CRP level between restenosis group and non-restenosis group wasn't statistically significant ($P > 0.05$); however, the differences in hs-CRP level at postoperative 7 days, 3 months, and 6 months were statistically significant between the above two groups, the hs-CRP level in restenosis group was significantly higher than that of non-restenosis group ($P < 0.001$). Δhs-CRP (the difference of hs-CRP between pre-operation and 6 months after stent implantation) in restenosis group was significantly lower than the non-restenosis group. Multivariate regression analysis showed that Δhs-CRP is a risk factor for restenosis after CAS (OR=12.355, P=0.000). Conclusion: The increased serum hs-CRP level after stent implantation may participate in the pathological process of restenosis after stent implantation. Monitoring dynamic change in postoperative serum level of hs-CRP can better predict and evaluate the occurrence of restenosis after stent implantation.

Keywords: Internal carotid stenosis, CAS, hs-CRP, postoperative restenosis

Introduction

At present, cardiovascular and cerebrovascular diseases is the first cause of death in Chinese population. Carotid stenosis is considered to be one of the major risk factors for ischemic cerebrovascular disease [1]. Since the late 1990s, stent implantation has become one of the important surgical methods for the treatment of carotid stenosis [2]. For a long time, carotid endarterectomy (CEA) was considered to be the "gold standard" for carotid stenosis. Compared to the traditional CEA, CAS has advantages such as significant therapeutic effect, less trauma and less complications etc. [3, 4]. In recent years, with the improvement in interventional devices and techniques as well as the developed quality of carotid artery stent, CAS has been widely used in clinical application. However, the effect of CAS is often affected by neointima hyperplasia and restenosis in stent [5, 6]. Studies have shown that [7], restenosis in stent is correlated with balloon dilatation and neointima hyperplasia plerosis and inflammation caused by stent implantation; abnormal hyperplasia and migration of vascular endothelial cells and smooth muscle cells causes the restenosis. Currently, the methods used to evaluate stent restnosis include vascular ultrasound, CT angiography, and cerebral

angiography. Among those, cerebral angiography is the standard for the diagnosis and assessment of restenosis [8], but its complications and risk cannot be ignored, including contrast media anaphylaxis, contrast-induced encephalopathy, and puncture sites bleeding and infection etc.

High-sensitive C-reactive protein (Hs-CRP) is an inflammatory mediator of atherosclerosis [9], which is widely concerned as a major inflammatory factor of cardiovascular and cerebrovascular diseases. Some studies have indicated that the increase of serum hs-CRP is an independent predictor of myocardial infarction (MI) and cerebral apoplexy risk [10]. However, it is not clear about the relationship between the expression change of hs-CRP after CAS and the restenosis. In this study, dynamic change of serum hs-CRP level and its action in the possession of restenosis in 57 patients of carotid artery stenosis with CAS were analyzed, which providing a basis for using serum hs-CRP as a monitoring indicator in predicting neointimal restenosis after CAS.

Research objects and methods

Object of research

57 patients, who were readmitted to review stent condition by angiography after CAS from January 2008 to December 2015, were selected in this study. There were 22 male patients and 35 female pateints, aged from 47 to 77 years old with an average age of (57.36±9.75) years old. Among them, 28 cases were complicated with hypertension, 22 cases with hyperlipidemia and 36 cases with diabetes; 28 cases with smoking history, 36 cases with family history of cardiovascular disease. Before the surgery, patients were with symptomatic carotid artery stenosis > 50% or asymptomatic carotid artery stenosis > 70%, and all the patients had good results after CAS (rate of residual stenosis was < 30%, lumen diameter increased 20% after operation). A total of 122 cases of patients underwent CAS in our hospital from January 2008 to December 2015, and 65 cases of patients couldn't be reviewed by angiography due to loss of follow-up or death.

Carotid artery stent implantation (CAS) After local anesthesia, puncture was performed on femoral artery, and 8F artery sheaths were placed at the intracranial and extracranial segments of internal carotid artery and, after whole body heparinization, 8F guiding catheter was placed at the distal of the affected side of carotid artery. The angioguard was inserted into catheter and guided to get through the narrow section, and then angioguard was unfolded in the straight vessel that at least 2 cm upper from the narrow section. After confirmation of completely fit of angioguard and internal carotid artery by angiography, balloon was pre dilated to expand the narrow segment, and then the balloon catheter was removed, stent was accurately positioned in the stenosis along the angioguard of the guide wire and released, then, angiopraphy was used again to confirm the morphology and position of stent. Perioperative treatment included 3 days of preoperative orally taking aspirin (300 mg/D) and polivy (clopidogrel (75 mg/D), 3 days of postoperative anticoagulation, and strict control of blood pressure level (110-120/70-80 mmHg).

