European Review for Medical and Pharmacological Sciences 2014; 18: 3029-3033

Dynamic changes of the various cytokines following carotid artery stenting

X.-J. JIA, S.-Z. FANG, Q.-F. ZHU, R.-T. XIE, Z.-Y. LIU

Department of Neurology, No. 264 Hospital, Taiyuan, Shanxi Province, China

Abstract. – OBJECTIVE: To observe the serum inflammatory and coagulation factors changes and clinical significance following carotid artery stenting.

PATIENTS AND METHODS: The expressions of serum inflammatory factors including IL-2, IL-6, IL-8, sICAM-1, hs-CRP, and TNF-α and serum coagulation factors including prothrombin time (PT), active partial thromboplastin time (APTT), fibrinogen (FIB), D-dimer (DD), and fibrin degradation products (FDP) were determined in 92 patients who had undergone carotid artery stenting before, 24h, 48h, 3 days and 1 week after the surgery. As well, 92 subjects who did not receive stenting were enrolled in the angiography group, amongst whom the same variables were determined.

RESULTS: In the stenting group, the expressions of hs-CRP, TNF-α, sICAM-1, IL-6, IL-8, FIB, and DD were significantly increased after the surgery ($p < 0.05$): hs-CRP reached a peak 48h after the surgery; TNF-α, sICAM-1, and IL-6 maintained at high levels at days 3-7; and FIB and DD increased 48h and 3d after the surgery. Compared with the angiography group, the expressions of hs-CRP, TNF-α, sICAM-1, and IL-8 (24h after the surgery) as well as FIB and DD (48h and 3d after the surgery) were significantly higher in the stenting group.

CONCLUSIONS: The hs-CRP, TNF-α, sICAM-1, IL-8, FIB, and DD increased after carotid artery stenting and, therefore, can serve as important factors for monitoring for acute postoperative complications.

Key Words:
Carotid artery stenting, Inflammatory factors, Coagulation factors.

Introduction

Carotid artery stenting is an effective intervention against carotid stenosis. Complications include acute cerebral infarction, cerebral hemorrhage and chronic vascular restenosis[1]. A close correlation between inflammatory cytokines [high-sensitivity C-reactive protein (hs-CRP), soluble intercellular adhesion molecule-1, (sICAM-1), coagulation factor D-dimer and fibrinogen degradation products (FDP)] versus carotid artery disease and stroke was demonstrated in recent studies[2]. The risk of complications post-carotid artery stenting can be associated to changes resulting from the cytokines as reported in a few studies. In this study, changes in serum inflammatory cytokines and coagulation factors were examined post carotid artery stenting.

Patients and Methods

Patients

Participants included patients who were admitted to our hospital's neurology department between January 2006 and December 2013. Ninety-two patients were placed into each of the groups (stenting group and angiography group). Another 92 patients who came to the clinic for a physical examination during the same period, were enlisted in the control group. The inclusion criteria were as follows: (1) symptomatic carotid stenosis < 50% or asymptomatic carotid stenosis < 70%; (2) carotid stenosis, as demonstrated by CT angiography (CTA) and ultrasound examination in combination; (3) absence of congestive heart failure or respiratory failure; and (4) creatinine levels < 6.4 mmol/L. The exclusion criteria included: (1) acute cerebral hemorrhage; (2) aortic occlusion or bilateral iliac artery occlusion; (3) previous history of hemorrhage or coagulopathy; (4) severe lung disease, unable to supine; (5) complete blockage of target vessels; (6) any myocardial infarction episodes within two months; (7) uncontrolled hypertension or diabetes mellitus; (8) stenosis site inaccessible to guide wire or catheter; (9) abdominal aortic aneurysm; and (10) inflammation in its acute stages.

Corresponding Author: Xiaojun Jia, MD; e-mail: jiating814@sina.com

Carotid Artery Stenting

Patients received 100 mg/day of aspirin and 75 mg/day of clopidogrel bisulfate three days prior to the procedure. Sodium phenobarbital 0.1 g i.m. was administered 30 minutes before surgery. The intervention was performed under local anesthesia and systemic heparinization. A catheter was placed into the carotid artery using a stiff Terumo guide wire with an arterial sheaths (8F). Other techniques (companion guide wire or coaxial guide wire) can be used if the catheterization procedure is unsuccessful. Stents were placed using the Angioguard (Plymouth, MN, USA) RX and SPIDERX (Minneapolis, MN, USA) devices. Enoxaparin 4 ml, bid was administered for three to five days continuously. A daily dose of 100 mg aspirin and clopidogrel bisulfate 75 mg/day was prescribed in combination for another six months.

