Pravastatin therapy fails to suppress post-PCI inflammatory response measured by serum neopterin and CRP levels

Pravastatin tedavisi serum neopterin ve CRP düzeyleri ile ölçülen PKG sonrası inflamasyonu baskılamakta yetersiz kalmaktadır

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ABSTRACT

Objective: Percutaneous coronary intervention (PCI) is known to induce both local and systemic inflammatory states. In addition to lowering lipid levels, statins exert well-proven anti-inflammatory effects. We investigated the effects of pravastatin on serum C-reactive protein (CRP) and neopterin levels in the short term after elective PCI.
Methods: In this randomized prospective study, 93 patients undergoing elective PCI were enrolled. Group 1 (n=30) received pravastatin at a dose of 10 mg/day, Group 2 (n=29) was given 40 mg/day, and Group 3 (n=34) served as the control group and received no lipid-lowering drugs. Blood samples were drawn before and after PCI to measure serum CRP and neopterin levels. Differences among the groups for continuous variables were evaluated by the ANOVA and the Kruskal-Wallis test as appropriate. The Chi-square test was used for comparison of categorical variables.
Results: Demographic features and the characteristics of the PCI, including the number of vessels and lesions and the duration and number of inflations, did not differ among groups (p>0.05). Serum CRP and neopterin levels were significantly increased after PCI (p<0.001). Mean serum neopterin levels before and after the PCI were as follows: Group 1: 13.3±5.9 vs 22.8±15.4 nmol/L, Group 2: 16.9±10.2 vs 22.0±14.9 nmol/L, controls: 15.2±11.9 and 18.8±11.5nmol/L. Prior pravastatin therapy had no significant effect on these inflammatory markers (F=0.5, p=0.6).
Conclusion: Percutaneous coronary intervention induces a pronounced inflammatory response. The pre-procedural administration of 2 different doses of pravastatin seems not enough to suppress this inflammation at the short-term follow-up. Further trials are needed to clarify this issue. *(Anadolu Kardiyol Derg 2011; 11: 207-12)*
Key words: Statin, C-reactive protein, neopterin, percutaneous coronary intervention

ÖZET

Amaç: Perkütan koroner girişim (PKG) sonrası hem lokal, hem de sistemik bir enflamatuvar yanıt meydana gelmektedir. Statinler lipit düşürücü etkilerinin yanında iyi tanımlanmış antienflamatuvar etkilere de sahiptirler. Bu çalışmada pravastatin tedavisinin elektif PKG yapılan hastalarda işlem sonrası serum C-reaktif protein (CRP) ve neopterin düzeyine olan etkisinin değerlendirilmesi amaçlanmıştır.
Yöntemler: Bu prospektif, randomize çalışmaya elektif PKG planlanan 93 hasta dahil edildi. Grup 1'e (n=30) pravastatin 10mg/gün, Grup 2'ye (n=29) 40 mg/gün başlandı; Grup 3 (n=34) kontrol grubu alındı ve bu gruba lipit düşürücü tedavi verilmedi. Hastalardan işlem öncesi, işlemden sonra kan örnekleri alınarak serum CRP ve neopterin düzeyleri çalışıldı. Devamlı değişkenlerin gruplar arası karşılaştırılması ANOVA ve Kruskal-Wallis testi ile yapıldı. Devamlı olmayan değişkenler ise Ki-kare testi ile değerlendirildi.
Bulgular: Hastaların demografik özellikleri ve PKG ile ilişkili verileri (işlem yapılan damar sayısı, balon şişirme sayısı ve süresi) gruplar arasında benzer idi (p>0.05). Serum CRP ve neopterin düzeylerinde işlemden sonra anlamlı artış saptandı (p<0.001). İşlem öncesi ve sonrası ortalama serum neopterin düzeyleri gruplar arasında şu şekilde idi: Grup 1: 13.3±5.9 ve 22.8±15.4 nmol/L; Grup 2: 16.9±10.2 ve 22.0±14.9 nmol/L; kontrol grubu: 15.2±11.9 ve 18.8±11.5nmol/L. İşlem öncesi başlanan pravastatin tedavisinin bu enflamasyon parametrelerine anlamlı bir etkisi saptanmadı (F=0.5, p=0.6).
Sonuç: Perkütan koroner girişim (PKG) belirgin bir enflamatuvar yanıta yol açmaktadır. İşlem öncesi 2 farklı dozda başlanan pravastatin tedavisinin kısa süreli izlemde bu inflamatuvar yanıtı baskılamada yetersiz kaldığı görülmüştür. Bu konunun daha iyi aydınlatılabilmesi için ileri çalışmalara ihtiyaç vardır. *(Anadolu Kardiyol Derg 2011; 11: 207-12)*
Anahtar kelimeler: Statin, C-reaktif protein, neopterin, perkütan koroner girişim

