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Original Article

Periprocedural plasma fibrinogen levels and coronary stent outcome

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ABSTRACT

Aim: Percutaneous intervention is one of the treatment option for coronary artery disease. Reinfarction and restenosis is one of the complication of the procedure. So this study was conducted to assess plasma fibrinogen levels pre- and post coronary stenting and its relation with outcome.

Methods: After obtaining informed consent, venous blood samples were collected at three timed points in relation to stenting – 24 h before, 24 h after and 72 h after stenting to assess fibrinogen levels. Patients were followed up for six months. Repeat revascularization, myocardial infarction and symptomatic angina were considered as major adverse clinical events.

Results: 57 patients who underwent successful stenting and followed up for six months up were included in the study. Mean age was 53 years and 87.7% were males and 29.8% were diabetics. Baseline plasma fibrinogen level was significantly high in patients who developed repeat angina and myocardial infarction after the stenting [288.64 ± 59.43 vs 393.75 ± 32.97 mg/dL, $p = 0.003$] and it remained high during serial assessment [322.74 ± 63.92 vs 422.00 ± 55.28 mg/dL, 326.23 ± 65.81 vs 419.50 ± 45.82 mg/dL, 0.008, 0.012 respectively]. Patients who developed adverse events denied any drug default.

Conclusion: We conclude that plasma fibrinogen plays a significant role in the development of adverse events following stenting shown by high level of plasma fibrinogen in patients who developed adverse events.

1. Background

Coronary heart disease [CHD] represents a major cause of morbidity and mortality in the world today. The etiology of CHD is multifactorial and is known to include diet, physical inactivity, obesity, diabetes, hypertension, lipid levels etc. In India, CHD is an epidemic and considered to be one of the major causes of disease-burden and deaths.[1]

Percutaneous Intervention [PCI] has become the commonly used treatment of symptomatic coronary artery disease with

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high success. Important drawback of PCI is development of in-stent restenosis.[2] Various factors are shown to affect the outcome of stenting in a patient. Early elastic recoil, late vessel remodeling, and neointimal proliferation have been proposed as important contributors to the restenosis after coronary angioplasty.[3]

Several studies have shown fibrinogen as a major cardiac risk factor. Fibrinogen affects platelet aggregation and blood coagulation. Also fibrinogen and its metabolites have direct effects on the vascular wall.[4,5]

Otsuka and his colleagues [2002] studied the relation between preprocedural fibrinogen level and stent outcome and occurrence of adverse cardiac events of patients undergoing PCI. They concluded that preprocedural fibrinogen level and stent length was an independent predictor of coronary stent outcome.[6] On the contrary, Pascalle and his colleagues [2005] in their GENDER project concluded that there is no association between preprocedural fibrinogen level and target vessel revascularization after coronary stenting.[7]

Since conflicting results were shown by various studies about baseline fibrinogen levels and stent outcome, present study was conducted with the idea to determine the relation between preprocedural fibrinogen levels and coronary stent outcome and to study fibrinogen level serially and coronary stent outcome.

2. Subjects and methods

2.1. Study subjects

70 cases undergoing elective PCI during the period 2009–2010 were enrolled in this study. Out of 70 cases, 62 cases had successful stenting. Five cases were lost to follow up.

Patients were included if they were stented successfully for stable or unstable angina and coronary heart disease with normal levels of CK-2 activity in the 24 h preceding the intervention. Exclusion criteria were Acute Coronary Syndrome [ACS], acute infections or previous PCI or Coronary Artery Bypass Graft CABG] of the target vessel. The study was approved by the institutional ethics committee. Written informed consent was obtained from each subject before the PCI procedure.

2.2. PCI procedure

Coronary stenting was done either using radial or femoral route under a local anesthetic. Use of glycoprotein IIb/IIIa receptor inhibitors and type of stent depended on the need of the interventional cardiologist. Patency of the vessel was assessed by angiography after the procedure was completed and TIMI flow 3 Normal blood flow filling coronary bed completely achieved.

All patients who underwent PCI received Clopidogrel 300 mg and aspirin 300 mg previous night and on the day of surgery and continued to followup after the procedure. Heparin 5000U and nitroglycerine were given during the procedure. Another 2500U heparin was given if procedure extends beyond one hour to maintain Activated Clotting Time of 250–300 s every hour. Tirofiban was the GP IIb/IIIa blocker used. Tirofiban was given to 25 patients out 57.