Determination of Serum Inflammatory and Coagulation Factors

Interleukin-2 (IL-2), IL-6, IL-8 and sICAM-1 concentrations were determined by ELISA. The hs-CRP and TNF-α levels were determined by immune nephelometry and radio-immunoassays. The PT, APTT, and FIB were measured according to the solidification method. The D-D was determined by turbidimetric immunoassays, while FDP was determined by emulsion agglutination turbidimetric method. The reagent kits were used according to their instructions.

Statistical Analysis

The statistical analysis was completed using the SPSS 10.0 software (SPSS Inc., Chicago, IL, USA). The count data were compared using c^2 test, and the measurement data and the carotid artery stenting results were compared using *t* test $p < 0.05$ was considered statistally significant.

Results

General Data of the Stenting Group

There were 52 males (56.5%) and 40 females (43.5%) in the stenting group (n=92), with a mean age of 72.2 ± 9.5 years. Among them, 43 patients had essential hypertension, 25 had diabetes; 11 were current smokers, and 26 had hyperlipidemia. Their body mass index (BMI) were (27.7 ± 3.2) kg/m^{2}and the hs-CRP level was 2.5 ± 0.4 mg/L. Compared with the angiography group, these indicators showed no significant differences (all $p > 0.05$). In the stenting group, 33 patients had coronary heart disease (CHD) and 16 had a history of cerebral infarction; compared with the angiography group, the occurrence of CHD was higher and that of cerebral infarction was lower in the stenting group (both $p < 0.05$) (Table I).

Changes of the Serum Inflammatory Cytokines Following Carotid Artery Stenting

The serum inflammatory cytokine levels in the control group were as follows: hs-CRP, 1.69 ± 0.56 mg/L; TNF-α, 1.13 ± 0.42 μg/L; sICAM-1, 189.2 ± 52.5 μg/L; IL-6, 16.16 ± 4.25 μg/L; IL-2, 173.88 ± 43.2 μg/L; and IL-8, 17.71 ± 1.32 μg/L. In the angiography group, the serum levels of hs-CRP, sICAM-1, IL-6, and IL-8 significantly increased 24 h after the procedure ($p < 0.05$). In the stenting group, the serum levels of hs-CRP, TNF-α, sICAM-1, IL-6, and IL-8 significantly in-

Table I. Baseline features of the patients.

	Angiography group (n = 92)	Stenting group (n = 92)	χ^2	*p*
Age ($\bar{x}$ ± s, y)	66.7 ± 7.3	72.2 ± 9.5	3.561*	0.016
Males	54 (58.7)	52 (56.5)	0.992	0.251
BMI ($\bar{x}$ ± s, kg/m^2)	25.1 ± 2.8	27.7 ± 3.2	1.927*	0.128
Current smokers	14 (15.2)	11 (12.0)	0.417	0.241
Essential hypertension	40 (43.5)	43 (46.7)	0.198	0.297
Diabetes mellitus	28 (30.4)	25 (27.2)	0.239	0.315
Hyperlipidemia	24 (26.1)	26 (28.3)	1.305	0.167
Coronary heart diseases	17 (18.5)	33 (35.9)	12.583	0.018
History of cerebral hemorrhage	10 (10.9)	11 (12.0)	0.682	0.395
History of cerebral infarction	19 (20.7)	16 (17.4)	8.614	0.023
hs-CRP ($\bar{x}$ ± s, mg/L)	2.2 ± 0.4	2.5 ± 0.4	2.038*	0.219

*Represents *t* value.

creased after the procedure ($p < 0.05$); the hs-CRP level reached a peak 48 hours after the procedure and then returned to normal, whereas the levels of TNF-α, sICAM-1, IL-6, and IL-8 remained high for three to seven days. Compared with the control group, the serum levels of hs-CRP, TNF-α, sICAM-1, IL-6, IL-2, and IL-8 24 hours after the procedures were significantly higher than those in the control group ($p < 0.05$) (Table II).

