Original Research Article

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A cross-sectional study of impact of dyslipidemia in stroke

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ABSTRACT

Background: Stroke is defined as abrupt onset of symptoms and/or sign of focal and global loss of cerebral function lasting for at least 24 hrs with no apparent cause other than of vascular origin. Dyslipidemia in stroke is not widely studied especially from the population of Northeast India (Manipur). Moreover, most prior studies did not specifically compare hemorrhagic stroke risk among those with elevated lipid levels to those with optimal or near optimal lipid levels. Therefore, we studied the levels of different Lipids in stroke patients (hemorrhagic and ischemic) to understand its role in pathogenesis of stroke.

Methods: This cross-sectional study was conducted in RIMS, Manipur from 2017-2019 and included 185 patients above 18 years with stroke within 48 hrs of onset of symptoms. NCCT brain and serum lipids, other related blood investigations were performed.

Results: We found that serum total cholesterol, LDL-C and triglycerides are significantly higher in infarction patients with average levels of 210.82 mg/dl, 143.64 mg/dl and 151.50 mg/dl respectively which is statistically significant (p<0.001). The average serum total cholesterol, LDL-C and triglycerides are significantly lower in ICH patients with average levels of 143.34 mg/dl, 84.67 mg/dl and 113.94 mg/dl respectively which is statistically significant. (p<0.001).

Conclusions: We concluded that raised level of serum total cholesterol, serum LDL-C, serum triglyceride are associated with cerebral infraction (p=0.001) and lower level of serum total cholesterol, serum LDL-C, serum triglyceride are associated with cerebral hemorrhage (p=0.001). Thus, serum lipid levels should be carefully monitored to prevent life threatening stroke.

Keywords: Cerebro vascular accidents, Hemorrhage, Infarction, Lipid profile, Stroke

INTRODUCTION

Stroke is defined as abrupt onset of symptoms and/or sign of focal and global loss of cerebral function lasting for at least 24 hrs with no apparent cause other than of vascular origin. Stroke is diagnosed based on history, clinical findings and the brain imaging. Stroke is classified on the basis of its etiology as either ischemic or hemorrhagic. In India, the prevalence of stroke is estimated as 203 per

100,000 above 20 years. In India, stroke incidence is 105 to 152/100,000 persons per year.³ Ischemic stroke accounts for about 85% of cases, primary intracerebral hemorrhage (ICH) for 10% and subarachnoid hemorrhage (SAH) for the remaining 5%.⁴

The role of lipid and lipoprotein biomarkers, such as of total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and triglycerides (TG), in risk prediction of

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ischemic heart disease is well established 1,2,4 but their value as independent predictors for ischemic stroke is less certain.⁵

In most epidemiological cohorts, the relationship between lipids and stroke is complex and varies by stroke subtype, with associations strongest for atherosclerotic subtypes. Conversely, there is an increased risk of ICH at low cholesterol levels, and there is evidence that small vessel disease may share a similar profile of inverse association with lipid levels. The associations also depend on the specific lipid component considered, with the data strongest for TC and LDL-C.⁶

Most prior studies had limited number of individuals with elevated lipid levels and did not specifically compare hemorrhagic stroke risk among those with elevated lipid levels to those with optimal or near optimal lipid levels. Hence, this study was undertaken with the aim to study the association of various components of lipid profile in cerebrovascular accident (CVA) and difference in subtypes of stroke as recent study have shown that low serum lipid levels also increases the risk of CVA.

METHODS

This cross-sectional study was conducted in RIMS, Imphal and includes those admitted in Medicine Wards or attending Medicine OPD. for a period of 2 years, from1st September 2017 to 31st August 2019. Patients diagnosed to have CVA either clinically or radiological examinations were taken for the study within 48 hours of onset of symptoms, based on the following criteria.

Inclusion criteria

Patients >18 years, diagnosed to have CVA both Ischemic and hemorrhagic.

Exclusion criteria

Exclusion criteria for the selection of process were transient ischemic attack, Patient already on lipid lowering drugs like statins, fibrates, any genetic disorder causing hypercholesterolemia like familial hypercholesterolemia etc, chronic alcoholics, nephrotic syndrome.

Sample size

Sample size (N) was calculated using the formula:

$$N = \frac{Z^2 PQ}{L^2}$$

Where,

Z = Critical standard score and taken as 1.96

P = Prevalence of cerebrovascular accidents (0.424%)

O = 100-P

L= Absolute allowable error (taken as 1)

$$N = \frac{1.962 \times 0.424 \times (100 - 0.424)}{1^2} = 168$$

Expecting non-response rate of 10% final sample size is 185. Prevalence of stroke in India is p=0.424% from Pandian JD et al 8 study.