Atorvastatin, aspirin and clopidogrel were continued for the patients for six months.

2.3. Lab analysis

2 ml of venous blood sample was collected in 3.8% citrate added tubes from the patients 24 h prior to coronary stenting. Two other venous blood samples were collected from the patients after 24 h of stenting and after 72 h of stenting.

Plasma fibrinogen was analyzed using Reagent kits from Tulip Diagnostics, India.

2.4. Dyslipidemia

Hypercholesterolemia is having serum cholesterol of 200 mg/dL and above. HDL less than 40 mg/dL was considered low HDL. LDL level $>$ 100 mg/dL was considered high.

2.5. Follow up and outcome measure

Patients were followed for six months. Outcome measure was taken to be freedom from cardiac related adverse events for six months. Cardiac related events included myocardial infarction, repeat revascularisation [either Percutaneous or Cardiac surgery] and recurrence of symptomatic angina. Occurrences of adverse events were collected from the patient's case records.

2.6. Statistical analysis

All data are expressed as mean $\pm$ standard deviation.

Repeated measures ANOVA followed by Mann Whitney test was used to compare means of the parameters of serial measurements.

p value of <0.05 was considered as significant for all statistical tests.

All analyses were performed with SPSS statistical software [SPSS Inc., Chicago, Illinois].

3. Results

3.1. Baseline patient characteristics

Mean age was 53 years and 87.7% were males and 29.8% were diabetics.

3.2. Serial assessment of plasma fibrinogen level

When compared to baseline level there is a significant increase in plasma fibrinogen after 24 h of the procedure [$p \leq 0.001$] and after 72 h [$p \leq 0.001$]. There is no significant change when plasma fibrinogen levels were compared between the samples collected after 24 h and 72 h of the procedure.

Changes in plasma fibrinogen level during serial assessment are given in Table 1.

Table 2 gives the details about the vessels involved and the number of stents used.

Table 1 – Periprocedural changes in plasma fibrinogen level [mg/dL].

Time	Fibrinogen [mg/dL]
a	296 ± 64
b	330 ± 68*
c	333 ± 69*

a – 24 h before stenting, b – 24 h after stenting, c – 72 h after stenting * – Significant on comparison with a $p < 0.05$ is significant.

Table 2 – Vessel involved and number of stents used in patients who underwent stenting.

S No.	Characteristics	Total $n = 57$
1	Vessel involved	
	LAD, *n* (%)	30 (53)
	RCA, *n* (%)	6 (11)
	LCx, *n* (%)	6 (11)
	LAD/RCA, *n* (%)	7 (12)
	LAD/LCx, *n* (%)	6 (11)
	RCA/LCx, *n* (%)	2 (4)
2	No. of Stents	
	1, *n* (%)	45 (79)
	2, *n* (%)	12 (21)

3.3. *Follow-up*

During follow up for 6 months, four patients developed adverse events. Two patients had acute myocardial infarction and two patients had unstable angina. There was no drug default among the patients.

Table 3 shows the baseline characteristics of patients who developed and did not develop adverse events.

18 patients had hypercholesterolemia. 43 out of 57 patients had low HDL. LDL was high in 44 patients out of 57. [LDL > 100 mg/dL in 44/57, LDL > 130 mg/dL in 24/57, LDL > 160 mg/dL in 7/57].

Table 3 – Baseline characteristics of patients who developed and did not develop adverse events.

Variable	Patients who did not develop adverse events, $n = 53$	Patients who developed adverse events, $n = 4$
Age [yrs]	52.8	53.2
Sex [F:M]	6:47	1:3
Smoking, *n* [%]	24 [45]	0 [0]
Diabetes, *n* [%]	15 [28]	2 [50]
Hypertension, *n* [%]	19 [36]	0 [0]
Obesity, *n* [%]	15 [28]	1 [25]
Dyslipidemia, *n* [%]		
Hypercholesterolemia	15 [28]	3 [75]
High LDL	44 [83]	3 [75]
Low HDL	40 [75]	3 [75]
Tirofiban use, *n* [%]	23 [43]	2 [50]
Type of stent		
Bare metal stent, *n* [%]	35 [66]	2 [50]
Drug eluting stent, *n* [%]	18 [34]	2 [50]
Fibrinogen level [mg/dL]	288.64 ± 59.43*	393.75 ± 32.97*

*$p = 0.003$.