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Introduction

Percutaneous coronary intervention (PCI) is a widely used method of revascularization for treating coronary artery disease (CAD). Balloon inflation during PCI injures the endothelium of the vessel and induces an inflammatory state, platelet activation, and thrombosis. A systemic inflammatory response (substantial elevations of CRP and other inflammatory markers) to PCI, whether coronary balloon angioplasty or stenting, has been well documented (1-3). The magnitude of the inflammatory response detected after those procedures has been shown to be related to long-term outcome (4, 5).

C-reactive protein (CRP), an acute-phase protein secreted by the liver in response to proinflammatory cytokines, is one of the most commonly used markers of inflammation. It has been clearly demonstrated that the CRP level increases in patients undergoing PCI (1, 2, 6). Evidence also shows that inflammation indicated by the post-procedural increase in CRP is a predictor of restenosis in patients after coronary stenting (7).

Neopterin, a pteridine derivative secreted by interferon-gamma–stimulated macrophages, is used as a biochemical marker for cellular immune response. It is a biologically stable molecule found in body fluids and can be measured in the serum or urine of patients.

Neopterin levels have been shown to be elevated in patients with CAD and associated with its severity, the complexity of atherosclerotic lesions and an increase in cardiovascular risk (8-10). Avanzas et al. (11) have documented that neopterin is an independent predictor of outcome in patients with CAD.

In addition to lowering cholesterol levels, statins have many useful pleiotropic effects, including anti-inflammatory actions, and are used to suppress inflammation associated with atherosclerosis (12). Data regarding the effects of statins on serum levels of inflammatory markers in patients undergoing PCI are limited.

In this study, we sought to investigate the acute effects of pre-procedurally administered pravastatin on the serum levels of inflammatory markers, CRP, and neopterin in patients with stable angina pectoris or old myocardial infarction undergoing elective PCI. We also compared the effects of 2 different doses of that treatment to evaluate whether the observed result, if any, was dose dependent.

Methods

Patients and treatment protocols

After the Ethics Committee approved the study protocol and informed consent had been obtained, 93 consecutive patients at Başkent University Hospital (21 women; age range, 30-80 years) in whom elective PCI had been planned and were not taking a statin were enrolled in this prospective randomized controlled study. All patients were randomized into 3 groups. Patients in group 1 (n=30) received pravastatin sodium (Pravachol®, Bristol-Myers Squibb) at a daily dose of 10 mg, and patients in group 2 (n=29) received pravastatin sodium 40 mg/d. The administration of pravastatin was initiated 1 week before the procedure and was continued afterwards. Subjects in group 3 (n=34), who served as the control group, were not treated with lipid-lowering medication. After completion of the study protocol these patients were also started a statin treatment.

All patients received aspirin 100-300mg/day, and clopidogrel started as a loading dose of 300 mg before the procedure and continued 75 mg/day thereafter. "Dyslipidemia" was defined as a total cholesterol level greater than 200 mg/dL, a low-density lipoprotein cholesterol level greater than 100 mg/dL, or a high-density lipoprotein cholesterol level less than 40 mg/dL. Patients with chronic liver disease, end-stage renal disease, decompensated heart failure, a history of acute coronary syndrome in the 4 weeks before the initiation of the study, elevated cardiac enzymes at baseline, or an acute infectious disease or malignancy were excluded from the study.

Laboratory methods

The results of the patients' routine laboratory evaluations and their clinical and demographic characteristics were recorded. Blood samples for CRP were drawn at baseline before PCI and 6, 24 and 36 hours after the procedure. Blood samples for neopterin were drawn at baseline and 36 hours after PCI, were centrifuged immediately at 3000 rpm for 10 minutes at 4°C, and were stored at -70°C until they were used. Serum neopterin levels were determined by ELISA testing (Cat No. RE 59321, IBL Hamburg, Germany). This assay has an analytical sensitivity (limit of detection) of 0.17 nmol/L. It's normal reference value in normal population is below 2.53 nmol/L. Serum CRP levels were measured by an immunoturbidimetric method (Roche Diagnostics, GmbH, Mannheim, Germany) which, as an analytical sensitivity, has lower detection limit of 0.25 mg/L. By this method the reference limit in normal population is less than 6 mg/L.