Changes of the Serum Coagulation Factors Following Carotid Artery Stenting

The serum coagulation factors in the control group were: PT, 12.8 ± 2.3 s; APTT, 29.6 ± 6.7 s; FIB, 3.2 ± 0.6 mg/dl; DD, 117.5 ± 26.8 mg/dl; and FDP, 1.9 ± 0.3%. In the angiography group, the levels of FIB and DD increased after surgery ($p < 0.05$), whereas PT and APTT increased one week after surgery ($p < 0.05$). In the stenting group, PT and APTT increased three days after surgery ($p < 0.05$), whereas FIB, DD, and FDP increased 48 hours after surgery ($p < 0.05$). Compared with the control group, the FIB and DD levels were higher in the angiography group and the stenting group ($p < 0.05$) (Table III).

Discussion

Changes in inflammatory and coagulation factors and their clinical relevance post-carotid artery stenting is described in the coronary artery stent procedure. It has been demonstrated that elevations of hs-CRP, IL-6, TNF-α and other inflammatory cytokines can be considered as sensitive indicators for post-operative assessment of inflammation in its early stages and disease state[3]. Post-operative elevation of inflammatory cytokines might be associated with the occurrence of important post-operative cardiovascular events, such as myocardial infarction, angina pectoris and death, as well the risk of restenosis[4]. The relevance of a single inflammatory cytokine or coagulation factor (such as hs-CRP, IL-6, sICAM-1, TNF-α, DD and FDP) to postoperative acute ischemic events or chronic restenosis has been described in many studies. However, changes of multiple inflammatory cytokines and coagulation factors were examined after vascular intervention, as investigated in this study. Profiles of inflammatory cytokines or coagulation factors following carotid artery stenting procedure were different to those of

Table II. Changes of the serum inflammatory cytokines following carotid artery stenting (n=92, $\bar{x} \pm s$).

Inflammatory cytokines	Before stenting	After stenting							
		24h		48h		3d		1w	
		t	*p*	*t*	*p*	*t*	*p*	*t*	*p*
Angiography group (n=92)									
hs-CRP(mg/L)	2.21 ± 0.43	3.06 ± 0.39	5.184-0.025	3.41 ± 0.58	7.369-0.017	2.43 ± 0.37	1.246-0.382	2.18 ± 0.26	0.653-0.726
TNF-σ (μg/L)	2.08 ± 0.37	2.36 ± 0.33	1.012-0.931	2.29 ± 0.18	0.658-0.383	2.32 ± 0.24	1.169-0.491	2.12 ± 0.13	0.962-0.208
sICAM-1 (μg/L)	263.75 ± 48.32	324.56 ± 52.17	4.264-0.009	268.60 ± 58.36	0.801-0.573	276.13 ± 42.83	0.461-0.308	283.09 ± 67.89	1.127-0.296
IL-2 (μg/L)	257.39 ± 50.18	199.42 ± 38.69	8.264-0.003	237.61 ± 47.23	1.062-0.816	264.94 ± 51.35	0.629-0.874	250.68 ± 47.32	1.302-0.309
IL-6 (μg/L)	98.35 ± 16.97	178.62 ± 34.29	9.863-0.002	116.12 ± 20.54	1.362-0.259	107.39 ± 23.87	0.715-0.460	91.67 ± 23.54	0.927-0.317
IL-8 (μg/L)	23.36 ± 4.18	34.28 ± 5.82	4.371-0.018	26.74 ± 4.09	0.742-0.084	24.03 ± 5.27	0.902-0.681	25.69 ± 5.42	0.234-0.750
Stenting group (n=92)									
hs-CRP (mg/L)	2.54 ± 0.38	4.37 ± 0.64	6.082-0.025	6.19 ± 0.52	8.829-0.014	2.63 ± 0.17	1.016-0.327	2.42 ± 0.23	0.723-0.135
TNF-α (∝g/L)	2.26 ± 0.27	1.09 ± 0.18	9.719-0.002	1.48 ± 0.27	3.003-0.027	1.36 ± 0.23	5.316-0.006	1.51 ± 0.28	2.988-0.038
sICAM-1 (∝g/L)	278.15 ± 39.26	452.20 ± 48.17	6.438-0.005	397.28 ± 43.54	3.065-0.016	332.36 ± 35.18	5.128-0.007	302.48 ± 58.75	1.006-0.232
IL-2 (∝g/L)	282.10 ± 54.65	196.25 ± 40.27	9.152-0.002	223.51 ± 42.83	5.655-0.014	276.49 ± 38.26	0.825-0.274	294.21 ± 43.37	0.740-0.363
IL-6 (∝g/L)	112.48 ± 35.84	184.19 ± 42.46	8.118-0.003	276.89 ± 47.85	9.428-0.001	218.35 ± 56.13	6.365-0.006	134.355 ± 32.71	0.709-0.428
IL-8 (∝g/L)	26.01 ± 4.52	44.05 ± 3.16	5.107-0.012	38.20 ± 5.17	6.394-0.002	32.98 ± 4.06	3.431-0.007	27.41 ± 5.02	0.827-0.267

