Preprocedural C-reactive protein predictive value in angiographic in-stent restenosis after coronary stent placement in patients with stable angina

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Submitted: 7 February 2008
Accepted: 8 May 2008

Arch Med Sci 2009; 5, 2: 166-171

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Abstract

Introduction: In spite of technological advances, restenosis after coronary stent implantation remains a long-term complication.
Material and methods: Elective stent placement in a native coronary artery and 6-month angiographic follow-up were performed in 128 patients with stable angina. Coronary angiograms were reviewed by two cardiologists who were blinded to the blood test results. In-stent restenosis was defined as ≥ 50% reduction in diameter of the target lesion. Demographic variables and past medical history of patients as well as biochemical data including plasma level of CRP, fasting blood sugar and lipid profile were collected prospectively, and compared in patients with and without in-stent restenosis.
Results: In-stent restenosis was observed in 46 patients (35.9%). The mean CRP concentration in restenotic and non-restenotic groups was 2.8 ±3.5 and 3.8 ±7.1 mg/l, respectively (p = 0.4) Restenosis rate in patients with high and low CRP concentrations were not statistically different (37.5 vs. 35%, respectively). The level of fasting blood sugar in restenotic patients was significantly higher than non-restenotic patients [102.3 ±39.7 vs. 84.5 ±28.9 mg/dl, OR 1.02 (1.00-1.04)]. Neither CRP level [OR 1.03, 95%CI (0.88-1.19)] nor other biochemical and clinical variables were associated with in-stent restenosis.
Conclusions: Preprocedural CRP may not predict in-stent restenosis, but strict control of diabetes may improve the outcome after elective coronary stenting.

Key words: C-reactive protein, stents, restenosis, diabetes, stable angina, bare-metal stent.

Introduction

In spite of advances in techniques, in-stent restenosis after coronary stent implantation remains the primary limiting factor in long-term vessel patency in 20-30% of treated lesions occurring 3-6 months after bare stent placement [1, 2]. Several clinical trials have suggested that inflammation plays an important role in the pathogenesis of restenosis [3, 4]. C-reactive protein (CRP) as the hallmark of systemic inflammation was proved to have predictive value for recurrent instability in patients with stable angina [5, 6], and acute coronary syndromes [7, 8], but data concerning the prognostic value of baseline CRP concentration for angiographic restenosis after coronary stenting are conflicting [9-12]. The treatment

of in-stent restenosis (ISR) remains difficult; therefore meticulous risk assessment before stent implementation is important to identify those patients who would benefit from other treatment modalities or drug- eluting stent placement.

This study was conducted to evaluate the predictive value of preprocedural level of CRP in 6-month angiographic coronary ISR in a cohort of patients undergoing elective single bare stent implantation.

Material and methods

Patients

Our study with $\alpha 1 = \alpha 2 = 0.5$, d = 0.2 has a 90% power for detecting differences between high and low serum CRP levels in restenosis. Considering 30% patient missing, we recruited 170 consecutive patients. This single centre prospective observational cohort study was conducted from July 2003 to April 2005. Patients were successfully treated with single elective bare-metal stent implantation in a native coronary artery. Patients were referred to our hospital for PCI because of refractory angina or angina with significant viability or high-risk sign in non-invasive tests. Exclusion criteria included contraindications to the use of anticoagulants, myocardial infarction during the last 3 months, unstable angina pectoris, cancer, rheumatoid arthritis, previous ISR, saphenous vein graft lesions, bifurcated lesion or DES implantation and inflammatory bowel disease or any other severe comorbid conditions. A written letter of consent was obtained from all patients before inclusion.

Angiographic assessment

Patients already taking daily chronic ASA therapy took 325 mg of ASA before BMS implantation was performed. If a patient was not already taking daily chronic ASA therapy, we gave 325 mg ASA at least 2 h and preferably 24 h before the procedure and continued it at least for 1 month, then changed it to 80-100 mg ASA per day lifelong [13]. Unfractionated heparin was administered as an intravenous bolus (10,000 units) followed by a continuous infusion at a dose of 1000 units/h. Patients were treated with ticlopidine 250 mg BID started at least 48 h before PCI or clopidogrel 75 mg daily started at least 1 week before the procedure and continued for one month after stent implantation [13]. Statins (lovastatin in 116 patients and simvastatin in 12 patients) were started for all patients at hospital admission and continued lifelong.