Study variable

The study included the demographic data like age, sex, symptoms, CNS examination, NCCT brain, lipid profile, complete hemogram, liver function test and kidney function test.

Operational definitions

Cerebrovascular Accidents were diagnosed from NCCT Brain Imaging, Dyslipidemia was diagnosed based on the NCEP-ATPIII Guidelines 9, T. Cholesterol: >200 mg% HDL: <40 (Male), <50 (Female), LDL: >100 mg% TG: >150 mg%

Sample collection and procedure

For diagnosis of CVA, NCCT Brain was done using PHILIPS BRILLIANCE 64 slice CT Axial Scanning with orbital view with slice thickness 3 mm, 120 kvp, 250 mA, rotation time 0.8 sec. With the participants consent blood samples were collected for serum lipid profile and other routine investigations. Serum lipid profile was done by using RANIBOX XIMOLA auto-analyser in RIMS biochemistry lab.

Statistical analysis

Statistical analysis was performed by using IBM: SPSS Statistics Version 21 and MINITAB Release 11.12, 32 Bit. Out of the parameters considered, all numerical/continuous variables were presented as Mean±SD (standard deviation) and those of qualitative/categorical variables were again described as number of cases and percentages. Independence Sample t-test, Fischer's exact T tests, Chi Square test were used and the p values of <0.05, <0.01 and <0.001 are taken as the cut off values for significant, highly significant and very highly significant respectively.

RESULTS

We enrolled 185 cases of CVA Patients both ischemia and ICH, above 18 years fulfilling the criteria. The average age of the patients was found to be 62.06 years with majority of them falling in the 55–64 year age group and minimum and maximum age were 48 and 80 years respectively. Only on the age group of 45-54 years.

ICH is more commonly seen than Infarct and in all other age group Infarct was more common than ICH among study population. Males are predominantly affected in both types of CVA, with Infarct (73%) and ICH (72.9%) as compared to females (50,7%) but no significant association with gender was observed (p=0.993). Though non-vegetarian were predominantly involved in both CVA, no significant association with dietary habits. (p=0.923) There exist strong association of hypertension as high risk factor with both CVA (p=0.003) (Table 1).

Table 1: Baseline characteristics of the study subjects (n=185).

	Results n (%) 1				
Parameters	Infract n=100(%)	ICH n=85(%)	p-value		
Age (in years)					
45-54	12 (12)	13 (15.3)			
55-64	48 (48)	41 (48.2)	0.550		
65-74	35 (35)	27 (31.8)	0.550		
≥75	5 (5)	4 (4.7)			
Gender		-			
Male	135 (73)	135 (73)	0.993		
Female	50 (27)	50 (27)	0.993		
Diet					
Non vegetarian	91 (91)	77 (90.6)	0.923		
Vegetarian	9 (9)	8 (9.4)			
Religion		-			
Christian	17 (17)	32 (37.6)			
Hindu	65 (65)	32 (37.6)			
Muslim	18 (18)	12 (14.1)	-		
Others	0 (0)	9 (10.6)			
Hypertension					
Yes	88 (88)	60 (70.6)	P=0.003		
No	12 (12)	25 (29.4)	1 -0.003		
Presenting symptoms Weakness of limb					
Left sided	44 (44)	55 (64.7)	P<0.005		
Right sided	55 (55)	30 (35.3)	1 <0.005		
Slurring speech					
Yes	90 (90)	75 (88.2)	P=0.700		
No	10 (10)	10 (11.8)			

Weakness of limbs are significantly associated with both cerebral infarction and ICH with p value <0.001. There is no significant association between distribution of slurring of speech and both types of CVA (Table1). Patients admitted with severe weakness of muscle with power of limb 1/5 shown better improvement in muscle power than who admitted with less weakness like power of limb 3/5 (Table 2 and 3). Power of limbs are significantly associated with both cerebral infraction and ICH (p<0.001). Patients admitted with severe weakness of muscle with power of limb 1/5 shown better

improvement in muscle power than those with power of limb 3/5 and cerebral infarction patients improved better than ICH patients. Among study population cerebral infarction patients improved better than ICH patients.

Table 2: Power of limbs and distribution at admission in two groups of patients studied (n=185).

