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Original Article

Internal Medicine Section

Is Low Cholesterol a Predisposing Factor for Primary Intracerebral Haemorrhage? A South Indian Perspective

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ABSTRACT

Introduction: Stroke is an important cause of mortality and morbidity in low-income and middle-income countries like India. Primary Intracerebral Haemorrhage (PICH) refers to Intracerebral Haemorrhage (ICH) in the absence of a single clear underlying lesion. Cholesterol levels are inconsistently associated with risk of ICH.

Aim: To assess their relationship between lipid parameters and PICH.

Materials and Methods: One hundred sixty patients with PICH were retrospectively recruited and compared with apparently healthy subjects. Low cholesterol was defined by Total Cholesterol (TC) <200 mg/dL; Low Density Lipoprotein Cholesterol (LDL-C) <100 mg/dL; High Density Lipoprotein Cholesterol (HDL-C) <40 mg/dL; and Triglyceride (TG) level <150 mg/dL.

Results: Out of 160 patients recruited majority of the patients were males (n=122). Mean age was 53.47±9.33 years. Most frequent risk factor of PICH was hypertension (72.5%). Most common site of bleed was in basal ganglion (n=63). The proportion of PICH patients with low TC was significantly higher than control (81.9% vs. 70%). TG levels and LDL-C were significantly low in PICH compared with controls (p-value<0.0001). Mean TC in PICH was 159 mg/dL vs. 180 mg/dL (p-value<0.0001); Mean TG level was 114 mg/dL vs. 168 mg/dL (p-value<0.0001); Mean LDL-C was 93 mg/dL vs. 119 mg/dL (p-value<0.0001). In a subgroup analysis, among older age (≥50 years) mean TC, TG levels and LDL-C were significantly low in PICH group compared to controls (p-value<0.0001). In multivariate analysis presence of low value of TG, LDL-C and TC remained a significant risk factor of PICH. Odds ratio for TG was 5.55 with 95% Confidence Interval (CI) of 3.295 to 9.36; odds ratio for LDL-C was 3.81 with 95% CI of 2.392 to 6.084.

Conclusion: Our present study confirms low cholesterol as risk factor for PICH especially in older individual and both sexes.

Keywords: Brain, Cholesterol levels, Stroke

INTRODUCTION

Stroke is the second leading cause of death worldwide, and one of the leading causes of disability [1]. ICH accounts for approximately 10%-20% of all strokes [2]. Stroke is an important cause of mortality and morbidity in low-income and middle-income countries like India. The estimated prevalence rate of stroke in India ranges, 84-262/100,000 38 in rural and 334-424/100,000 population in urban areas [3]. The pooled data incorporating all the studies from India reveal haemorrhagic stroke in 20-32% cases [4,5] which is higher than western registry. In Asian societies cholesterol level is low and this may contribute to higher frequency of ICH, in addition to other risk factors [6].

ICH occurs when a blood vessel within the brain parenchyma ruptures. ICH can also occur as a complication of vascular malformation or tumour or venous thrombosis, or bleeding diathesis which is then referred to as secondary intracerebral haemorrhage. PICH refers to ICH in the absence of a single clear underlying lesion. PICH is the most frequent type of ICH. Evidences shows that hypertension is the single most important risk factor for ICH [7,8]; followed by cerebral amyloid angiopathy [9]. High alcohol intake is another risk factor for ICH [7,8].

Association of altering lipid level such as TC, TG, LDL-C and HDL-C in patients with ICH were demonstrated previously by various studies [7-15]. Most studies have shown that lower TC [12-15] and lower LDL-C [8,12] and higher HDL-C [8,12] are associated with increased risk of ICH, however, the relationship between TG and ICH was observed to be controversial. Present study is the largest case series from India that depicts association of lipid subfractions with PICH patients.

MATERIALS AND METHODS

This research was a retrospective, case-control, single centre study conducted between January 2014 and May 2017. PICH was defined as sudden onset of neurological event with Computed Tomography (CT) brain showing ICH in the absence of single clear underlying lesion. Low cholesterol was defined by Total Cholesterol (TC) <200 mg/dL; Low Density Lipoprotein Cholesterol (LDL-C) <100 mg/dL; High Density Lipoprotein Cholesterol (HDL-C) <40 mg/dL; and Triglyceride (TG) level <150 mg/dL. The above reference cut-off was considered as per a previous study [16]. Atherogenic Index of Plasma (AIP) was calculated as log (TG/HDL-C) [17]. In patients on statin more stringent cut-off was considered for TC i.e., ≤160 mg/dL in concordance with a previous study [13].

