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Effect of Various Clinical Parameters and Oxidative Stress Markers on TIMI Flow in Patients Undergoing Percutaneous Coronary Interventions

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Abstract

There is limited literature regarding effect of various clinical parameters on TIMI flow in ACS patients who underwent PCI. Also, it is not well known whether oxidative stress which is produced at local site can influence TIMI flow. Our study was done to evaluate role of various clinical parameters and oxidative stress markers on TIMI flow. The TIMI flow showed significant ($r = -0.27$, $p<0.01$) inverse relation with the disease severity i.e. as disease progresses, TIMI flow decreases. 100% occlusion showed highest and significant inverse relation with the TIMI flow, followed by LV dysfunction, diabetes, thrombus and least by smoker and ACS. The gender has no relation with the TIMI flow and similar influence on TIMI flow. Pre PCI level of all antioxidants and free radical marker did not show any association ($p>0.05$) with TIMI flow. Pre PCI scores of TIMI flow are much dependent on clinical characteristics rather than antioxidants and free radical marker.

***Keywords**: PCI, OXIDATIVE STRESS, TIMI Flow.*

Introduction

Ischemic heart disease (IHD) is one of the major causes of mortality and morbidity in the world. The most common cause of IHD is atherosclerotic coronary artery disease with erosion or rupture of a plaque causing transient, partial or complete arterial occlusion. [1]

The main goal of therapy for acute myocardial infarction is the early restoration of coronary flow to limit myocardial necrosis. Even after successful percutaneous coronary intervention (PCI), insufficient reperfusion is often present despite successful opening of occluded artery and microcirculatory failure remains challenge. Coronary flow can be reduced following PCI by several mechanisms including dissection, spasm, visible thrombus distal to lesion and generation of free radicals leading to oxidative bursts and stress. Oxidative stress is one of the major contributors to atherosclerotic plaque instability with inflammation process. [2]

Oxidative stress, defined as the impaired balance between oxidant and antioxidant systems, plays a crucial role in the pathogenesis of both atherosclerosis and acute coronary syndromes. Over the last decade, oxidative stress following restoration of myocardial flow in humans has been studied in detail but the results are conflicting. While ischemia-reperfusion studies in animals have shown protective effects of antioxidants, the use of antioxidants in acute coronary syndromes (ACS) in humans has been disappointing. Literature data about oxidative stress in percutaneous coronary interventions are still controversial.

Myocardial reperfusion in ACS patients undergoing PCI is primarily assessed using the angiographic thrombolysis in myocardial infarction (TIMI) flow grade. Various clinical parameters like gender, smoking, diabetes, LV dysfunction, thrombus, type of occlusion, type of ACS can affect TIMI flow. [3] There is less data

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about role of various clinical parameters and oxidative stress markers on TIMI flow before and after PCI.

Patients undergoing PCI had various degrees of TIMI flow. TIMI flow grade was assessed before and after PCI. Successful PCI had TIMI 3 flow, while in complicated PCI, TIMI 0,1,2 flow was seen. Mechanical causes for reduced/no flow e.g. dissection, spasm, visible thrombus distal to lesion etc. were ruled out.

This study was designed to observe role of various clinical parameters on TIMI flow on patients undergoing PCI and role of oxidative stress markers on TIMI flow on patients undergoing PCI.

Material and Method

This study was conducted at Department of Cardiology in patients admitted to coronary care unit with acute coronary syndrome (ACS) and their samples were analyzed at Department of Biochemistry, CSM Medical University, Lucknow between December 2009 and October 2010.

Inclusion Criteria

1. 18 year or more of age and of either sex.
2. ACS patients (Unstable angina (UA), non ST elevation MI (NSTEMI), ST elevation MI (STEMI) undergoing PCI for infarct related artery.

