The effects of iodixanol and iopamidol on adhesion molecule serum levels in patients with angina pectoris undergoing coronary angiography: a randomized study

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Abstract

Objective: To compare intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) serum levels between patients with stable (SAP) and unstable angina pectoris (USAP) undergoing coronary angiography (CAG), investigate effects of CAG on ICAM-1, VCAM-1 levels in SAP, USAP patients; probable different effects of non-ionic radiocontrast media (RCM), iso-osmotic iodixanol and low osmolar iopamidol, on these adhesion molecules (AM).

Methods: In this randomized, prospective study, 2 groups consisting of patients with SAP (n=22) and USAP (n=22) undergoing CAG were included. For halves of each group iopamidol, for the other halves iodixanol were used as RCM, in turn for randomization. The patients were divided into 4 subgroups according to clinical presentations and used RCM(SAP-iodixanol, SAP-iopamidol USAP-iodixanol, USAP-iopamidol). ICAM-1, VCAM-1 levels were measured just before and 12 hours after CAG. Repeated measurements were compared with two-way ANOVA test.

Results: Baseline VCAM-1 concentration was higher in USAP group than SAP group (p=0.001). ICAM-1, VCAM-1 concentrations increased significantly following CAG in SAP, USAP groups. ICAM-1, VCAM-1 concentration increments; didn't reach statistical significance in SAP-iodixanol subgroup, reached a borderline significance in SAP-iopamidol subgroup (p=0.06, p=0.06). In USAP-iodixanol subgroup; only VCAM-1 (p<0.001), in USAP-iopamidol subgroup; ICAM-1 (p=0.009), VCAM-1 (p=0.006) levels increased significantly following CAG. No complication was observed.

Conclusion: To our knowledge, this is the first study indicating ICAM-1, VCAM-1 inducing effect of CAG in patients with SAP, USAP and differential effects of iodixanol and iopamidol on ICAM-1, VCAM-1 serum levels. Further studies are needed to clarify the effects of CAG and different RCM on vascular inflammation, vessel injury, serum AM levels and their clinical significance. This study should be taken as a pilot, hypothesis-generating study. *(Anadolu Kardiyol Derg 2014; 14: 156-61)*

Key words: angina pectoris, intercellular adhesion molecule-1, vascular cell adhesion molecule-1, coronary angiography, iodixanol, iopamidol

Introduction

Atherosclerosis is a multifactorial, multistep disease that involves chronic inflammation at each step, from initiation to progression (1). Early phase of atherosclerosis involves the recruitment of inflammatory cells from the circulation. This process is predominantly mediated by cellular adhesion molecules (CAMs), which are expressed mainly on the vascular endothelium in response to inflammatory stimuli (2). Soluble forms of CAMs have been detected in plasma and have been reported to be indicative of the expression of membrane bound adhesion molecules (AMs) (3).

In recent years, special attention has been paid to the potential value of soluble CAMs (sCAMs) as biomarkers for coronary artery diseases (CADs) (2). There has been a large number of clinical studies about the relationship between sCAMs and CADs' manifestations (3). In some previous studies, patients with stable angina pectoris (SAP) usually had higher serum levels of CAMs than control groups (4-7). Additionally, various studies consistently found that intercellular adhesion molecule-1 (ICAM-1) and/or vascular cell adhesion molecule-1 (VCAM-1) levels were elevated in patients with unstable angina pectoris (USAP) or Non-Q-wave infarction (4-10). Comparison of the CAMs' levels between patients with SAP and USAP, have revealed conflicted results previously (4-7, 10). The coronary angiography (CAG) is being performed increasingly in patients with CAD. Increased levels of serum systemic inflammatory

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markers (SIMs) have been shown in patients with SAP (11) and USAP (12) following diagnostic CAG previously. In a previous study, while these markers increased following exposure to both ionic and non-ionic radiocontrast media (RCM), there was a consistent trend towards lower serum inflammatory markers (SIM) release with non-ionic RCM (13). Nowadays non-ionic low osmolar (LO) and iso-osmotic (IO) radiocontrast media (RCM) are being widely used in CAG because of their fewer side effects. Currently there hasn't been comparison between LO and IO RCM for their effects on serum levels of CAMs.