Coronary intervention and angiographic assessment were performed with a digital angiographic system (Advantx LCV, GE Medical Systems, Milwaukee, WI, USA), and quantitative coronary analysis (QCA) with an edge-detection algorithm [13, 14] was performed on a digital angiographic workstation (DLX, GE Medical Systems). Angiographic success was considered to be the placement of the stent in the target lesion, with a thrombolysis in myocardial infarction (TIMI) grade 3 coronary flow and residual stenosis < 50%. Coronary angiograms were reviewed by two cardiologists who were blinded to the blood test results. Seven patients had unsuccessful angioplasty. Of the remaining 163 patients, 128 patients agreed to follow-up angiography being performed. The second angiography was performed within 6 (median 5.4) months after angioplasty. In-stent restenosis was defined as ≥ 50% stenosis of the target lesion (including 0.5 cm on either side of the stent). Call visits were performed every two weeks during the follow-up period, and in the case of angina pectoris, patients were candidated for earlier follow-up angiography.

Clinical and laboratory assessment

Data were collected regarding the patients' age, sex, body mass index, current smoking habits (> 10 cigarettes/day), history of dyslipidaemia, hypertension and diabetic patients on oral anti-diabetic agents or insulin.

Blood samples were obtained after at least 8-h fasting from the sheath of the femoral artery just before PCI. C-reactive protein measurements were performed with nephelometric assay (Dade Behring Diagnostics). C-reactive protein concentrations > 3 mg/l were considered high. Lipid profile and blood glucose level were assessed with enzymatic-colorimetric methods.

Statistical analysis

Univariate analysis of continuous variables was performed with two-sample independent *t*-test or Mann-Witney U test, as required. Relative frequencies were compared between restenotic and non-restenotic groups with χ^2 test. Multiple logistic regression analysis was used to identify the predictive value of respected variables for restenosis and univariate variables with significant impact ($p < 0.05$). Known predictive variables were entered in the model. In order to increase the normality of variables, logarithmic transformed CRP values were used in regression analysis. ROC curve analysis was also performed to assess the predictive value of CRP concentrations for restenosis. *P* values less than 0.05 were considered significant. Statistical analysis was performed using Statistical Package for Social Sciences software version 11.0 (SPSS Inc, Chicago, IL, USA).

