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Study of Platelet Functions and Prothrombotic Factors in Cerebrovascular Accidents: A Tertiary Care Centre Experience

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Abstract

Introduction: *According to WHO, globally cerebrovascular accident is third commonest cause of mortality and fourth leading cause of disease burden. Ischemic cerebrovascular accident is the most common cerebrovascular disease, most often due to atherothrombotic disease and uncommonly by disorder of hyper-coagulation. Disorders of coagulation leading to thrombosis are approximately 1% of all ischemic cerebrovascular accident and 4-8% of young cerebrovascular accident. Similarly combined deficiency lead to hypercoagulable state and rarely present as cerebrovascular accident.*[1]

Aims and Objectives: *The present study was undertaken to assess the role of platelet functions (Platelet Count, platelet volume and platelet aggregation) and antithrombotic factors (protein C, protein S and Homocysteine) in the pathogenesis of cerebrovascular accident.*

Materials and Methods*: A total of 50 patients coming to Neurology emergency with cerebrovascular accidents and 50 age and sex matched controls were included.*

The cases and controls included in this study were investigated for following parameters: Protein C and protein S were estimated by Coagulometric Assay, Homocysteine estimation was done by Semi-auto analyser, Platelet count and platelet volume were estimated by automated cell counter, Platelet aggregation with ADP by using optical Aggregometer and for PT/APTT estimation.

Results: *Levels of Protein C and Protein S were significantly decreased whereas Homocysteine was significantly raised in stroke patients.*

Mean platelet Volume was increased and platelet count reduced in ischemic stroke patients. Platelet aggregation with 5µM ADP was reduced in ischemic and hemorrhagic stroke.

Conclusion: *Protein C, Protein S, MPV and Homocysteine levels may be useful in diagnosing the ischemic stroke. Platelet count and MPV are inversely proportional to each other in case of ischemic stroke whereas platelet aggregation with 5µM ADP is reduced in both ischemic and hemorrhagic stroke.*

Key words: *Cerebral stroke, Risk factors, Platelets; Aggregation; MPV, Ischemia*

Introduction

According to WHO, globally cerebrovascular accident is third commonest cause of mortality and fourth leading cause of disease burden. Ischemic cerebrovascular accident is the most common cerebrovascular disease, most often due to atherothrombotic disease and uncommonly by disorder of hyper-coagulation. Disorders of coagulation leading to thrombosis are approximately 1% of all ischemic cerebrovascular accident and 4-8% of young cerebrovascular accident. Similarly combined deficiency lead to hypercoagulable state and rarely present as cerebrovascular accident. [1]

A prothrombotic state caused by deficiency of protein C and S, each an inhibitor of coagulation cascade, increases the risk of ischemic cerebrovascular accident in young adults. Protein S deficiency has been associated with cerebral arterial ischemia more often than protein C deficiency.

Abnormally high levels of Homocysteine in the serum, predispose to increased risk of thrombosis.

This study was aimed to assess the role of platelet functions (Platelet count, Mean platelet volume and platelet aggregation) and antithrombotic factors (protein C, protein S and Homocysteine) in the pathogenesis of cerebrovascular accident

Material and methods

A total of 50 Patients were selected after being diagnosed as a case of ischemic and hemorrhagic stroke on the basis of history, clinical examination and CT/MRI findings. Those presenting with first episode within one week were included.

Patients receiving drugs interfering with platelet functions were excluded.

Normal healthy individuals (50) who were not receiving drugs interfering with platelet functions or coagulation were selected as controls. The controls were age and sex matched with respect to the cases

History and clinical examination

A detailed history was obtained. Past and present therapeutic history was also recorded. History of smoking, alcohol intake, hypertension and diabetes was noted. General examination was done. Findings of CT/MRI noted.

Sample collection

Blood sample were collected in EDTA vial and citrate vial. Citrate vial were centrifuged at 800-1000 g for 2 min and obtained platelet rich plasma. Remaining citrated blood was centrifuged at 3000 g for 15 minutes and obtained platelet poor plasma. Platelet aggregation tests were estimated within 3 hrs after taking citrated blood. PC and MPV were estimated by automated cell counter while PC was also checked manually.