In this study, we aimed to compare baseline ICAM-1 and VCAM-1 serum levels between patients with SAP and USAP undergoing diagnostic CAG, to investigate effects of CAG on basal ICAM-1 and/or VCAM-1 levels in patients with SAP and USAP; probable different effects of non-ionic RCM, IO iodixanol and LO iopamidol, on these sCAMs. If a lower impact on the CAMs can be detected for one of these RCM, it may be reasonable to prefer that agent for coronary procedures.

Methods

Study design

This randomized, prospective study was carried out between June 2009 and October 2009 at our hospital. Totally 44 consequent patients with SAP (SAP group, n=22) or USAP (USAP group, n=22) were included according to inclusion and exclusion criteria. For halves of patients in each group iopamidol, for the other halves of patients, iodixanol were used as RCM, during CAG.

Study population

Patients with either SAP or USAP undergoing diagnostic CAG within the next 24 hours after admission were screened. SAP was diagnosed with the patients who had typical effort chest pain, no resting angina pectoris for more than two months history. USAP was diagnosed according to the Braunwald classification (14). Patients with SAP and any coronary diameter stenosis of ≥50% or patients with USAP (Braunwald class IB, n=4; IIB, n=6; IIIB, n=12) and any culprit coronary lesion were included. Totally 44 patients (29 men,15 women; mean age 59.45±9.37 years) with SAP (SAP group, n=22) or USAP (USAP group, n=22) were included. Patients under the age of 18 and over the age of 75, patients with infectious and active inflammatory diseases (rheumatoid arthritis, inflammatory bowel disease, etc); renal failure (creatinine ≥1.2 mg/dL); malignancy; history of previous coronary artery bypass surgery or myocardial infarction; documented cardiovascular disease; structural heart disease, currently receiving anti-inflammatory; immunosuppressive or cytostatic agents, history of receiving RCM in the last fifteen days were excluded from this study. Patients for whom additional procedures were needed during diagnostic CAG such as ventriculography, aortography or urgent PCI or patients who received >100 mL RCM during CAG procedure weren't enrolled to limit the amount of RCM and probable effects of these procedures on the AM levels.

Study protocol

First peripheral venous blood samples to measure ICAM-1 and VCAM-1 serum levels were drawn from all the patients in SAP and USAP groups just before the sheath insertions in the catheterization laboratory. For the halves of each group iodixanol, for the other halves iopamidol were used as angiographic RCM, in turn for randomization. Finally, patients were divided into 4 subgroups according to the clinical presentations and used RCM (SAP-iodixanol, SAP-iopamidol, USAP-iodixanol, USAP-iopamidol). Each subgroup consisted of 11 patients. Levels of ICAM-1 and VCAM-1 were also measured 12 hours after CAG. All subjects gave their written, informed consent. This study was approved by the local Ethics Committee.

Contrast agents

In the study, for the halves of each group, non-ionic, iso-osmolar iodixanol (Visipaque 320, GE Healthcare Ireland Cork, Ireland), for the other halves of patients, non-ionic low osmolar iopamidol (iopamiro 300, Bracco Spa, Italy) were used as angiographic radiocontrast agent.

Coronary angiography

After administration of local anesthesia, selective CAG was performed using the standard Seldinger technique through the percutaneous right femoral artery puncture (Philips, H3000, The Netherlands). Coronary diameter stenosis was measured by means of quantitative coronary angiography. Angiograms were evaluated by an experienced cardiologist for the detection of culprit lesions in patients with USAP. Gensini scores (15) were calculated to determine the severity of atherosclerosis. The volume of given RCM recorded in each procedure.

Laboratory analysis

Levels of circulating soluble adhesion molecules ICAM-1 and VCAM-1 were investigated in patients immediately before and 12 hours after CAG. Blood samples were 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 coefficient of variation (CV) 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.

