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Original Research Article

Circadian variation in stroke: a hospital-based study

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ABSTRACT

Background: Proof of a circadian rhythm in the occurrence of cerebral infarction and other types of stroke might provide clues to factors which immediately precipitate these events, which in turn might lead to more rational treatments. The aims of the current study were to find out the circadian variation of stroke onset and to determine the risk factors related to circadian variation.
Methods: This cross-sectional study was conducted in a tertiary hospital of Bangladesh from July to December 2014 among 67 diagnosed cases of ischemic and hemorrhagic stroke of first attack. Times of onset of stroke and wake-sleep state were recorded.
Results: The mean age of the study subjects was 62.1 years, 64.2% were male. Among them, 59.7% had an ischemic stroke and 40.3% had a hemorrhagic stroke. The occurrence of stroke was most common during 6 am to 12 pm (47.8%), followed by 12 am to 6 am (25.4%), 12 pm to 6 pm (17.9%), and 6 pm to 12 am (9.0%). Circadian variation of stroke was homogenous and statistically insignificant in association with age group when categorized as below 65 years and 65 years or above years, sex, smoking habit, and presence or absence of diabetes mellitus, atrial fibrillation, and dyslipidemia. But hypertension and ischemic heart disease (IHD) were significantly associated with circadian variation of stroke. The occurrence of ischemic stroke and hemorrhagic stroke was most common from 6 am to 12 pm (47.5% and 48.1%) respectively. When considered separately, significant circadian variation noted for ischemic stroke and hemorrhagic strokes were also noted.
Conclusions: The study contributes further evidence for the circadian variation in the occurrence of ischemic stroke and hemorrhagic stroke. Attempts to prevent their occurrence must take into account this circadian variation.

Keywords: Circadian rhythm, Hemorrhagic stroke, Hypertension, Stroke, IHD, Ischemic stroke

INTRODUCTION

Stroke is the third leading cause of death in developed countries after coronary heart disease and malignancy and important cause of hospital admission in a global perspective.[1] Stroke may be broadly classified into either ischemic stroke or hemorrhagic stroke. Stroke is characterized by the sudden loss of blood supply to the brain with concomitant loss of neurologic function due to either rupture (hemorrhagic stroke) or occlusion

(ischemic stroke) of blood vessels in the brain. These events deprive the brain of essential nutrients and oxygen, leading to brain necrosis with loss of function and irreparable damage.[2,3]

Data suggest the existence of a particular pattern in circadian variation of cardiovascular and cerebrovascular diseases.[4-7] Chronobiological variations such as circannual (annual) variation and circaseptan (weekly) variations also have been reported.[8]

This study was conducted to discover whether there is a period during the 24 hours of the day when stroke onset is more likely, to estimate the level of excess risk, and to determine whether this period of increased risk is different for various subtypes of stroke (ischemic or hemorrhagic).

METHODS

This cross-sectional study was conducted in the Departments of Neurology and Medicine, Sylhet MAG Osmani Medical College Hospital, Sylhet, Bangladesh from July to December 2014.

Consecutive cases of acute ischemic or hemorrhagic stroke regardless of age and gender experiencing stroke for the first time admitted in the Neurology and Medicine units of the hospital during the study period were included in the sample.

Stroke was diagnosed as a clinical syndrome consisting of rapidly developing clinical signs of focal (or global in case of coma) disturbance of cerebral function lasting more than 24 hours or leading to death with no apparent cause other than a vascular origin.

Patients with the transient ischemic attack, those having a history of previous stroke, and patients with a history of head injury were excluded. A sample size of 67 was calculated using Cochran's formula considering 5% level of significance, 6% precision level (marginal error) and prevalence of stroke of 4.6%.

Purposive sampling was employed as the sampling technique in this study. Data were collected in a pre-designed case record form. Informed written consent was obtained from the patients or guardians after full explanation of the details of the disease process and purpose of the study. Clinical diagnosis of stroke was established from history and thorough physical examination. Each day was divided into four sections of 6 hours duration each. Time calculation was started from 00:00 hrs (12 midnight).

Time of stroke onset was noted and each patient was bracketed in a particular 6 hour time period. The exact time was noted for patients who awake at the time of stroke onset. Information about the onset of stroke in patients, who were in asleep, was collected from their attendants. Past medical and personal history for cigarette smoking, arterial hypertension, diabetes mellitus, and ischemic heart disease and other associated disease condition were also sought.

