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Original Research Article

Markers of inflammation following percutaneous coronary intervention (PCI) and its effect on adverse events

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ABSTRACT

Background: Number of markers of inflammation has been associated with coronary artery disease and various studies have shown increased levels during chronic stable angina, acute myocardial infarction, and percutaneous coronary intervention. However, co-relation to final outcomes of percutaneous coronary intervention with these markers has not been studied. Aim of this study was to try and find a correlation between markers of inflammation released during percutaneous coronary intervention and incidence of restenosis on follow up at 06 moths on patients undergoing percutaneous coronary intervention with Bare Metal Stent (BMS).
Methods: 36 consecutive only Bare Metal Stent (BMS) angioplasties done at our centre between July 2015 and June 2016 were analysed for markers of inflammation from peripheral venous sample before the procedure and coronary sinus sample after the procedure. Pts were kept on follow up for 6 months and assessed as per their clinical symptoms and Coronary Angiogram was done where indicated and results tabulated.
Results: There was increase in the studied markers of inflammation post percutaneous coronary intervention but they did not correlate with or predict possible restenosis.
Conclusions: This study showed that markers of inflammation are elevated during percutaneous coronary intervention but none of these markers correlates with subsequent restenosis.

Keywords: Acute coronary syndrome, Coronary artery disease, Inflammatory markers, Percutaneous coronary intervention

INTRODUCTION

Recent research has shown that inflammation plays a key role in coronary artery disease (CAD) and other manifestations of atherosclerosis. Immune cells dominate early atherosclerotic lesions, their effector molecules accelerate progression of the lesions, and activation of inflammation can elicit acute coronary syndromes.[1]

Studies done earlier by other workers had shown that in the systemic circulation of patients undergoing acute percutaneous coronary intervention for AMI, inflammatory markers such as CRP, serum amyloid A SAA, and IL-6 were elevated. At the site of the ruptured plaque, however, serum concentrations of the inflammatory markers CRP, IL-6, and SAA differed from those in the systemic circulation.[1]

Therefore, we hypothesized that the elevated markers of inflammation in patients undergoing percutaneous coronary intervention would correlate with incidence of future restenosis and if identified correctly can be used as a routine test during all percutaneous coronary intervention to predict restenosis.

METHODS

36 consecutive patients presenting with chronic stable angina who underwent Bare Metal Stent (BMS) angioplasties between July 2015 and June 2016 were enrolled in the study after a written and informed consent. Pre procedure venous blood sample were obtained and analysed for markers of inflammation. After angioplasty and stenting, coronary venous sinus sample was obtained by right heart catheterisation. The markers tested were Interleukin -2(1L-2), Interleukin -6(1L-6), C reactive Protein (CRP), serum amyloid A (SAA) and Tumour necrosis factor -alpha (TNF-a).

The results were tabulated. Patients were kept on monthly follow up and were re- studied with Coronary Angiogram only if they had fresh symptoms. Of the 36 patients 04 were lost to follow up and at the end of 06 months 07 patients were detected to have in-stent restenosis. The incidence of clinical and angiographic restenosis were then analysed with their initial markers of inflammation. Value of $p < 0.05$ was considered significant.

RESULTS

Total number of cases: 36, Lost to follow up: 04, in-stent restenosis at 06 months: 07.

Table 1: Levels of serum, 1L-2, 1L-6, CRP, SAA and TNF-a comparison of all cases pre and post percutaneous coronary intervention.

	Pre PCI	Post PCI	p value
IL-2(pg/ml)	12.97 ± 4.58	30.58 ± 10.57	<0.05
IL-6 (pg/ml)	1.305 ± 0.190	4.452 ± 2.456	<0.05
CRP (mg/ml)	0.755 ± 0.64	1.34 ± 1.58	<0.05
SAA (mg/ml)	14.083 ± 1.679	21.027 ± 6.513	<0.05
TNF-a (pg/ml)	15.888 ± 1.617	21.555 ± 3.093	<0.05

Table 2: Levels of serum, 1L-2, 1L-6, CRP, SAA and TNF-a Comparison of all cases all post percutaneous coronary intervention with those cases detected to have in-stent restenosis.

	Post PCI	ISR	P value
IL-2(pg/ml)	30.58 ± 10.57	33.42 ± 5.79	NS
IL-6 (pg/ml)	4.452 ± 2.456	4,485 ± 1.56	NS
CRP (mg/ml)	1.34 ± 1.58	0.914 ± 0.566	NS
SAA (mg/ml)	21.027 ± 6.513	25.857 ± 9.06	NS
TNF-a (pg/ml)	21.555 ± 3.093	22.57 ± 1.39	NS

All the markers of inflammation studied - IL-2, IL-6, CRP, SAA, and TNF-a showed a significant elevation post percutaneous coronary intervention compared to baseline levels, as shown in Table 1.