Percutaneous coronary intervention

Procedures were performed by 3 experienced operators. Patients who underwent laser angioplasty or rotational and/or excisional atherectomy, those in whom debulking devices were used and those in whom the PCI was not successful were excluded from the study. In all patients, bare metal stents with or without balloon angioplasty were used. "Procedural success" was defined as less than 30% residual stenosis after the procedure and the achievement of thrombolysis in myocardial infarction (TIMI) III flow. Procedural characteristics were noted as the number of vessels and/or lesions, the total duration and number of inflations, and the number and type of stents used.

Statistical analysis

For statistical analysis, the computer program SPSS 9.0 for Windows (SPSS Inc, Chicago, Ill, USA) was used. The distribution of continuous variables for normality was tested with one-

sample Kolmogorov-Smirnov test and data are presented as mean±standard deviation (S.D.) or median and interquartile ranges, as appropriate. Categorical variables are reported as frequencies and group percentages. Differences among the groups in normally and non-normally distributed variables were evaluated by the analysis of variance (ANOVA) for repeated measures and the Kruskal-Wallis test respectively. The Chi-square test was used for comparison of categorical variables. A value of $p<.05$ was considered statistically significant.

Results

The mean age of the study population was 58.9±11.0 years. Patients in all groups were similar with regard to age, clinical and demographic characteristics, and laboratory findings except for platelet counts (Table 1). Patients in the treated and control groups had similar prevalence of hypertension, diabetes mellitus, dyslipidemia, tobacco smoking, and family history of premature CAD. Baseline levels of CRP and neopterin also did not differ significantly among the groups ($p>0.05$).

As we had expected, serum CRP and neopterin levels were increased significantly ($p<0.05$) after PCI in all groups (Table 2 and 3). Although the increase in CRP levels was most pronounced in the control group as opposed to groups 1 and 2, that difference did not reach statistical significance ($p>0.05$) (Table 2). The degree of elevation in neopterin levels after the procedure also did not differ among the groups (Table 3) ($p>0.05$).

In subgroup analysis, no differences in serum CRP and neopterin levels were detected among the groups with regard to the operator who performed the procedure ($p>0.05$), the number and type of stents used ($p>0.05$), or the total duration of balloon inflation ($p>0.05$) (Table 1). Home medications use rate that the patients were taking, including aspirin, clopidogrel, β-adrenergic blocking agents, angiotensin-converting enzyme inhibitors, calcium channel blocking agents, and oral nitrates, were similar among the groups ($p>0.05$). Patients' functional class according to the New York Heart Association classification and left ventricular ejection fraction indicated by echocardiography did not differ among the groups ($p>0.05$).

Discussion

The main findings of this study are 2-fold. First, PCI was found to induce a marked systemic inflammatory state characterized by substantial elevations in serum levels of CRP and neopterin. Second, although it had a mild limiting effect on the increase in the post-procedural CRP level, the pre-procedural administration of pravastatin at 2 different doses was ineffective in suppressing that inflammatory response at short-term follow-up after elective successful PCI.

Inflammation plays a crucial role in both the pathogenesis and the progression of the atherosclerotic heart disease. Percutaneous coronary intervention is accepted as a source of programmed damage to the endothelium of the coronary arteries that leads to a systemically measurable inflammatory state. Mechanisms proposed for the inflammatory response after PCI include disruption of atherosclerotic plaque, which contain inflammatory cells; vascular injury; myocardial necrosis; the release of inflammatory and chemoattractant factors resulting from the ischemia-reperfusion cycle induced by balloon inflation; and direct trauma by the procedure itself (5, 13, 14).

Data show that CRP usually increases 6 to 8 hours after PCI, reaches a peak concentration at 24 to 48 hours (6, 7). Study by Gasparadone et al. (15) revealed that atorvastatin therapy (80 mg/d) initiated at the time of coronary stenting decreases CRP levels as early as 24 to 48 hours after that procedure. Patients untreated with a statin had the most marked inflammatory response. Our findings are not in accordance to this study. We think that the main reason was that the statin dose we used was too low. Because 10 mg of atorvastatin seems to be as potent as 40mg of pravastatin (16).

Data regarding the effects of statins on serum neopterin levels are limited and reveal challenging findings. Neurauter et al. (17) conducted *in-vitro* investigations on the effects of atorvastatin on the T-cell-macrophage system in peripheral blood mononuclear cells and in human monocytic cell lines. Neopterin production and tryptophan degradation were monitored in cytokine-treated mononuclear cells after treatment with atorvastatin. The investigators found that atorvastatin at high doses (100 μM) inhibited neopterin formation and tryptophan degradation completely but that low doses (10 μM) of that drug were only partially effective (17). That finding is important because statins were shown to suppress the cellular immune system.