Laboratory investigation

The cases and controls included in this study were investigated for following parameters: Protein C and protein S were estimated by Coagulometric Assay, Homocysteine estimation was done by Semi-auto analyser, Platelet count and platelet volume were estimated by automated cell counter, Platelet aggregation with ADP (5µ mol) by using optical Aggregometer and for PT/APTT estimation.

Results

A total of 50 cases and 50 controls were included in this study. Irrespective of groups (cases and controls), majority of subjects were males (73%). Statistically, there was no significant difference between the two groups (χ^2=0.051 (df=1); p=0.822). Majority of cases were ischemic stroke cases (n=34; 68%). There were 16 (32%) cases of haemorrhagic stroke.

Age of subjects ranged from 24 to 65 years. Majority of subjects were aged above 50 years (78%). Only 2% of cases were aged 21-30 years. Mean age of patients was 55.30±9.94 years.

Comparison of Protein C, Protein S and Homocysteine levels among cases and controls:

No significant difference between haemorrhagic and ischemic stroke was observed for any of the three parameters studied. Mean protein C and protein S levels were found to be lower in both the types of stroke cases as compared to controls but difference was significant statistically only between stroke and controls for Protein C levels. Homocysteine levels were higher in both types of cases as compared to controls and the difference was significant statistically ($p<0.05$) **(Table 1).**

In both the stroke types and controls, lower Protein C levels was observed in younger age groups. However no association was found between Protein S and age. Gender-wise comparison between ischemic stroke and controls was significant statistically with males having more mean Homocysteine levels than females.

Haematological profile of Different types of cases and controls:

No significant difference in haematological parameters was observed between hemorrhagic stroke and ischemic stroke. Platelet Count (PC) was lower in both haemorrhagic and ischemic stroke groups as compared to controls but difference was significant statistically only between ischemic stroke and controls **(Table 2).**

Comparison of Conventional Coagulation marker levels among Different types of cases and controls:

Mean Prothrombin time (PT) was significantly lower in ischemic stroke cases as compared to hemorrhagic stroke cases and controls ($p<0.05$). No significant difference between hemorrhagic and ischemic stroke cases was observed for activated partial thromboplastin time (APTT). APTT was significantly higher in ischemic stroke cases as compared to controls **(Table 3).**

Comparison of Mean Platelet Volume (MPV) among Different types of cases and controls:

MPV was significantly higher in ischemic stroke cases as compared to both hemorrhagic stroke and control groups ($p<0.001$). Statistically, no significant difference in MPV of hemorrhagic stroke cases and controls could be seen ($p=0.054$) **(Table 4).**

Comparison of Platelet Aggregation (%) between Cases and controls:

Platelet aggregation was significantly reduced in both haemorrhagic and ischemic stroke as compared to controls ($p<0.001$). But aggregation was more reduced in haemorrhagic stroke. There was no significant difference in aggregation between ischemic and haemorrhagic stroke cases (Figure 1) **(Table 5).**