Computed tomography (CT) scan of the brain was done within 24 h after stroke onset to stratify the patient into each category of ischemic and hemorrhagic stroke. The diagnosis and subtypes of stroke were confirmed on neuroimaging (CT Scan/MRI brain). Strokes were classified into ischemic stroke and intracerebral hemorrhage (ICH).

Fasting plasma glucose (FPG) and lipid profile were measured within 24 h after stroke onset after overnight fasting for at least 8 hours. A Sellectra 2 auto-analyzer (Vital Scientific, Spankeren, Netherlands) was used in the laboratory. Diabetes mellitus was diagnosed according to American Diabetes Association (ADA) criteria.[9]

Arterial hypertension was diagnosed when its presence was documented in medical records or when at least two readings of blood pressure was >140mm Hg (systolic) or >90mm Hg (diastolic) after the acute phase of stroke.[10] Ischemic heart disease was diagnosed when there was a history of angina pectoris or myocardial infarction.

According to the American diabetic association, hypercholesterolemia refers to a total cholesterol level of ≥200mg/dl; HDL-C considered low when the level was <40 mg/dl in male and <50 mg/dl in female; LDL considered high when the level was ≥100mg/dl; triglyceride considered high when the level was ≥ 150mg/dl.[9]

Ethical Consideration

Informed written consent was taken from each of the patients before taking any interviews after describing the purpose and methods of the study, confidentiality of the interviews, risks, and benefits of participating in the study. A pre-designed study protocol was submitted and approved by the Bangladesh College of Physicians and Surgeons (BCPS). All information was collected confidentially with complete respect to the patient with and without any force or pressure.

Statistical Analysis

Data were processed manually and analyzed with the help of SPSS version 16.0. Quantitative data were expressed as mean and standard deviation. Qualitative data were expressed as frequency and percentage and compared by using Chi-square test and Fisher's Exact test. p-value ≤0.05 was considered as statistically significant.

RESULTS

The mean age of the study subjects was 62.1 years, the majorities were in the age group ≥65 years, 64.2% were

male, 49.3% were smoker, 58.2% were hypertensive, 20.9% had DM, 20.9% had atrial fibrillation, 24.8% had IHD, and 41.8% had dyslipidemia. Stroke was ischemic in 59.7% and hemorrhagic in 40.3% of cases. 37.3% of the stroke events occurred during sleep (Table 1). The occurrence of stroke was most common during 6 am to 12 pm (47.8%), followed by 12 am to 6 am (25.4%), 12 pm to 6 pm (17.9%), and 6 pm to 12 am (9.0%) (Figure 1).

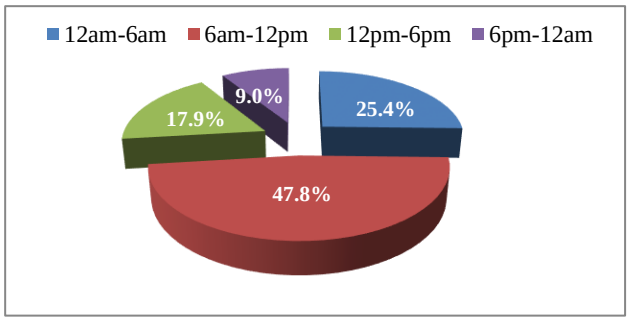

Figure 1: Distribution of the patients by time of occurrence of stroke (n=67).

The circadian variation of stroke was homogenous and statistically insignificant in association with age group (below 65 years and 65 years or above), gender, smoking habit, diabetes mellitus, atrial fibrillation, and dyslipidemia. But hypertension and ischemic heart disease were significantly associated with circadian variation of stroke (Table 2). The occurrence of ischemic stroke was most common during 6 am to 12 pm [19 (47.5%)] and hemorrhagic stroke was most common during 6 am to 12 pm [13 (48.1%)]. There was significant circadian variation noted for ischemic stroke ($p<0.001$) and hemorrhagic stroke ($p<0.05$) (Table 3).

Table 1: Characteristics of the study participants (N=67).

