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Laboratory Evaluation of Hypercoaguable State in Myocardial Infarction

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Abstract: ***Myocardial infarction is the most important form of ischaemic heart disease and alone is the leading cause of death. Hypercoagulability is well established risk factor for thrombosis that occurs in MI. Hypercoagulability is the condition in which coagulation system is out of balance and prone to thrombus formation. Such hypercoagulable state is due to increased levels of coagulation factors or reduced fibrinolytic action. In present study the subjects were divided into 3 groups. Group A - 26 healthy controls, Group B- 22 patients of Acute MI and Group C- 52 patients of Old MI. The battery of test selected were Bledding time, Prothrombin time test, Partial thromboplastin time with Kaolin, and Quantitative determination of fibrinogen in plasma. Present study concludes coagulation parameters especially fibrinogen and PTTK have predictive value in detecting hypercoagulable state in patients of MI, at the same time BT and PT has not shown predictive changes. Thus patients of acute and old MI who are in state of hypercoagulability need preventive measures and appropriate treatment for reduction in mortality and morbidity from such a disastrous disease.***

Keywords: Myocardial infarction, Bleeding time, Prothrombin Time, Partial thromboplastin time with Kaolin, Cardiovascular disease

1. Introduction

Ischaemic heart disease in its various forms is responsible for 80 to 90% of all deaths caused by heart diseases. Myocardial infarction, also known as heart attack, is overwhelmingly the most important form of ischaemic heart disease and alone is the leading cause of death in United States and industrialized nations.

According to Global Burden of Disease study age - standardized estimates, approximately 24.8% of all deaths in India are attributable to Coronary Vessel Disease. The age – standardized CVD death rate of 272 per 1,00,000 population in India is higher than 235 per 1,00,000 population . The years of life lost attributable to CVD in India increased from 23.2 million to 37 million over 1990 to 2010. Overall prevalence of MI is 3.6% (4.7% in men & 2.6% in women). Estimated annual incidence of MI 935000 which includes 6,10,000 new and 3,25,000 recurrent infarctions. Lifetime risk of developing CHD after age 40 is 49% for men & 32% for women Lloyd-Jones et al, 2011[1]**.** This rising prevalence of CVD has become a menace associated with social, personal and economic burden among world population Deaton et al, 2011[2]**.** Considering a leading threat and on the rise in India. Emphasis should be given on prevention, early detection, and treatment with the use of both conventional and innovating techniques to combat this epidemic and a multi-pronged effort to scale up interventions is mandatory.
MI can occur virtually at any age but the frequency rises sharply with increasing age especially when risk factors predisposing to atherosclerosis like hypertension, diabetes, cigarette smoking, genetic hypercholesterolemia etc. are present.

Woolf and Davie[3] suggest that among 85 to 90% of cases of MI, coronary thrombosis to be the dominant cause. Mcaik BG et al (1995) [4]found hypercoagulable states which lead to thrombosis occur in Patients of MI. Hypercoagulability is the condition in which coagulation system is out of balance and prone to thrombus formation. Such hypercoagulable state is due to increased levels of coagulation factors or reduced fibrinolytic action. Hypercoagulability is a well-established risk factor for thrombosis that occurs in MI.

Thus, if thrombosis is the initiating event and hypercoagulable state is a cause, it is beneficial to identify a hypercoagulable state in patients of MI to reduce the morbidity and mortality of this catastrophic disease.

2. Literature Survey

Hypercoagulable state
Macik BG et al (1995)[4] defined hypercoagulable state as any alteration of the coagulation pathways that predispose to thrombosis and can be divided into primary (genetic) and secondary (acquired) disorder. Individuals with primary hypercoagulable state are associated with mutations in factor V, and lack of anticoagulants (eg. Antithrombin III, protein C, or protein S). Gheye S et al (1999) [5] found that hereditary elevated levels of homocysteine and fibrinogen level proved independent risk factors for coronary artery diseases.

Myocardial Infarction- A hypercoagulable state-
The increase in coaglability of blood in coronary thrombosis has been reported long back by Molten SE et al (1949) [6]. Lot of work since then has been carried out by various workers Mcdonald and Edgill (1975) [7] could demonstrate an element of hypercogulability in patients of MI. Thus patients who had multiple infarcts presumably thrombotic in origin is clearly at risk of further thrombosis either all the time or at least episodically.

Role of various abnormal tests – Either single or multiple or even single risk factor is responsible for thrombosis. In

such cases even if a single test is found to be highly abnormal, it would be argued that the patient is at increased risk. More probably a patient is likely to develop a thrombus because several or indeed half a dozen factors are slightly abnormal, but all activities may summate and potentiate each other O'brien and green (1985) [8]. So, combinations of test may help to discriminate person at risk and even better results may be obtained if abnormal tests results are combined with other risk factors such as smoking, Diabetes, hypertension and increased cholesterol levels.