Two hundred fifteen patients were admitted with a diagnosis of ICH during this period. Patients were considered eligible when they met the following inclusive criteria: patients with age ranging from 18-80 years; diagnosis of PICH where secondary causes of haemorrhage such as trauma, tumour bleed, vascular malformation, and use of oral anticoagulant were ruled out based on Magnetic Resonance Imaging (MRI) brain and history; all fasting lipids done within 48 hours of admission. After initial review 160 patients were enrolled as case. Patients with lobar haemorrhage had undergone vascular imaging to rule out other causes of haemorrhage. All the patients with PICH had undergone routine bleeding parameters including platelet count and prothrombin time. Control groups consisted of 160 apparently healthy individuals prospectively recruited, who came for health check-up, and were age and sex matched to patient group.

Baseline characteristics of age, sex, smoking history, alcohol use, and vascular risk factors including diabetes mellitus, hypertension,

prior stroke, Coronary Artery Disease (CAD) were assessed using a proforma.

STATISTICAL ANALYSIS

All data were analysed by means of SPSS 17.0. All data of cholesterol fraction were shown as the mean and Standard Deviation (SD) and compared between case and control group using unpaired t-test. Differences in baseline factors (sex, age, vascular risk factors) and proportion of individual with low cholesterol among groups were compared using 2×2 tables with Fishers-exact test for significance. Odds ratio was calculated for proportion of patients with low cholesterol. All CI were set at 95%. Multiple logistic regression analysis was performed. Potential covariates examined were age, alcohol use and presence or absence of hypertension. All significance tests were two-sided, with $p<0.05$ designated as significant.

RESULTS

Baseline Characteristics of the Patient

Of the 160 patients (PICH group), the median age was 54 years, mean age was 53.47±12.36 years and 122 (76.2%) patients were males. A total of 107 (66.8%) patients were ≥50 years of age. There was no difference of baseline characteristics between study and control groups [Table/Fig-1].

Parameter	PICH GROUP (n=160)	Control Group (n=160)	Statistics	p-value
Male	122 (76.2%)	118 (73.8%)	χ^2=0.267	0.606
Females	38 (23.7%)	42 (26.2%)		
Mean age (years)	53.47±12.36	51.43±12.12	t=1.488	0.138
Age range (years)	18-82 years	18-76 years		
Age <50 years	53 (33.1%)	54 (33.8%)	χ^2=0.014	0.906
Age >50 years	107 (66.9%)	106 (66.3%)		

[Table/Fig-1]: Baseline characteristics of study group.

Risk Factor Profile

The most prevalent risk factor in these two groups were hypertension (PICH: 72.5% vs. control: 5.6%), alcohol use (PICH: 42.5% vs. control: 7.5%), diabetes mellitus (PICH: 20.1% vs. control: 10.6%) and smoking (PICH: 25.6% vs. control: 5.6%) respectively. Among PICH group 13.1% patient had history of prior stroke; 15% had statin use and 8.1% patients had history of CAD. There was significant difference ($p<0.05$) in this risk factor in PICH group compared to controls. Risk factor profile in the study is shown in [Table/Fig-2].

Risk factors	PICH (n=160)	Control (n=160)	p-value
Hypertension	116 (72.5%)	9 (5.6%)	<0.0001
Diabetes	32 (20.1%)	17 (10.6%)	0.02
Alcohol use	68 (42.5%)	12 (7.5%)	<0.0001
Smoking	41 (25.6%)	9 (5.6%)	<0.0001
Prior stroke	21 (13.1%)	0	<0.0001
Statin use	24 (15%)	0	<0.0001
Coronary artery disease	13 (8.1%)	0	<0.0002

[Table/Fig-2]: Risk factor profile of study group (PICH versus control).

