Research Article

Circadian, circaseptan and circannual onset in stroke

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Abstract

Background and Objective: This study was done to evaluate circadian, circaseptan, and circannual rhythms in onset of stroke subtypes along with influence of risk factors, in local population. **Subjects and Methods:** 294 stroke patients, subtyped as Ischemic Stroke (IS), Intracerebral hemorrhage (ICH) and Subarachnoid hemorrhage (SAH) with Circadian (time in a day), circaseptan (day in a week) and circannual (season in a year) onset and risk factors were studied between January 2009 and December 2010 **Results:** 229 (77.89%) had IS, 63(21.42%) ICH and 2(0.68%) SAH. Bimodal peak of stroke onset noted, with bigger (51.7% patients) morning peak (4:01 am to 8:00 am), smaller (19.38% patients) evening peak (4:01 pm to 8:00 pm).Stroke subtypes and risk factors had similar pattern except diabetics (34 patients), had bigger peak in evening than morning. Stroke onset (circaseptan) was, on Wednesday (24.01%), Monday (21.83%), least on Sunday (14.87%) and similar in stroke subtypes. Seasonal (circannual) onset of stroke was highest in monsoon (34.01%), summer (33.67%), post monsoon (17%) and least in winter (15.30%) for all subtypes of stroke. **Conclusion:** Stroke onset has bimodal circadian peak (morning and evening), and attenuation of morning peak in diabetics and Circannual (seasonal) onset in monsoon and summer in local population.

Keywords: Circadian, circaseptan, circannual rhythm, Ischemic stroke (IS), Intra cerebral hemorrhage (ICH) and Subarachnoid hemorrhage (SAH).

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INTRODUCTION

Stroke is the culmination of a heterogeneous group of cerebrovascular diseases that is manifested as ischemia or hemorrhage of one or more blood vessels of the brain. The incidence of stroke exhibits the circadian, circaseptan and circannual pattern. Although ischemic and hemorrhagic strokes are different entities and are characterized by different pathophysiological mechanisms, they share an identical double-peak 24 h pattern. A constellation of endogenous circadian rhythms and exogenous cyclic factors are involved. The staging of the circadian rhythms in vascular tone, coagulative balance, and blood pressure plus temporal patterns in posture, physical activity, emotional stress, and medication effects play central and/or triggering roles. Features of the circadian rhythm of blood pressure, in terms of their chronic and acute effects on cerebral vessels, and of coagulation are especially important. Clinical medicine has been most concerned with the prevention of stroke in the morning, when population-based studies show it is of greatest risk during the 24 h; however, improved protection of at-risk patients against stroke in the early evening, the second most vulnerable time of cerebrovascular accidents, has received relatively little attention thus far[1].

MATERIALS AND METHODS

The study was carried out on 294 patients of stroke admitted to BRIMS Hospital, Bidar, over a period of two years, during January 2009 to December 2010. The diagnosis of stroke was defined, according to the World Health Organization criteria, as rapidly developing clinical symptoms or signs of focal or global loss of cerebral function, with symptoms lasting more than 24 hours or leading to death, with no apparent cause other than a vascular origin.[2]. Exclusions included major brain trauma, neoplasm, coma attributable to metabolic disorders, vasculitis involving the brain, peripheral

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neuropathy, hematological abnormalities, or central nervous system infections like tuberculoma and others. Transient ischemic attacks and silent brain infarctions (cases without clinical symptoms and signs) and patients whose stroke onset time was unknown were not included. **STROKESUBTYPES:** were then grouped into 3 major categories: Ischemic stroke ((IS): including thrombotic brain infarction, cardioembolic stroke, and lacunar infarcts), Intracerebral hemorrhage (ICH), or Subarachnoid hemorrhage (SAH).Clinical examination and CT scan was done to establish the diagnosis of stroke along with other appropriate investigations. **TIME OF ONSET:** Stroke onset time was defined as the earliest time the patient or a witness noted definite neurological symptoms or signs. It was obtained from patients, their relatives, or bystanders. For calculations of frequency of onset, the day was divided into six equal – 4 hour periods as follows:4:01 am to 8:00 am; 8:01 am to 12:00 noon;12:01 noon to 4:00 pm;4:01 pm to 8:00 pm;8:01 pm to 12:00 midnight;12:01 midnight to 4:00 am. **DAY OF ONSET:** The day of onset of stroke symptom was defined as the particular day in a week when onset of symptoms were noted. **SEASONAL ONSET:** The seasonal onset of stroke symptom was defined as the particular season in a year when onset of symptoms were noted. The season of onset was split into groups based on seasonal trends prevailing in Bidar as **WINTER:** December 1st o February 7th; SUMMER: February 8th to May 31st; **MONSOON:** June 1st to September 30th; POST MONSOON: October 1st to 30th November Age, gender, history of smoking/tobacco and alcohol consumption, diabetes, hypertension, cardiovascular disease, transient ischemic attack, results of CT scan brain were noted for each subject and the patient was followed up till discharge from the hospital. The observations were tabulated and statistical analysis was performed on the results applying non parametric chi square test.