3. Methods/Approach

The present study was conducted in Department of Pathology in Tertiary Care Hospital in Central India in total duration of 2 yrs. The subjects of the study were divided into 3 groups:

Group A - Around 26 in number (21 males and 5 females) healthy controls free from diabetes, hypertension and obesity. They were unrelated to the patients, mostly either staff members or visitors to the hospital.

Group B - Included 22 patients (15 males and 7 females) who were admitted to Indira Gandhi govt. Medical College and Hospital, Nagpur, in the Intensive Coronary Care Unit and who were diagnosed as patients of Myocardial Infarction which required typical history, acceptable electrocardiographic changes and raised level of serum cardiac markers.

Group C - The patients 52 (42 Males and 10 Females) who had an attack of acute myocardial infarction three months earlier or more attending the Cardiology Clinic for follow up.

Inclusion Criteria for selection of patients were - Adult patient (less than 75 yrs) of either sex having no history of smoking, Diabetes mellitus, hypertension or renal failure.

4. Procedure

The pre -requisite for accurate results in coagulation test system is the proper collection of samples, including subsequent handling and storage if necessary. Since anyone of the coagulation factors can become rate limiting in the enzymatic process of blood clotting, therefore all the blood samples were collected, handled and stored as per criteria laid by the National committee for clinical laboratory standards (NCCLS). The battery of test selected were Bledding time (Ivy's method), Prothrombin time test (Modified Quick's one stage method), Partial thromboplastin time with Kaolin, and Quantitative determination of fibrinogen in plasma.

5. Discussion

In our Study total 100 cases were analysed in three Groups – A, B and C.

Table 1: Showing age and sex wise distribution in patients of acute and old myocardial infarction (n=74)

Sr. no	Age group	Sex		Total
		Male	Female	
1	31- 40	7	1	8
2	41-50	8	7	15
3	51-60	14	7	21
4	61-70	22	3	25
5	71-80	4	1	5
	Total	55	19	74

(Mean age – 57.11)

The prevalence of MI was found most in fifth to seventh decade with male preponderance as compared to females.

Table 2: Showing coagulation parameters in control (Group A) n=26

Parameters	BT (min)	PT (sec)	PTTK (sec)	Fibrinogen (mg/dl)
Range	1.40 to 4.20	12-20	33-52	252-342
Mean	3.28	15.81	44.15	294
SD	+1.02	+1.86	+9.04	+34

Group A- Control group consisted of 26 healthy subjects belonged to 41 -70 years (mean 52.92) age group. There was no significant difference seen in coagulation parameters in respect to gender or age group. (Table 2)

Table 3: showing coagulation parameters in patients of Acute Myocardial Infarction (Group B) n=22

Parameters	Range	Mean + SD	t Value	P Value	Significance
BT (min)	1.20-4.10	3.37 =1.26	1.4332	> 0.05	Nonsignificant
PT (sec)	9-20	14.55 =3.1	1.7429	> 0.05	Nonsignificant
PTTK (sec)	23-52	33.72=9.33	3.1698	< 0.05	Significant
Fibrinogen (mg/dl)	302-378	358=22	7.6050	< 0.05	Significant

Group B – It consisted of 22 patients of acute myocardial infarction admitted in ICCU. Blood sample collected within 2 hrs of hospitalization and before heparinisation or thrombolization. When these patients were compared with the control group, out of 4 tests, 2 tests revealed statistically significant values. The test with significant changes included PTTK and Plasma Fibrinogen level. Out of 22 patients of Acute MI 19 Patients showed a variable coagulation abnormality in favour of hypercoagulable state. Each test, meaning thereby, that the tests were in different permutations and combinations. These data were analysed and as per the number of tests abnormal, a spectrum of patients from low risk to high risk was discovered.

Table 4: Showing analysis of various coagulation parameters in patients of acute MI. Group B (n=22)

*	Tests				No. of Patients	Total	% age	Group
	PT	PTTK	Fibrinogen	BT				
4	↓	↓	↑	↓	1	1	4.54	5
3	↓		↑	↓	2	5	22.72	4
	↓	↓	↑		3			
2		↓	↑		4	6	27.27	3
			↑	↓	1			
	↓		↑		1			
1			↑		7	7	31.81	2
0					3	3	13.63	1
	7	8	19	4	22	22		
% age	31.81	36.36	86.36	18.18			% age	Group

* - Number of positive test favoring diagnosis of hypercoagulable.
↑- Increased level.
↓ - Shortened time

Table 4 which comprises of patients of acute MI depicts different groups with respect to number of tests abnormal. Thus 5 groups were isolated –
Group 1 – 13.63% did not show any abnormality.
Group 2- 31.81% of patients showed 1 test abnormality.
Group 3- 27.27 % of patients showed 2 test abnormality.
Group 4- 22.72 % of patients showed 3 test abnormality.
Group 5- 4.54 % of patients showed 4 test abnormality.

