Circadian Variation in the Onset of Acute Ischemic Stroke

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Abstract

Background: To evaluate the relation of circadian variation on onset of acute ischemic stroke.

Methods: In this descriptive study 181 patients with ischemic stroke were included. The time of onset of symptoms to determine the circadian variation was noted. In order to determine the frequency of acute ischemic stroke associated with circadian variation, the time of day was divided into four equal intervals of 6 hours each. Time of stroke onset was noted and each patient was bracketed in a particular six hour time period. These six hour periods were 0-6, 6:00-12, 12:00-18, and 18:00-24 hours.

Results : Out of 181 patients, majority (44.8%) had acute ischemic stroke during 6:00-12:00 hours. Mean age of the study population was 69.09 ±12.607 with age range from 36 to 97 years. Majority (74.6%) were male.

Conclusion: Incidence of ischemic stroke is significantly increased in the morning 6:01-12:00 hours.

Key Words: Circadian variation, stroke onset, ischemia.

Introduction

Stroke is the third leading cause of disability and death. According to World Health Organization (WHO), annually 15 million people worldwide suffer a stroke. Stroke caused an estimated 5-7 million deaths in 2005 and 87% of these deaths were in low-income and middle-income countries. In Asian countries the average age of patients with stroke is 15 years younger than in developed countries. In Pakistan, stroke not only increases mortality and morbidity, but also puts a great economic burden on the society. Estimated annual incidence is 250/100,000, translating to 350,000 new cases every year.

Recent data indicates that major unfavorable cerebrovascular events are not randomly distributed over time, but show a peculiar distribution along the day, the week, and the months of the year. Several studies have demonstrated that the onset of acute ischemic stroke occurs much more often in the morning hours. Chronobiological variations such as circannual (annual) variation, circaseptan (weekly) variation and circadian (diurnal) variation have also been reported. Although a well-defined pattern of ischemic stroke onset has been proved, there is insufficient information about circadian pattern amongst subtypes of stroke. Thrombotic strokes could result from an increase in platelet aggregation and a reduction in fibrinolytic activity, which both occur during the morning. Changes in platelet aggregation correlate with changes in plasma catecholamine levels, which actually increase between 6 and 9 AM. On the other hand, the fibrinolytic system represents reciprocal changes in the concentrations of tissue plasminogen activator (tPA) and its fact-acting inhibitor (PAI) during the morning. Early morning high plasminogen activator inhibitor with a low tissue plasminogen activator activity and a reversal of it in evening, substantiates the early morning occurrence of ischemic stroke. Blood pressure estimation also demonstrates a circadian rhythm that overlaps that of stroke onset.

Patients and Methods

This descriptive study was conducted at Shifa International Hospital, from March 2013 to September 2013. With the help of WHO Sample Size Calculator calculations measured were confidence level= 95%, anticipated population proportion = 8.2%, absolute precision required = 4% and sample size = n = approximately 181 patients. Inpatients (n=181), fulfilling the inclusion criteria were included. The time of onset of symptoms to determine the circadian variation was noted. In order to determine the frequency of acute Ischemic stroke associated with circadian variation, the time of day was divided into four equal intervals of 6 hours each. Time of stroke onset was noted and each patient was bracketed in a particular six hour time period. These six hour periods were 0-6, 6:01-12, 12:01-18, and 18:01-24 hours. Start of symptoms was considered as time of onset. Patients, with an age more than 25 years, presenting with acute ischemic stroke for the 1st time, within first 24 hours of onset of focal neurological deficit, were included. Patients with old ischemic stroke, recurrent ischemic stroke, hemorrhagic stroke on brain imaging, were
Acute ischemic stroke was defined as presentation within 24 hours from the onset of any one of the focal neurological deficit, i.e., muscle weakness (paresis), paralysis, lost/abnormal sensation on one side of the body, difficulty speaking, confusion, problems with vision, dizziness, loss of balance and co-ordination along with Imaging (showing acute ischemic changes/may be normal excluding bleeding) which includes CT scan brain (hypodense area) and MRI brain (hypoperfusion).

Results

Maximum number of acute ischemic strokes occurred between 6:01-12:00 hours. Two peaks of onset of symptoms were observed, first during 6:01-12:00 hours in 44.8% patients and the second between 12:01-18:00 hours in 24.9% (Table 1). A significant association was observed in time of onset of acute Ischemic stroke. The trough was evening time during the interval from 18:01 to 24:00 hours when only 10.5% had acute ischemic stroke. In addition, 19.9% patients had developed symptoms of acute ischemic stroke during 0-6:00 hours. It was observed that patients presented 4.0 times more during morning 6:01-12:00 hours as compared to evening 18:01-24:00 hours. Mean age of the study population was 69.09 ±12.607, with age range from 36 to 97 years. Male patients were more (74.6%) (Table 2). During the interval from 0 to 6:00 hours out of 36 patients, there were 69.4% male patients and 36.5% female patients; during the interval from 6:01 to 12:00 hours out of 81 patients, 72.8% were male patients while 27.2% were female patients. Patients who developed symptoms of acute ischemic stroke during the interval from 12:01 to 18:00 hours, were 45 in total out of which 80% were male and 20% were females. Similarly, male patients were greater in number i.e. 78.9% than female patients (21.1%) out of 19 patients who had their symptoms of acute ischemic stroke during the interval from 18:01 to 24:00 hours (Table 3).

