An important role for VCAM-1, but not for ICAM-1 in restenosis following coronary stent implantation

Koroner stent implantasyonu sonrası restenozda ICAM-1'e göre VCAM-1'in önemli rölü

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ABSTRACT

Objective: In this study, we evaluated the possibility that, levels of circulating adhesion molecules following direct stent implantation may be a marker of restenosis.

Methods: This prospective, observational study investigated levels of circulating intercellular (ICAM-1), and vascular cell (VCAM-1) adhesion molecules in 15 patients with stable angina pectoris before and after coronary stent implantation for single vessel-single lesion disease in proximal left anterior descending artery. All patients received bare-metal stents. Patients underwent repeat coronary angiography for detection of restenosis at 6 month. Continuous data between patients with and without restenosis were compared using Mann-Whitney U test. Repeated measurements were compared using Wilcoxon T test. Categorical data were compared using Chi-square statistics.

Results: Baseline ICAM-1 and VCAM-1 concentrations before percutaneous coronary intervention (PCI) were 4.89±2.28 and 46.35±22.96 ng/ml respectively. Levels of ICAM and VCAM increased nonsignificantly 24 hours after PCI (5.01±2.35 ng/ml and 52.57±19.40 ng/ml, respectively). Six patients (40%) developed restenosis within 6 months. Mean stent length, mean stent diameter, and mean dilatation pressure were comparable in patient groups with and without restenosis. Levels of plasma VCAM-1 measured before and after PCI did not change significantly in patients without restenosis. However, these levels increased significantly in the group of restenosis. At 6 months, patients who developed restenosis, had higher VCAM-1 levels, as compared to baseline values (from 45.1±21.0 to 57.2±14.3 ng/ml, $p<0.05$). Plasma levels of pre and post PCI ICAM-1 did not differ significantly between groups with and without restenosis.

Conclusion: These results suggest a more dominant role for VCAM-1, but not for ICAM-1 in development of restenosis following coronary stent implantation. *(Anadolu Kardiyol Derg 2010; 10: 405-9)*

Key words: Restenosis, stenting, inflammation, vascular cell adhesion molecule-1, intercellular adhesion molecule-1

ÖZET

Amaç: Bu çalışmada stabil koroner arter hastalığı nedeni ile stent implante edilen olgularda, adezyon moleküllerinin seviyesi ile restenoz arasındaki ilişki araştırılmıştır.

Yöntemler: Stabil angina pectoris nedeni ile proksimal sol ön inen artere stent implante edilen 15 olguda işlem öncesi ve sonrasında dolaşımdaki hücreler arası adezyon molekül-1 (ICAM-1) ve vasküler hücre adezyon molekül -1 (VCAM-1) seviyeleri prospektif gözlemsel olarak araştırılmıştır. Hastalarda çıplak metal stent kullanılmıştır. Tüm hastalara restenoz değerlendirmesi amacı ile tespiti için implantasyonun 6. ayında tekrar koroner anjiyografi yapıldı. Çalışma sonunda restenoz saptanan ve saptanmayan hastalara ait sürekli değişkenler Mann-Whitney U testi ile karşılaştırıldı. Tekrarlanan ölçümlere ait sürekli değişkenlerin karşılaştırılmasında Wilcoxon T testi kullanıldı. Kategorik veriler ise Ki-kare testi ile karşılaştırıldı.

Bulgular: Perkütan koroner girişim (PKG) öncesi bazal ICAM-1 ve VCAM-1 konsantrasyonları sırası ile 4.89±2.28 ve 46.35±22.96 ng/ml bulunmuştur. Ölçülen ICAM-1 ve VCAM-1 seviyeleri PKG' den 24 saat sonra istatistik olarak anlamsız derecede artış göstermiştir (5.01±2.35ng/ml ve 52.57±19.40 ng/ml). Altı olguda (%40) 6. ayda restenoz tespit edilmiştir. Restenoz gelişen ve gelişmeyen hasta grupları arasında ortalama stent uzunluğu, çapı ve balon şişme basıncı bakımından fark bulunmamıştır. Stent implantasyonundan önce ve sonra ölçülen VCAM değerleri restenoz olmayan grupta anlamlı değişiklik göstermemiş, bununla birlikte restenoz grubunda anlamlı artış göstermiştir (45.1±21.0' den 57.2±14.3 ng/ml'ye, $p<0.05$). Bazal ve post PKG ICAM-1 değerleri restenoz olan ve olmayan gruplarda anlamlı değişiklik göstermemiştir.