Tables 5: Showing coagulation parameters in patients of old MI (Group C) n=52

Parameters	Range	Mean + SD	t Value	P Value	Significance
BT (min)	1.8 to 4.38	3.03 =1.29	1.3965	> 0.05	Nonsignificant
PT (sec)	10-18	14.94 +2.43	1.59	> 0.05	Nonsignificant
PTTK (sec)	23-56	36.40+10.73	3.1595	< 0.05	Significant
Fibrinogen (mg/dl)	320-372	362 +12	13.0382	< 0.05	Significant

Group C – It included 52 patients, who had suffered an episode of acute MI, at least 3 months before the coagulation studies were done.

Same battery of coagulation tests were performed and here too, statistically significant values were obtained in the same two tests.

Table 6: Showing analysis of various coagulation parameters in patients of old MI. Group C (n=52)

*	Tests				No.of Patients	Total	%	Group
	PT	PTTK	Fibrinogen	BT				
4	↓	↓	↑	↓	1	1	1.92	5
3	↓	↓	↑		1	6	11.53	4
	↓		↑	↓	4			
		↓	↑	↓	3			
2		↓	↑		12	19	36.53	3
	↓		↑		5			
			↑	↓	2			
1			↑		21	22	42.30	2
				↓	1			
0					4	4	7.69	1
	8	18	47	9	52	52		
%	15.38	34.61	90.38	17.30			Percentage	Group

The above data when analyzed gives information as follows –
Group 5 at highest risk of thrombosis with all the 4 abnormal tests.
Group 2 at relatively low risk has maximum 42.30% of patients.
Risk of thrombosis rises from group 1 to group 5.

Individual tests pertained to coagulation profile –

Bleeding time – Bleeding time apparently a simple test that has a great theoretical advantage that it is a global in vivo test. Whatever it measures, if abnormal, it is likely to be a clinical importance. It must reflect the interaction of the platelets with the damaged endothelium but blood coagulation is hardly involved, since the patients with gross clotting defect after have normal bleeding time. Though the present study show Bleeding time is not statistically significant test , 4 patients of Acute MI and 9 patients of old MI show significantly shortened bleeding time associated with other abnormal coagulation profile tests. (Table 4 & 6). Thus this enhances the thrombotic risk by adding one or more ingredient to activate coagulation.

Prothrombin time –Prothrombin time gives an idea of the extrinsic system of coagulation. This system gets activated by the action of tissue factor (a cofactor) on factor VII in presence of calcium ions. PT shortened in 31.81% and 15.38% of patients of acute and old MI respectively.(Table 4 & 6).

Partial Prothrombin time with Kaolin- PTTK measures the time taken to form a clot by accelerating the contact activating process by kaolin. The reduction in time to form the clot in patients than the control group only suggest either the factors are in an activated states or there is reduction in the inhibitory substances of coagulation. Both these would lead to brisk clot formation and possibly thrombosis. 8 out of 22 (36.36%) patients in Group B and 36.41% (18 out of 52) patients from group C showing statistically significant shortened PTTK which follows high fibrinogen levels (Table 4 & 6). Thus on the whole PTTK appears to be a simple and reliable test to give an idea of activated coagulation.

Plasma fibrinogen Level –

Table 7 showing plasma fibrinogen levels in all three Groups.

			Mean fibrinogen level in mg/dl	
Sr.no.	Age Group	Control	Acute MI	Old MI
1	31-40	275	333	351.16
2	41-50	278.38	352.6	356.8
3	51-60	312.5	358.57	366.35
4	61-70	330	368.25	364
5	71-80	-	-	367.4

Fibrinogen is an acute phase protein and is elevated in infections, malignancy, postoperative procedures and in other forms of stress. Many of these clinical conditions are themselves associated with increasing risk. It is therefore difficult to decide if the clinical condition itself predisposes to thrombosis and raised fibrinogen is a secondary event, or whether the fibrinogen is itself an independent risk factor. Present study observed that both the group B and Group C had a significantly higher levels of fibrinogen. The patients of the group C, however , had mean fibrinogen (362 +12 mg/dl) more than the group B (358 =22 mg/dl). Control group A had lowest fibrinogen level (294 +34 mg/dl).

