Original Article

Association of Low Serum Cholesterol With Hemorrhagic Stroke

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Abstract

Background: *Stroke is the second cause of death and third cause of disability in worldwide so control of risk factor is the best option for prevention of stroke and stroke related disability.* ***Objectives:*** *The study is to know the relation of low serum cholesterol with hemorrhagic stroke.* ***Materials and Methods:*** *This Study is a case control study carried out at Neurology and Medicine ward Mymensingh Medical college hospital (MMCH) from july2017 to December 2018 to see the association of low serum cholesterol with hemorrhagic stroke. A total number of 120 subjects more than 18 years were considered for the study. Among them 60 were study group and 60 were control group. The study population has been selected following some exclusion and inclusion criteria.* ***Results:*** *Result showed that hemorrhagic stroke was more in male than female, common after the age of 60 years. Lower middle classes are more sufferers. Hypertension was 76.7% of study group and serum cholesterol was significantly lower in study group than the control group.* ***Conclusion:*** *This study found that the serum total cholesterol level of study group is less than that of the healthy control group and the difference is statistically highly significant (p< 0.001). So it can be concluded that low serum cholesterol is associated with hemorrhagic stroke.*

Key words: *Low Serum Cholesterol, Hemorrhagic Stroke.*

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Introduction

Stroke is defined as rapidly developing symptoms and sign of focal and global loss of cerebral function lasting at least 24 hours with no apparent cause other than of vascular origin. Stroke is the sudden death of some brain cell due to lack of oxygen when the blood flow to the brain is lost by blockage of artery or rupture of an artery to the brain .[1] Stroke is one of the leading causes of death in the world. Moreover, it is the leading cause of acquired disability in adult in most regions.[2] Countries with low and middle income population have the largest burden of stroke, accounting for more than 85% of stroke mortality worldwide. However few reliable data are available to identify risk factors for stroke in most of these regions.

Stroke is the third most common cause of death after coronary heart disease and all cancer death.[3] According to World Health Organization (WHO), 15 million people suffer from stroke worldwide each year. Among them 85% is ischemic and 15% is hemorrhagic stroke. Of these, five million die and another five million are disabled permanently (WHO, 2007). The immediate outcome of hemorrhagic stroke is poor, about 50% died immediately. On contrary, ischemic stroke has less than 20% of immediate death rate (Neurology illustrated 5th edition).The prevalence rate of stroke in India is 250-350 per 100000 in last decade.[4] Estimated annual incidence in Pakistan is 250/100000 translating to 350000 new cases every year.[5] In Asia, the problem of stroke has a particular strong impact, not only because more than half of the world's population lives in Asia, In Asian population, where plasma cholesterol level are low, hemorrhagic stroke may form up to 30 % of all stroke.[6]

Incidence of stroke in Bangladesh is 2.55 per 1000 population per year in both sexes (Bangladesh Bureau of Statistics, 2009). Another study showed prevalence of stroke is 46.2% in rural area, 27.4% in

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semi- urban area and 26.4% in urban population.[7] The high number of disability adjusted life-years lost due to stroke (485 per 10000 people) show that stroke severely impacts Bangladesh's economy.[8]

Due to the tremendous burden that stroke places on our society, there have been major efforts to identify modifiable risk factors that could reduce the incidence of stroke. Multiple risk factors for stroke have been identified. The most prevalent of these include hypertension, diabetes mellitus, smoking, atrial fibrillation, coronary artery disease and disorder of lipid metabolism. Epidemiologic studies suggest that elevated total cholesterol and low density lipoprotein cholesterol (LDL-C) are possible risk factors for ischemic stroke,[9,10] Other studies suggest low serum total cholesterol levels are associated with an increased risk of symptomatic intracerebral hemorrhagic and with presence of asymptomatic cerebral micro bleeds. The relative contribution of lipid fraction to these associations is unclear and requires investigation. In Asian society low cholesterol levels have been proposed as one explanation for the high incidence of intracerebral hemorrhage, In a population based study from North East India, hemorrhagic stroke was found in about 32% of the cases having low serum cholesterol level.[11,12] Since the introduction of highly effective means of lowering serum cholesterol by the use of statins, the potential importance of this relationship has increased. The present study is intended to define the relationship between primary intracerebral hemorrhage and low total cholesterol so that the effective preventive measure of hemorrhagic stroke can be planned.

General objectives

To see the association of serum total cholesterol level with hemorrhagic stroke.

Materials and Methods

This was a case control study.

The study duration was 18 months from the date of approval of protocol, from July 2017 to December 2018.

The study was carried out at Neurology and Medicine ward of Mymensingh Medical College Hospital, Mymensingh.