RESULTS

The total numbers of patients included in the study are 294. **AGE INCIDENCE:** The youngest patient with stroke, in this study was a 20 year old female and the oldest patient was a 95 year old male. The incidence of stroke was highest (83 cases) in the 7th decade (61-70 years), which are 28.23% of all cases followed by 73 cases in the 6th decade (51-60 years), which are 24.83% of all cases, were statistically found significant $p<0.001$. **SEX INCIDENCE:** Out of 294 patients, 172 (58.5%) were males and 122 (41.5%) were females, was found statistically significant $p<0.001$.The ratio of male: female is 1.4:1. **SUBTYPES OF STROKE:** Out of 294 patients, 229 (77.89%) had Ischemic stroke (IS), 63 (21.42%) had intracerebral hemorrhage (ICH) and 2(0.68%) had subarachnoid hemorrhage (SAH), significant statistical association was found between stroke subtype, hypertension, mortality but not with gender, history of smoking/tobacco, alcohol, diabetes, cardiovascular disease, transient ischemic attack. **CIRCADIAN VARIATION IN ONSET OF STROKE:** A bimodal peak of onset of symptoms of stroke was seen with highest peak of 152 cases (51.74%) in morning between 4:01 am and 8:00 am. A second lesser peak of 57 cases (19.38%) in evening between 4:01 pm and 8:00 pm followed by 22 patients (7.48%) between 8:01 am and 12:00 pm, 30 patients (10.20%) between 12:01 pm to 4:00 pm and 26 patients (8.84%) between 8:01 pm and 12:00 midnight had onset of stroke. The lowest incidence 7 (2.38%) patients was seen between 12:01 midnight and 4:00 am. **CIRCADIAN VARIATION IN PATIENTS WITH IS:** 229 patients with IS, presented with bimodal peak of onset of symptoms with highest (124 patients-54.14%) morning peak of onset between 4:01 am and 8:00 am. A second lesser evening peak (57 patients-24.89%) between 4:00 pm to 8:00 pm (statistically found not significant) **CIRCADIAN VARIATION IN PATIENTS WITH ICH and SAH:** 63 patients with ICH had bimodal peak of onset, with first morning peak (26 patients-41.26%) between 4:01 am and 8:00 am. A second evening peak (18 patients-28.57%) between 4:00 pm and 8:00pm. Both cases of SAH had onset between 4:01 am to 8:00 am (statistically found not significant). **CIRCADIAN VARIATION AND ASSOCIATED RISK FACTORS:** Of the total 294 cases, the number of patients having associated risk factors was 250, which is 85.03% of all cases. The commonest risk factor is hypertension (179 patients-71.60%) followed by smoking (169 patients-67.60%) and diabetes mellitus (34 patients-13.60%).However only 14 (5.60%) patients with past history of TIA and 6 (2.40%) patients with cardiovascular disease was statistically significant. All the patients with risk factors exhibited higher morning and lesser evening circadian peak except in diabetics (34 patients) the highest (17 patients-50%) of onset of stroke was observed between 4:01 pm to 8:00 pm followed by 7 patients-20.58% between 4:01 am to 8:00 am and 6 patients-17.64% which was statistically fond significant $P<0.001$. **MORTALITY:** Out of the total 294 patients, 46 expired during their stay in hospital. The presence of circadian variation is evident in the mortality due to stroke .Out of the total 46 patients, who expired, 21 (45.65%) patients had onset of symptoms between 4:01 am and 8:00 am and lesser second peak of onset of symptoms between 4:01 pm to 8:00 pm. Table no. 3 shows the relation between Circadian (the time of onset of symptoms) and the number of deaths. Out of 46 patients who had expired 15 (32.60%) had ICH, whereas 30 (65.2%) had ischemic