Method of cerebral angiography

The right side of the inguinal region was disinfected for local anesthesia, then puncture was performed on femoral artery and 5F vascular sheath was successfully inserted; 2000 U heparin was intravenous-injected, then a whole brain DSA examination was carried on. The angiographic equipment included bidirectional digital subtraction machine and automatic high-pressure injector that produced by SIEMENS, Germany. The contrast media was iopamidol 370. Criteria for stent restenosis: compared with lumen from last CAS, the diameter loss of lumen > 50% was considered as stent restenosis. In addition, the diameter loss of 30%-50% was determined to be mild stent restenosis in this study.

The detection method of hs-CRP

The content of serum hs-CRP was detected by immune transmission turbidity method. 3 ml peripheral blood was extracted from patients, and then centrifuged to separate the serum after placed at room temperature for about half an hour, then stored at -20°C. Hs-CRP kit was purchased from Dade Behring Company (USA).

Statistical treatment

SPSS 17.0 software was used for data analysis. Measurement data were expressed with mean

Table 1. Comparison of the general condition in two groups of patients

Parameter	Restenosis group (n=11)	Non-restenosis group (n=46)	Statistic	*P* value
Gender male (%)	5 (45.45)	20 (43.48)	χ^2=0.232	0.454
Age (year)	57.45±4.66	61.34±7.35	t=0.156	0.345
Hypertension (%)	23.55	26.35	χ^2=0.455	0.656
Diabetes (%)	34.45	41.77	χ^2=0.356	0.356
Dyslipidemia (%)	66.45	34.35	χ^2=5.775	0.015
Smoking history (%)	52.24	51.45	χ^2=0.466	0.556
Family history of cerebrovascular disease (%)	33.55	32.46	χ^2=0.566	0.677

Table 2. Comparison of the pathological changes of carotid artery and CAS between stenosis group and non-restenosis group

Item	Stenosis group (n=11)	Non-restenosis group (n=46)	Statistic	*P* value
Degree of carotid artery stenosis				
50-70%	3 (27.27%)	14 (30.43%)	χ^2=0.156	0.667
70-90%	6 (54.54%)	24 (52.17%)	χ^2=0.056	0.946
90-99%	2 (18.18%)	8 (17.39%)	χ^2=2.356	0.118
Stent length/mm	38.34±5.34	37.32±2.45	t=0.532	0.595
Stent diameter/mm	8.34±0.64	8.37±0.56	t=0.122	0.903
Sent categories			χ^2=0.486	0.481
Closed loop stent	2	9		
Open loop stent	9	37		

Table 3. Level of blood lipid in restenosis group and non-restenosis group and its single factor analysis

Item	Restenosis (n=11)	Non-restenosis (n=46)	Statistic	*P* value
TC (mmol/L)	5.35±0.34	4.25±0.76	t=10.146	0.002
TG (mmol/L)	1.45±0.57	1.65±0.67	t=0.157	0.343
LDL-C (mmol/L)	2.66±0.87	2.68±0.84	t=0.345	0.465
HDL-C (mmol/L)	1.57±0.46	1.67±0.57	t=0.354	0.477

± standard deviation, and t test was used for the comparison between two groups; enumeration data were expressed with percentage, and chi-square was used for the comparison between two groups. Logistic regression analysis was used in multivariate analysis. The difference was statistically significant with $P < 0.05$.

Results

The basic clinical features of patients

Among the 57 patients with carotid artery stenting, after being reviewed by cerebral angiography, 11 cases (19.3%) had stent restenosis, including 5 patients (8.8%) with stenosis > 50% and 6 cases (10.5%) with stenosis of 30%-50%; the rest 46 patients didn't have stent restenosis. According to the results of angiography, the patients were divided into restenosis group and non-restenosis group. Comparison of the general condition in the two groups of patients is shown in **Table 1**, the blood lipid significantly increased (χ^2=5.775, P=0.015) in restenosis group. All the patients were followed up for (188±28.6) days, and there was no new cerebral infarction, transient ischemic attack or cerebrovascular events during the follow-up.