Study group: Hemorrhagic stroke patients admitted in Neurology & Medicine wards of Mymensingh Medical College Hospital, Mymensingh.

Age and sex matched apparently healthy people and patient having no family history of hemorrhagic stroke.

According to case-control study due to limitation of time, resources, accessibility and availability, out of 120 sample only 60 patients were taken for study group during the study period and age sex matched apparently 60 subject were taken for control group.

The Purposive sampling technique was done for selecting both study and control group, who fulfilled the inclusion criteria were included in the study until target sample size achieved.

- Patients with WHO defined stroke confirmed by CT scan that the stroke was hemorrhagic.
- Age 18 years and above.
- Patients/ attendants who have given written consent and willing to comply with the study procedure.
- Patients with ischemic stroke.
- Patients receiving drugs that affect on cholesterol levels (e.g. Statin).
- Low serum cholesterol due to Malabsorption syndrome.
- Known thyroid disorders (either hypo or hyperthyroid).
- Apparently healthy adult
- Having no history of hemorrhagic stroke
- Age more than 18 yrs
- Respondents of both gender
- Respondents who refused to be included in the study
- Having apparent cardiovascular, renal, hepatic disease
- Patients receiving drugs that affect on cholesterol levels.
- Low serum cholesterol due to Malabsorption syndrome.
- Known thyroid disorders (either hypo or hyperthyroid).

Data were collected from hemorrhagic stroke patients admitted in neurology and medicine wards of Mymensingh Medical College Hospital in a data collection sheet of formed questionnaire

A case control study on the association of serum total cholesterol level with hemorrhagic stroke. The study was carried out for duration of 12 months. After obtaining the ethical committee's clearance, a total number of 120 subjects more than 18 years were considered for the study. Among them 60 were study group and 60 were control group. Hemorrhagic stroke patient diagnosed both clinically as well as by CT scan of head was taken as study group and control group were age, sex, matched apparently healthy people and patient attendants having no hemorrhagic stroke. Study and control group were selected 1:1 ratio and compared accordingly. All the cases and control were selected from the Neurology and Medicine department of Mymensingh Medical College Hospital. CT scan of head was carried out in the Department of Radiology and Imaging of MMCH and serum cholesterol level was studied in the department of Biochemistry MMC. After obtaining the informed consent of the cases and controls, fasting blood was drawn under all aseptic precautions. Measures were taken to prevent hemolysis. Samples were sent to the Biochemistry Department, MMC. The statistical analysis was done by using computer with SPSS version 20 to estimate the association of hemorrhagic stroke with serum cholesterol level.

Results

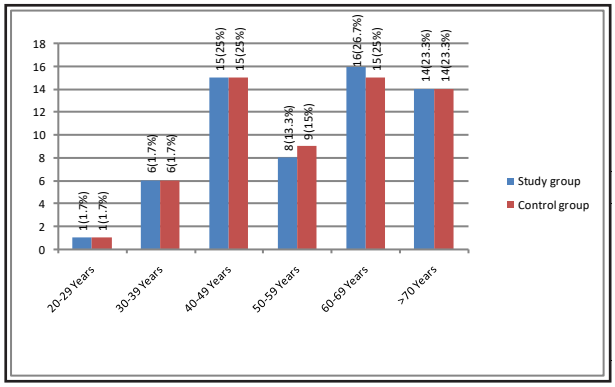
This case control study were carried out in the department of Neuro medicine in collaboration with department of Biochemistry, MMC. In this study sixty (60) is hemorrhagic stroke patients were enrolled as study group taken from Neuro medicine and Medicine department of MMCH. Sixty (60) age and sex matched healthy adults were enrolled as control group. Those control groups were taken from attendance of patients.

Table l: Distribution of the respondents by sex (n=120)

Sex	Study group		Control group		Male &Female ratio
	Number	Percentage	Number	Percentage	
Female	19	31.7%	19	31.7%	
Male	41	68.3%	41	68.3%	2.15:1
Total	60	100	60	100	

Table I shows the distribution of the respondents by sex. Out of 120 respondents in study group and control group 31.7% were female, 68.3% were male and male & female ratio was 2.15:1.

Figure 1: Distribution of the respondents by age groups (n=120)



* Chi square test was done to measure the level of significant

Figure I shows the age distribution of the respondents of both groups. A total of 120 patients were included in the study. They were divided into six groups according to their age. The mean age was found 56.41 (15.06) years and range were 26-85 years in study group and mean age was 56.20 (14.79) years and range were 22-75 years in control group which was found statistically non-significant. Most of the respondents 26.3% in both groups belonged to 60-69 years age group.