stroke and 1 (2.17%) had SAH (Statistically not significant). **CIRCASEPTAN (Weekly) VARIATION IN ONSET OF STROKE:** Out of total 294 patients, 55(18.70%) had onset of symptoms on Wednesday 50 (17.00%) on Monday and least 34 (11.56%) on Sunday. Which was similar in stroke subtypes IS, 43 (18.77%) patients on Wednesday and 39 (17.03%) on Monday. ICH 12 (19.04%) patients on Wednesday and 11 (17.46%) patients on Monday. Irrespective of the day patients exhibited bimodal circadian rhythm. The circaseptan incidence of stroke along with sub types was statistically not significant. **MORTALITY:** Out of 46 numbers of deaths 9(19.56%) patients who had stroke onset on Thursday died while 8(17.39%) patients with onset on Monday died. However out of 30 deaths due to IS, 6(20.00%) cases with onset on Monday died while 5 (16.66%) patients each, on Thursday, Friday and Saturday died. Out of 15 patients of ICH 5 (33.33%) patients with onset on Wednesday died, while 4 (26.66%) patients died with onset on Thursday. Among 2 SAH cases 1 with onset on Sunday died. All these associations were statistically significant. **CIRCANNUAL (SEASONAL) VARIATION IN ONSET OF STROKE:** Out of 294 patients, 100 patients (34.01%) had onset of stroke symptoms during monsoon season and 99 (33.67%) had onset during summer, applying goodness of fit chi square test the above findings were highly significant p<0.001.Similar seasonal onset was found in stroke subtypes Out of 229 patients with IS, 80 (34.93%) had onset in monsoon and 78 (34.06%) in summer. Out of 63 patients with ICH, 21 (33.33%) had onset in summer and 20 (31.74%) in monsoon. Out of 2 SAH cases 1 had onset in winter and another had onset in post monsoon season (statistically found not significant) **MORTALITY:** Out of 46 patients who died, 17 (36.95%) patients had stroke onset in monsoon and 16 (34.78%) in summer. Out of 30 deaths with IS, 13 (43.33%) had onset in monsoon and 10 (33.33%) had onset in summer. However out of 15 deaths with ICH, 6 (40%) had onset in summer and 4 (26.66%) had onset in monsoon. One SAH death had onset in post monsoon season (statistically significant).

Table 1: Age and Gender Distribution of Stroke

AGE	<30	31-40	41-50	51-60	61-70	71-80	81-90	>91	TOTAL
Male	5	15	31	47	50	20	3	1	172
Female	3	5	7	26	33	37	9	2	122
Total No. of Cases	**8**	**20**	**38**	**73**	**83**	**57**	**12**	**3**	**294**
Percentage (%)	**2.72**	**6.80**	**12.93**	**24.83**	**28.23**	**19.39**	**4.08**	**1.02**	

X^2 = 30.977, P= 0.0001, Highly Significant

Total no. of cases: 294.

Table 2: Sub types of stroke and variables

	TYPE OF CVA			P Value
	Ischemic stroke	Intra cerebral hemorrhage	Subarachnoid hemorrhage	
Male	134	39	0	
Female	95	24	2	X^2=3.13 P<0.05 Not Significant
TOTAL No of Cases	**229**	**63**	**2**	
PERCENTAGE	**77.89%**	**21.42%**	**0.68%**	
Smoking/Tobacco	134	35	0	X^2=0.451 P<0.05 Not Significant
Alcohol	74	24	0	X^2=0.74 P<0.05 Not Significant
Diabetes	29	4	1	X^2=1.22 P<0.05 Not Significant
Hypertension	130	47	1	X^2=7.36 P<0.05 Significant
Cardiovascular disease	4	2	0	X^2=0.128 P<0.05 Not Significant
TIA	12	2	0	X^2=0.522 P<0.05 Not Significant
Mortality (In-hospital)	30	15	1	X^2=5.086 P<0.05 Significant