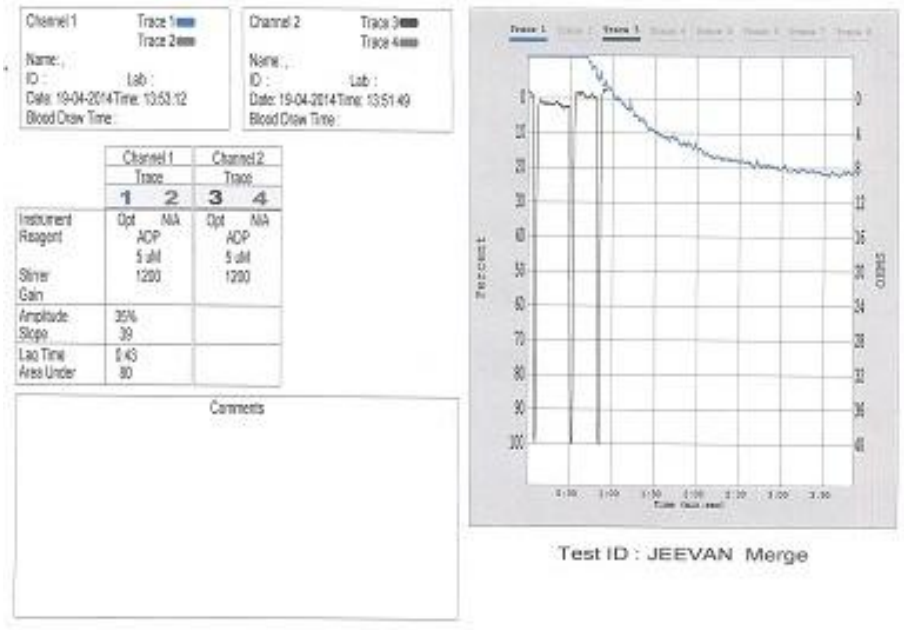

Figure 1: Platelet aggregation studies with 5µM ADP , showing markedly reduced aggregation

Table 1: Comparison of Protein C, Protein S and Homocysteine levels among cases and controls

SN	Parameter	Haemorrhagic stroke (n=16)		Ischemic stroke (n=34)		Controls (n=50)		Statistical significance (ANOVA)	
		Mean	SD	Mean	SD	Mean	SD	F	P
1	Protein C	86.5	20.7	86.4	31.8	101.5	22.0	4.313	0.016
2	Protein S	89.2	34.0	90.1	39.2	95.1	18.1	0.407	0.667
3	Homocysteine	9.0	5.0	12.4	7.3	5.6	2.5	18.811	<0.001

Between Group Comparisons (Tukey HSD test)

SN	Parameter	Hemorrhagic vs Ischemic stroke			Hemorrhagic stroke vs Control			Ischemic stroke vs Controls		
		Mean Diff.	SE	p	Mean Diff.	SE	p	Mean Diff.	SE	P
1	Protein C	0.085	7.768	1.000	-14.99	7.359	0.109	-15.08	5.695	0.025
2	Protein S	-0.862	8.934	0.995	-5.873	8.464	0.768	-5.010	6.550	0.725
3	Homocysteine	-3.392	1.528	0.073	3.458	1.448	0.049	6.849	1.120	<0.001

Table 2: Demographic and haematological profile of Different types of cases and controls

SN	Parameter	Haemorrhagic stroke (n=16)		Ischemic stroke (n=34)		Controls (n=50)		Statistical significance (ANOVA)	
		Mean	SD	Mean	SD	Mean	SD	F	P
1	Age	55.6	8.7	55.1	10.6	55.3	10.0	0.010	0.991
2	TLC (thousands)/mm^3	6.9	1.2	6.6	1.1	6.7	1.4	0.347	0.708
3	Polymorph (%)	64.7	4.5	65.7	4.6	68.3	2.4	8.529	<0.001
4	Lymphocyte (%)	32.4	4.4	31.0	3.7	29.5	1.9	6.525	0.002
5	Eosinophil (%)	2.1	0.8	1.5	1.0	1.5	1.0	2.456	0.091
6	Monocyte (%)	0.8	0.7	1.0	0.7	0.7	0.7	1.165	0.316
7	Platelet count (lakhs/cumm)	2.2	0.7	2.1	0.7	2.8	1.1	5.205	0.007

Between Group Comparisons (Tukey HSD test)

SN	Parameter	Hemorrhagic vs Ischemic stroke			Hemorrhagic stroke vs Control			Ischemic stroke vs Controls		
		Mean Diff.	SE	P	Mean Diff.	SE	p	Mean Diff.	SE	P
1	Age	0.415	3.042	0.990	0.243	2.882	0.996	-0.173	2.231	0.997
2	TLC (thousands)/mm^3	0.328	0.394	0.683	0.223	0.373	0.821	-0.105	0.289	0.930
3	Polymorph (%)	-0.989	1.105	0.645	-3.613	1.047	**0.002**	-2.624	0.810	**0.005**
4	Lymphocyte (%)	1.438	0.929	0.273	2.978	0.880	**0.003**	1.540	0.681	0.066
5	Eosinophil (%)	0.592	0.289	0.106	0.563	0.273	0.104	-0.029	0.212	0.989
6	Monocyte (%)	-0.158	0.207	0.725	0.073	0.196	0.927	0.231	0.151	0.285
7	Platelet Count (lakhs/cumm)	0.018	0.284	0.998	-0.593	0.269	0.076	-0.611	0.208	**0.012**

Table 3: Comparison of Conventional Coagulation marker levels among Different types of cases and controls