Lipid Profile

Proportion of patients with low TC (TC<200 mg/dL) was significantly higher ($p=0.01$) in PICH group compared to controls (81.9% vs. 70%). The proportion of patients with low TG (83.7% vs. 48.1%); low LDL-C (60.6% vs. 28.7%); low VLDL-C (81.2% vs. 48.1%) were significant ($p<0.0001$) in PICH group compared to control group. Odds ratio was higher for low TG (odds ratio=5.55 with 95% CI=3.295-9.36) followed by LDL-C (odds ratio=3.81, 95% CI=2.392-6.084). Odd's ratio for low TC was 1.93 (95%CI=1.144-3.274) [Table/Fig-3].

Parameter	PICH group	Control group	t-value	p-value
	Mean±SD	Mean±SD		
TC	159±52.1	180±39.8	4.01	<0.0001
Triglycerides (TG)	114.4±79.3	168±82.9	5.94	<0.0001
LDL-C	93.2±43.1	119.7±36.7	5.94	<0.0001
HDL-C	39.6±13.2	39.6±12.2	0.06	1
VLDL	22.8±15.8	33.6±16.5	5.94	0.0001
TC in age<50years	170.9±54.3	178.5±37	0.85	0.39
TG in age <50 years	141.6±103.8	172.8±75	1.78	0.07
LDL in age<50 years	99.8±44.5	119±34.2	2.50	0.018
Atherogenic index in age <50 years	0.14±0.3	0.27±0.23	2.40	0.018
TC in age >50 years	153.3±49.9	180.6±41.2	4.34	<0.0001
TG in age >50 years	100.9±59.5	165.7±86.5	6.37	<0.0001
LDL in age >50 years	89.6±42.1	119.9±38	5.50	<0.0001
Atherogenic index in age >50 years	0.025±0.25	0.23±0.03	5.27	<0.0001
TC in females	173±58.2	187.2±37.3	1.29	0.1
TG in females	107.6±48.5	170.6±78.1	4.27	<0.0001
LDL in females	98.3±44.2	126.8±33.8	3.25	0.0017
Atherogenic index in females	0.023±0.21	0.22±024	3.83	<0.0001
TC in males (n=122)	154.7±49.2	177.3±40.4	4.34	0.0001
TG in males	116.5±86.5	167.2±84.5	6.37	<0.0001
LDL in males	91.3±42.7	117±37.4	5.50	<0.0001
Atherogenic index in males	0.076±0.29	0.25±0.3	5.27	<0.0001

[Table/Fig-3]: Comparison of mean and standard deviation of cholesterol fractions in study group.

Mean TC for PICH patients were significantly low (159 mg/dL vs. 180 mg/dL, p-value<0.0001) compared to control group. Mean TG and mean LDL-C were also significantly low in PICH group compared to control ($p<0.0001$). There was no significant mean difference for HDL observed between both groups. In the subgroup analysis females had low mean TG (107 mg/dL vs. 170 mg/dL; $p<0.0001$), low mean LDL-C (98 mg/dL vs. 126 mg/dL; $p=0.0017$) in PICH group compared to control group. There was no significant difference in mean TC in females among both groups. Men had low mean TC (154 mg/dL vs. 177 mg/dL, ($p=0.0001$), low mean TG levels (116 mg/dL vs. 167 mg/dL, $p<0.0001$), and low mean LDL (91 mg/dL vs. 117 mg/dL, ($p<0.0001$) in PICH group compared to control group. In a separate analysis based on patient age, older individual (age ≥50 years) had significantly low mean TC ($p<0.0001$), low mean TG ($p<0.0001$), and low mean LDL (p-value<0.0001) among PICH group compared to controls. There was no significant difference in mean TC, TG, LDL-C in young individuals (age <50 years) in both groups. Mean atherogenic index was significantly low in PICH group compared to control ($p<0.0001$) [Table/Fig-4].

Subgroup analysis of PICH group based on presence of hypertension as risk factor showed lower mean of TC, LDL, TG levels and atherogenic index in the non hypertensive group compared to hypertensive group. This difference was statistically significant in mean LDL in 129 non hypertensive group (p-value=0.02) compared to hypertensive group of PICH. Based on location of bleed patients of PICH group were further differentiated into lobar (involving predominantly the cortex and underlying white matter of the cerebral hemisphere) and non lobar bleed. Non lobar bleed included deep parenchyma (involving predominantly the basal ganglia, periventricular white matter, thalamus, or internal capsule), brainstem and cerebellar bleed. It was observed that mean TC was lower in lobar bleed group (152 mg/dL vs. 160 mg/dL) compared to non lobar bleed group, while mean LDL and mean TG levels were lower in non lobar bleed. These differences were not statistically significant [Table/Fig-5].