Sonuç: Bu sonuçlar koroner stent implantasyonunu takip eden restenozda adezyon moleküllerinden ICAM-1'e göre VCAM-1'in daha önemli rolü olduğunu düşündürmektedir. *(Anadolu Kardiyol Derg 2010; 10: 405-9)*

Anahtar kelimeler: Restenoz, stent, inflamasyon, vasküler hücre adezyon molekül -1, hücreler arası adezyon molekül-1

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Introduction

Percutaneous coronary intervention (PCI) has become a safe and effective treatment modality for coronary artery disease. Despite considerable progress, restenosis remains a major limitation of PCI. Many clinical, angiographic, and procedural variables have been studied as predictors for restenosis (1-7). The prediction of restenosis with the existing variables is poor. Restenosis is determined by many factors. Injury of the vessel wall caused by balloon dilation or stent placement and 'response to injury' plays a central role in pathogenesis of restenosis. Many studies have supported the pathogenetic role of vascular cell adhesion molecule 1 (VCAM-1) and inter-cellular adhesion molecule-1 (ICAM-1) in inflammation and response to injury (8, 9). Beyond the development of atherosclerotic plaques, adhesion molecules may be important in restenotic neointima formation.

In this study, we therefore evaluated the possibility that baseline or intervention-induced circulating VCAM-1 and ICAM-1 levels may be the markers for restenosis risk after direct stent implantation.

Methods

In this prospective, observational study, 15 patients with stable angina pectoris who undergo PCI for single vessel, single lesion disease in proximal left anterior descending artery (LAD) were included (10 men, mean age 59±12 years). Patients treated for unstable coronary syndromes were excluded. Current study also excluded patients with infectious and active inflammatory diseases (rheumatoid arthritis, inflammatory bowel disease, etc) to prevent confounding effect of preexisting inflammation on restenosis. Patients who needed predilation and postdilation were excluded to create a similar and uniform degree of vessel injury. The study enrollment criteria also excluded patients with renal failure, malignancy, previous coronary artery bypass surgery or previous myocardial infarction. All lesions to be dilated were de-novo lesions of native coronary arteries. An informed consent was obtained from all patients.

PCI

Patients received a 300mg loading dose of clopidogrel followed by clopidogrel 75 mg/day for at least 6 months and 300 mg/day acetylsalicylic acid continuously. Direct stent implantation was performed by femoral approach. A 7F guiding catheter was used for the procedure. At the beginning of the intervention, all patients were administered 100U/kg of unfractionated heparin intravenously. During the PCI procedure non-ionic contrast agent iopamidol (Iopamiro 300, Bracco Spa, Italy) was used. All patients received bare-metal Ephesos stents (Nemed, Istanbul, Turkey). Stents were deployed at an average pressure of 14 atm in about 30 seconds.

A repeat angiographic study was performed after for detection of angiographic restenosis at 6 months, and ≥ 50% diameter stenosis at the site of intervention was considered indicative of restenosis.

Laboratory analysis

Levels of circulating soluble adhesion molecules ICAM-1, and VCAM-1 were investigated in patients immediately before and after direct stent implantation. Blood samples were drawn from all patients just before heparin administration and 24 hours after the PCI. Blood was collected into Vacutainer tubes. VCAM-1 and ICAM-1 measurements were made with the use of a commercially available enzyme-linked immunosorbent assay kit (Biosource, California, USA). Intra-assay CV (coefficient of variation) values of the measurements are 6.1% and 4.0% for ICAM and VCAM analysis. Inter-assay CV values for ICAM and VCAM are 7.8% and 5.1% respectively. Analysis was performed at a dilution of 1:50 for VCAM and dilution of 1:100 for ICAM as recommended. Data presented as post-dilution measurements. Undiluted values can be calculated multiplying these post-dilution measurements by dilution factors of 50 and 100 for VCAM and ICAM respectively.