Table 3: Circadian Rhythm (Time of Onset) and Variables

	4:01 AM to 8:00 AM	8:01 AM to 12:00 PM	12:01 PM to 4:00 PM	4:01 PM to 8:00 PM	8:01 PM to 12:00 AM	12:01 AM to 4:00 AM	P Value
Male	88	15	17	33	14	5	X^2=1.36 P<0.05 Not Significant
Female	64	7	13	24	12	2	
Total	152	22	30	57	26	7	
Ischemic stroke	124	16	22	39	23	5	X^2=9.51 P<0.05 Not Significant
Intracerebral Hemorrhage	26	6	8	18	3	2	

Subarachnoid hemorrhage	2	0	0	0	0	0	
Smoking/ Tobacco	86	12	18	30	17	5	X^2=1.95 P<0.05 Not Significant
Alcohol Consumption	48	9	12	17	8	4	X^2=3.55 P<0.05 Not Significant
Diabetes Mellitus	6	3	2	15	7	1	X^2=27.59 P<0.001 Significant
<5 Years	4	2	2	6	4	0	
>5 Years	2	1	0	9	3	1	
Hypertension	90	12	20	36	18	3	X^2=2.81 P<0.05 Not Significant
Cardio Vascular Disease	1	0	0	3	1	1	X^2=11.17 P<0.05 Significant
Transient Ischemic Attack	6	0	1	5	1	1	X^2=4.92 P<0.05 Not Significant
Mortality (In-Hospital)	21	5	3	12	3	2	X^2=4.24 P<0.05 Not Significant

Total no. of patients: 294.

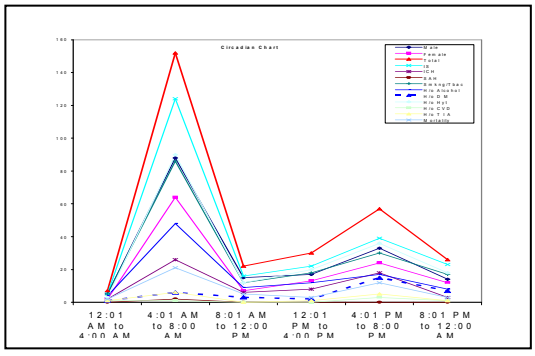
Table 4: Circaseptan (Day) and Circannual (Season) Onset of stroke

Day of Onset	Ischemic stroke (Mortality)	ICH (Mortality)	SAH (Mortality)	Stroke (Mortality)	P Value
MONDAY	39 (6)	11 (2)	0 (0)	50 (8)	
TUESDAY	30 (4)	7 (1)	0 (0)	37 (5)	
Wednesday	43 (2)	12 (5)	0 (0)	55 (7)	X2=8.255 P<0.05 Not Significant and
Thursday	33 (5)	6 (4)	0 (0)	39 (9)	(Mortality)
Fri Day	27 (5)	9 (0)	1 (0)	37 (5)	X2=29.46 P<0.01 Significant
Saturday	33 (5)	9 (2)	0 (0)	42 (7)	
Sunday	24 (3)	9 (1)	1 (1)	34 (5)	
Season of Onset	229 (30)	63 (15)	2 (1)	294(46)	
WINTER	30 (1)	14 (4)	1 (0)	45 (5)	X2=7.86 P<0.05 Not Significant
SUMMMER	78 (10)	21 (6)	0 (0)	99 (16)	And
MONSOON	80 (13)	20 (4)	0 (0)	100(17)	(Mortality)
POST MONSOON	41 (6)	8 (1)	1 (1)	50 (8)	X2=15.33 P<0.05 Significant

Table 5: Circannual (seasonal) variation in onset of stroke

	Winter	Summer	Monsoon	Post monsoon
Number of Cases	45	99	100	50

X2 = 36.96, P<0.001 Highly Significant.



