Changes in Serum Copeptin and Sphingosine 1-Phosphate in Patients with Restenosis after Stent Implantation of Symptomatic Intracranial Artery Stenosis

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ABSTRACT

Objective: To determine the changes of serum copeptin and sphingosine 1-phosphate (S1P) in patients with restenosis after stent implantation of symptomatic intracranial artery stenosis.

Study Design: An observational study.

Place and Duration of Study: Changyi people's Hospital, China, from February 2016 to November 2019.

Methodology: A total of 76 patients with symptomatic intracranial artery stenosis and stent implantation were divided into the restenosis group (n = 16) and the non-restenosis group (n=60) according to the intracranial artery restenosis occurred after the follow-up of 1 year. Levels of serum copeptin and S1P were compared between the groups.

Result: There were significant differences in diabetes mellitus and hypertension between the two groups ($p<0.001$ and $p = 0.017$, respectively). There were no significant differences in serum copeptin and S1P levels between the two groups before and 3 days after the operation ($p = 0.927$, 0.792, 0.776, and 0.906, respectively). Postoperative follow-up of one year, levels of serum copeptin in the restenosis group were higher than those in the non-restenosis group ($p<0.001$), and levels of serum S1P in the restenosis group were lower than those in the non-restenosis group ($p = 0.003$).

Conclusion: High serum copeptin level, low serum S1P level, hypertension, and diabetes mellitus are independent risk factors promoting restenosis after stent implantation in patients with symptomatic intracranial artery stenosis.

Key Words: *Copeptin, Sphingosine 1-phosphate (S1P), Symptomatic intracranial artery stenosis, Stent implantation, Restenosis.*

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INTRODUCTION

Symptomatic intracranial artery stenosis refers to intracranial artery stenosis caused by atherosclerosis accompanied with ischemic stroke or transient ischemic attack in the blood supply area of the narrow artery. Intracranial artery stenosis is one of the main causes of the attack and recurrence of ischemic stroke.[1] At present, medication, surgical treatment, and intravascular interventional therapy are the main treatment methods for intracranial artery stenosis. Stent implantation of intracranial artery stenosis is one of the main methods of intravascular interventional therapy.[2] The safety and effectiveness of stent implantation for intracranial artery stenosis have been verified.[3]

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Although stent implantation of the intracranial artery stenosis can effectively alleviate clinical symptoms, the challenge of short-term and long-term complications such as in-stent restenosis of the intracranial artery cannot be ignored. Restenosis after stent implantation for symptomatic intracranial artery stenosis is a key issue in clinical research.[4] It is very important to avoid and prevent restenosis after stent implantation.

Copeptin is the carboxy peptide of arginine vasopressin precursor.[5] It has the advantages of good stability and is convenient to be detected. Blood copeptin was not elevated in coronary artery ectasia cases.[6] However, studies have shown that copeptin may be a useful serum marker for stroke risk assessment in patients after carotid endarterectomy.[7] It has been confirmed that serum copeptin may be a sensitive index of early subclinical peripheral arterial disease.[8] It has also been reported that copeptin is an independent risk factor for intracranial and extracranial artery stenosis, especially for intracranial artery stenosis.[9]

Sphingosine 1-phosphate (S1P) is a sphingolipid substance that circulates *in vivo* with biological activity.[10] Previous studies have confirmed that S1P has a vascular protective effect by

preventing the overproduction of inflammatory factors and inhibiting inflammatory reactions.[11] The mechanism of restenosis after stent implantation is related to inflammatory factors.[12]It has been found that patients with a high level of S1P have a lower risk of in-stent restenosis.[13] However, there are few reports on the changes of serum copeptin and S1P in restenosis after stent implantation for symptomatic intracranial artery stenosis.

The purpose of this study was to determine the changes in serum copeptin and S1P in patients with restenosis after stent implantation of symptomatic intracranial artery stenosis.

METHODOLOGY

This observational study was approved by the Ethics Committee of Changyi People's Hospital, China. A total of 76 patients with symptomatic intracranial artery stenosis and stent implantation in the hospital, from February 2016 to November 2019, were selected as the subjects (The deadline for follow-up was November 2020).

The inclusion criteria were patients diagnosed with symptomatic stenosis ≥50% by CT angiography and digital subtraction angiography before operation and undergone stent implantation; aged 18-80 years; with complete follow-up data; and with the informed consent of patients and their families. The exclusion criteria were patients with brain tumors, severe bleeding tendencies, serious cardiovascular diseases, blood system diseases, or unable to tolerate stent implantation; patients diagnosed with symptomatic stenosis by carotid ultrasound and transcranial Doppler ultrasound but not examined by CTA or DSA; surgical failure, *i.e*. stents not completely covering the lesions or residual stenosis ≥50%; lost visitors; and patients with stent thrombosis after the operation. Restenosis was judged by the coronary angiographic results within one year after the operation. According to the ACC/AHA coronary angiography guidelines, restenosis was diagnosed as the degree of stenosis ≥50% at both ends of the stent (≤5 mm from the edge of the stent) or both ends of the stent and the diameter of the lumen between both ends.

Patients were divided into the restenosis group (n=16) and the non-restenosis group (n=60) according to the intracranial artery restenosis that occurred after the follow-up of one year. All the patients were followed up before operation, 3 days after the operation, and 1 year after the operation. Five ml fasting venous blood samples were taken from the elbow vein in the early morning. The levels of serum copeptin and S1P were measured by enzyme-linked immunosorbent assay method.