Statistical analysis

Statistical analysis was performed using SPSS software (SPSS software for Windows, version 11.5 Chicago, IL, USA). Categorical data were compared with Chi-square statistics. Continuous data were presented as mean±standard deviation and/or median (minimum-maximum) and compared with Mann-Whitney U test between groups. Repeated measurements in the same group were compared with Wilcoxon T test. A p value <0.05 was considered statistically significant.

Results

The baseline concentrations of ICAM-1 and VCAM-1 before PCI were 4.89±2.28 and 46.35±22.96 ng/ml respectively. Levels of ICAM-1 and VCAM-1 increased nonsignificantly 24 hours after PCI (5.01±2.35ng/ml and 52.57±19.40ng/ml respectively).

All patients underwent repeat angiographic study for detection of angiographic restenosis at 6 month. Six patients (40%) developed restenosis within 6 months, defined as a >50% reduction of the lumen diameter at the site of stent implantation. Baseline characteristics of patients with and without restenosis are shown in Table 1. Anatomical and procedural variables during coronary angiography and PCI are summarized in Table 2. These angiographic and interventional variables were not significantly different between patient groups with and without restenosis.

We also compared treatment differences between groups during the study duration. All patients received clopidogrel and acetylsalicylic acid. There were no statistical significant differences between groups for statin, beta-blocker and ACE inhibitor or angiotensin receptor blocker administration during the study period (Table 3).

Table 1. Baseline clinical characteristics of patients with or without subsequent restenosis

Variables	Patients with restenosis (n=6)	Patients without restenosis (n=9)	p*
Age, years	57±10 59 (46-72)	59±13 61 (45-76)	ns
Male gender, n (%)	5 (83)	8 (88)	ns
Diabetes, n (%)	1 (16)	1 (11)	ns
Hyperlipidemia, n (%)	4 (66)	7 (77)	ns
Smoking, n (%)	4 (66)	8 (88)	ns

Continuous data are expressed as median (minimum-maximum) and mean±SD values
Categorical data are expressed as numbers (percentage)
*Chi - square and Mann - Whitney U tests.
ns - not significant

Table 2. Comparison of selected angiographic and procedural parameters determining restenosis in patients with and without subsequent restenosis

Variables	Patients with restenosis (n=6)	Patients without restenosis (n=9)	p*
Type B and C lesion, n (%)	1 (16)	2 (22)	ns
Stent length, mm	16.5 (12.0-25.0) 18.3±4.4	17.0 (12.0-25.0) 17.8±5.1	ns
Stent diameter, mm	3.5 (3.0-3.5) 3.4±0.4	3.5 (2.5-3.5) 3.3±0.5	ns
Inflation pressure, atm	14.0 (12.0-18.0) 14.3±2.7	14.0 (10.0-20.0) 13.5±4	ns

Continuous data are expressed as median (minimum-maximum) and mean±SD values
Categorical data are expressed as numbers (percentage)
*Chi - square and Mann - Whitney U tests.
ns - not significant

Table 3. Treatment regimens in both groups

Variables	Patients with restenosis (n=6)	Patients without restenosis (n=9)	p*
Clopidogrel, n (%)	6 (100)	9 (100)	na
ASA, n (%)	6 (100)	9 (100)	na
Statin, n (%)	5 (83)	7 (77)	ns
Beta-blocker, n (%)	3 (50)	5 (55)	ns
ACEI or ARB, n (%)	3 (50)	6 (66)	ns

Categorical data are expressed as numbers (percentages)
*Chi - square test
ACEI - angiotensin converting enzyme inhibitor, ARB - angiotensin receptor blocker, ASA - acetyl salicylic acid, na - not applicable, ns - not significant

Levels of plasma VCAM-1, measured before and after PCI, did not change significantly in patients without restenosis. However, these levels increased significantly in the group of restenosis. At 6 months, those who developed restenosis had higher VCAM-1 levels following PCI, compared with their baseline values ($p< 0.05$). Plasma levels of pre and post PCI ICAM-1 did not differ significantly both in patient groups with and without restenosis (Table 4). The difference between post VCAM-1 levels in patients with restenosis and without restenosis was found statistically nonsignificant ($p>0.05$).