Variables	Subgroups	Values Mean±SD or n (%)
Age (years)		62.1±9.5
Age group (years)	Below 45	2 (3.0%)
	45-54	11 (16.4%)
	55-64	20 (29.9%)
	65 and above	34 (50.7%)
Gender	Male	43 (64.2%)
	Female	24 (35.8%)
Smoking status	Smoker	33 (49.3%)
	Non-smoker	34 (50.7%)
Hypertension	Present	39 (58.2%)
	Absent	28 (41.8%)
Diabetes mellitus	Present	14 (20.9%)
	Absent	53 (79.1%)
Arial fibrillation	Present	14 (20.9%)
	Absent	53 (79.1%)
Prior IHD	Present	19 (28.4%)
	Absent	48 (71.6%)
Dyslipidaemia	Present	28 (41.8%)
	Absent	39 (58.2%)
Sleep-Awake state	Sleep	25 (37.3%)
	Awake	42 (62.7%)
Stroke type	Ischemic	40 (59.7%)
	Haemorrhagic	27 (40.3%)

Table 2: Association of various risk factors and circadian variation of stroke (n=67).

Risk factors	Subgroups	12am-6am n (%)	6am-12pm n (%)	12pm-6pm n (%)	6pm-12pm n (%)	P-value
Age	<65 years	7 (41.2)	17 (53.1)	6 (50.0)	3 (50.0)	>0.05
	≥65 years	10 (58.8)	15 (46.9)	6 (50.0)	3 (50.0)	
Sex	Male	9 (52.9)	24 (75.0)	7 (58.3)	3 (50.0)	>0.05
	Female	8 (47.1)	8 (25.0)	5 (41.7)	3 (50.0)	
Smoking habit	Smoker	7 (41.2)	14 (43.8)	9 (75.0)	3 (50.0)	>0.05
	Non-smoker	10 (58.8)	18 (56.2)	3 (25.0)	3 (50.0)	
Hypertension	Present	6 (35.3)	24 (75.0)	7 (58.3)	2 (33.3)	<0.05
	Absent	11 (64.7)	8 (25.0)	5 (41.7)	4 (66.7)	
Diabetes mellitus	Yes	3 (17.7)	5 (15.6)	4 (33.3)	2 (33.3)	>0.05
	No	14 (84.4)	27 (84.4)	8 (66.7)	4 (66.7)	
Atrial fibrillation	Yes	4 (23.5)	3 (9.4)	5 (41.7%)	2 (33.3%)	>0.05
	No	13 (76.5)	29 (90.6)	7 (58.3%)	4 (66.7%)	
Prior IHD	Yes	1 (5.9)	14 (43.8)	2 (16.7)	1 (16.7)	<0.05
	No	16 (76.5)	18 (90.6)	10 (83.3)	4 (83.3)	
Dyslipidaemia	Yes	8 (47.1)	10 (31.2)	6 (50.0)	4 (66.7)	>0.05
	No	9 (52.9)	22 (68.8)	6 (50.0)	2 (33.3)	

Fisher's Exact test was applied to assess the level of significance.

Table 3: Association of types and circadian variation of stroke (n=67).

Types of stroke	12am-6am n (%)	6am-12pm n (%)	12pm-6pm n (%)	6pm-12pm n (%)	p-value
Ischemic	13 (32.5)	19 (47.5)	6 (15.0)	2 (5.0)	<0.01
Haemorrhagic	4 (14.8)	13 (48.1)	6 (22.2)	4 (14.8)	<0.05

Chi-Square test was applied to assess the level of significance.