Exclusion Criteria

1. Chronic stable angina
2. Any mechanical complication occurred during PCI e.g. dissections, visible thrombus distal to lesion.
3. Chronic inflammatory disorders e.g. Rheumatoid arthritis, SLE.
4. Recent /ongoing infection or fever
5. Chronic renal failure or Creatine> 2 mg/dl
6. Severe LV dysfunction (Ejection fraction < 30%)
7. Cardiogenic shock
8. Uncontrolled diabetics

Study design

After taking detailed history and physical examination, routine blood tests and echocardiogram, subjects were divided into three groups:

Control groups (n= 11, healthy subjects): Normal coronary angiogram with TIMI 3 flows, normal LV function, non-smoker and non-diabetes.

PCI was confined to infarct related artery and was performed using standard techniques. One balloon inflation (15-45 sec) was usually enough to restore coronary artery patency, although further inflation or application of stent was performed to optimize angiographic appearance of underlying stenosis.

Uncomplicated group (n= 76): Patients undergoing PCI had successful procedure with TIMI 3 flow.

Complicated group (n= 32): Patients undergoing PCI after balloon inflation/stent implantation had TIMI 0, 1, 2 flows with no mechanical cause for reduced flow e.g. dissection, spasm, visible thrombus distal to lesion etc. None of the subjects (patients or controls) were taking antioxidant or vitamin supplements, probucol, allopurinol, quinidine, disopyramide, or other drugs known to affect serum lipid peroxidation and antioxidant values. Oral consent was obtained from the patients and normal subjects, prior to study.

Blood Collection and Estimation of free radical markers

Collection of blood sample (5ml) prior to PCI and within 30 min. of balloon inflation was done through guiding catheter hooked in coronary artery and collected in heparinised tubes and the plasma was separated by centrifugation at 3000 rpm for 15 min. Estimation of free radical markers e.g. MDA and antioxidants assay like Catalase (CAT), Superoxide Dismutase (SOD), Glutathione Peroxidase (GPx) and Glutathione Reductase (GR) were done at biochemistry lab, CSSMU, Lucknow. [4]

TIMI Grade Flow [5]

'TIMI Grade Flow' is a scoring system from 0-3 referring to levels of coronary blood flow assessed during percutaneous coronary angioplasty:

Grade 0 (no perfusion): There is no antegrade flow beyond the point of occlusion.

Grade 1 (penetration without perfusion): The contrast material passes beyond the area of obstruction but "hang up" and fail to opacify the entire coronary

bed distal to the obstruction for the duration of the cineangiographic filming sequence.

Grade 2 (partial perfusion): The contrast material passes across the obstruction and opacifies the coronary bed distal to the obstruction. The rate of entry of the contrast material into the vessel distal to the obstruction or the rate of clearance from the distal bed are perceptibly slower than its entry into or clearance from comparable areas not perfused by the previously occluded vessel—e.g., the opposite coronary artery or the coronary bed proximal to the obstruction.

Grade 3 (complete perfusion): Antegrade flow into the bed distal to the obstruction occurs as promptly as antegrade flow into the bed proximal to the obstruction, and clearance of contrast material from the involved bed is as rapid as clearance from an uninvolved bed in the same vessel or the opposite artery.

Statistical analysis

Association among clinical parameters, pre PCI levels of antioxidants and free radical marker and pre PCI scores of TIMI flow was assessed by Pearson correlation method while predictors of pre PCI TIMI flow from clinical variables and pretreatment levels of antioxidants and free radical marker were identified by multiple regression analysis considering the scores of TIMI flow the dependent variable and scores of clinical variables and levels of antioxidants and free radical marker the independent variables.

Assessment of relative risk (Odds ratio) after PCI in patients with positive (uncomplicated group: 0) and negative (complicated group: 1) response of TIMI flow was done by binary logistic regression analysis considering the response of TIMI flow the dependent variable and scores of clinical variables and change (pre to post or post to pre) in antioxidant and free radical marker levels the independent variables. A two- tailed (α=2) probability values $p<0.05$ was considered to be statistically significant. All analyses were performed on Graph Pad Prism (version 3.0) and Minitab (version 13.0).