Statistical analysis

All statistical procedures were performed using Statistical Package for Social Sciences (SPSS) Windows Version 11.5 (SPSS Inc, Chicago, IL, USA). Categorical data were expressed as numbers (n) and percentages (%) and continuous data as mean±standard deviation (SD). Categorical data were analyzed using chi-square test. Normality tests were performed for variables. Statistically

significant differences between continuous variables of two groups were determined by using the Mann-Whitney U test or independent samples t-test, as appropriate. Repeated measurements in the same group were compared with two-way analysis of variance (ANOVA) test according to results of normality test. A p value <0.05 was considered statistically significant.

Results

Baseline variables are shown in Table 1. Baseline clinical characteristics, current medications and laboratory findings were comparable between SAP and USAP groups except for significantly higher angiotensin converting enzyme inhibitor/angiotensin receptor blocker (ACEI/ARB) and heparin use in the USAP group (p=0.035 and p<0.001 respectively). There was no statistical difference between SAP and USAP groups on baseline ICAM-1 concentrations (p=0.66). In contrast, baseline VCAM-1 concentration was higher in the USAP group than SAP group (p=0.001). There was no significant difference between two groups on volume of RCM used in CAGs (p=0.90) (Table 1).

Baseline ICAM-1 and VCAM-1 concentrations increased significantly after CAG in both SAP (for ICAM-1 p=0.023, for VCAM-1 p=0.010) and USAP (for ICAM-1 p=0.020, for VCAM-1 p<0.001) groups (Table 2). In subgroup analyses; in SAP-iodixanol subgroup neither ICAM-1 nor VCAM-1 concentration changed significantly after CAG comparing with basal measurements (p=0.16 and p=0.10 respectively, Table 3). In contrast, in SAP-iopamidol subgroup both ICAM-1 and VCAM-1 concentrations increased with a borderline significance (p=0.06 and p=0.06 respectively, Table 3). In USAP-iodixanol subgroup ICAM-1 level did not changed significantly but VCAM-1 serum level increased significantly following CAG (p=0.547, p<0.001, respectively, Table 4). In USAP-iopamidol subgroup in comparison with basal values, both ICAM-1 and VCAM-1 concentrations increased significantly after CAG (p= 0.009, p=0.006 respectively, Table 4). No complication was observed.

Discussion

The results of this study indicate that baseline VCAM-1 concentration was higher in the USAP group than SAP group. ICAM-1 and VCAM-1 serum levels increased significantly following diagnostic CAG in both SAP and USAP groups. In patients who received non-ionic RCM, LO Iopamidol during CAG, ICAM-1 and VCAM-1 levels increased (significantly in USAP group, with a borderline significance in SAP group). In contrast, non-ionic RCM, IO iodixanol administration did not result in a significant change of serum levels of both adhesion molecules except a significant VCAM-1 elevation in patients with USAP.

Inflammation plays a pivotal role in atherosclerosis (16). Various risk factors trigger an inflammatory response leading to the initiation and progression of atherosclerotic vascular disease. Several CAMs, cytokines and growth factors secreted from the endothelium aggravate inflammation and increase subendothelial lipid accumulation (17). Inflammatory processes of the coronary arterial wall are involved in plaque formation, progression and finally, plaque instability consecutively leading to the clinical manifestations of stable CAD or acute coronary syndromes (ACSs). ACSs result from plaque rupture or erosion leading to local thrombus formation with consecutive necrosis of myocytes (16). The role of CAMs in the pathogenesis of atherosclerosis has now been clearly demonstrated. Plasma levels of CAMs, have also been associated with the presence of clinical atherosclerotic disease, cardiovascular risk factors and ACSs (18).