Group B and Group C did not show a significant variation, but found significantly raised as compared to control group A. it means a dynamic process is occurring in the body as regards the fibrinogen production. Whether this change is a cause or/and effect ? present study does help in giving a possible clue to the casual role of fibrinogen in evoking a thrombosis. This is apparently due to the highly increased

levels in both group B and group C. If increasing fibrinogen were to be an effect then perhaps we should not be able to see such a rise in fibrinogen level long after the attack of acute myocardial infarction, when the infarcted area is supposed to have healed by the third month of the episode of acute myocardial infarction. Thus we can say that this sustained rise in fibrinogen (362 mg+12mg/dl) one or other time with other growth factors is likely to go for thrombus formation. That explains why probably the fibrinogen levels in group B is lower than that of group C, but still significantly higher than that the control subjects, related to the consumption during coronary thrombosis. Hence we can say that despite consumption, the fibrinogen levels continue to be on higher side for two reasons – 1. High level of fibrinogen before the episode and 2. Increased production, as it is an acute phase reactant. After summing all the facts it appears that fibrinogen is probably in an increased quantity before the thrombosis occurs. Keshavamurthy CB et al 2000[10]

Mc Donald and Edgill[8] , Khare A et al[11], Lisman T et al[12], Nada Mohammad Ali et al[13] demonstrated activated coagulation in acute MI by registering increased fibrinogen, increased prothrombin activity and increased thromboplastin generation. Repeated test performed on these patients showed an unalteration which indicated hypercoagulability in these patients. Their study does confirm hypercoagulability which is more in patients of MI then angina pectoris. They also remarked that relative hypercoagulability of the blood vessel exist in some normal persons, but there is no evidence as yet that this predisposes to ischaemic heart disease. Hypercoagulation might be an effect of ischaemic heart disease rather than a cause.

In fact the study has been done to detect a hypercoagulable state in a survivors of Myocardial infarction with a view of findingout the patients who are at high risk of getting recurrent coronary thrombosis.

6. Conclusion

It has been observed in present study that there is an element of hypercoagulability in patients of acute myocardial infarction group as determined by various abnormal coagulation parameters as compared to normal healthy control.

The presence of similar degree of abnormal coagulation parameters has also been found in patients with old myocardial infarction, suggesting a hypercoaguable state which may lead to re-infarction.

Plasma fibrinogen is an independent risk factor for MI as indicated by significantly raised plasma fibrinogen level in present study.

Present study concludes coagulation parameters especially fibrinogen and PTTK have predictive value in detecting hypercoagulable state in patients of MI. at the same time BT and PT has not shown predictive changes.

Thus patients of acute and old myocardial infarction who are in state of hypercoagulability need preventive measures and appropriate treatment for reduction in mortality and morbidity from such a disastrous disease.

References

[1] Loyd – Jones et al : Heart disease and stroke statistics – 2010 update, A report from American Heart association, Circulation 2010,121(7)948-54.
[2] Deaton et al :The global burden Of Cardiovascular diseases. Eur J. Cardiovascular Nurs.2011, 10 supp2 ,5-13.
[3] Woolf,N and Davie,Mj: Myocardial variants of acute myocardial necrosis and their relationship to coronary artery thrombosis. Acta med. Scand 1980 (suppl) 642:92.
[4] Macik B.G, Ortel T.L : clinical and laboratory evaluation of the hypercoagulable states. Clin chest Med. 1995,16:375.
[5] Gheye S, Lakshmi A V, Krishni T P, Krishnaswamy K . : Fibrinogen and Homocystine levels in coronary artery disease. Indian Heart Journal, 1999, Vol51, P 499 -502.
[6] Molten S E, Vromen L, Uromen G M S, : the adhesiveness of blood platelet and thromboembolism and haemorrhagic disorders. Amer. Jour. Clinical Path 1949,19 :701.
[7] Mc Donald and Edgill M, : Blood coagulation in Ischaemic Heart Disease. Lancet, 1957, 2:457
[8] Mc Donald and Edgill M, : Blood coagulation studies during various phase of Ischaemic Heart Disease. Lancet, 1959, 1:1115.
[9] O'Brien J R, and Green P J, the investigations of the prothrombotic state, blood Coagulation and Hemostasis, Practicle guides; Jean M, Thompson.Edinb, Churcill – Livingstone. Edn 36rd ,1985.
[10] Keshavamurthy C B, Kane G R, Magdum A P, Sahoo P K, serum fibrinogen and C reactive protein levels predict major adverse cardiac events in unstable cardiac angina, Indian Heart Jr.2000, Vol 52, p 36-39.
[11] Khare. A, Ghosh K, Shetty S. Combination of thrombophilia markers in acute MI of young in Indian. Journal Med Sci,2004, September,58(9) : 381-8
[12] Lisman T et al. "Decreased Plasma Fibrinolytic Potential as a risk for venous and arterial thrombosis." Semin Thromb Hemostat. 2017 Mar,43(2): 178-184.
[13] Nada Mohammed Ali et al. "Alteration in D- dimer, Prothrombin Time 7 APTT as Thrombogenesis activity markers in patients with Acute MI." Open Journal of Blood diseases, Jan,2016, Vol.6 1-5