SN	Parameter	Haemorrhagic stroke (n=16)		Ischemic stroke(n=34)		Controls (n=50)		Statistical significance (ANOVA)	
		Mean	SD	Mean	SD	Mean	SD	F	P
1.	PT (sec)	13.3	4.7	10.7	2.1	13.9	1.1	19.974	<0.001
2.	APTT (sec)	35.7	11.4	37.4	3.4	33.7	2.6	4.987	0.009

Between Group Comparisons (Tukey HSD test)

SN	Parameter	Hemorrhagic vs Ischemic stroke			Hemorrhagic stroke vs Control			Ischemic stroke vs Controls		
		Mean Diff.	SE	P	Mean Diff.	SE	p	Mean Diff.	SE	P
1	PT	2.615	0.717	**0.001**	-0.663	0.679	0.594	-3.278	0.526	**<0.001**
2.	APTT	-1.650	1.583	0.552	1.992	1.500	0.383	3.642	1.161	**0.006**

Table 4: Comparison of MPV among Different types of cases and controls

SN	Parameter	Haemorrhagic Stroke (n=16)		Ischemic stroke (n=34)		Controls (n=50)		Statistical significance (ANOVA)	
		Mean	SD	Mean	SD	Mean	SD	F	P
1.	MPV	8.0	0.5	8.6	0.5	7.8	0.4	37.25	<0.001

Between Group Comparisons (Tukey HSD test)

Hemorrhagic vs Ischemic stroke			Hemorrhagic stroke vs Control			Ischemic stroke vs Controls		
Mean Diff.	SE	P	Mean Diff.	SE	p	Mean Diff.	SE	P
-0.515	0.126	<0.001	0.280	0.119	0.054	0.795	0.092	<0.001

Table 5: Comparison of Platelet Aggregation (%) between Cases and controls

SN	Group	Total			Male			Female			Signi- ficance of difference (Within group)	
		n	Mean	SD	n	Mean	SD	N	Mean	SD	"t"	"p"
1.	Cases	43	63.93	11.63	29	64.07	11.62	14	63.64	12.09	0.111	0.912
2.	Control	50	76.86	5.55	37	77.08	5.64	13	76.23	5.46	0.471	0.640
Significance of difference (between groups)		t=6.992; p<0.001			t=3.438; p=0.002			t=5.980; p<0.001				
1.	Ischemic stroke	31	65.19	11.97	18	64.94	13.39	13	65.54	10.20	0.134	0.894
2.	Control	50	76.86	5.55	37	77.08	5.64	13	76.23	5.46	0.471	0.640
Significance of difference (between groups)		t=5.923; p<0.001			t=3.333; p=0.003			t=4.749; p<0.001				
1.	Hemorrhagic stroke	12	60.67	10.49	11	62.64	8.36	1	39.00	-	-	-
2.	Control	50	76.86	5.55	37	77.08	5.64	13	76.23	5.46	0.471	0.640
Significance of difference (between groups)		t=7.481; p<0.001			t=6.645; p<0.001			-				
1.	Ischemic stroke	31	65.19	11.97	18	64.94	13.39	13	65.54	10.20	0.134	0.894
2.	Hemorrhagic stroke	12	60.67	10.49	11	62.64	8.36	1	39.00	-	-	-
Significance of difference (between groups)		t=1.149; p=0.257			t=0.512; p=0.613			-				

Table 7: Association of Mean HCY levels with age

SN	Age Group	Overall (n=100)			Hemorrhagic stroke (n=16)			Ischemic stroke (n=34)			Controls (n=50)		
		N	Mean	SD	n	Mean	SD	n	Mean	SD	n	Mean	SD
1.	≤50	22	8.25	4.66	4	10.13	4.57	7	10.10	6.04	11	6.39	3.13
2.	51-60	41	9.06	6.64	5	9.48	6.97	16	13.31	7.88	20	5.55	2.31
3.	61-70	37	7.95	5.71	7	8.11	4.25	11	12.65	7.55	19	5.16	2.42
ANOVA (F)		0.362			0.208			0.459			0.813		
P		0.697			0.815			0.636			0.450		

Mean platelet volume and count: - comparison between present and previous studies