Figure 2: Distribution of the respondents by Occupational Status (n=120)

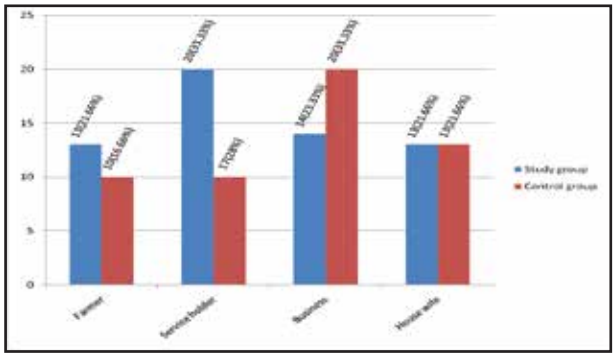


Figure 2 shows the distribution of the respondents by occupational status. Among study and control groups, farmer were 13(21.66%) vs 10(16.66%), service holder 20(33.33) vs 17(28.00), businessman 14(23.33%) vs 20 (33.33%) and house-wife were 13(21.66%) vs 13 (21.66%). No statistically significant difference was observed between two groups in terms of occupational status.

Figure 3: Distribution of the respondents according to economical status (n=120)

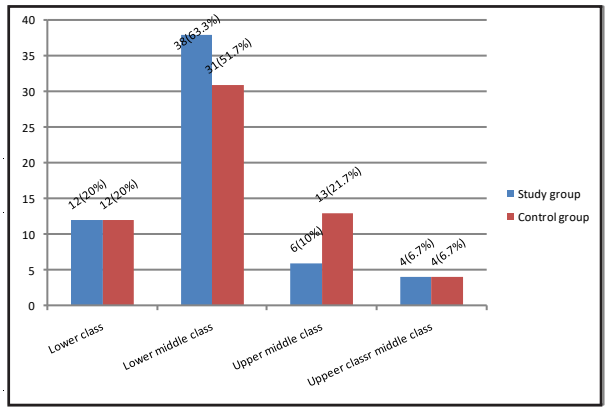


Figure 3 shows that the distribution of respondents according to the economical status in study vs control groups, Lower class both groups are 20%, lower middle class 63.3% vs 51.7%, upper middle class 10% vs 21%, upper class was 4% in both groups. The differences between the two groups were statistically insignificant.

Figure 4: Distribution of the respondents by Residence (n=120)

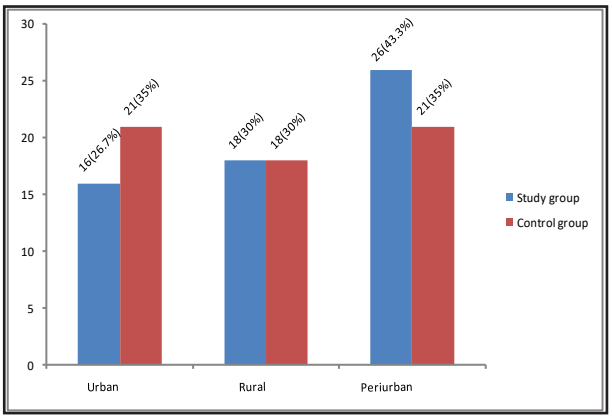


Figure 4 shows the age distribution of the respondents by residence. Out of all patients in study group 26.7% was urban dweller and 30% rural and 43.3% periurban. In control group 35% were urban dweller and 30% in rural and 35% periurban. No statistically significant difference was observed between two groups in terms of residence.

Table II: Distribution of the respondents by Risk factors (n=120)

Risk factors		Study group	%	Control group	%	P-value
	Smoker	39	65	32	53.3	
Smoking	Non smoker	21	35	28	46.7	0.194 NS
	Total	60	100	60	100	
	Absent	53	88.3	50	83.3	
DM	Present	7	11.7	10	16.7	0.432 NS
	Total	60	100	60	10	
	Absent	14	23.3	52	86.7	
HTN	Present	46	76.7	8	13.3	0.001NS
	Total	60	100	60	100	

* Chi square test was done to measure the level of significant

Table II shows that there were 39 smokers in study group and 32 in control group. There were 21 non-smokers in study group and 28 in control group. The study shows that there were 53 non-diabetics in study group and 32 in control group. There were 7 diabetics in study group and 10 in control group. There was statistically no significant difference between study and control groups in smoker vs non-smoker and diabetics vs non-diabetics population. It also shows that there were 14 non-hypertensive in study group and 52 in control group. There were 46 hypertensive in study group and 8 in control group. There was statistically significant difference between study and control groups.