ICAM-1 continuously present in low concentrations in the membranes of leukocytes and endothelial cells. Upon cytokine stimulation, the concentrations greatly increase. ICAM-1 can be induced by interleukin-1 and tumor necrosis factor-alpha (TNF-α) and is expressed by the vascular endothelium, macrophages and lymphocytes. ICAM-1 is a ligand for leukocyte function-associated antigen-1 (LFA-1), a receptor found on leukocytes. When activated, leukocytes bind to endothelial cells via ICAM-1/LFA-1 and then transmigrate into tissues (19). VCAM-1 is an immunoglobulin-like AM expressed on activated endothelial cells. VCAM-1 binds to $\alpha 4\beta 1$ integrin, which is expressed on lymphocytes, monocytes and eosinophiles. Interestingly, VCAM-1 can mediate both rolling-type adhesion and firm adhesion, depending on the avidity status of $\alpha 4\beta 1$ integrin. Although it is structurally similar to ICAM-1 and other CAMs, VCAM-1's patterns of regulation are unique. VCAM-1 is not expressed under baseline conditions but is rapidly induced by pro-atherosclerotic conditions (20). Although two AMs have similar structures because of their different expression patterns, ligands and functions, it is reasonable to expect them to be effected differently in some situations.

In the recent study, comparison between patients in SAP and USAP groups did not reveal any significant difference in terms of clinical, laboratory parameters. Concomitant medications were also found comparable in both groups except ACEI/ARB and heparin. Drugs, such as aspirin, probucol, statins, ARBs, ACEIs, peroxisome prolipherator-activated reseptor-α and γ ligands, calcium channel blockers, beta-blockers, may affect endothelial CAM expression (21). Studies have shown that angiotensin II has pro-inflammatory actions and induces the production of inflammatory cytokines and CAMs (22). More recent data have demonstrated that, treatments with ACEIs or ARBs may decrease serum CAM levels (23-26). Coagulation also augments inflammation. Thrombin has been reported to induce ICAM-1 and VCAM-1 (27). Heparin also has some anti-inflammatory activity (28). In our study in spite of significantly higher ACEI /ARB and heparin administrations in USAP group, patients with USAP had higher baseline VCAM-1, but similar basal ICAM-1 levels with SAP group. Serum levels of ICAM-1 and/or VCAM-1 have been compared between patients with SAP and USAP previously (4-7, 10). In some of these studies, serum levels of

Table 1. Comparison of baseline clinical characteristics, current medications, laboratory findings and volume of used radiocontrast media between SAP and USAP groups

	SAP (n=22)	USAP (n=22)	*P
Clinical characteristics			
Age, years	60.2±8.4	58.6±10.3	0.56
Male gender, %	15 (68.2)	14 (63.6)	0.85
Diabetes mellitus, %	7 (31.8)	7 (31.8)	1.00
Hypertension, %	13 (59.1)	15 (68.2)	0.53
Dyslipidemia, %	17 (77.3)	16 (72.7)	0.72
Current smoking, %	9 (40.9)	10 (45.5)	0.76
Obesity, %	8 (36.4)	8 (36.4)	1.00
Current medications,%			
Statin	11 (50.0)	12 (54.5)	0.76
ACEI-ARB	8 (36.4)	15 (68.2)	0.035
Antiplatelet agents	22 (100)	22 (100)	1.00
Beta blocker	16 (72.7)	10 (45.5)	0.07
Nitrate	13 (59.1)	9 (40.9)	0.22
Insulin	1 (4.5)	1 (4.5)	1.00
OAD	5 (22.7)	3 (13.6)	0.43
Fibrate drugs	1 (4.5)	2 (9.1)	0.55
Diuretic	6 (27.3)	5 (22.7)	0.72
CCB	9 (40.9)	7 (31.8)	0.53
Heparin	0 (00.0)	22(100)	<0.001
Laboratory findings			
WBC count	7981±1445	7798±1530	0.68
Creatinin, mg/dL	0.83±0.17	0.75±0.14	0.11
HbA1c (%) of patients with DM	7.2±0.8	7.3±0.7	0.80
TCL of patients with DPL, mg/dL	195.3±30.4	189.6±30.3	0.59
LVEF, %	60.2±3.9	60.6±5.1	0.74
Gensini score	33.5±19.0	32,1±22.2	0.82
Multivessel disease, %	15 (68.2)	14 (63.6)	0.85
Adhesion molecule levels			
Pre-CAG ICAM-1, ng/dL	563.7±170.9	579.0±134.3	0.66
Pre-CAG VCAM-1, ng/dL	465.7±191.2	720.6±277.4	0.001
Radiocontrast media			
Volume of used RCM, mL	53.95±5.43	53.05±3.89	0.90