Motor system Examination power Limbs	Infract (%)	ICH (%)	Total N (%)	P value
Left upper & lower limb POWER: 1/5	49 (49)	40 (47.1)	89 (48.1)	
Left upper & lower limb POWER: 2/5	0 (0)	36 (42.4)	36 (19.5)	
Right upper & lower limb POWER: 2/5	20 (20)	0(0)	20 (10.8)	<0.001
Right upper & lower limb POWER: 3/5	31 (31)	9 (10.6)	40 (21.6)	
Total	100 (100)	85 (100)	185 (100)	

Table 3: Power of limbs at Discharge distribution in two groups of patients studied (n=185).

Motor system examination power Limbs	Infract (%)	ICH (%)	Total N (%)	P value
Left upper & lower Limb POWER: 1/5	0 (0)	17 (20)	17 (9.2)	
Left upper & lower Limb POWER 2/5	49 (49)	11 (12.9)	60 (32.4)	
Left upper & lower Limb POWER: 3/5	0 (0)	48 (56.5)	48 (25.9)	<0.001
Right upper & lower limb POWER 3/5	51 (51)	9 (10.6)	60 (32.4)	
Total	100 (100)	85 (100)	185 (100)	

In NCCT brain the most commonly involved area in both CVA was basal ganglia and it is significantly associated with both infarction and ICH (p<0.001). The most common vessel involved was middle cerebral artery in both CVA and it is statistically significant. (p<0.003) (Table 4). In biochemical investigations, KFT, LFT, RBS except serum urea, other tests are not significantly associated with CVA (Table 5).

Table 4: ECG/NCCT brain/territory/ECHO/X-ray chest distribution in two groups of patients studied.

Parameters	Infract (%) (n=100)	ICH (%) (n=85)	Total (%) (n=185)	P value
ECG			•	
LVH	1 (1)	1 (1.2)	2 (1.1)	1.000
NAD	99 (99)	84 (98.8)	183 (98.9)	1.000
NCCT brain				
Left internal capsule infarct	56 (56)	0 (0)	56 (30.3)	
Right basal ganglia hemorrhage	0 (0)	85 (100)	85 (45.9)	0.001**
Right internal capsule infarct	42 (42)	0 (0)	42 (22.7)	<0.001**
Right internal capsule & corona radiata	2 (2)	0 (0)	2 (1.1)	
Territory				
Left MCA territory	56 (56)	30 (35.3)	86 (46.5)	
Right MCA tTerritory	42 (42)	55 (64.7)	97 (52.4)	0.003**
Right cortical lacunar infarct	2 (2)	0 (0)	2 (1.1)	
Artery involved				
LEFT MCA	56 (56)	30 (35.3)	86 (46.5)	
RIGHT CO	39 (39)	39 (45.9)	78 (42.2)	0.002**
Right MCA	5 (5)	16 (18.8)	21 (11.4)	
Echo				
Grade 1DD	1 (1)	1 (1.2)	2 (1.1)	
LVH	2 (2)	2 (2.4)	4 (2.2)	1.000
NAD	97 (97)	82 (96.5)	179 (96.8)	
X-ray chest				
NAD	100 (100)	85 (100)	185 (100)	1.000
Yes	0 (0)	0 (0)	0 (0)	-1000

In NCCT brain the most commonly involved area in both CVA was basal ganglia and middle cerebral artery was the commonly involved vessel and is significantly associated with both CVA.

Table 5: Comparison of clinical variables in two groups of patients studied (N=185).

variables	Infract	ICH	P value	Total
Hemoglobin (g/dl)	13.51±1.32	13.41±1.27	0.608	13.46±1.29
Total Count cells/mm ³	6649.00±1211.77	6532.94±1212.28	0.517	6595.68±1210.09
Platelet Count cells/mm ³	200979.00±35089.04	200069.41±35493.17	0.861	200561.08±35182.06
Total bilirubin mg%	0.84 ± 0.19	0.82±0.19	0.686	0.83±0.19
Total protein g%	6.55±0.43	6.50±0.45	0.466	6.53±0.44
Serum albumin g%	3.98±0.31	3.94±0.33	0.376	3.96±0.32
Serum globulin g%	2.58±0.27	2.58±0.29	0.993	2.58±0.28
Serum Urea mg/dl	43.21±5.08	40.76±6.34	0.004**	42.09±5.81
Serum Creatinine mg/dl	0.98±0.13	0.96±0.15	0.330	0.97±0.14
RBS mg/dl	124.84±19.41	126.48±18.62	0.560	125.59±19.01

**In biochemical investigations, except serum urea, other test are not significantly associated with CVA.

Table 6: Lipid parameters distribution in two groups of patients studied.