SPSS 25 statistical software was used for data processing. The measurement data in accordance with the normal distribution were expressed by mean ± standard deviation, and the independent sample t-test was used for comparison. The counting data were expressed as percentage (%) and chi-square or Fisher's Exact test was used for comparison. P <0.05 was the threshold of significant difference.

RESULTS

There were no significant differences in gender, age, drinking history, and smoking history between the two groups (p=0.875, 0.952, 0.763, and 0.835, respectively, Table I), but there were significant differences in diabetes mellitus and hypertension between the two groups (p <0.001 and p = 0.017 respectively, Table I).

Table I: Comparison of demographic data between the two groups before treatment.

Parameter	Restenosis group (n=16)	Non-restenosis group (n=60)	p-value
Male [n (%)]	11 (68.75)	40 (66.67)	0.875
Age (years)	66.63±8.67	66.73±5.59	0.952
Drinking history [n (%)]	4 (25.00)	19 (31.67)	0.763
Smoking history [n (%)]	7 (43.75)	28 (46.67)	0.835
Diabetes mellitus [n (%)]	11 (68.75)	13 (21.67)	<0.001
Hypertension [n (%)]	9 (56.25)	15 (25.00)	0.017

There were no significant differences in serum copeptin and S1P levels between the two groups before and 3 days after the operation (p= 0.927, 0.792, 0.776, and 0.906, Table II). Postoperative follow-up of one year, the levels of serum copeptin in the restenosis group were higher than those in the non-restenosis group (p <0.001, Table II), and the levels of serum S1P in the restenosis group were lower than those in the non-restenosis group (p= 0.003, Table II).

DISCUSSION

Stent implantation has become one of the main methods for the treatment of intracranial artery stenosis, but there remain some shortcomings of restenosis. Previous studies have found that hypertension is a risk factor for vascular restenosis after stent implantation for intracranial arterial stenosis.[14]Restenosis rates between diabetics and nondiabetics were similar in carotid artery stenting and carotid endarterectomy patients.[15] The results of this study showed that there were significant differences in the proportion of hypertension and diabetes between the restenosis group and the non-restenosis group. Therefore, we speculated that hypertension, diabetes mellitus, and restenosis after stent implantation may be related to symptomatic intracranial artery stenosis.

Copeptin is a stable precursor C-terminal part of posterior pituitary vasopressin, which is a biomarker for the diagnosis and prediction of diabetes mellitus.[16] It has been found that the increase of serum copeptin level is related to systolic and diastolic blood pressure.[17] A study found that elevated serum copeptin was associated with increased major adverse cardiac events (including recurrent myocardial infarction and death *etc*.) incidence.[18]

The results of this study showed that the levels of serum copeptin in the restenosis group were higher than those in the non-restenosis group after follow-up for 1 year.

Table II: Comparison of serum copeptin and S1P levels between the two groups.

Parameter	Time	Restenosis group (n=16)	Non-restenosis group (n=60)	p-value
Serum copeptin (pmol/L)	Before operation	17.47±2.04	17.51±1.46	0.927
	Three days after operation	24.29±2.80	24.13±2.01	0.792
	Postoperative follow-up one year	19.15±2.24	13.42±1.12	<0.001
Serum S1P (ng/mL)	Before operation	104.38±10.86	103.65±8.64	0.776
	Three days after the operation	97.92±10.01	98.21±8.17	0.906
	Postoperative follow-up one year	90.74±7.89	97.39±7.70	0.003

The result of this study was basically consistent with the result reported in a previous study that serum copeptin levels of cases with intracranial vertebrobasilar artery stenosis and restenosis after stenting were significantly higher than those without restenosis one year after surgery.[19] It can be seen that the relationship between copeptin and diabetes mellitus and hypertension may also be a potential mechanism of its correlation with restenosis after stent implantation in symptomatic intracranial artery stenosis.

In-stent restenosis is considered to be a self-repair response after local vascular injury. The disorder of the re-endothelial process is closely related to the occurrence of restenosis.[20] S1P plays an important role in regulating the vascular formation, barrier protection and vascular tension through S1P1, S1P2, and S1P3.[21] The results of this study showed that the serum S1P level in the restenosis group was lower than that in the non-restenosis group after follow-up for 1 year. The result of this study was basically consistent with the result reported in a previous study that serum S1P levels decreased in cases with cerebral vascular restenosis after stent implantation.[22] It is speculated that the lower the S1P is, the higher the risk of restenosis will be. S1P plays a protective role after stent implantation for symptomatic intracranial artery stenosis.

It should be pointed out that this study is a retrospective study with small sample size. To further clarify the specific mechanism of restenosis after stent implantation in symptomatic intracranial artery stenosis, studies with a large sample size combined with basic experiments are needed.

CONCLUSION

High serum copeptin level, low serum S1P level, hypertension, and diabetes mellitus are independent risk factors promoting restenosis after stent implantation in patients with symptomatic intracranial artery stenosis. As to the critical level of serum copeptin and S1P at which suspect stenosis considering a single patient when do not have a comparison, it needs further confirmation in the future.

ETHICAL APPROVAL:

This study was approved by the Ethical Committee of Changyi people's Hospital, China.

PATIENT'S CONSENT:

Informed consents were obtained from the patients to publish the data.

COMPETING INTEREST:

The authors declared no competing interest.

AUTHORS' CONTRIBUTION:

XJ: Writing result interpretation, and discussion.
ZL: Data collection, analysis, and final approval.
SW: Revising it critically for important intellectual content.

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