		Ischemic stroke cases	controls	P value
D'Erasmo et al. (1990)	MPV	11.26 +/- 1.29	8.93 +/- 0.93	P<.001
	PC($X10^9$)/L	213.61±65.65	299.52±60.61	P<.001
T.O.Malley et.al. (1994)	MPV (fL)	11.3	10.1	P<.001
	PC($X10^9$)/L	255	299	P<0.01
Farahnaz et al. (2013)	MPV	9.36±0.95	8.55±0.65	P=0.020
	PC($X10^9$)/L	283.7±59.2	238±89.2	P<0.001
Ozlem Sahin Balcik et al (2013	MPV	8.6	**7.7**	P=0.001
	PC($X10^9$)/L	224.80	290.94	P=0.005
Present study	MPV	8.6	7.8	P<0.001
	PC($X10^9$)/L	220	280	P=0.012

Association of Mean Homocysteine levels with age:

No significant association between Homocysteine and age was observed either for overall as well as all the three groups independently (p>0.05).

Although in ischemic stroke cases with increasing age an increasing trend was observed for Homocysteine levels, but the difference was statistically not significant.

In cases of haemorrhagic stroke no statistically significant correlation was found with Homocysteine **(Table 6).**

Discussion

In the present study various hemostatic parameters (platelet aggregation, MPV and Platelet Count, protein C, S and homocysteine) were evaluated in 50 cases of ischemic and hemorrhagic stroke and 50 age and sex matched controls.

Our study was in concordance with the study of D'Erasmo et al (1990), T.O.Malley et al (1994), Ozlem Sahin Balcik et al (2013), farahnaz et al (2013).[2-5]

D'Erasmo et al. performed a study on patients with ischemic cerebral stroke in order to obtain information on serial changes of some platelet parameters and to test their prognostic significance. Platelet count, obtained within 48 h after cerebral stroke, was significantly lower than in the control group, reaching the normal level on the ninth day and thereafter. The MPV was significantly greater than in the controls, and normalization generally occurred on the forty-fifth day. The mean PC was significantly lower in the patients who died than in those who survived (P less than 0.025 and P less than 0.05 respectively on the first to second and fourth day after stroke). The reduction of PC and the increase of MPV appear to be related to an increased platelet consumption in the stroke area, associated with an in vivo platelet activation, as larger platelets are more responsive to platelet activity and aggregability tests. They concluded that lower mean PC observed in the patients who died suggests that the platelet value might be considered as a prognostic index of cerebral stroke.[2] **T.O Malley et al**. found that MPV was higher in acute stroke (11.3 compared with 10.1 fL in control subjects; $P<.001$, Student's t test). In addition, PC was reduced in stroke patients (255×10^9/L) compared with control subjects (299×10^9/L; $P<0.01$). There was a significant negative ($r=-.37$, $P<0.003$; n=58) correlation between PC and MPV in stroke patients. There was no such relation in control subjects. [3] **Ozlem Sahin Balcik et al.** conducted a study on 50 patients and concluded that PC was inversely associated with MPV.[4] **Farahnaz Ghahremanfard** concluded that MPV is associated with ischemic stroke severity and has a high value for discriminating severe from mild ischemic stroke. [5]

Platelet aggregation and ischemic stroke

In present study the mean platelet aggregation was (%) 65.19±11.97 for all cases of ischemic stroke which was significantly lower as compared with 76.86±5.5 for all controles (n=31; p<0.001). These results were similar to the study of Tohgi H et al. (1991).[6] **Tohgi H et al** compared whole blood platelet aggregation and MPV during the acute, subacute, and chronic periods of cerebral thrombosis in 22 patients with 29 controls. During the acute and subacute periods, platelet aggregation, PC, platelet crit, and MPV were significantly less in the patients than in the controls. There results suggest that platelet aggregation is reduced during the acute period due to the consumption of platelets during thrombogenesis and the remaining individual platelets are hyperactive. Platelet consumption during the acute period increases with stroke size.

Our study was in discordance with study done by Kenneth K et al, Nicholas M Smith et al, Rajiv Joseph et. al.[7-9]. There results suggested that patients with transient ischemic attacks had increased platelet aggregation.