At 6 months follow up 07 cases out of 36 were found to have instent restenosis. Comparison of these cases with instent restenosis with the rest of cases did not show any significant difference in the levels of inflammatory biomarkers (Table 2).

DISCUSSION

Recent research has shown that inflammation plays a key role in coronary artery disease (CAD) and other manifestations of atherosclerosis. Immune cells dominate early atherosclerotic lesions, their effector molecules accelerate progression of the lesions, and activation of inflammation can elicit acute coronary syndromes. The evidence that atherosclerosis, the main cause of CAD, is an inflammatory disease in which immune mechanisms interact with metabolic risk factors to initiate, propagate, and activate lesions in the arterial tree is established.[1]

A decade ago, the treatment of hypercholesterolemia and hypertension was expected to eliminate CAD by the end of the 20th century, but cardiovascular diseases are expected to be the main cause of death globally within the next 15 years owing to a rapidly increasing prevalence in developing countries and eastern Europe and the rising incidence of obesity and diabetes in the Western world. Cardiovascular diseases cause 38 percent of all deaths in North America and are the most common cause of death in European men under 65 years of age and the second most common cause in women. These facts force us to revisit cardiovascular disease and consider new strategies for prediction, prevention, and treatment.[1]

Atherosclerotic lesions (atheromata) are asymmetric focal thickenings of the innermost layer of the artery, the intima. They consist of cells, connective-tissue elements, lipids, and debris.[2] Blood-borne inflammatory and immune cells constitute an important part of an atheroma, the remainder being vascular endothelial and smooth-muscle cells. The atheroma is preceded by a fatty streak, an accumulation of lipid-laden cells beneath the endothelium. Most of these cells in the fatty streak are macrophages, together with some T cells. Fatty streaks are prevalent in young people, never cause symptoms, and may progress to atheromata or eventually disappear.

In the center of an atheroma, foam cells and extracellular lipid droplets form a core region, which is surrounded by a cap of smooth-muscle cells and a collagen-rich matrix. T cells, macrophages, and mast cells infiltrate the lesion and are particularly abundant in the shoulder region where the atheroma grows.[2] Many of the immune cells exhibit signs of activation and produce inflammatory cytokines.[1-4]

Myocardial infarction occurs when the atheromatous process prevents blood flow through the coronary artery. It was previously thought that progressive luminal narrowing from continued growth of smooth-muscle cells in the plaque was the main cause of infarction. Angiographic studies have, however, identified culprit lesions that do not cause marked stenosis, and it is now evident that the activation of plaque rather than stenosis precipitates ischemia and infarction. Coronary spasm may be involved to some extent, but most cases of infarction are due to the formation of an occluding thrombus on the surface of the plaque.[4]

There are two major causes of coronary thrombosis: plaque rupture and endothelial erosion. Studies in animals and humans have shown that hypercholesterolemia causes focal activation of endothelium in large and medium-sized arteries. The infiltration and retention of LDL in the arterial intima initiate an inflammatory response in the artery wall. Modification of LDL, through oxidation or enzymatic attack in the intima, leads to the release of phospholipids that can activate endothelial cells, preferentially at sites of hemodynamic strain.[5] Patterns of haemodynamic flow typical for atherosclerosis-prone segments (low average shear but high oscillatory shear stress) cause increased expression of adhesion molecules and inflammatory genes by endothelial cells. Therefore, haemodynamic strain and the accumulation of lipids may initiate an inflammatory process in the artery.[6]

The inflammatory process in the atherosclerotic artery may lead to increased blood levels of inflammatory cytokines and other acute-phase reactants. Levels of C-reactive protein and interleukin-6 are elevated in patients with unstable angina and myocardial infarction, with high levels predicting worse prognosis.[6,7] The levels of other inflammatory markers are also elevated in these patients, including fibrinogen, interleukin-7, interleukin-8, soluble CD40 ligand, and the C-reactive protein–related protein pentraxin 3. Levels of C-reactive protein are elevated in patients with unstable angina, a condition that is probably dependent on coronary thrombosis of atherosclerotic plaques, but not in those with variant angina caused by vasospasm. Therefore, elevated C-reactive protein levels in patients with acute coronary syndromes likely reflect inflammation in the coronary artery rather than in the ischemic myocardium. Activated T cells are also present and subgroups of inflammatory T cells are increased in the blood of patients with acute coronary syndromes. Collectively, these findings suggest that inflammatory immune activation in coronary arteries initiates acute coronary syndromes, with circulating levels of inflammatory markers reflecting the clinical course of the condition.[7]