Comparison of carotid artery stenosis and parameters of carotid stent

57 carotid stents were used in 57 patients, including 46 open loop stents with 9 restenosis, 11 closed loop stents with 2 restenosis. No statistically significant difference was observed

Table 4. Dynamic change of hs-CRP after CAS (mg/L)

	n	Before operation	7 days after operation	3 months after operation	6 months after operation
Restenosis group	11	7.69±0.35	8.45±0.46	8.57±0.35	7.35±0.45
Non-restenosis group	46	7.91±0.57	6.94±0.34	5.35±0.95	4.56±0.56
Statistic		0.665	3.456	10.354	13.456
P value		0.245	0.001	0.000	0.000

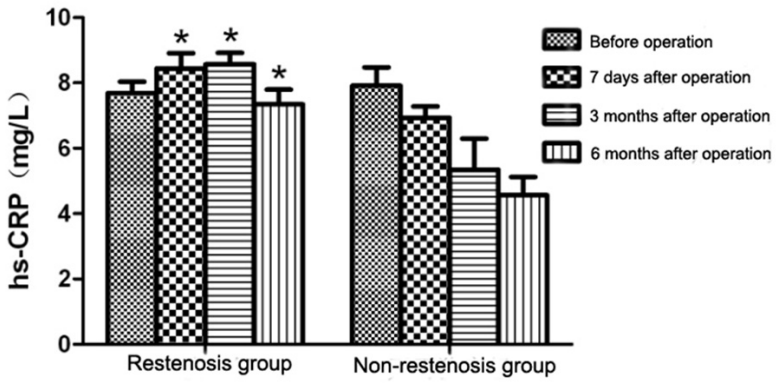

Figure 1. Expression level of hs-CRP at different time point in two groups of patients, *$P < 0.05$.

Table 5. Restenosis after CAS and Δhs-CRP

	n	Δhs-CRP (mg/L)
Restenosis group	11	0.34±0.55
Non-restenosis group	46	3.35±1.45
Statistic		8.455
P value		0.000

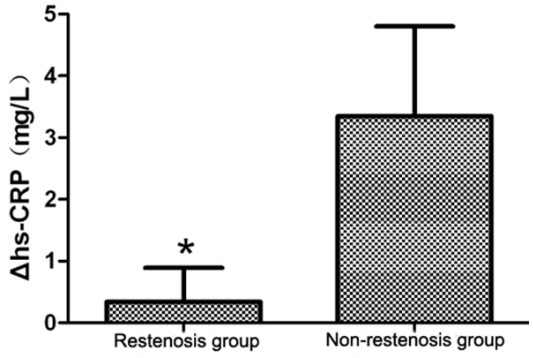

Figure 2. Comparison of difference in hs-CRP between the two groups of patients, *$P < 0.05$.

by comparing the sent categories of two groups. There was no significant difference in the degree of carotid artery stenosis, stent diameter and stent length between the two groups, see **Table 2**.

Comparison of level of blood lipid in the two groups of patients

The level of blood lipid in the two groups of patients is shown in **Table 3**. We can see that there was no significant difference in hyperlipidemia (TG), low density lipoprotein-cholesterol (LDL-C) and high density lipoprotein-cholesterol (HDL-C) between restenosis group and non-restenosis group ($P > 0.05$). However, total cholesterol concentration in restenosis group was significantly higher than that of non-restenosis group ($P < 0.05$).

Dynamic change of hs-CRP and stent restenosis in two groups

There was no significant difference in preoperative hs-CRP level between the two groups (p=0.245). However, hs-CRP levels at postoperative 7 days, 3 months and 6 months in restenosis group were significantly higher than those in patients of non-restenosis group, see **Table 4**, **Figure 1**. Δhs-CRP (the difference of hs-CRP between pre-operation and 6 months after stent implantation) in restenosis group was significantly lower than the non-restenosis group (t=8.455, $P < 0.001$), see **Table 5**, **Figure 2**.

Multivariate regression analysis

Binary logistic regression analysis in stenosis group and non-restenosis group: age, hypertension, hyperlipidemia, diabetes, smoking history, family history of cerebrovascular disease, Δhs-CRP were included in logistic regression analysis. The results showed that Δhs-CRP (OR= 12.355, P=0.000) is a risk factor for restenosis after CAS, see **Table 6**.