Walter and associates (18) measured serum neopterin levels in stable CAD patients and found that statin use was associated with lower neopterin concentrations.

In a study involving stable atherosclerotic disease and hypercholesterolemia, fluvastatin therapy at a daily dose of 80 mg was shown to decrease serum levels of CRP and neopterin after 3 months of follow-up (19). Unlike CRP, however, the decrease in neopterin disappeared at 12th month of therapy. In another study, however, treatment with fluvastatin failed to decrease neopterin levels (20). Ray et al. (21) in a recent paper reported their data obtained from 3946 patients with acute coronary syndrome who were followed over 2 years. They found no significant difference in absolute neopterin levels in patients treated with pravastatin 40 mg/d vs atorvastatin 80 mg/d at 30 days, 4 months or at the end of the study. In that study neopterin level, as a marker of activation of monocyte-macrophage system, was identified as predictor of long-term mortality and recurrent cardiovascular events. Another large trial enrolling 1801 participants who underwent coronary angiography and followed for a median of 8 years revealed that neopterin is an independent predictor of all cause and cardiovascular mortality in patients with and without CAD (22).

Table 1. Patient characteristics and laboratory findings

Variables	Group 1 (n=30)	Group 2 (n=29)	Control group (n=34)	F/Chi-square*	p*
Gender	10 F, 20 M	4 F, 25 M	7 F, 27 M		0.1
Age, years	58.4±11.9	56.6±9.5	61.7±11.0	1.5	0.2
Atherosclerotic risk factors					
Hypertension, %	66.7	41.4	55.9		0.1
Diabetes mellitus, %	26.7	17.2	21.2		0.6
Dyslipidemia, %	70.0	58.6	55.9		0.4
Smoking, %	43.3	41.4	58.8		0.3
Family history of CAD, %	26.5	20.7	26.5		0.3
Body mass index, kg/m^2	25.1±2.3	26.6±2.0	27.4±4.1	1.6	0.2
Laboratory variables					
Total cholesterol, mg/dL	212±52	181±44	200±47	2.7	.069
HDL cholesterol, mg/dL	43.4±13.6	39.4±11.9	46.9±11.8	2.3	.08
LDL cholesterol, mg/dL	129±52	101±40	116±41	1.8	.09
Triglycerides, mg/dL	138 (90-242)	135 (98-167)	135 (95-221)	0.6	0.7
Glucose, mg/dL	117±41	108±30	116±32	0.5	0.5
Hemoglobin, g/dL	14.2±1.4	14.0±1.6	13.5±1.7	1.3	0.2
Leukocytes, K/mm^3	4.7±3.6	6.4±4.0	7.6±5.2	3.1	0.054
Platelets, K/mm^3	268 (215-321)	252 (203-329)	191 (180-240)	12.6	0.02
BUN, mg/dL	20.0±8.4	17.3±5.9	19.0±5.8	1.0	0.3
Creatinine, mg/dL	0.9±0.2	0.9±0.2	1.0±0.2	1.0	0.3
AST, U/L	27.5±9.2	21.6±5.2	26.4±10.2	3.7	0.05
ALT, U/L	28.0±16.1	24.7±10	26.5±10.5	0.4	0.6
Medications					
Beta-blocker, n (%)	46.6	51.7	42.5		0.8
ACEI/ARB, %	26.6	27.5	38.2		0.4
Calcium channel blocker, %	36.6	34.4	44.1		0.7
Nitrate, %	16.6	24.1	20.5		0.5
Procedural characteristics					
Lesions intervened, n	1.37±0.5	1.55±0.8	1.27±0.5	1.3	0.2
Stents per patient used, n	1.39±0.6	1.22±0.8	0.96±0.4	2.3	0.08
Total balloon inflation, sec	151±90	147±85	129±107	0.03	0.9

Data are expressed as the mean±SD, the median (interquartile range), or frequency counts (percentages)

*ANOVA test, Kruskal-Wallis test, Chi-square test

ACEI - angiotensin converting enzyme inhibitor, ALT - alanine aminotransferase, ARB - angiotensin receptor blocker, AST - aspartate aminotransferase, BUN - blood urea nitrogen, CAD - coronary artery disease F - female, HDL - high-density lipoprotein, LDL - low-density lipoprotein, M - male

In our study, pravastatin therapy did not limit the post-procedural increase in neopterin level in the short term, perhaps because the treatment period was brief, the dose of the statin used was low, or the inflammatory response induced by PCI was too pronounced to be controlled with statin therapy alone.