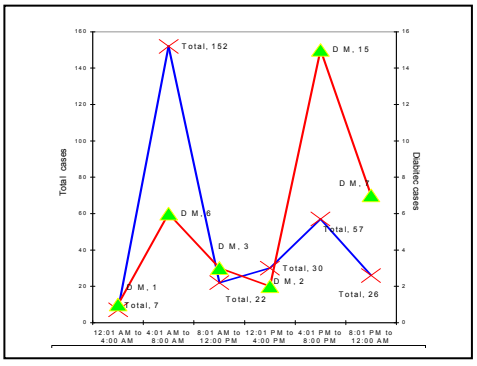


Figure 1:

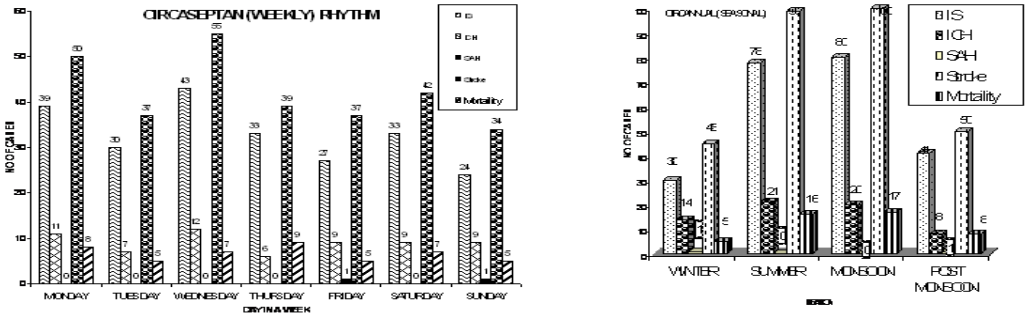


Figure 2:

DISCUSSION

The marked circadian rhythm in the onset of stroke is supposed to occur secondary to complex interplay between protective and trigger factors. These events occur throughout the day but at a relatively lesser rate than morning hours[3-6].These physiological changes are raised levels of catecholamines, raised blood pressure, increased platelet aggregability and decreased endogenous fibrinolytic activity. As we getup and attain an upright posture during early morning various physiological changes occur which can be grouped into hemodynamic changes, vascular changes and hematorrheologic changes[4,7]. The most important hemodynamic change is rise in heart rate and blood pressure. Along with decreased vagal tone, rise in catecholamine level and activation of rennin angiotensin system, make the atherosclerotic plaque more liable to rupture and thrombosis[4,7,8]. The vascular changes like increased vascular receptor sensitivity, increased vascular tone also contribute to the damage[3,7]. Increased platlet aggregability, increased blood viscosity and a fall in the fibrinolytic activity, are hematorrheologic changes which add fuel to the fire[3,5,7,9,10].Apart from these, various trigger factors act in conjunction with physiological changes in the early morning hours, like start of activity, bursts of anger, sexual activity and heavy physical exertion[4,6,8]. These trigger factors can precipitate an attack any time of the day. However getting up late, shift in time of awakening, starting activity at a later hour shifts the physiological effect of these to later hours[11]. In the hospital based study by Bhalla *et al*[12] of 146 patients, with 64.25% males and 35.8% females, is comparable to our study of 58.5% males (mean age 58.94yrs) and 41.5% females (mean age 66.81yrs) with change in male to female ratio(1.4:1), when compared to them (1.80:1).While subtypes of stroke in our study were 77.89%(IS) ,21.42%(ICH), they reported 55% hemorrhagic and45% ischemic. The mean age in our study is 62 ±14years, whereas they reported 58.5 ±6.5 years. In the meta analysis of 31 publications reported by William[13]Ischemic stroke 8250 (78.9%), Hemorrhagic 1801(17.22%) and 405 (3.87%) TIA were reported. In a community based-cohort (Framingham study) study[14] 45% were men (286 of 635), and mean ages were 69.7 years for men and 73.4 years for women. 61% were Acute Brain Infarcts (390 of 635), 25% were Cardiac Embolisms (156 of 635), 7% were IntraCerebral Hemorrhages (43 of 635), and 7% were Subarachnoid Hemorrhages (46 of 635). The above findings are comparable with our study. Our study had 85% patients with risk factors. Hypertension (60.54%), Smoking/Tobacco (57.48%), Alcohol (33.33%) consumption, Diabetes mellitus (11.56%), TIA (4.76%) and Cardio vascular disease (2.04%). In the study done by Cafagna D[20] *et al* the commonest risk factor was Hypertension (35%) followed by Diabetes mellitus (32%) and smoking (26%). In our study we noted that the risk factors had no influence on bimodal circadian rhythm except in diabetes there was a higher evening peak and attenuation of morning peak which was statistically significant P<0.001 finding. Similarly however diabetic subject did not show a significant circadian variation in the onset of acute myocardial infarction[18] The Bimodal peak of stroke onset in a day (Circadian rhythm), with higher peak in morning hours and lower peak in evening hours were reported in hospital based studies[12,15] and significantly morning peak was reported in all.[12-15] The subtypes of stroke, Ischemic stroke showed single morning peak in some studies and ICH,SAH showed double morning peak[16]. In Framingham study all cases of stroke had morning peak but ICH continued to peak till 4 pm. In meta-analysis[13] of stroke All three subtypes of stroke had a significantly higher risk between 6 AM and noon (55% for 8250 ischemic strokes; 34% for 1801hemorrhagic strokes, and 50% for 405 transient ischemic attacks). Framingham study[14] reported with Winter as the peak season for cerebral embolic strokes. Significantly more stroke events occurred on Mondays than any other day, particularly for working men. For intracerebral hemorrhages, a third happened on Mondays in both genders. A seasonal effect was found for IS, but not for hemorrhagic stroke. The peak occurrence was in