Table 6. The result of multivariate regression analysis of restenosis after stenting

Variable	Regression coefficient	OR value	95% CI	*P* value
Δhs-CRP	3.455	12.355	1.466-4.357	0.000

Discussion

Cerebral ischemic stroke is one of the main cardiovascular and cerebrovascular diseases that cause death. Studies found that carotid stenosis is one of the main causes of cerebral ischemic stroke, and the degree of carotid stenosis is positively related with the occurring risk of cerebral ischemic stroke [11, 12]. In recent ten years, CAS has been widely used in the clinic and gradually replaced CEA to become the main method for the treatment of carotid stenosis [13, 14]. However, CAS has complications of neointima hyperplasia and restenosis in stent, which seriously affect the curative effect and long-term prognosis [15, 16].

Studies at home and abroad have reported that the rate of restenosis after CAS is about 20%-40%, which mainly occurred in 6-18 months after surgery, and severe stenosis (> 50%) usually occurred within 15 months after surgery [17-19]. This research showed that, in 57 patients underwent carotid artery stenting, after being reviewed by cerebral angiography 6 months after surgery, 11 cases (19.3%) had stent restenosis, including 5 patients (8.8%) with stenosis > 50% and 6 cases (10.5%) with stenosis of 30%-50%; 46 cases didn't have stent restenosis. This is basically similar to the research at home and abroad. At the same time, these results also showed that the rate of restenosis for CAS was high, and this problem seriously affected the long-term effect of CAS. Therefore, it is necessary for patients to carry on long-term follow-up and to find index for evaluating the prognosis after CAS.

Hs-CRP is an inflammatory mediator of atherosclerosis [20], which is an independent predictor of clinical outcome in patients with coronary heart disease and MI. However, the analysis for the role of hs-CRP in patients with CAS is not sufficient. The results of this study showed that there was no significant difference in preoperative hs-CRP level between restenosis group and non-restenosis group (P > 0.05), however, the hs-CRP level at postoperative 7 days, 3 months, and 6 months in restenosis group was significantly higher than that of non-restenosis group. Δhs-CRP (the difference of hs-CRP between preoperation and 6 months after stent implantation) in restenosis group was significantly lower than that of non-restenosis group (t=8.455, P < 0.001), indicating that the dynamic change of hs-CRP level plays an important role in the pathological process of stent restenosis. Lower level of hs-CRP reflects lower level of inflammation in the body, so the chance of stent restenosis is smaller. After CAS, the carotid endangium and whole body will have inflammatory reaction. Massive proliferation of carotid endangium and smooth muscle cells will lead to restenosis. hs-CRP, as an acute inflammatory reaction factor, is mainly synthesized and secreted in the liver cells [21]. There is study found that within 24-48 hours after acute inflammation, the concentration of serum hs-CRP would increase nearly 100 times [22]. Therefore, under most circumstances, hs-CRP can be used as a molecular marker for predicting and evaluating the state of inflammation in the body [23]. This study found that the level of hs-CRP is closely related to the occurrence and development of carotid restenosis. The mechanism may be due to the direct effect of hs-CRP on carotid endangium, activating the complement system, and promoting the local inflammatory reaction [24]. In addition, hs-CRP can also cause aggregation of monocytes, which infiltrate the carotid endangium and further develop into macrophages [25, 26]. Macrophages will be transformed into foam cells after phagocytosis of lipids, and massively deposite, which further result in the stenosis.

Patients with carotid stenosis tend to have other diseases, such as coronary heart disease, hypertension, diabetes, hyperlipidemia and so on [27, 28]. This study found that the proportion of hyperlipidemia was significantly higher in the restenosis group compared with the non-restenosis group. It is found that there is a certain relationship between the level of blood lipid and the occurrence and development of carotid restenosis. The abnormal lipid metabolism in the body makes blood lipid more likely to be deposited on the vascular wall, so as to promote the occurrence and development of restenosis after CAS [29, 30]. But the binary

Logistic regression analysis results showed that Δhs-CRP is a risk factor for restenosis after CAS.

In conclusion, the inflammatory reaction may play an important role in the restenosis after CAS. The increased serum hs-CRP after stent implantation may participate in the pathological process of restenosis after stent implantation. Therefore, closely monitoring preoperative and postoperative changes of serum hs-CRP level can better predict the occurrence of restenosis for patients.

Disclosure of conflict of interest

None.

Address correspondences to: Guoquan Wang and Shuiting Zhai, Department of Vascular and Endovascular Surgery, Henan Province People's Hospital, No. 7, Weiwu Road, Zhengzhou, Henan Province 450000, P.R. China. Tel: +86-37187160229; E-mail: guoquan_wang@sina.cn (GQW); E-mail: shuiting_zhai@sina.cn (STZ)

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