Results

1. Correlation and Regression between clinical parameters and free radicals.

The baseline scores of all clinical variables i.e. Disease severity (1- controls, 2- uncomplicated PCI , 3- complicated PCI), Gender (1- male, 2- female), Smoker (0- No, Yes-1), Diabetes (0- No, Yes-1), LV dysfunction (0- No, Yes-1), Thrombus (0- No, Yes-1), 100% occlusion (0- No, Yes-1), ACS (1-UA,2-NSTEMI,3-STEMI) and TIMI flow (0,1,2,3) and pre PCI level of antioxidants (CAT, SOD, GPx, GR) and free radical marker (MDA) were correlated with each other and summarized in Table 1a.

Table 1: Inter correlation (n=119) among all studied variables

Variables	Disease severity	Gender	Smoker	Diabetes	LV dysfunction	Thrombus	100% occlusion	ACS	CAT	SOD	GPx	GR	MDA	TIMI flow
Disease	1.00													
Gender	-0.01^{ns}	1.00												
Smoker	0.29**	-0.43**	1.00											
Diabetes	0.27**	-0.25**	0.21*	1.00										
LV dysfunction	0.34**	-0.30**	0.31**	0.72**	1.00									
Thrombus	0.41**	-0.15^{ns}	0.35**	0.46**	0.43**	1.00								
100% occlusion	0.43**	-0.19*	0.34**	0.59**	0.61**	0.75**	1.00							
ACS	0.50**	-0.32**	0.32**	0.38**	0.40**	0.20*	0.25**	1.00						
CAT	-0.15^{ns}	0.14^{ns}	-0.02^{ns}	0.01^{ns}	-0.01^{ns}	0.02^{ns}	-0.01^{ns}	-0.13^{ns}	1.00					
SOD	-0.33**	-0.23**	0.00^{ns}	0.09^{ns}	0.18*	0.07^{ns}	0.14^{ns}	-0.06^{ns}	0.01^{ns}	1.00				
GPx	-0.23*	0.02^{ns}	-0.10^{ns}	-0.16^{ns}	-0.14^{ns}	-0.13^{ns}	-0.05^{ns}	-0.05^{ns}	-0.03^{ns}	0.07^{ns}	1.00			
GR	-0.11^{ns}	0.06^{ns}	-0.06^{ns}	0.06^{ns}	0.03^{ns}	-0.01^{ns}	-0.06^{ns}	-0.01^{ns}	0.00^{ns}	0.14^{ns}	0.09^{ns}	1.00		
MDA	0.41**	-0.07^{ns}	0.17^{ns}	0.04^{ns}	0.15^{ns}	0.06^{ns}	0.15^{ns}	0.37**	-0.04^{ns}	-0.09^{ns}	-0.14^{ns}	-0.14^{ns}	1.00	
TIMI flow	-0.27**	0.08^{ns}	-0.19*	-0.49**	-0.56**	-0.47**	-0.66**	-0.19*	0.11^{ns}	0.00^{ns}	0.04^{ns}	-0.11^{ns}	0.02^{ns}	1.00

ns- $p>0.05$, *- $p<0.05$, **- $p<0.01$

Table 2: Regression (n=119) of TIMI flow with other studied variables

Predictor	Coefficients	Standard Error	t Stat	p-value	95% CI	
					Lower	Upper
Intercept	1.76	0.70	2.53	0.013	0.38	3.14
Disease severity	0.08	0.08	1.08	0.282	-0.07	0.24
Sex	-0.07	0.07	0.97	0.335	-0.21	0.07
Smoker	0.02	0.07	0.26	0.792	-0.12	0.16
Diabetes	0.02	0.10	0.24	0.814	-0.17	0.22
LV dysfunction	-0.31	0.11	2.88	**0.005**	-0.52	-0.10
Thrombus	0.06	0.14	0.40	0.688	-0.22	0.33
100% occlusion	-0.71	0.14	5.03	**0.000**	-1.00	-0.43
ACS	-0.01	0.04	0.35	0.728	-0.09	0.07
CAT	0.01	0.01	1.88	0.062	0.00	0.02
SOD	0.54	0.24	2.23	**0.028**	0.06	1.03
GPx	0.00	0.01	0.32	0.748	-0.02	0.02
GR	-0.02	0.01	1.95	0.054	-0.04	0.00
MDA	0.11	0.07	1.49	0.139	-0.04	0.26