Table III. Changes of the serum coagulation factors following carotid artery stenting (n = 92, $\bar{x} \pm s$).

Coagulation factors	Before stenting	After stenting							
		24h		48h		3d		1w	
		t	*p*	*t*	*p*	*t*	*p*	*t*	*p*
Angiography group (n=92)									
PT(s)	11.7 ± 2.6	12.3 ± 2.1	0.615-0.292	10.9 ± 2.8	0.826-0.351	11.6 ± 3.1	1.037-0.095	15.7± 2.8	3.351-0.024
APTT(s)	30.5 ± 8.6	33.6 ± 7.5	0.392-0.280	31.8 ± 5.2	0.714-0.562	32.6 ± 6.4	0.948-0.127	39.3 ± 8.1	7.002-0.016
FIB (mg/dl)	4.1 ± 0.4	4.2 ± 0.4	0.305-0.763	4.8 ± 0.5	4.127-0.038	3.8 ± 0.6	0.619-0.062	4.0 ± 0.5	0.332-0.502
DD (mg/dl)	208.9 ± 34.6	265.2 ± 30.9	8.249-0.013	323.6 ± 41.8	6.230-0.007	212.5 ± 22.8	1.009-0.397	192.3 ± 42.7	0.692-0.316
FDP (%)	1.5 ± 0.2	0.7 ± 0.3	7.370-0.006	0.6 ± 0.2	5.217-0.003	1.2 ± 0.4	0.947-0.169	1.4 ± 0.3	0.842-0.242
Stenting group (n=92)									
PT(s)	11.9 ± 3.2	10.1 ± 3.6	1.169-0.352	12.2 ± 2.0	0.281-0.284	18.6 ± 4.8	4.916-0.007	10.5 ± 2.8	0.883-0.149
APTT(s)	27.1 ± 10.4	29.5 ± 8.1	0.851-0.125	31.2 ± 8.5	1.002-0.264	39.8 ± 8.2	6.983-0.007	29.1 ± 7.6	0.872-0.308
FIB (mg/dl)	4.0 ± 0.6	4.3 ± 0.5	0.831-0.582	5.8 ± 0.7	6.341-0.027	4.9 ± 0.8	4.270-0.035	4.1 ± 0.8	0.529-0.231
DD (mg/dl)	193.5 ± 30.7	213.4 ± 35.0	0.381-0.229	354.7 ± 42.8	9.209-0.001	283.6 ± 32.9	6.135-0.003	208.1 ± 27.6	0.273-0.516
FDP (%)	1.7 ± 0.8	2.2 ± 0.9	0.714-0.163	2.2 ± 0.4	3.453-0.008	1.6 ± 0.7	0.529-0.246	1.9± 0.3	0.294-0.268

pre-operative conditions or controls. These factors were important to monitor the occurrence of relevant complications.