Table 4 – Serial measurement of plasma fibrinogen levels in patients who developed and did not develop adverse events.

Time	Patients who did not develop adverse events, $n = 53$ [mg/dL]	Patients who developed adverse events, $n = 4$ [mg/dL]	*p*
a	288.64 ± 59.43	393.75 ± 32.97	0.003
b	322.74 ± 63.92	422.00 ± 55.28	0.008
c	326.23 ± 65.81	419.50 ± 45.82	0.012

a – 24 h before stenting, b – 24 h after stenting, c – 72 h after stenting.

Comparison of baseline characteristics like diabetes, hypertension, obesity and dyslipidemia between patients who patients who developed and did not develop adverse events did not provide significant results. No significant difference in incidence of adverse events with tirofiban use. The rise in plasma fibrinogen level after stenting is similar in both bare metal and drug eluting stents, but no significant difference between the types of stents. No statistically significant changes in CK2 following stenting or its association with fibrinogen.

The mean levels of plasma fibrinogen at 24 h before procedure is significantly high in patients who developed adverse events [393.75 ± 32.97 mg/dL vs 288.64 ± 59.43 mg/dL, $p = 0.003$].

The plasma fibrinogen levels of the 2 groups were compared in Table 4.

Plasma fibrinogen levels in patients who developed and did not develop adverse events after 24 and 72 h of procedure were 322.74 ± 63.92 mg/dL vs 422.00 ± 55.28 mg/dL and 326.23 ± 65.81 mg/dL vs 419.50 ± 45.82 mg/dL [$p = 0.008$ and 0.012 respectively].

4. Discussion

Fibrinogen is an acute phase reactant protein and a proinflammatory marker which plays an important role in platelet aggregation, increases plasma viscosity, causes the release of vasoconstrictor mediators and growth factors and also leads to fibrin deposits.[7]

In the present study, plasma fibrinogen level was increased following stenting and the level remained elevated at 72 h. This may be due to disruption of the vascular wall by stenting which may attract various inflammatory cells which may result in cytokine production. This leads to increased production of acute phase proteins including fibrinogen.[8]

Plasma fibrinogen level increased after stenting irrespective of type of stent used [both bare metal and drug eluting stents], but no significant difference between types of stents indicating that the stenting procedure induced an inflammatory response.

In the present study, patients who developed adverse events during six month follow up had their baseline plasma fibrinogen level more than 350 mg/dL. Various studies has shown that patients with baseline plasma fibrinogen level more than 350 mg/dL during follow up had more restenosis and adverse events when compared to patients with plasma fibrinogen level below 350 mg/dL[6,9]

Restenosis after coronary stenting is thought to be mainly due to neointimal proliferation. The migration and proliferation of smooth muscle cells, induced by the production and release of growth factors, cytokines and extracellular matrix synthesis, result in neointimal formation and eventually represents the restenosis.[3,10] Stent implantation induces a vascular inflammatory response which also contributes to restenosis.[10]

Increased fibrinogen causes alterations in fibrin clot structure and this is shown to impair fibrinolysis and increase the risk of cardiovascular events following stent procedure including stent thrombosis.

Fibrinogen may be considered a risk factor for restenosis because fibrin degradation products stimulate smooth muscle cell outgrowth which is seen in neointimal proliferation leading to restenosis.[7,9] For example, fibrinogen can promote endothelial-cell migration and extracellular accumulation of low-density lipoproteins. Fibrinogen can promote platelet aggregation by interacting with GP IIb/IIIa receptors on the platelet membrane. In addition, an elevated level of plasma fibrinogen increases blood viscosity,[5] which causes impaired microcirculatory flow, endothelial shear-stress damage, and predisposition to thrombosis.[11]

Recently Enright k *et al* studied measurement of fibrinogen and platelet reactivity with adverse events following PCI procedure and showed that fibrinogen measurements before procedure adverse cardiac related events.[12]

In the present study, only incidence of adverse events during six month follow up was assessed. Angiographic follow up was not done and hence percentage of restenosis was not determined. Two of the four patients who developed adverse events following stenting were diabetic. Effect of uncontrolled or poorly controlled diabetes on stent outcome is to be studied.

We conclude that there is an increased inflammation following stenting and high baseline plasma fibrinogen level can be used to assess risk for development of adverse cardiac events following PCI.

Conflicts of interest

The authors have none to declare.

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