2.Binary logistic regression

The baseline scores of all clinical variables and change levels of all antioxidants and MDA after PCI were again regressed against TIMI flow to investigate the effect of PCI on TIMI flow response (positive (0): TIMI 3; negative (-1): TIMI 0,1,2) and were summarized in **Table 2.**

Table 3: Binary logistic regression (n=108) of TIMI flow with other studied variables

Predictor	Coeff	SE Coeff	Z value	p- value	Odds ratio	95% CI	
						Lower	Upper
Constant	-4.05	2.48	1.63	0.103			
Sex	1.26	0.94	1.33	0.183	3.51	0.55	22.28
Smoker	0.11	0.74	0.15	0.879	1.12	0.26	4.74
Diabetes	-3.89	1.53	2.53	0.011	0.02	0.00	0.41
LV dysfunction	2.44	1.38	1.76	0.078	11.43	0.76	171.32
Thrombus	0.85	1.28	0.67	0.505	2.35	0.19	28.89
100% occlusion	3.47	1.50	2.31	0.021	32.22	1.70	611.16
ACS	-0.30	0.58	0.51	0.607	0.74	0.24	2.30
CAT	0.57	0.34	1.69	0.092	1.76	0.91	3.41
SOD	-14.19	6.47	2.19	0.028	0.00	0.00	0.22
GPx	-0.01	0.32	0.02	0.987	0.99	0.53	1.86
GR	0.44	0.24	1.83	0.068	1.56	0.97	2.51
MDA	4.76	1.84	2.59	**0.010**	116.41	3.19	4251.87

Discussion

There is limited literature regarding effect of various clinical parameters present in ACS patients on TIMI flow who underwent PCI. Also, it is not well known whether oxidative stress which is produced at local site can influence TIMI flow (Berg 2006). [6] Our study was done to evaluate role of various clinical parameters and oxidative stress markers on TIMI flow.

We correlated various clinical parameters i.e. disease severity, gender, smoking, diabetes, LV dysfunction, thrombus, type of occlusion of infarct related artery, ACS and pre PCI level of antioxidants (CAT, SOD, GPx, GR) and MDA on TIMI flow.

In table 1, the TIMI flow showed significant (r= -0.27, p<0.01) inverse relation with the disease severity i.e. as disease progresses, TIMI flow decreases. The gender has no relation (r= 0.05, p>0.05) with the TIMI flow i.e. both the sexes have similar influence on TIMI flow. However, 100% occlusion showed highest and significant (r= -0.61, p<0.01) inverse relation with the TIMI flow, followed by LV dysfunction (r= -0.56, p<0.01), then diabetes (r= -0.49; p<0.01), then thrombus (r= -0.47; p<0.01) and least by smoker and ACS (r= -0.19, p<0.05). Interestingly, pre PCI level of all antioxidants and free radical marker did not show any association (p>0.05) with TIMI flow. In conclusion, the pre PCI scores of TIMI flow are much dependent on clinical characteristics rather than antioxidants and free radical marker. Role of clinical variables like diabetes, LVdysfunction,100% occlusion, ACS play important role in outcome of any PCI as described by Cura FA,2001. [7]

The regression analysis (Table 2) showed LV dysfunction, 100% occlusion and SOD are the significant (p<0.05 or p<0.01) predictors of TIMI flow and among these 100% occlusion which showed maximum influence (β= -0.71, t=5.03; p<0.01) on TIMI flow can be considered as independent predictor of pre PCI TIMI flow and were observed similar by Kammler et.al 2006, Luca et.al 2004. [8,9]