Platelets in acute haemorrhagic stroke

The mean platelet aggregation (%) was 60.67±10.49 for hemorrhagic stroke which was

significantly lower than compared with 76.86±5.5 for all controls (n=12; p<0.001). In 4 patients aggregation was not done because of decreased PC (<150x10^9/l). Since hemorrhagic stroke accounts for only about 15% of all strokes it is unsurprising to find that relatively little research into the role of platelets in this syndrome has been carried out. Our study was similar to the study done by **Gaur SP et al.** [10] They studied twenty patients of transient ischaemic attacks, 22 of thrombotic stroke and 26 of hemorrhagic stroke and 21 control subjects. They concluded that Mean platelet aggregation values were significantly lower in hemorrhagic stroke patients as compared to controls. Conversely, Lui and colleagues found that aggregation was increased in hemorrhagic stroke and also noted significantly elevated levels of plasma β-TG (though not as high as in non-hemorrhagic stroke) compared with controls. These findings possibly reflect pre-existing ischaemic vascular disease or other vascular risk factors present in our patient cohort. Hence, the role of platelets in the pathogenesis of haemorrhagic stroke is far from clear. That elevated levels of β-TG are present post-stroke suggests that platelets may be important in controlling the bleeding.[11]

Protein C and Protein S

Mean protein C level was 86.4±31.8 in cases of ischemic stroke which was found to be significantly lower when compared with 101.5±22 for controls (n=34,p=0.016). Mean protein S level was 90.1±39.2 in cases of ischemic stroke which was found to be significantly lower when compared with 95.1±18.1 for all controls. This level was not significant statistically (p=0.667). There was no significant correlation between hemorrhagic stroke cases in protein C & S levels. In our 34 patients of ischemic stroke 4 patients were having decreased protein C and S both while only 2 were having isolated protein S deficiency. Only one was having isolated protein C deficiency. The patients having decreased protein C and S were chiefly of younger age group (4 patients aged 24-45 years). Our study was similar to study done by **Stanford K. Shu et al.** found that very low free protein S (<15% normal total protein S) was more frequent among patients than control subjects (11% versus5%), but this trend failed to reach statistical significance.[12] Our study showed similar results to study done by **F Barinagarrementeria et al.** They studied 36 patients under 40 years of age and found that in 10% to 23% patients no cause for stroke was found. Although 4% of cerebral strokes in the young can be attributed to hematologic disturbances that predispose to thrombosis. 9 patients (25%; 5 women, 4 men) had a deficiency of one natural anticoagulant. In these isolated protein S deficiency was present in 5 cases. Only one was having isolated protein C deficiency.[13]

Homocysteine

The mean homocysteine level in cases of hemorrhagic stroke (n=16) was 9.04±5.01 which was significantly higher when compared with 5.59±2.54 for controls (n=50, p=0.001). The mean homocysteine level in all male cases of hemorrhagic stroke (n=16) was 9.27±5.10 which was significantly higher when compared with 5.59±2.54 for all controls (n=50, p=0.001). For females comparison could not be done as only one female in this group. The mean homocysteine level in cases of ischemic stroke (n=34) was 12.43±7.73 which was significantly higher when compared with 5.59±2.54 for controls (n=34,p<0.001). The mean Homocysteine levels were 13.49±8.21 for male cases of ischemic stroke which was significantly increased compared with 5.55±2.30 for all control males. The mean Homocysteine levels were 10.73±5.49 for female cases of ischemic stroke which was significantly increased compared with 5.70±3.22 for all control females. Present study was similar to the study of Zolianthanga Zongte et.al, AG Bostom et al, Gudrun Boysen et al and Ralph L. Sacco, MD et.al.[1, 14-16]

Conclusion

Ischemic stroke are more common than hemorrhagic stroke. There is male predominance

in cases. Deficiency of protein C and S is associated with ischemic stroke but not a common cause of it. However if these are deficient, manifestations appear in younger age group. Increased levels of Homocysteine are associated with ischemic stroke; however it may also increase in cases of hemorrhagic stroke. High MPV is associated with ischemic stroke and platelet count is inversely proportional to it. Aggregation is more reduced in cases of hemorrhagic stroke as compared to ischemic stroke.

However being a time bound study and having small sample size significance of all these parameters and association with diagnosis need to be explored by more studies having larger sample size and good follow up with a more time period.

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