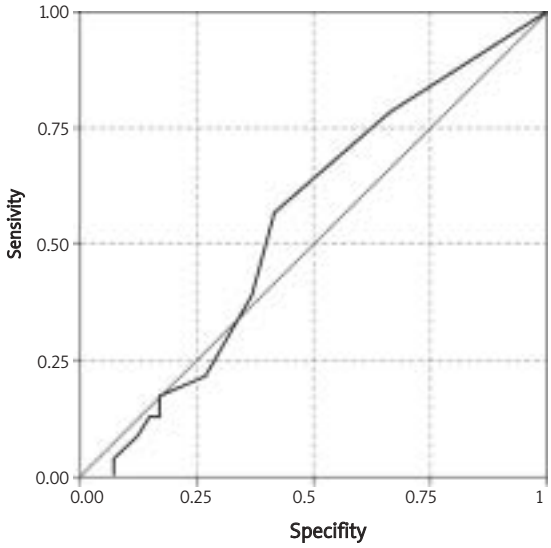

Figure 1. ROC curve of CRP concentration for prediction of in-stent restenosis

Results

In-stent restenosis (ISR) rate was 46/128 (35.9%). In-stent restenosis rate according to the type of coronary vessels and univariate analysis of baseline characteristics and possible risk factors for restenosis in 128 patients are shown in Table I. The mean CRP concentration in restenotic and non-restenotic groups were 2.8 ±3.5 and 3.8 ±7.1 mg/l, respectively (p = 0.4). In-stent restenosis rate in patients with high and low CRP concentrations were not statistically different (37.5 vs. 35% respectively). ROC curve analysis also showed the absence of a cut-off point in preprocedural CRP concentration to distinguish a distinct predictive value for the occurrence of restenosis [area under the curve 0.55 (95% CI 0.45-0.65), p = 0.35] (Figure 1). Of respected variables, only FBS showed a significant difference between restenotic and non-restenotic groups. Logistic regression analysis also showed that FBS is a predictor of restenosis (OR 1.02, 95% CI 1.00-1.04) but CRP (OR 1.03, 95% CI 0.88-1.19) and other serological and demographic parameters may not predict restenosis after PCI (Table II).

Table I. Univariate analysis of baseline characteristics and possible risk factors for restenosis

	Total (n = 128)	No-restenosis group (n = 82)	Restenosis group (n = 46)	P value
Age [years]	55 ±9	55 ±9	53 ±8	0.15
Male sex [%]	80 (62.5)	54 (65.9)	26 (56.5)	0.34
Diabetes mellitus	20 (15.6)	11 (13.4)	9 (19.6)	0.45
Hypertension	21 (16.4)	15 (18.3)	6 (13.0)	0.62
Dyslipidaemia	52 (40.6)	34 (41.5)	18 (39.1)	0.85
Smoker	22 (17.2)	14 (17.1)	8 (17.4)	1.0
Family history of CAD	9 (7.0)	5 (6.1)	4 (8.7)	0.72
BMI	26.4 ±3.6	26.3 ±3.9	26.6 ±3.0	0.65
CRP	3.47 ±6.07	3.8 ±7.1	2.8 ±3.5	0.40
Total cholesterol	221 ±57 208 (138-439)	216 ±56 208 (145-405)	231 ±57 215 (138-439)	0.16
HDL- cholesterol	37.5 ±8.9 37 (20-56)	37.9 ±8.5 39 (24-55)	36.7 ±9.7 36 (20-56)	0.44
Triglycerides	197 ±74 186 (90-447)	189 ±73 180 (90-447)	211 ±75 202 (111-380)	0.11
FBS	90.8 ±34.2 85 (47-198)	84.5 ±28.9 77 (47-172)	102.3 ±39.7 89 (52-198)	< 0.01
LAD*	96 (75%)	58 (60.4%)	38 (39.6%)	
LCX**	26 (20.3%)	20 (76.9%)	24 (23.1%)	
RCA***	6 (5%)	4 (66.6%)	2 (33.3%)	

**LAD – left anterior descending artery*
***LCA – left circumflex artery*
****RCA – right coronary artery*
¶ continuous variables have been are shown as mean ± standard deviation and median (range)

Discussion

A few studies have investigated the relationship between preprocedural CRP and angiographic in-stent restenosis after coronary stenting, which yielded conflicting results. Yip *et al*. [15] reported that there is no evidence proving a positive association between elevated CRP and late restenosis, but preprocedural CRP is strongly associated with the progression of moderately obstructive lesions in non-culprit vessels. Segev *et al.* [16] after 6 months' follow-up of 216 patients, reported that neither preprocedural nor peak CRP concentration obtained after coronary stenting may predict late angiographic restenosis. A recent study using intravenous ultrasound reported that elevated CRP is significantly associated with ISR only in patients with soft plaque [17]. Another study on 276 patients reported that restenosis rates were significantly higher in the two upper tertiles compared with CRP levels in the lowest tertile (45.5 vs. 38.8 vs. 18.5%, respectively) [10]. However, the present study found no significant association between baseline serum concentration of CRP and late angiographic restenosis. The discrepancy in results among different studies may be attributed to the differences in the spectrum of patients, the methods used to measure CRP, or in the use of statins [18].

It has been demonstrated that local inflammation of coronary vessels due to atherectomy and local sustained inflammatory response due to stent placement is associated with plaque instability and restenosis [19-21]. There was no relationship between plasma CRP concentration and plaque CRP in these studies. These findings clearly suggest that local sustained inflammatory response plays a role in neointimal hyperplasia after coronary stent implantation [21], but this may not be reflected by an increased baseline plasma CRP concentration, which signifies activation of systemic inflammation.