In table 3, Binary logistic regression was applied to investigate the effect of PCI on TIMI flow response. The response (positive (0): TIMI 3; negative (-1): TIMI 0, 1, 2) of TIMI flow after the PCI significantly affected by Diabetes (β= 3.47, Z=2.31; p<0.05), SOD (β= -14.19, Z=2.19; p<0.05), and MDA (β= 4.76, Z=2.59; p<0.05). Patients with Diabetes and 100% occlusion respectively have 0.02 (95% CI: 0.00 - 0.41) and 32.2 (95% CI: 1.70 – 611.16) times more risk (odds ratio) of having decrease TIMI flow post PCI than those without these. Our finding was similar as by Suenari K et.al. [10] In contrast, decrease in SOD after PCI minimally effects the response of TIMI flow (odds ratio=0.00, 95% CI: 0.00 - 0.22) but the increase in MDA induced 116.4 times more risk on TIMI flow (odds ratio=116.41, 95% CI: 3.19 – 4251.87). But the increase in our study was small and had taken 2 samples just prior to and after PCI for oxidative stress. So, we cannot evaluate rise and fall of these markers in ACS. Long term follow-up is required in those patients with decreased TIMI flow. Also, study included all ACS patients going for PCI irrespective of their index events.

Conclusion

The TIMI flow showed significant (r=-0.27, p<0.01) inverse relation with the disease severity i.e. as disease progresses, TIMI flow decreases. 100% occlusion showed highest and significant inverse relation with the TIMI flow, followed by LV dysfunction, diabetes, thrombus and least by smoker and ACS. The gender has no relation with the TIMI flow and similar influence on TIMI flow. Pre PCI level of all antioxidants and free radical marker did not show any association (p>0.05) with TIMI flow. Pre PCI scores of TIMI flow are much dependent on clinical characteristics rather than antioxidants and free radical marker.

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References

1. Benjamin EJ, Blaha MJ, Chiuve S, et al. Heart Disease and Stroke Statistics - 2017 Update: A Report from the American Heart Association. Circulation 2017.
2. Paterson JR, Oldroyd KG, Rumley AG, Eteiba H, Rae AP, Hutton I, et al. Free radical activity during percutaneous transluminal coronary angioplasty. Biochem Soc Trans 1990; 18: 1183-1184.
3. R.W. Harrison, A. Aggarwal, F.S. Ou, L.W. Klein, J.S. Rumsfeld, M.T. Roe, et al., Inci- dence and outcomes of no-reflow phenomenon during percutaneous coronary intervention among patients with acute myocardial infarction, Am. J. Cardiol.

111 (2) (2013) 178–184.

4. Devasagayam TPA, Boloor KK and Ramsarma T. Methods for estimating lipid peroxidation: Analysis of merits and demerits (mini review). Indian J Bioche Biophys 2003;40:300-8
5. TIMI Study Group. The Thrombolysis in Myocardial Infarction (TIMI) trial. Phase I findings. N. Engl. J. Med. 1985 Apr 04;312(14):932-6.
6. Berg K, Wiseth R, Bjerve K,Brurok H, Gunnes S, Skarra S, Jynge P, Basu S.Oxidative stress and myocardial damage during elective percutaneous coronary interventions and coronary angiography. Free Radical Research 2004; 38 (5): 517-525.
7. Cura FA, L'Allier PL, Kapadia SR, et al. Predictors and prognosis of suboptimal coronary flow after primary coronary angioplasty in patients with acute myocardial infarction. Am J Cardiol 2001;88:124–8.
8. KAMMLER Juergen TIMI 3 flow after primary angioplasty is an important predictor for outcome in patients with acute myocardial infarction Clinical research in cardiology 2009, vol. 98, n°3, [Note(s): 165-170 [6 p.]]
9. De Luca G, Ernst N, Zijlstra F, van't Hof A, Hoorntje J, Dambrink J, Gosslink AT, de Boer MJ, Suryapranata H. Preprocedural TIMI flow and mortality in patients with acute myocardial infarction treated by primary angioplasty. J Am Coll Cardiol 2004;43:1363–7.
10. K. Suenari, N. Shiode, K. Shirota, H. Ishii, K. Goto, A. Sairaku, et al., Predictors and long-term prognostic implications of angiographic slow/no-flow during percutane- ous coronary intervention for acute myocardial infarction, Intern. Med. (Tokyo, Japan) 47 (10) (2008) 899–906 .