The carotid artery stenting procedure is recognized by the medical community as an important intervention against carotid artery stenosis. Maximizing its outcome and minimizing related complications represent important unmet medical needs. Changes in inflammatory cytokines or coagulation factors following carotid artery stenting are of a concern. Gupta et al[5] described that the vascular intima-media thickness post-carotid artery stenting was associated with pre-operative hs-CRP elevation. A high preoperative level of hs-CRP could be considered as an indicator for postoperative vascular intima-media thickness. We were interested in the correlation between postoperative changes of hs-CRP level and recurrence of restenosis. As described researchers[6], TNF-α might play a role in the course of the inflammatory cell proliferation and the extracellular matrix hyperplasia following carotid artery stenting. Liu et al[7] investigated the changes in the platelet function following carotid artery stenting and observed the platelet function activation within one week following carotid artery stenting. This might be associated with postoperative cerebral infarction and deep vein thrombosis, despite of the preoperative dual antiplatelet treatment of aspirin and clopidogrel bisulfate. Understanding the inflammatory cytokines and the changes in coagulation factor post-carotid artery stenting are important in the preventing postoperative complications. Therefore, changes to the hs-CRP, IL-6, sICAM-1, TNF-α and other inflammatory cytokines, as well as coagulation factors such as DD and FDP, should be monitored before and after the procedure to analyze its fluctuating pattern and clinical importance.

In this study, the hs-CRP, IL-6, sICAM-1, TNF-α levels and other inflammatory cytokines, as well as coagulation factors such as DD and FDP were higher than those of the controls ($p < 0.05$). As shown by these results, these factors could be considered as indices for carotid atherosclerotic stenosis, representing the extent of atherosclerotic lesions. These results were consistent with those described in the literature[8]. Moreover, the levels of hs-CRP, IL-6, sICAM-1, TNF-α and other inflammatory cytokines, as well as coagulation factors such as DD and FDP were significantly higher than those of the control group, which persisted for one week after

the procedure. The levels of hs-CRP, TNF-α, sICAM-1 and IL-8 at 24 hours after the procedure were significantly higher than those of controls, to those of three days FIB and DD at 24h, 48h, and three days FIB hours after the procedure.

Conclusions

The evidence suggested that relevant postoperative inflammatory responses might persist for one week, which is also the highest risk period of transient ischemic attack (TIA), cerebral infarction, and acute myocardial infarction. Inflammatory cytokines and coagulation factors were important when monitoring for acute postoperative complications.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

References

1) Jia XJ, Zhou HD, Zhang M, Yang H, Chen Y. Discussion of characteristics and treatment of complications after carotid artery stenting. Chongqing Medicine 2008; 7: 718-721.
2) Tzoulaki I, Murray GD, Lee AJ, Rumley A, Lowe GD, Fowkes FG. Relative value of inflammatory, hemostatic, and rheological factors for incident myocardial infarction and stroke: the Edinburgh Artery Study. Circulation 2007; 16: 2119-2127.
3) Wang SX, Zhou LH, Wang FF, Zhao L, Gao YJ, Mi YJ, Chen QD. Role of inflammatory cytokines in the restenosis after stent angioplasty for intra- and extra-cranial stenosis. J Chengde Med Coll 2007; 2: 179-182.
4) Zhao YM, Ji SD, Zhang W, He Y, Shen WH, Ruan CG. Effect of coronary stent implantation on coagulation and platelet function of rabbits. Shanghai Laboratory Animal Science 2004; 4: 224-226.
5) Gupta R, Bhatt A, Kassab M, Majid A. elevated levels of pre-procedural high-sensitivity c-reactive protein is associated with midterm restenosis after extra- and intracranial stenting. J Neuroimaging 2010; 20: 74-77.
6) Miyahara T, Koyama H, Miyata T, Shigematsu H, Inoue J, Takato T, Nagawa H. Inflammatory responses involving tumor necrosis factor receptor-associated factor 6 contribute to in-stent lesion formation in a stent implantation model of rabbit carotid artery. J Vasc Surg 2006; 3: 592-600.
7) Liu F, Wang DM, Liu JC, Li J, Xu XD, Hao HJ, Huang YN. Serial changes in circulating platelet activation and platelet aggregation after carotid artery stenting. Chinese J Thromb Hemost2008; 2: 60-64.
8) Ridker PM, Silvertown JD. Inflammation, C-reactive protein, and atherothrombosis. J Periodontol 2008; 79(8 Suppl): 1544-1551.