In a recent trial Probasco et al. (23) examined the effect of atorvastatin therapy on serum neopterin levels in patients with HIV-1 infection. Eight weeks of atorvastatin 80mg/day therapy failed to suppress neopterin levels in this pilot study. Another research by Mulder et al. (24) revealed that both atorvastatin (40mg/day for the first 8 and 80mg/day for 8 weeks, defined as aggressive therapy) and simvastatin (40 mg/day, for 16 weeks) therapies had no decreasing effect on serum neopterin levels. Our study is the first prospective study evaluating the effects of

Table 2. Serum levels of CRP at baseline and after PCI

Variables	Group 1 (n=30)	Group 2 (n=29)	Control group (n=34)
Baseline			
CRP, mg/dL	10.1±5.8	8.5±5.0	9.6±6.5
Post-PCI 6 h			
CRP, mg/dL	13.2±5.3	14.4±12.3	13.8±9.4
Post-PCI 24 h			
CRP, mg/dL	18.5±9.9	19.3±12.3	21.4±13.5
Post-PCI 36 h			
CRP, mg/dL	21.7±9.4	20.4±9.9	24.8±14.5
Tests of within group effects: F=65.7, p<0.001 Tests of between group effects: F= 0.3, p= 0.7			
Tests of within group contrasts: Baseline vs post-PCI 6 h: F= 21.4, p<0.001 Post-PCI 6 h vs post-PCI 24h: F=39.7, p<0.001 Post-PCI 24 h vs post-PCI 36h: F=7.1, p=009			
Group effect on CRP: Baseline vs post-PCI 6 h: F=0.7, p=0.4 Post-PCI 6 h vs post-PCI 24h: F=0.7, p=0.4 Post-PCI 24 h vs post-PCI 36h: F= 0.5, p=0.5			
Pairwise Comparison: Group 1 vs 2; P= 0.9, Group 1 vs 3; P= 0.7, Group 2 vs 3; P= 0.7			
Data are expressed as the mean±SD *ANOVA for repeated measurements CRP - C-reactive protein, PCI - percutaneous intervention			

Table 3. Serum levels of neopterin at baseline and after PCI

Variables	Group 1 (n=30)	Group 2 (n=29)	Control group (n=34)
Baseline			
Neopterin, nmol/L	13.3±5.9	16.9±10.2	15.2±11.9
Post-PCI 36 h			
Neopterin, nmol/L	22.8±15.4	22.0±14.9	18.8±11.5
Tests of within group effects: F=6.3, p=0.01 Tests of between group effects: F=0.2, p=0.7			
Tests of within group contrasts: Baseline vs post-PCI 36 h: F=6.3, p=0.01			
Group effect on Neopterin: Baseline vs post-PCI 36 h: F=0.5, p=0.6			
Pairwise Comparison: Group 1 vs 2; p=0.9, Group 1 vs 3; p=0.9, Group 2 vs 3; p=0.7			
Data are expressed as the mean±SD *ANOVA for repeated measurements CRP - C-reactive protein, PCI - percutaneous intervention			

statins on serum levels of neopterin in patients undergoing PCI. Our results showed that neopterin levels increased significantly after that procedure. The endothelial damage and fragmentation of the atheromatous plaque during PCI might lead to the migration of macrophages to that region. The resulting local and systemic inflammatory reaction; mediated by the cellular immune system, might be the reason for the increased serum neopterin level after PCI, but unexpectedly, it seems likely not suppressed with prior pravastatin use.

We know that inflammation is an integral part of atherosclerotic vascular disease, and it seems very likely that the post-PCI local and systemic inflammatory responses detected by serum markers have clinical implications. Although in our study, pravastatin exerted a mild limiting effect on the post-procedural increase in the CRP level, we believe that additional trial of different statins and other anti-inflammatory agents at various doses and with long-term follow-up should be conducted.

Study limitations

Our study had several limitations. The number of patients in each group was low, and both the pre-procedural treatment and the follow-up periods after PCI were brief because all measurements were obtained during the patients' hospital stay. If the study period had been prolonged, we might have observed a difference in the outcome of treatment with pravastatin. In addition, a study using high-sensitive CRP instead of conventional CRP would have provided more valuable information and could make a difference in favor of pravastatin use. Finally, the dose of statin we used was low, which might have masked the anti-inflammatory effects of those drugs.

Conclusion

In this study, we found that PCI induced a pronounced inflammatory response. The pre-procedural use of pravastatin at 2 different doses seems not sufficiently suppress that inflammation at short-term follow-up after elective successful PCI. Additional studies with greater numbers of patients are needed to better clarify that issue.

Conflict of interest: None declared.

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