Moreover, all patients in our study received statins, while previous studies have shown that statin therapy interferes with the detrimental effects of inflammation on accelerated neointimal hyperplasia following coronary stenting, in such a way that it significantly attenuates the increased risk of major adverse cardiac events in patients with elevated CRP levels undergoing coronary stent implantation [22].

However, these beneficial effects remain controversial regarding the restenotic process [23, 24]. Importantly, in our study, the physicians were blinded to CRP value. Therefore, these values did not influence the clinical decision-making process concerning statin therapy during follow-up. Our study, in accordance with some previous surveys [25-29], did not demonstrate any predictive values for total cholesterol, HDL and triglycerides in restenosis after coronary stenting. Some prior studies reported a relationship between diabetes and restenosis [30-32], but others did not [33-36]. In the present study, the relative frequency of restenosis between diabetic and non-diabetic patients was not statistically different, probably due to the fact that in this study only 15.6% of the included patients had diabetes. Therefore a lack of association between diabetes and restenosis might be explained by the low percentage of diabetic patients. However, fasting blood sugar level showed a significant association with restenosis after coronary stenting. These findings might be due to the strict control of blood glucose in some of our known diabetic patients [37].

Table II. Logistic regression analysis of possible risk factors for restenosis

	Univariate	Multivariate
CRP*	0.97 (0.90-1.03), 0.40	1.03 (0.88-1.19), 0.68
Total cholesterol	1.00 (0.99-1.01), 0.17	1.00 (0.98-1.02), 0.83
HDL cholesterol	0.98 (0.94-1.02), 0.43	0.93 (0.85-1.00), 0.06
Triglycerides	1.00 (0.99-1.00), 0.11	0.99 (0.98-1.01), 0.43
FBS**	1.02 (1.00-1.02), < 0.01	1.02 (1.00-1.04), < 0.01

**CRP – C-reaction reactive protein, **FBS – fasting blood sugar*

However, it seems reasonable to conclude that poorly controlled diabetes may worsen the outcome after coronary stenting. Its mechanism of action might be due to an increased neointimal hyperplasia because of the stimulatory effects of growth factors [30].

The role of other known cardiovascular risk factors such as age, sex, hypertension and smoking for restenosis after coronary stenting is controversial [38-41]. Although we did not find any differences in univariate analysis, further prospective studies with more meticulous quantitative assays, especially for hypertension and smoking, are suggested.

Study limitations

First, our study population consisted of a homogeneous group of patients with stable angina who underwent elective stenting, while some other studies used patients with unstable angina pectoris [15, 16], or a mixed group of patients including patients with acute coronary syndrome and stable angina pectoris [10]. Although the homogeneity of the study population increases the reliability of the findings, the results obtained

from our low-risk patients may not be applicable to different subsets of patients such as acute coronary syndromes.

Second, we used a turbidimetric method instead of the recently recommended high-sensitive CRP assay. Although some other large-scale cohorts using the same method did not demonstrate a predictive value for CRP [10], this factor may explain at least part of the discrepancies in the results.

Third, we did not measure serial CRP concentrations in the follow-up period, so our study is unable to demonstrate the predictive value of sequential changes in the CRP level for restenosis after coronary stent placement.

In conclusion, our findings do not support any association between plasma levels of CRP and angiographic in-stent restenosis in patients with stable angina undergoing elective bare-metal stent implantation. The present study revealed that among traditional risk factors for CAD, only the blood glucose concentration can predict restenosis after coronary stenting. Further prospective studies with larger sample size and more sensitive CRP assay methods which critically consider the role of statins, atherosclerotic risk factors and the nature of angiographically documented lesions may help risk stratification for restenosis. The results of the suggested studies would help identify patients who are at an increased risk of ISR, are poor candidates for bare-metal stent implantation and could benefit from other treatment modalities including drug-eluting stents.

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