Continous data are expressed as mean±SD. Categorical data are expressed as n (%).
*Chi-square; Mann-Whitney U test or independent samples t-test
ACEI/ARB - angiotensin converting enzyme inhibitor/angiotensin receptor blocker; CAG - coronary angiography; CCB - calcium channel blocker; DLP - dyslipidemia; ICAM-1 - intercelluler adhesion molecule-1; LVEF - left ventricular ejection fraction; OAD - oral antidiabetic; RCM - radiocontrast medium; SAP - stable angina pectoris; TCL - total cholesterol level; USAP - unstable angina pectoris; VCAM-1 - vascular cell adhesion molecule 1; WBC - white blood cell

Table 2. Comparison between pre and post coronary angiography adhesion molecule levels in SAP and USAP groups

	SAP Group (n=22)		*P
	Pre-CAG	Post-CAG	
ICAM-1, ng/dL	563.7±170.9	648.0±209.7	0.023
VCAM-1, ng/dL	465.7±191.2	673.8±313.6	0.010
	USAP Group (n=22)		*P
	Pre-CAG	Post-CAG	
ICAM-1, ng/dL	579.0±134.3	626.1±115.0	0.020
VCAM-1, ng/dL	720.6±277.4	1176.3±419.1	<0.001

Data are expressed as mean±SD
*Two-way ANOVA test
ICAM-1 - intercelluler adhesion molecule 1; CAG - coronary angiography; SAP - stable angina pectoris; USAP - unstable angina pectoris; VCAM-1 - vascular cell adhesion molecule-1

Table 3. Comparison between pre and post coronary angiography adhesion molecule levels in SAP-iodixanol and SAP-iopamidol subgroups

	SAP-iodixanol subgroup (n=11)		*P
	Pre-CAG	Post-CAG	
ICAM-1, ng/dL	588.5±178.1	674.2±236.6	0.16
VCAM-1, ng/dL	507.7±188.6	683.0±318.9	0.10
	SAP-iopamidol subgroup (n=11)		*P
	Pre-CAG	Post-CAG	
ICAM-1, ng/dL	538.8±168.2	621.7±186.7	0.06
VCAM-1, ng/dL	423.7±193.2	664.6±323.5	0.06

Data are expressed as mean±SD
*Two-way ANOVA test
CAG - coronary angiography; ICAM-1 - intercelluler adhesion molecule 1; SAP - stable angina pectoris; VCAM-1 - vascular cell adhesion molecule 1

Table 4. Comparison between pre and post coronary angiography adhesion molecule levels in USAP-iodixanol and USAP-iopamidol subgroups

	USAP- iodixanol subgroup (n=11)		*P
	Pre-CAG	Post-CAG	
ICAM-1, ng/dL	626.0±118.3	642.5±126.8	0.547
VCAM-1, ng/dL	678.8±171.2	1091.2±250.8	<0.001
	USAP- iopamidol subgroup (n=11)		*P
	Pre-CAG	Post-CAG	
ICAM-1, ng/dL	532.0±137.9	609.7±105.5	0.009
VCAM-1, ng/dL	762.3±358.3	1261.4±538.6	0.006

Data are expressed as mean±SD
*Two-way ANOVA test
CAG - coronary angiography; ICAM-1 - intercelluler adhesion molecule 1; USAP - unstable angina pectoris; VCAM-1 - vascular cell adhesion molecule 1

VCAM-1 were found to be higher in patients with USAP than SAP (4, 5, 7, 10) and in most of them there was no difference in ICAM-1 levels between patients with USAP and SAP (4, 6, 7, 10). The findings of our study are parallel with most of data in current literature (4, 7, 10). In one study, higher VCAM-1 serum levels were found only in patients with Braunwald class II and III USAP

than patients with SAP (5). In contrast, neither VCAM-1 nor ICAM-1 level was significantly different between patients with SAP and USAP in another study (6). However, because of very small sample size, caution must be applied to the results of this study. In the light of different expression, function, ligand characteristics of the CAMs and different pathophysiologies of the SAP and USAP, these findings may be interpreted as VCAM-1 level is more useful parameter for detecting increased inflammation, plaque destabilization and culprit lesion. If our findings will be supported by further studies, VCAM-1 serum level can be a useful biochemical marker to discriminate USAP from SAP.