DISCUSSION

Previous data suggest the existence of a particular pattern in circadian variation of cardiovascular and cerebrovascular diseases. Several studies have demonstrated that the onset of acute ischemic stroke occurs much more often in the morning hours.[11-14] The circadian pattern of onset is less certain for hemorrhagic stroke. However, a study of 137 cases of intracerebral hemorrhage between 1960 and 1989 noted a significant increase in the time of onset of intracerebral hemorrhage and subarachnoid hemorrhage between 8.00 and 16.00 hours.[15] Speculations about underlying physiological factors include relationship to diurnal variations observed in the production of hormones such as cortisol, insulin, and catecholamines, as well as sympathetic tone affecting heart rate and blood pressure (BP), platelet agreeability, blood viscosity, and fibrinolytic activity. The abrupt change in physical activity on awaking and arising is believed to be the major determinant of the diurnal variation of most of the above factors.[16,17] The current study conducted among 67 patients with acute stroke showed that the occurrence of stroke was most common from 6 am to 12 pm (47.8%), followed by 12 am to 6 am (25.4%), 12 pm to 6 pm (17.9%) and 6 pm to 12 am 6 (9.0%). This result was in agreement with the study of Argentino et al, that the frequency of onset of stroke was 56.1% during the interval from 6:01 am to Noon; 20.2% during the interval from 12:01 to 6 pm, 8.2% from 6:01 pm to midnight, and 15.5% from 12:01 to 6.00 am.[14] The rate of occurrence of stroke was highest in the late morning (0600–1159 hours) was reported by several other studies.[12,13] In the current study, 62.7% of patient's onset of stroke was during awake; while 37.3% occurred during sleep. Bassetti et al. found 79.1% of ischemic stroke occurred during awake and 20.9% during sleep.[18] Argentino et al. also found 78.6% of patients were awake when their stroke occurred (onset between 6:01 AM and 11 PM), and the remaining 21.4% awoke with stroke symptoms (onset between 11:01 PM and 8 AM).[14] In a minority of cases, which varies in the literature from less than 10% to as much as 44%, stroke occurs at night.[19] This suggests that sleep, although "protective" for most cerebrovascular events, may represent a vulnerable state for a subset of patients at risk for stroke. Nocturnal blood pressure swings, cardiac arrhythmias, and sleep-disordered breathing have been suggested as possible explanations for the nocturnal onset of stroke.

Circadian variation of stroke was homogenous and statistically insignificant in association with age group when categorized as below 65 years and 65 years or above years; sex; smoking habit, diabetes mellitus, atrial fibrillation, and dyslipidemia. But hypertension and ischemic heart disease were significantly associated with circadian variation of stroke. In this regards, Gupta et al. found that the age and sex distribution in morning strokes was not different from other groups.[6] They also found amongst the associated vascular risk factors, the only significantly associated vascular risk factor with late morning strokes was the association with IHD and hypertension. This suggests that hypertension and IHD could have an important associated role in the circadian pattern of stroke onset. Indeed, this circadian pattern is similar to that as observed in acute myocardial infarction, myocardial ischemia, sudden cardiac death, and other vascular events and has previously been reported.[20] A study has reported that between 6.00 hours and 12.00 hours there is a 40% higher risk of myocardial infarction, 29% increased risk of cardiac death and 49% increased risk of stroke.[21] This similarity in circadian pattern between cardiac and cerebral vascular events suggests a common underlying pathophysiological mechanism.[6]

In this study the occurrence of ischemic stroke was most common from 6 am to 12 pm (47.5%) and hemorrhagic stroke was also most common from 6 am to 12 pm (48.1%). There was significant circadian variation noted for ischemic stroke and hemorrhagic stroke. Butt et al. also observed significant circadian variations for both ischemic and hemorrhagic strokes.[8] Argentino et al. also found a significant circadian variation for ischemic stroke.[14] Passero et al. found a clear circadian variation of hemorrhagic stroke, with a peak of incidence between 6:00 AM and noon.[22] Thrombotic strokes could result from an increase in platelet aggregation and a reduction in fibrinolytic activity, which both occur during the morning. In fact, changes in platelet aggregation correlate with changes in plasma catecholamine levels, which actually increase between 6 and 9 AM.10 On the other hand, the fibrinolytic system represents reciprocal changes in the concentrations of tissue plasminogen activator (t-PA) and its fast-acting inhibitor (PAI) during the morning; Kluft et al. found high PAI activity in contrast to low tPA activity during the early morning, while this pattern was completely reversed at noon, when an increase in tPA activity and a decrease in PAI activity were observed; while hemorrhagic stroke events in the morning are due to the increase in sympathetic tone on awakening and the associated increase in blood pressure Passero et al.[14,22,23]

CONCLUSION

The study contributes further evidence for the circadian variation in the occurrence of ischemic stroke and hemorrhagic stroke. The findings of this study conclude that the incidence of ischemic stroke and hemorrhagic stroke are significantly increased between 6 am and noon. Attempts to prevent their occurrence must take into account this circadian variation. Appropriate preventive measures may be needed during these vulnerable periods.

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