Table 4. Levels of circulating adhesion molecules before and after intervention

Variables	Patients with restenosis (n=6)	Patients without restenosis (n=9)
Pre-PCI ICAM-1, ng/ml	4.7±2.1 4.6 (2.0-7.4)	4.9±2.4 5.1 (1.8-7.8)
Post-PCI ICAM-1, ng/ml	4.8±1.9 4.7 (2.3-7.5)	5.1±2.7 5.3 (1.7-8.0)
p*	ns	ns
Pre-PCI VCAM-1, ng/ml	45.1±21.0 46.0 (16.9-73.1)	47.3±23.4 46.3 (18.1-75.8)
Post-PCI VCAM-1, ng/ml	57.2±14.3 58.5 (34.4-74.0)	50.1±27.8 47.6 (18.0-83.2)
p*	<0.05	ns

Data are expressed as mean±SD and median (minimum-maximum) values
* Wilcoxon T test
ICAM - intracellular adhesion molecule, ns-not significant, PCI - percutaneous coronary intervention, VCAM - vascular cell adhesion molecule

Discussion

The results of this study suggest that, levels of circulating adhesion molecules, mainly VCAM, may be a marker of restenosis following direct stent implantation.

PCI has become a commonly used procedure for the treatment of severe coronary artery disease. Restenosis is a significant limitation to the long-term efficacy of this procedure. Identifying patients at increased risk for restenosis may improve stratification of patients to individually tailored treatment. Thus far, however, it has proven difficult to stratify patients with regard to risk for coronary restenosis based only upon clinical, angiographic or procedural risk factors.

The predominant pathology in restenosis is intimal hyperplasia. Intervention-induced vascular injury and response to injury are critical factors in the development of intimal hyperplasia. Inflammation is the early phase of response to injury and wound healing phenomenon. This is followed by cellular proliferation phase, and a late phase of remodeling which involves extracellular matrix protein synthesis. These three phases eventually lead to intimal hyperplasia.

The role of inflammation in the development of restenosis after coronary interventions has been investigated extensively. Several studies have supported the critical role of inflammation in this process. There are some animal and human studies implicating pre-exiting inflammation in the development of restenosis (10-12). Current study excluded patients with infectious and active inflammatory diseases (rheumatoid arthritis, inflammatory bowel disease, etc). We also excluded patients with unstable coronary syndromes to prevent confounding effect of preexisting inflammation on restenosis.

In addition to inflammatory status prior to PCI, inflammatory response to PCI has also been implicated in restenosis (13-16). There are differences between balloon angioplasty and stenting in the type and degree of arterial injury (17). The widespread use

of coronary stents has fundamentally altered the vascular response to injury by causing a more intense and prolonged inflammation comparing with balloon angioplasty. Because of this different impact in the local inflammatory activation after stenting and balloon angioplasty, we only included patients who underwent direct stenting. To obtain a uniform degree of arterial injury, patients who needed predilation and postdilation were excluded. In this study, mean stent length, mean stent diameter, mean dilatation pressure are comparable in patient groups with and without restenosis.

Leukocyte recruitment and infiltration are hallmark of inflammation. Further evidence linking leukocytes and restenosis has been provided by the study of Moreno et al. (18) in which the authors found a positive correlation between the number of macrophages in directional atherectomy specimen and subsequent propensity for restenosis. Adhesion of these circulating inflammatory cells to the site of vascular injury is mediated mainly by adhesion molecules. Upon cytokine stimulation, VCAM-1 and ICAM-1 are upregulated and expressed by endothelial cells. Evidence from animal and human studies have supported the pathogenetic role of VCAM-1 and ICAM-1 in inflammation and atherosclerosis (8, 9). Beyond the development of atherosclerotic plaques, adhesion molecules may be important in restenotic neointima formation. In an animal model of wire-induced vascular injury, VCAM-1 expression is highly induced in the neointimal smooth muscle cells (19). In another study, VCAM-1 antibody has protected from neointima formation in genetically hypercholesterolemic mice (20). The NF-KB transcription factors modulate the expression of inflammatory mediators including VCAM-1. Plant extract andrographolide blocks the binding of NF-KB transcription factor to the promoter regions of target genes, prevents NF-KB activation and inhibits inflammation. Interestingly it has been reported that andrographolide attenuates neointimal hyperplasia in a murine model of restenosis (21).