Parameter	PICH group (n=160)	Control group (n=160)	Odd's ratio	Confidence interval (95%CI)	p-value
Number of patients with low TC (<200 mg/dL)	131 (81.9%)	112 (70%)	1.93	1.144-3.274	0.01
Number of patients with low TG (<150 mg/dL)	134 (83.7%)	77 (48.1%)	5.55	3.295-9.36	<0.0001
Number of patients with low HDL (<40 mg/dL)	88 (55%)	88 (55%)	1.00	0.643-1.553	1
Number of patients with low LDL (<100 mg/dL)	97 (60.6%)	46 (28.7%)	3.81	2.392-6.084	<0.0001
Number of patients with low VLDL (<30 mg/dL)	130 (81.2%)	77 (48.1%)	4.67	2.822-7.730	<0.0001

[Table/Fig-4]: Comparison of proportions of patients with low cholesterol levels among PICH and control groups.

PICH group	Hypertensive group (n=115)	Non hypertensive group (n=45)	t-value	p-value
	Mean±STD	Mean±STD		
TC	161.8±53.8	152.2±48.0	1.04	0.29
TG	120.4±83.3	98.9±45.4	1.63	0.1
LDL	97.7±46.0	80.9±31.7	2.24	0.02
Atherogenic index	0.43±0.29	0.39±0.22	0.83	0.40
PICH group	Lobar bleed group (n=24)	Non-lobar bleed group(n=136)		
Mean TC	152.5±70.2	160.3±48.2	0.67	0.49
Mean TG	137.8±105.3	110.2±73.8	1.5	0.11
Mean LDL	93.3±61.2	92.2±39.3	0.04	0.96

[Table/Fig-5]: Subgroup analysis of the PICH group and comparison of mean and standard deviation of cholesterol fractions.

In a subgroup analysis of patients with PICH, 24 patients had used statin either due to underlying CAD or prior history of ischemic stroke. Among statin group TC≤160 mg/dL was observed in 23 (95.83%) patients while non-statin group TC≤160 mg/dL was observed in 66 (41.25%) patients. These differences among statin and non-statin group was statistically significant (p-value<0.0001).

Location of Bleed

Non lobar bleed was found in 85% (n=136) of the patients. Dominant hemisphere (left sided) bleed was predominant (n=105). Most frequent location of bleed was basal ganglion (n=63) followed by thalamus (n=47). Lobar bleed was observed in 24 patients, brainstem bleed in 17 patients and 9 patients had cerebellar bleed.

Clinical Features

Majority of the patient had focal neurological deficit in the form of hemiplegia or hemiparesis isolated or combination with other features (n=145). All the patients had mild headache and 6 patients showed severe headache. Sixteen patients were in altered sensorium. Seizure occurred in 9 patients. Death occurred in 6 (3.75%) hospitalised patients.

DISCUSSION

Low serum cholesterol is a less well established risk factor for ICH. The Multiple Risk Factor Intervention Trial (MRFIT) [18], Honolulu heart studies [19] and Kaiser Programme cohort [20] have confirmed that low cholesterol is associated with high incidence of ICH in the Americans.

The heart protection study [21] and SPARCLE trials [22] reported higher rates of ICH in participants assigned to statin therapy. In addition, higher rates of ICH were observed in participants with low cholesterol levels. Rotterdam study reported low TG levels were associated with increased risk of ICH [23]. Low serum cholesterol has been reported as risk factor for ICH in elderly men [20]. The relative contribution of lipid fractions to these associations is unclear and requires further investigation among Indians. Hence present study was conducted whether TC, TG, LDL-C, and HDL-C were associated with risk of PICH in men and women of younger and older age groups in our region.

Our findings in patients with PICH confirm the population-based observation that individuals with lower cholesterol levels are at increased risk of ICH. We observed inverse association between TC, LDL-C and TG levels and risk of PICH. This association was strongly significant in older individual, both men and women. Our findings are consistent with prior studies [14,15] which confirms lower TC, LDL-C and TG levels as risk factor for PICH among Indians.