Lipids	Infract n=100(%)	ICH n=85(%)	Total n= 185(%)	P value
Total cholester	rol (mg/dl)			
<200	36 (36)	85 (100)	121 (65.4)	
200-240	64 (64)	0 (0)	64 (34.6)	<0.001**
>240	0 (0)	0 (0)	0 (0)	
LDL (mg/dl)				
<100	0 (0)	8 (9.4)	8 (4.3)	<0.001**

Continued.

Lipids	Infract n=100(%)	ICH n=85(%)	Total n= 185(%)	P value
100-120	94 (94)	77 (90.6)	171 (92.4)	
>120	6 (6)	0 (0)	6 (3.2)	
HDL (mg/dl)				
<40	56 (56)	41 (48.2)	97 (52.4)	
40-60	44 (44)	44 (51.8)	88 (47.6)	0.305
>60	0 (0)	0 (0)	0 (0)	
TGL (mg/dl)				
<150	32 (32)	83 (97.6)	115 (62.2)	
150-500	68 (68)	2 (2.4)	70 (37.8)	<0.001**
>500	0 (0)	0 (0)	0 (0)	_

Table 7: Comparison of lipids in two groups of patients studied (N=185).

Variables	Infract	ICH	Total	P value
Total Cholester ol (mg/dl)	210.82 ±28.23	143.34 ±20.99	179.82 ±42.04	<0.001 **
LDL	143.64	84.67	116.55	<0.001
(mg/dl)	±24.87	±15.25	±36.16	**
HDL	34.44	34.42	34.43	0.988
(mg/dl)	±6.92	±8.17	±7.50	
TGL	151.50	113.94	134.24	<0.001
(mg/dl)	±39.4	±29.71	±39.88	**

In our study we found that serum total cholesterol, LDL-C and triglycerides are significantly higher in infarction patients with average levels of 210.82 mg/dl, 143.64 mg/dl and 151.50 mg/dl respectively which is statistically significant (p value<0.001). The average serum total cholesterol, LDL-C and triglycerides are significantly lower in ICH patients with average levels of 143.34 mg/dl, 84.67 mg/dl and 113.94 mg/dl respectively which is statistically significant. (p value <0.001) (Table 6, 7).

DISCUSSION

Dyslipidemia as a major risk factor for CVA has been a recurring area of research worldwide. Recent studies show that not only raised lipid level but also low lipid levels are risk factor for ICH. It is being suggested that there is difference in the lipid levels between Ischemic and ICH. Our study was conducted to ascertained whether this relationship also exist in Indian subcontinent and especially in the population of central India.

ICH

In our study,9.4% of ICH patients having LDL-C level <100 mg/dl. Most of patients (90.6%) of ICH have LDL-C level of 100 -160 mg/dl and major portion of Infarction patients (94%) also fall in the same LDL-C range. The findings were statistically significant with p<0.001.

Similar correlation where found by Gurol et al10 who reported that participants with LDL-Concentrations <100 mg/dl had a significantly higher risk of developing ICH. Adjusted hazard ratios were 1.65 (95% confidence interval [CI] 1.32–2.05) for LDL-C concentrations of 70 to 100 mg/dL and 2.69 (95% CI 2.03–3.57) for LDL-C concentrations <50 mg/dl. These results indicate that patients with low LDL-C <100 mg/dl has higher chance of developing ICH.

Infarct

In our study, 64% of cerebral infarction patients have total cholesterol 200-280 mg/dl, 94% have LDL-C between 70-120 mg/dl and 68% have triglyceride between 150-500 mg/dl. The findings were statistically significant with "P" value of 0.001. Argade DS et al who studied lipid profile of 90 CVA patients including both cerebral infraction and hemorrhage found that total cholesterol, triglyceride and LDL- cholesterol levels were significantly raised while HDL- cholesterol levels were low in ischemic stroke than control.² Regarding TG, a direct association between increased triglyceride levels and ischemic stroke (adjusted Relative Risk= 1.05; 95% CI, 1.03 to 1.07) for each 10-mg/dl increase in triglycerides levels were reported in a meta-analysis involving 64 studies.¹¹ .Many other studies have shown that triglycerides levels are inversely associated with hemorrhagic stroke risk. 12,13 Another study showed higher TC being associated with higher risk of ischemic stroke, whereas lower levels were associated with higher risk of brain hemorrhage.⁶