In this study, we therefore evaluated the possibility that level of circulating adhesion molecules following direct stent implantation may be a marker of restenosis. In an early study, Inoue et al. (22) demonstrated a significant increase in the serum levels of adhesion molecules immediately after angioplasty. The maximum increase was seen 24 h after angioplasty and continued during the 48-hour observation period. For this reason, in our study, blood samples for adhesion molecules were drawn just before and 24 hours after the PCI. Tsakiris et al. (23) evaluated circulating cell adhesion molecules before and after transluminal angioplasty of peripheral arteries. This study has shown that elevated baseline values and postintervention levels of these adhesion molecules were associated with an increased risk for restenosis after peripheral angioplasty. But there are differences in the extent of inflammation in response to intervention in elastic iliac arteries and mainly muscular coronary arteries (24). More recently Heider et al. (25) investigated the distribution pattern of adhesion molecules after peripheral percutaneous transluminal angioplasty in peripheral arterial occlusive disease. Authors assessed the levels of adhesion molecules before the procedure and 24 hours to 2 and 4 weeks after angioplasty. Both the levels of ICAM-1 and VCAM-1 were higher in patients with restenosis, but without reaching statistical significance for ICAM-1 at all time points. Studies of Tsakiris et al. (23) and Heider et al. (25) included patients who underwent peripheral PTA. In contrast, our study included patients who underwent stent implantation for coronary artery disease. In an early study study by Kamijikkoku et al. (26), the role of ICAM-1 in the prediction of coronary restenosis was evaluated. The authors have demonstrated a significant increase in ICAM-1 levels in patients who developed early restenosis following primary angioplasty for acute myocardial infarction. In our study, in a patient population with stable coronary artery disease, those who developed restenosis had higher VCAM-1 levels following PCI compared with their baseline values ($p<0.05$). In contrast, pre and post PCI ICAM-1 levels were comparable both in patient groups with and without restenosis. Results suggest a more dominant role for VCAM-1, but not ICAM-1 in restenosis following coronary stent implantation for stable coronary artery disease. ICAM-1 and VCAM-1 molecules have different structure, function, and ligands. Therefore, it might be expected that they also have different clinical significance.

Study limitations

As a limitation, current study has been conducted with bare metal stents and these results can not be applied to restenosis following drug-eluting stent (DES) implantation. However Karabela et al. (27) have reported recently VCAM-1 elevation following DES implantation in patients with stable and unstable coronary artery disease. However, they found a positive correlation only between IL-10 levels and in-stent restenosis. Major limitation of the study is the small sample size of 15 patients. Larger studies will be necessary to clarify and prove the role of adhesion molecules and their usage in restenosis prediction. This study should be seen as a pilot, hypothesis-generating study.

Conclusion

Our results suggest a dominant role for VCAM-1 in restenosis development following coronary stent implantation.

If future studies confirm our results, cellular adhesion molecules may be potential targets to prevent restenosis in clinical practice. These results may lead to a more tailored therapy for patients with identified increased risk of restenosis after PCI. Future studies, with novel agents directed towards blocking VCAM-1 are needed to establish the effectiveness of this approach. These VCAM-1 antagonists may be a welcome addition to our limited armamentarium to fight against restenosis. A promising approach may be genetic transfer of fusion proteins. In this field, VCAM-1-mediated cell adhesion and transmigration has been shown to be inhibited by genetic transfer of a fusion protein in a recent study (28).

Conflict of interest: None declared.

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