This study has also found that, baseline ICAM-1 and VCAM-1 concentrations increased significantly after CAG in both SAP and USAP groups. This increase in USAP group was observed, in spite of significantly higher ACEI/ARB and heparin administrations. In patients with USAP, in addition to higher basal VCAM-1 levels, not only the CAG procedure itself, but ongoing atherothrombotic process and more pronounced inflammation might be responsible for the more pronounced increment in VCAM-1 levels. In an early study, CAG didn't elevate levels of serum inflammatory markers (SIM) in patients with SAP, but there were substantial increases in SIMs in patients with USAP following CAG (12). Later, a small clinical study showed that CAG also caused elevation of serum SIMs in patients with SAP (11). One study didn't find a substantial change in serum ICAM-1 level in SAP patients following CAG (29). In another earlier study, ICAM-1 levels were investigated in subjects undergoing peripheral angiography. Compared with basal values, levels of ICAM-1 were increased 24 hours after angiography, but increments in ICAM-1 levels didn't reach statistical significance (30). Endothelial expression of VCAM-I and ICAM-1 in vitro peaks by ~6 hours and 12 hours, respectively, and both proteins persist for at least 72 hours after induction by TNF-α (27). For these reasons in our study, peripheral venous blood samples to measure the CAM serum levels were taken just before and 12 hours after CAG. In a previous different study, inflammatory markers increased following exposure to both ionic and non-ionic RCM during CAG. The level of increase was lower with non-ionic RCM (13).

In current study's subgroup analyses; in patients who received non-ionic RCM, LO iopamidol during CAG, levels of both ICAM-1 and VCAM-1 increased significantly in patients with USAP and increased with a borderline significance in patients with SAP. These findings suggest that LO iopamidol may induce release of both AMs in patients with unstable and stable atherosclerotic plaque. In contrast, non-ionic RCM, IO iodixanol administration did not result in a significant change of serum levels of both AMs except a significant VCAM-1 elevation in patients with USAP. As a mechanism, higher basal VCAM-1 levels, more pronounced inflammation may be responsible and may facilitate this iodixanol-induced VCAM-1 release in patients with USAP. Following administration of IO iodixanol, ICAM-1 levels did not changed significantly in patients with SAP or USAP. Taken together, these findings suggest LO iopamidol is a more potent inducer of AMs comparing with IO iodixanol. The results of this study also indicate that, VCAM-1 release may be more sensitive indicator of RCM induced vessel injury. The issue that, with which mechanisms, the RCM, used in angiography increase AM levels can only be speculated. The RCM may increase levels of AMs by means of increasing expression, increasing release or decreasing the clearance of AMs existing in the serum.

Study limitations

Major limitation of the study is relatively small subgroup of patients. Although associations between increments in soluble ICAM-1 (31, 32) or VCAM-1 (33) levels following percutaneous coronary intervention and restenosis have been detected, there have been studies about the relationship between AM levels and stent thrombosis (34); clinical significance of pro-inflammatory or AM inducing effects of CAG and its long-term consequences have not been studied. Our study is not a follow up study so that it can't shed light to clinical significance of AM elevations secondary to CAG. Furthermore, blood samples were taken only twice as just before and 12 hours after CAG, serial blood sampling was not made in our study. Hence, it isn't possible to know the trend of AM serum levels. The maximum blood levels of CAMs and the time for sampling after the procedure may cause bias.

Conclusion

To our knowledge, this is the first study which indicates, ICAM-1 and VCAM-1 inducing effect of diagnostic CAG in patients with SAP or USAP and differential effects of iodixanol and iopamidol on ICAM-1 and VCAM-1 serum levels. Further studies are needed to clarify the effects of coronary angiography and different contrast agents on vascular inflammation, vessel injury, serum AM levels and their clinical significance. This study should be taken as a pilot, hypothesis-generating study.

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