mid-May. Neither the region (i.e., climate) nor the race of the patient substantially modified the seasonal trend[15] However our study demonstrated all stroke subtypes had circadian rhythm with bimodal peaks in morning and evening but circannual rhythm showing peak 100 (34.01%) in monsoon (june-september) followed by summer (8thfebruary-may) 99 (33.67%) and least cases 30(10.20%) in winter(december-february7th) which is contrary to above study. In a study, the occurrence of ischemic stroke was the highest in summer, but the occurrence of hemorrhagic stroke was the highest in winter[16]. Berginer *et al*.[17] suggested that exposure to heat is likely to cause dehydration, increasing the viscosity of the blood. Also peripheral vasodilatation cause a reduction of blood supply to the central nervous system during heat exposure. These effects in persons without vascular disease might cause no damage, while in older patients with vascular disease the effects could predispose to thromboembolic episodes.

MORTALITY

In our study, out of the total 294 patients, 46 expired. The presence of circadian variation is evident in the mortality due to cerebrovascular accidents with 21(45.65%) had onset of symptoms between 4:01 am to 8:00 am. and second peak 12(26.08%) was found between 4:01PM to 08:00PM. Which was statistically not significant. Mortality was 30(65.21%) in IS, 15(32.60%) in ICH and 1(2.17%) in SAH.

CONCLUSION

Circadian, circaseptan, and circannual rhythms are found in stroke onset in the present study, though only circadian and circannual rhythms were statistically significant. Gender, history of smoking, alcohol, hypertension, TIA, CVD had no influence on these rhythms, except diabetics had attenuation of morning peak. The possible factors involved in temporal distribution of stroke for a morning peak has been elucidated in various studies but the evening peak cannot be explained on the basis of physiological changes. The evening peak may be a result of trigger factors like stress, anger or other such factors. These observations could be useful for a better understanding of the pathogenesis and treatment of stroke. As two distinctive peaks are seen the preferred timing of scheduling dose would be after lunch to cover the evening peak between and another dose of long acting drug to be taken after dinner to cover the morning. Further larger studies from different parts of the country and from rural areas and amongst different ethnic groups are needed for analyzing the presence of circadian, circaseptan and circannual variation to plan and change treatment strategies.

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ABBREVIATIONS

IS	: Ischemic Stroke
ICH	: Intracerebral Hemorrhage
SAH	: Subarachnoid Hemorrhage
BRIMS Hospital	: Bidar Institute of Medical Sciences Hospital
CT scan	: Computerised Tomographic Scan
TIA	: Transient Ischemic Attack
CVD	: Cardio Vascular Disease

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