Table III: Serum lipid profile (mg/dl) in case and control groups. (n=120)

	Mean	SD	Mean	SD	
Serum lipid	Study group		Control Group		P value
S.Chol (mg/dl)	174.53	26.64	195.15	26.04	0.001 **
HDL (mg/dl)	37.01	4.87	37.95	3.53	0.122NS
LDL (mg/dl)	113.93	9.20	127.15	20.10	0. 001 **
TG (mg/dl)	169.73	42.12	158.60	26.99	0. 88 NS

* Independent Sample test was done to measure the level of significance.

This table III shows that distribution of serum lipid profiles in respondents. The mean value of serum total cholesterol was the focus of this study. It was found 174.53±26.64 mg/dl in study group and 195.15±26.05 mg/dl in control group which was statistically significant (p< 0.001). There was also statistically significant difference in LDL parameters in study group 113.93± 9.2 mg/dl and in control group it was 127.15±20.10 mg/dl. The other parameters were HDL 37.O1± 4.87 VS 37.95± 3.53 mg/dl and TG was 169.73± 42.12 VS 158.60± 26.99 mg/dl. No statistically significant difference was observed in serum level of HDL and TG between the two groups.

Table IV: Risk factors for hemorrhagic stroke

Risk factors	Unadiusted odd ratio (95% CI)	Adjusted odd ratio (95% CI)
Smoking Status		
Non-smoker (Ref).	1	1
Smoker	2.59(1.24-5.41)	0.85(0.57-2.82)
DM		
Absent (Ref).	1	1
Present	3.24(1.24 - 8.49)	.88(0.36-3.06)
HTN		
Absent (Ref).	1	1
Present	4.37(1.8710.21)	3.66(1.1412.12)
TC		
Up to 189 mg/dl (Ref)	1	1
less than 189 mg/dl	4.27(1.99.61)	6.24(2.07-22.83)
TG		
Up to 150 mg/dl (Ref)	1	1
less than 150 mg/dl	0.66(2.1- 4.46)	.90 (1.17-5.86)
HDL		

* Adjusted odd ratio derived from logistic regression model – Enter method.

Table IV shows that different risk factors of stroke. In unadjusted odds, being smoker (unadjOR. 2.59, 95% CI (1.24 – 5.41); DM (unadjOR. 3.24, 95% CI (1.24 – 4.49); HTN (unadjOR. 4.38, 95% CI (1.88 – 10.21); Low level of serum TC [unadjOR. 4.28, 95% CI (1.91 – 9.61); TG [unadjOR. 0.67, 95% CI (2.10 – 4.46); LDL (unadjOR. 1.63, 95% CI (1.08 – 6.42); and decreased level of HDL (unadjOR. 3.00, 95% CI (2.23 – 6.13); were found significant predictors. All the significant independent variables were entered in Enter Logistic Regression model for adjusted odds. This logistic regression model revealed having hypertension [adjOR (95% CI), 3.66 (1.11 – 12.12); Decreased level TC bellow 189mg/dl [adjOR (95% CI), 6.24 (1.17 – 22.83); and decreased level of LDL belloe115mg/dl [adjOR (95% CI), 4.45 (0.10 – 8.05); as significant risk for hemorrhagic Stroke.

Discussion

In this study, 60 patients of hemorrhagic stroke were enrolled as study group. For better precision, 60 age and sex matched healthy adults were also taken as control group. Among them

41 were male and 19 were female. According to analysis of age distribution, there was no significant difference among both groups.

Advancing age was found to be associated with hemorrhagic stroke. Analysis of age distribution showed that more respondents of study group were in elder age groups which were of 60 to 69 years. In the study group it was 26.4% and in control 25%. The mean age of study and control groups was 56.41±15.06 and 56.20 ±14.79 respectively. Anwarullah et al found 34 percent patients in the sixth decade and 27 percent in the seventh decade.[13] This observation was in conformity with that of Haque and Mannan and Liu and Chia.[14,15]

In this study, 33.33% hemorrhagic stroke patient were service holder both govt. and non government. Majority ware retired persons. Farmers were 21.66% and businessmen were 23.66%. Among the female 68% were house wives. There were no available data regarding stress, anxiety, work hour and physical exertion in their respective jobs, to compare in this study so it is a potential space for further study of hemorrhagic stroke in association with occupation.

In this study, among the peri urban dweller hemorrhagic stroke was more than the urban and rural area. In peri urban it was 43.30% and urban 26.70% and rural 30%. Data were not available to compare this result.

