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Evaluation of Risk Factors for Hemorrhagic Stroke: A study in a tertiary care hospital of Bangladesh

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Abstract
Background: *Stroke is the second cause of death and third cause of disability in worldwide. Control of risk factors is the best option for prevention of stroke and decreasing the stroke related disability. So, knowledge regarding the risk factors is very important for treating and preventing hemorrhagic stroke.*
Aim of the study: *The aim of this current study was to evaluate the risk factors for hemorrhagic stroke.*
Materials and Methods: *This study was a case control study carried out at Neurology and Medicine ward Mymensingh Medical College Hospital (MMCH) from July 2017 to December 2018 to see the association of low serum cholesterol with hemorrhagic stroke. A total number of 120 subjects of more than 18 years were considered for the study as the study subjects. Among them 60 were in study (Case) group and 60 were in control group. The study population had been selected according to the pre-defined exclusion and inclusion criteria.*
Results: *In analyzing the risk factors between the groups, it was found 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 diabetic patients 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 was also found that, there were 14 non-hypertensive patients in study group and 52 in control group. There were 46 hypertensive patients in study group and 8 in control group. There were statistically significant differences between study and control groups regarding hypertension and total serum cholesterol.*
Conclusion: *According to the findings of this study we can conclude that, hypertension as well as low total serum cholesterol are potential risk factors of hemorrhagic stroke.*
Key words: *Hemorrhagic stroke, Risk factors, DM, HTN.*

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I. Introduction

Stroke is the second cause of death and third cause of disability in worldwide. 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. 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[1]. Estimated

annual incidence in Pakistan is 250/100000 translating to 350000 new cases every year[2]. 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 is low, hemorrhagic stroke may form up to 30 % of all stroke[3]. 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 semi- urban area and 26.4% in urban population[4]. The high number of disability adjusted life-years lost due to stroke (485 per 10000 people) show that stroke severely impacts Bangladesh's economy[5]. 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[6], 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[7]. 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 major objective of this current study was to evaluate the risk factors for hemorrhagic stroke.

II. Objectives

The objective of this study was to asses and compare the risk factors between hemorrhagic stroke and healthy population.

III. Material and Methods

This was a case control study was conducted during the period from July 2017 to December 2018 at the Neurology and Medicine ward of Mymensingh Medical College Hospital (MMCH), Mymensingh, Bangladesh. Study or case group was formed by 60 hemorrhagic stroke patients admitted in the Neurology & Medicine wards of MMCH, Mymensingh. On the other hand, the **c**ontrol group was formed 60 age and sex matched apparently healthy people and patient attendants' having no history of hemorrhagic stroke. 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. According to the inclusion criteria of this study, 18 years and above aged patients with WHO defined stroke confirmed by CT scan that the stroke was hemorrhagic were included as the case group participants. On the other hand, according to the exclusion criteria of this study, ischemic stroke patients, patients receiving drugs that affect on cholesterol levels, patients with, malabsorption syndrome and patients with known hypo or hyperthyroid patient were excluded. In control group, apparently healthy adults of similar ages of both gender having no history of hemorrhagic stroke were included. 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. 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. 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. All data were processed, analyzed and disseminated by MS Office and SPSS program as per need.

IV. Results

In this study 60 hemorrhagic stroke patients were enrolled as study group taken from Neuro medicine and Medicine department of MMCH. On the other hand, 60 age and sex matched healthy adults were enrolled as control group. Those control groups were taken from attendance of patients. 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. The mean age was found 56.41 (15.06) years and the range was found 26-85 years in study group. On the other hand, the mean age was found 56.20 (14.79) years and the range was 22-75 years in control group which was statistically non-significant. In analyzing the risk factors between the groups, it was found 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-diabetic patients 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 was also found that, there were 14 non-hypertensive patients in study group and 52 in control group. There were 46 hypertensive patients in study group and 8 in control group. There was statistically significant difference between study and control groups. The mean value of serum total cholesterol was the focus of this study. Total cholesterol 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 37.01 ± 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. In unadjusted odds, being smoker (unadj OR. 2.59, 95% CI (1.24–5.41); DM (unadj OR. 3.24, 95% CI (1.24–4.49); HTN (unadj OR. 4.38, 95% CI (1.88–10.21); Low level of serum TC [unadj OR. 4.28, 95% CI (1.91–9.61); TG [unadj OR. 0.67, 95% CI (2.10 – 4.46); LDL (unadj OR. 1.63, 95% CI (1.08–6.42); and decreased level of HDL (unadj OR. 3.00, 95% CI (2.23–6.13); were found significant predictors.

Table 1: Age distribution of both group participants (N=120)

Age (Year)	Study group (n=60)		Control group (n=60)		Total (n=120)		*P* value
	n	%	n	%	n	%	
20-29	1	1.67%	1	1.67%	2	1.67%	
30-39	6	10.00%	6	10.00%	12	10.00%	
40-49	15	25.00%	15	25.00%	30	25.00%	
50-59	8	13.33%	9	15.00%	17	14.17%	3.764
60-69	16	26.67%	15	25.00%	31	25.83%	
≥70	14	23.33%	14	23.33%	28	23.33%	
Total	60	100%	60	100%	120	100%	

Independent Sample test was done to measure the level of significance

Table 2: Serum lipid profile (mg/dl) in case and control groups (N=120)

Serum lipid	Study group	Control Group	P value
	Mean ± SD	Mean ± SD	
S. Chol. (mg/dl)	174.53±26.64	195.15±26.04	0.001^{Sig}
HDL (mg/dl)	37.01±4.87	37.95±3.53	0.122^{NS}
LDL (mg/dl)	113.93±9.2	127.15±20.1	0. 001^{Sig}
TG (mg/dl)	169.73±42.12	158.6±26.99	0. 880^{NS}

Table 3: Chi square test results of the factors between the groups (N=120)

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

Table 4: Logistic regression between risk factors for hemorrhagic stroke

Risk factors	Unadjusted 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(1.87-10.21)	3.66(1.11-12.12)
TC		
Up to 189 mg/dl (Ref).	1	1

less than 189 mg/dl	4.27(1.9-9.61)	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)	0.90 (1.17-5.86)
HDL		
30 and above (Ref).	1	1
less than 30mg/dl	3.00 (2.23-6.13)	0.67 (0.33-2.25)
LDL		
Up to 130(Ref).	1	1
less than 115	1.63(1.07-6.41)	4.45(0.10-8.05)

V. Discussion

The aim of this current study was to evaluate the risk factors for hemorrhagic stroke. 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. Analysis of age distribution showed that out of all patients, 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. 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. 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%. This study re-evaluated that 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 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.[8] Jafre et al (2014) 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[9]. 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 was nonsmoker 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)[10]. 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 Honolulo 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)[11]. 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 increases 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)[12]. 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)[13]. 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 37.01±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.

VI. Conclusion

According to the findings of this study we can conclude that, hypertension as well as low total serum cholesterol are potential risk factors of hemorrhagic stroke. Basically, this was a single centered study with a small sized sample. So, the findings of this study may not reflect the exact scenario of the whole country. For getting more specific result, we would like to recommend for conducting similar more studies in several places with lager size samples.

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