Our study also showed that 52.4% of patients having HDL-C <40 mg/dl are affected by either cerebral infarction or ICH but it is not significantly associated. (p=0.305). However, Pikula et al who studied participants of Framingham Study for 9 years for incident of cerebral infarction reported HDL-C <40 mg/dl and TC/HDL ratio >5 were associated with increased risk of cerebral infarction.⁵ It is well known that HDL has an inverse correlation with ischemic stroke.⁶ There is 11-15% decreased risk of ischemic stroke for each 10 mg/dl increase in HDL-C 14. Of the 2 types of HDL:HDL-2 is larger and less dense and HDL-3 is

smaller and denser. HDL3 is more important than HDL2 as it inhibit formation of atherosclerosis in vessels by inhibiting LDL oxidation and thereby protects against stroke such as lacunar infarcts and ICH15

Mention may be made here about a rarer lipid molecule, lipoprotein A (LPA). It is found that in Atherosclerosis Risk in communities, Lp(a) levels ≥30 mg/ml were associated with increased risk of ischemic stroke in black and white women, but not in white men.⁶ Lp(a) levels ≥30 mg/dl at baseline were associated with an increased risk of ischemic stroke. This association was more pronounced among men and blacks.⁶

Hyperlipedemia in CVA: mechanism

In brain ischemia, increased lipids cause accelerated endothelial injury, oxidative stress to neurons and subsequent inflammation and neuronal loss in animal studies. Apo lipoprotein E (ApoE) is an important gene which is involved in metabolism and transport of lipids. Its absence leads to hyperlipedmia and resultant accelerated atherosclerosis. At the time of ischemic stroke, it worsens the neuronal loss and death by damaging the neurovascular coupling, decreased cerebral blood flow, dysregulates the reflex vasodilator mechanism, and worsens cerebral perfusion deficits. Moreover, hyperlipidemia also increases impairs Blood Brain Barrier permeability, augments brain parenchymal swelling in acute ischemia through lipid peroxidation, matrix metalloproteinases (MMPs) activation, and RhoA overactivation in wildtype mice, and not ApoE-/- mice. It also instigates inflammatory cascades in form of endothelial cell activation, and infiltration of the circulating immune cells into the brain, platelet activation and adhesion to the injured endothelial cells.¹⁶

Lipids and stroke subtypes

In our study, most of patient diagnosed to have infarct of various degree were found to have moderately elevated lipids levels. Moderately high Total cholesterol, LDL triglycerides levels where found in 64%, 94% and 68% of the patients respectively. On the contrary, in our study, ICH patients had low or almost normal lipids levels. All the ICH patients (100%) had normal total cholesterol levels and whereas 97.6% of ICH patients had normal trigylcerides levels. Many literatures suggested significant association between lipids and large vessel occlusive/atherosclerosis strokes (OR, 3.2).¹⁷ However for dyslipidemia and lacunar stroke, variable association exist. Few studies showed lacunar stroke being associated with levels of TC17 and LDL18 while many other showed no relationship between them. 19,20 Regarding the small vessel disease (White matter hyperintensity (Leukoariosis), cerebral microbleeds), it is inversely proportional to lipids such that decreased lipids predisposes to hampers functions of small vessels.²¹⁻²³

Limitations

Further studies are needed to confirm our finding and since this is as cross-sectional study and hospital-based territory care study so there may be chances of selection bias with confound factor. Hence, a long-term pros pective study including peoples from various ethnic groups and finding out the target serum lipid levels for every age group and specific diseases is the need of the hour.

CONCLUSION

The concept of aggressive management of dyslipidemia is changing dramatically in the past few years, as results of evidences from recent studies, very low lipid levels are also harmful to health. In developing countries like ours where there is very high prevalence of dyslipidemia because of various reasons like improper dietary habits, unhealthy life style etc. there should be a specific cut off level of lipids for treatment. In this study we found that raised level of serum total cholesterol, serum LDL-C, serum triglyceride are associated with cerebral infraction (p=0.001) and lower level of serum total cholesterol, serum LDL-C, serum triglyceride are associated with cerebral hemorrhage (p=0.001). On the other hand, there is no relationship between serum HDL-C levels and both CVA in our study. Thus, serum lipid levels should be carefully monitored and it should be maintained within the normal range as there exist hazards of low serum lipid levels.

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Institutional Ethics Committee

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