Proportions of patients with low TC, low TG and low LDL were significantly higher in PICH group compared to control group. We also observed strongly significant difference in mean TC, mean TG and mean LDL-C in PICH group compared to control. In the subgroup analysis females had significantly lower mean TG levels and mean LDL-C in PICH group compared to controls. Although mean TC was lower in females in PICH group, however mean difference was not statistical significant compared to control. Men had lower mean TC, LDL-C and TG levels in PICH group and difference was statistical significant compared to control men.

Literature review showed that serum cholesterol has protective effect against ICH. Cholesterols are the essential components of cell membrane needed to maintain the stabilisation of endothelial cells and intern integrity of cerebral small vessels [24]. Hence lower lipids are risk factor for ICH. Epidemiological and case control studies found a correlation between ICH and change of blood cholesterol fraction. Findings are not consistent and vary region wise. Present study found that low TC, LDL-C, and TG levels are associated with risk of PICH. Findings were similar to prior studies from India [14,15] but vary when compared to western studies [20,23]. Level of HDL cholesterol positively correlated with risk of ICH, suggesting that increased level of HDL cholesterol may be related to higher risk of ICH [12]. However, in the present study there was no significant difference in HDL-C in PICH group compared to control. Level of HDL-C remained same in both group, indicating no role of HDL-C either low or high as a risk factor of PICH in Indians.

Iribarren C et al., in a cohort of aged 40-89 years, observed excess risk of ICH in men aged 65 years or older [20]; similar findings were observed in present study were older individual aged 50 years or more especially men had significant lower mean TC, LDL, TG and atherogenic index in PICH group. Younger individuals showed significant lower mean LDL and atherogenic index in PICH group compared to control group. We also observed significant lower mean LDL-C and TG levels in women in PICH group compared to control group. Difference in mean cholesterol was not significant in women with PICH compared with control group.

Another fact is that mean TC was lower in lobar bleed group, while mean TG and LDL-C was lower in non lobar bleed group in present study. However there was no significant difference among these subgroups. While literature review showed that reduction of cholesterol using statin was associated with highest risk of ICH recurrence in survivors of lobar bleed [25]. In a subgroup analysis of PICH group, mean of TC, LDL-C, TG and atherogenic index was lower among non hypertensive group compared to hypertensive group, indicating low cholesterol as an independent risk factor for PICH in non hypertensive group.

We further observed a significant lower mean LDL-C in non hypertensive patients compared to hypertensive among PICH group (p-value=0.02). Mortality rate in this case series is only 3.75% as compared to 30-40% mortality in other comparative studies [26]. This can be explained by the referral of patients with low Glasgow coma scale for emergency decompression surgery.

Although we obtained significant evidences to confirm our hypothesis, there remained certain drawback in the present study. First, study was a retrospective one and sample size was small, although largest from India. Second drawback of the study was lipid levels were determined in first 48 hours after PICH. This we have done referring the prior studies from India [14,15]. Studies have shown that cholesterol levels tend to decline in the first 24-48 hours after stroke, with a nadir of 1-2 week and return to baseline at 3 months [27]. The cause of the drop in cholesterol following ICH has been attributed to non specific increase in catecholamines. The decrease in cholesterol levels within 48 hours after ICH appears to occur earlier than when compared to myocardial infarction or ischemic stroke [18,27]. Further patients were recruited from one centre and sub group population, and follow-up period was short (till hospital stay). Hence randomised trials in larger multicentres with larger sample size and longer time observation are mandatory for understanding further relationship between serum cholesterol fractions and PICH for both prevention of ICH and safety of statin therapy on ICH patient. Current data provides guidance for clinicians approaching ICH.

CONCLUSION

Taken together our data confirms that lower cholesterol levels are associated with increased risk of PICH. The contribution of lipid fractions TC, LDL-C and TG levels to these associations are clear from the present study. LDL-C was significantly lower in all age group and both sexes in PICH group compared to control. TC were significantly lower in statin group compared to non statin group. Therefore, patients with low LDL-C, and cardiovascular risks, there should be cautious use of statin. Henceforth lipid lowering agents should be avoided in PICH patients. Compared to western stroke registry where low TG levels are associated with ICH, Indians have lower TC, LDL-C and TG level as a risk factor for ICH.

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