Inflammatory markers and the risk of CAD

Although the degree of active inflammation is increased in activated plaques of patients with acute coronary syndromes, smoldering inflammation characterizes silent plaques. Such lesions may also release inflammatory mediators into the systemic circulation. A moderately elevated C-reactive protein level on a highly sensitive immunoassay is an independent risk factor for CAD in a healthy population.[8] Whether this test should be used to screen asymptomatic persons is a matter of debate. Other measures of acute-phase reactants, including the erythrocyte sedimentation rate and levels of fibrinogen and other plasma proteins, also provide information about the inflammatory risk of CAD, as do levels of circulating, soluble adhesion molecules such as soluble intercellular adhesion molecule 1, soluble VCAM-1, and soluble P-selectin, which are shed by activated cells. The fact that several different inflammatory markers, with different biologic activities, contribute to the statistical risk of CAD makes it unlikely that C-reactive protein or any of the other markers actually causes the disease. Instead, they all reflect the local inflammatory process in the artery and, perhaps, other tissues (e.g., adipose tissue). Further research will be needed to clarify the role of these molecules as markers of risk as well as contributors to disease progression.

Therapeutic opportunities

The knowledge that atherosclerosis is an inflammatory disease offers new opportunities for the prevention and treatment of CAD. Powerful immunosuppressant or anti-inflammatory agents could represent attractive treatments for acute coronary syndromes.[8] For long-term prevention of atherosclerosis; a more specific approach is desirable, such as vaccination with disease-related antigens. Experimental results in both these areas are encouraging.

The immunosuppressive drugs cyclosporine and sirolimus block the activation of T cells and, at high levels, smooth-muscle proliferation. They inhibit intimal lesions, and sirolimus-coated stents are currently used to prevent restenosis after angioplasty. Whether this family of compounds can be used in acute coronary syndromes is not known. [9]

In the systemic circulation of our patients undergoing acute PCI for AMI, inflammatory markers such as CRP, SAA, and IL-6 were elevated, in line with work of others. At the site of the ruptured plaque, however, serum concentrations of the inflammatory markers CRP, IL-6, and SAA differed from those in the systemic circulation. Indeed, although the local coronary levels of IL-6 and SAA at the culprit lesion were markedly elevated compared with systemic levels, those of CRP were decreased. Because levels of Lp(a) remained unchanged, local dynamics of CRP, IL-6, and SAA reflect ongoing biological processes at the site of coronary occlusion. Any impact of the collateral circulation on the inflammatory reaction is unlikely. Although about half of the patients (52%) showed some collaterals at angiography, by definition (the patients presented with AMI and chest pain), the collateral circulation must have

been functionally negligible. In an extension of the work of Liuzzo et al in the systemic circulation, the patients without preceding symptoms before AMI also exhibited lower local coronary levels of inflammatory markers compared with those with periods of transient unstable angina before the index event, suggesting that local mechanisms of coronary occlusion also may differ identified by immunohistochemistry in atherectomy specimens and was found to be elevated in the vessel wall of unstable compared with stable patients.[10] These results show that inflammatory mediators locally released within the culprit coronary artery are important in AMI. This is further supported by in vitro findings in human vascular cells demonstrating biological activity of IL-6 at concentrations measured in the culprit artery.[11]

Various studies reviewed have proven that.[12-14]

- The plaque is a storehouse of markers of inflammation confirmed during biopsies.
- Studies during in acute myocardial infarction revealed a rise in markers of inflammation.
- The process of percutaneous coronary intervention is akin to acute myocardial infarction and there should logically be release of markers of inflammation.
- These markers of inflammation may be responsible for endothelial proliferation detected post percutaneous coronary intervention.

CONCLUSION

This study was conceptualized on the hypothesis that tackling raised markers of inflammation detected during percutaneous coronary intervention may help in preventing in-stent restenosis while using bare metal stent (BMS). The idea was to identify specific markers of inflammation correlating with in-stent restenosis. Once this has been done the second study was to be on administration of antibodies to the raised markers of inflammation and see whether this helped in reducing in-stent restenosis while using bare metal stent (BMS).

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