This study re-evaluated the association between having a history of smoking and hemorrhagic stroke. It was significant with unadjusted odd ratio 2.59 and 95% confidence interval ranging from 1.248 to 5.41 and but in adjusted odd ratio model, it is .85 with 95% confidence interval ranging from (0.57 to 2.82) (p=0.521). It is non-significant. Tan et al (2008) also found cigarette smoking as risk factor of stroke with an OR 2.3 and 95% CI=1.10 to 4.96.[16] Albucher et al (2000) showed that smoking as a risk factor of stroke in a multivariate analysis, this study had given more emphasis in ischemic stroke than hemorrhagic stroke.[17] All these studies are not consistent with the present study result. So, it needed further studies with large sample size to establish this factor. It may also a cause that in this study both the case and control females, maximum were non smoker as for socio cultural and religious background , But in case of referral studies the female smoker were more.

The person having associated risk factor like diabetes mellitus and hypertension, were more vulnerable to develop stroke. It was proved by logistic regression model. In unadjusted DM (OR. 3.24, 95% CI but adjusted OR .88 but in adjusted model only HTN adj OR. 3.66, 95% CI was significant risk factor for hemorrhagic stroke. Hypertension and diabetes mellitus (DM) were found to be significant risk factor for ischemic stroke (P<0.01 and P<0.05 respectively) in a study by Uddin et al (2009).[18] In a multivariate analysis by Albucher et al (2000) showed that hypertension as a risk factor of hemorrhagic stroke. The odd ratio of hypertension in a study by Tan et al (2004) was 2.7 with 95% confidence interval ranging from 1.53 to 4.80, which is consistent with this study.

In this study, Serum total cholesterol between case and control groups was [173.53 (39.57) mg/dl Vs 195.15. (22.08) mg/dl; p value <0.001]. The difference between study and control group was statistically significant. Low total cholesterol levels were found in 55.7% (33/60) of the study group and 20.0% (12/60) of the control group. There was 6.2 times risk of development hemorrhagic stroke in study of having low cholesterol level and with the range of (2.07-22.83); 95% CI. In Honolulu Heart Program they studied serum cholesterol and hemorrhagic stroke, there was a significant (p=0.001) inverse association between serum cholesterol and hemorrhagic stroke. This inverse association was nonlinear, with a higher incidence rate only for serum cholesterol in lowest quintile was < 189mg/dl, The RR was 2.55 (95% CI 1.58-4.12).[19] In study of Malaber Institute kerala, India, 2012, showed that the proportion of ICH patient with low cholesterol was significantly higher than the control group (68% VS 43%). Mean total cholesterol was significantly low in ICH patient compared with controls (177mg/dl vs 200mg/dl; p value 0.0006), which is consistent with the present study. Mercola.com 2008 found that as cholesterol dropped, the risk of hemorrhagic stroke increase significantly.

A person with a cholesterol level below 180mg/dl had twice the risk of hemorrhagic stroke compared with someone at 230mg/dl. Larry B. Goldstein showed that ICH was 3 times more common (p=0.04) in men with serum cholesterol <160mg/dl compared with those with higher levels, where higher levels were associated with increased risk of ischemic stroke (p=.007) .[20] The Green Med Info published an article on January 2001. Stroke. Carlos Iribarren , David R.Jackob, Stephen Sidney 1996 showed among 386 events by multivariate proportional hazards life table regression analysis, serum cholesterol level bellow 10th percentile (178mg/dl) compared with higher cholesterol level, was associated with a significantly increased risk of ICH in men aged 65years or older (RR, 2.7; 95% CI , 1.4 to 5.0) ,[21] All these study results are in accordance with this study findings.

In this study, it was also found that level of LDL between study and control was 113.93(9.2) mg/dl vs 127.15(20.10) mg/dl; P=0.001 which was statistically significant and in logistic regression test adjustable odds 4.45 (0.10-8.05). In the study of Malaber Institute kerala, India, 2012 showed that the proportion of ICH patient have low level serum LDL-c which is consistent with this study. The other parameters were HDL 37.O1±4.87 vs 37.95± 3.53 and TG was 169.73± 42.12 mg/dl vs 158.60± 26.99 mg/dl statistically non significant. In that study Indian study 2012 showed that the proportion of ICH patient has low level serum TG, which is not consistent with the present study. But there was no significant difference in high-density lipoprotein level in both groups which is consistent with this study.

Conclusion

This study found that the serum total cholesterol level of study group is less than that of the healthy control group and the difference is statistically highly significant (P< 0.001). So it can be concluded that low serum cholesterol is associated with hemorrhagic stroke. Including this, others several risk factors were found like hypertension and low level of LDL. Further studies to evaluate the mechanism of this observation are required.

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