Table 3: Circadian rhythm in acute ischemic stroke-Gender distribution

<table>
<thead>
<tr>
<th>Gender of patient</th>
<th>0-6</th>
<th>6:01-12</th>
<th>12:01-18:00</th>
<th>18:01-24:00</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>25(69.4%)</td>
<td>9(27.2%)</td>
<td>6(18.2%)</td>
<td>15(78.9%)</td>
<td>135(74.6%)</td>
</tr>
<tr>
<td>Female</td>
<td>11(30.6%)</td>
<td>13(37.5%)</td>
<td>9(27.2%)</td>
<td>17(81.1%)</td>
<td>66(25.4%)</td>
</tr>
<tr>
<td>Total</td>
<td>36(100.0%)</td>
<td>22(100.0%)</td>
<td>15(100.0%)</td>
<td>19(100.0%)</td>
<td>181(100.0%)</td>
</tr>
</tbody>
</table>

Discussion

Stroke is the third leading cause of death and main cause of adult disability worldwide. Data show that stroke onset is not random during 24 hours but it has a characteristic distribution. The clinical onset of myocardial infarction and stroke occurs more frequently in the early morning. Identification of high risk periods for vascular events may have important therapeutic implications, such as matching drug effects with vulnerability. Studies confirm the circadian variation in cases of cerebral infarction and intra cerebral bleed. In this local study, time of the day (24 hours) was divided into six equal intervals of 4 hours each. But Elliot found the results of the smaller time periods (3- or 4-hour “slices”) may underestimate the true circadian variation in stroke onset because statistical power of the meta-analysis diminishes as the number of time periods increases. Therefore, the time of day (24 hours) was divided into four equal intervals of 6 hours each in our study in order to determine the frequency of acute ischemic stroke associated with circadian variation.

A local study on 800 patients, where 55% cases were of ischemic stroke, 41% were of intracranial bleed and 4% were of subarachnoid haemorrhage, showed circadian variation on the onset of acute ischemic stroke. Of all acute ischemic stroke cases, 19.4% patients from 12am to 4am, 28.5% 4am to 8am, 12.6% 8am to 12pm, 16% 12pm to 4pm, 20% 4pm to 8pm, 3.4% 8pm to 12am.

Omama et al found that 20% of all CIF occurred during sleep. In their study, 44.8% ischemic cases developed stroke during sleep or at the time of awakening. Studies revealed that over 50% of ischemic stroke were either present on awakening or developed during earlier hours of the morning. A smaller peak in late after-noon in patients is probably attributed to the habit of afternoon nap (siesta) common in this part of world. Thrombotic strokes

Table 1: Acute ischemic stroke - circadian rhythm

<table>
<thead>
<tr>
<th>Hours</th>
<th>No</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-6</td>
<td>36</td>
<td>19.9</td>
</tr>
<tr>
<td>6:01-12</td>
<td>81</td>
<td>44.8</td>
</tr>
<tr>
<td>12:01-18:00</td>
<td>45</td>
<td>24.9</td>
</tr>
<tr>
<td>18:01-24:00</td>
<td>19</td>
<td>10.5</td>
</tr>
<tr>
<td>Total</td>
<td>181</td>
<td>100.0</td>
</tr>
</tbody>
</table>

Table 2: Acute ischemic stroke-Patients’ sex

<table>
<thead>
<tr>
<th></th>
<th>Frequency</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>135</td>
<td>74.6</td>
</tr>
<tr>
<td>Female</td>
<td>46</td>
<td>25.4</td>
</tr>
<tr>
<td>Total</td>
<td>181</td>
<td>100.0</td>
</tr>
</tbody>
</table>
could result from an increase in platelet aggregation and a reduction in fibrinolytic activity, which both occur during the morning. Changes in platelet aggregation correlate with changes in plasma catecholamine levels, which actually increase between 6 and 9 AM. The presence of late night second peak in present study could be a result of trigger factors like stress, anger, hot humid climate, intake of heavy night meals and other unidentifiable factors. 

A recent meta-analysis showed circadian variation in the stroke onset in both male and female patients in all groups. But the number of male patients was greater than female patients in each group. The frequency of atherosclerosis is lower in premenopausal women than men of similar age unless they have major stroke risk factors. Whether circadian variation on the onset of ischemic stroke is same for the patients with the risk factors or it differs, needs to be explored.

Finding of the early morning highest risk of the onset of stroke symptoms has broad implications. There is an evidence that acute emergent treatments for cerebral ischemia can be delivered in a timely fashion and result in improved long-term outcomes. This study indicates that irrespective of the type of stroke, most patients will be awake when the onset of stroke symptoms occurs. Blood pressure is often considered one of the most powerful risk factors for stroke and has a circadian variation that parallels the circadian variation in stroke onset. Antihypertensive agents administered in the morning ought to have a long duration of action to still have an effect on the early morning rise in blood pressure. It can be hypothesized that antihypertensive agents that specifically target the early morning rise in blood pressure and heart rate, without reducing blood pressure severely during the night, might be more advantageous in controlling the 20% rise in blood pressure during the hours around awakening. This appears also to be the time of day associated with an increased risk of stroke, myocardial infarction, and sudden cardiac death.

Conclusion
1. Incidence of ischemic stroke is significantly increased in the morning 6:01-12:00 hours. 2. Strategies to control blood pressure and coagulation, in accordance with the circadian variation of stroke onset, can have a positive impact on stroke prevention.

References