CLINICAL CHARACTERISTIC AND BLOOD PRESSURE MANAGEMENT IN ACUTE STROKE PATIENTS

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ABSTRACT

Introduction: Clinical characteristics to differentiate stroke subtype may be helpful to make sound decision in managing blood pressure in clinically stroke patients. This is more important while en route patient to tertiary centre for neuroimaging facility and neurosciences services. The objective of this study is to determine the distinction between ischaemic and haemorrhagic stroke based on the clinical characteristics. Time of presentation was also calculated to determine the feasibility of thrombolytic therapy among stroke patients in Malaysia.

Methods: A cross-sectional observational study of all stroke patients presented to Hospital Kuala Lumpur from January 2005 to May 2005. All patients were subjected to brain CT. Clinical characteristics – age, gender, loss of consciousness (LOC), headache, vomiting, Glasgow coma scale (GCS), systolic blood pressure and diastolic blood pressure – were assessed. Time of presentation was also determined. Multiple logistic regression analyses with the stroke types as the outcome (ischaemic=1 vs haemorrhagic stroke=0) were performed.

Results: A total of 143 patients (88 male and 55 female) were included. The mean age for haemorrhagic stroke was 51.1 (± 14.9) years old and mean age for ischaemic stroke was 56.8 (± 9.7) years old. Our logistic model shows five clinical characteristics were associated with types of stroke – age, GCS, sex, headache and LOC. Male (adj. OR 0.18, 95% CI 0.05-0.59), headache (adj.OR 0.16, 95% CI 0.06-0.47), LOC (adj.OR 0.20, 95% CI 0.06-0.66), age in years (adj OR 1.06, 95% CI 1.01-1.11) and GCS (adj.OR 1.44, 95% CI 1.14-1.82) were all significant (p-value < 0.05) in our model. Only 4.9% patients presented less than 3 hours and most of them (64.3%) presented more than 6 hours.
Conclusion: Male patients, having LOC and headache were the clinical characteristics predictive of lower chance of having ischaemic stroke. But, increasing age and higher GCS were more likely to associate with ischaemic stroke. BP in clinically stroke patients that have higher odds for haemorrhagic stroke should be lowered with a target of SBP $\geq 140$mmHg. There was significant delayed of presentation for stroke patients. Many factors need to be improved to reduce the time of presentation in the future.

*Key words: acute stroke, clinical characteristic, blood pressure, time of presentation*
INTRODUCTION:

Stroke causes dire consequences. It is one of the top five leading causes of death and one of the top 10 causes for hospitalization in Malaysia. Stroke is also in the top five diseases with the greatest burden of disease, based on disability-adjusted life years. The incidence and prevalence of stroke in Malaysia increased dramatically in the 5-year study period.

Clinical characteristic of stroke subtype - ischaemic or haemorrhagic stroke- is always challenging even for experienced physicians. The Allen and Siriraj scores were previously introduced to help physicians to clinically differentiate between ischaemic and haemorrhagic stroke. However, their clinical use is questionable as it has conflicting results in a few validation studies. The SCAN rule was introduced to help physicians to identify minor stroke patients who are likely to have haemorrhagic stroke. These clinical scores or rule are helpful to prioritise patients in the area where neuroimaging facility is limited, early referral to neurologists is almost impossible and prompt initiation of antiplatelet is crucial for secondary stroke prevention.

Management of blood pressure in stroke patients has better understanding with the published evidence of large clinical trials. Based on the studies, BP lowering is recommended in acute hemorrhagic stroke and is safe in ischaemic stroke. For patients with ischemic stroke, results of the China Antihypertensive Trial in Acute Ischemic Stroke (CATIS) trial showed that BP reduction does not improve or worsen the outcome. For patients with hemorrhagic stroke, SBP reduction around 140mmHg showed clinically feasible, well tolerated and seems to reduce the haematoma growth.

Since the emergence of thrombolytic therapy, the usage of intravenous recombinant tissue plasminogen activator (rt-PA) is indicated for carefully selected ischaemic stroke patients. Initial study showed rt-PA was limited to less than 3 hours, but with the third European Cooperative Acute Stroke Study (ECASS 3) trial, this treatment can be extended within 4.5 hours. The time of patients’ presentation to the hospital in Malaysia in relation to thrombolytic therapy has not been widely studied. The objectives of this study were to determine the time of presentation of stroke patients to the Emergency Department (ED) and to determine the distinction between ischaemic and haemorrhagic stroke based on the clinical characteristics. Hence this may guide primary or secondary health care centre to manage the blood pressure while en route patients to tertiary centre for CT scan and further management.

METHODS:

This cross-sectional observational study was conducted in ED, Hospital Kuala Lumpur (HKL) from January 2005 to May 2005. All patients, either new cases or referred cases who presented to ED HKL with suspected stroke were triaged by paramedics at triage zone. Detailed history, physical examination and complete neurological assessment were done for each patient.
by doctor in-charge. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured at triage by the nurse or medical assistant blinded to the study. Basic blood investigations were done for each patient to exclude any electrolyte and metabolic abnormality. All clinically diagnosed stroke patients underwent computed tomography (CT) scan of the brain to confirm the diagnosis. The results of the CT scan were reviewed by the emergency doctors and managed accordingly. Patients were then referred to neurology team on-call for further assessment and management. All the CT scans were also reviewed by the radiologist either on the same day or the next working day with a written report.

Time of presentation was defined as time from symptoms onset to the time of the assessment by doctor in-charge in ED HKL. Time of onset was defined as the time that the patients or family member noticed the symptoms. If the symptoms occurred during sleep, the time of onset was considered to be the time when the patient went to bed. Demographic data including gender, age group and ethnicity was obtained. Statistical analyses were done using the Statistical Package for Social Sciences (SPSS) where Pearson chi-square and independent t-test were performed for univariable analyses. Next, for multivariable analysis, we used binary logistic regression and set the outcome as stroke types; ischaemic (coded as 1) and haemorrhagic stroke (coded as 0).

**RESULTS:**

A total of 143 patients were included in the study with 88 (62%) and 55 (38%) of them were male and female respectively. Malay ethnic (54.5%) was the majority of the study population followed by Chinese (26.6%) and Indians (18.9%) patients. The youngest patient was 20 years old and the eldest was 89 years old. The mean age for haemorrhagic stroke was 51.1 (± 14.9) years old and mean age for ischaemic stroke was 56.8 (± 9.7) years old. The mean SBP for haemorrhagic stroke and ischaemic stroke were 174.8 mmHg and 166.6 mmHg respectively. Age, symptoms of loss of consciousness (LOC), headache and vomiting were significantly associated with haemorrhagic stroke. Poor Glasgow coma scale (GCS) and higher SBP were significantly associated with haemorrhagic stroke. There was no statistical significant difference between DBP among patients with haemorrhagic and ischaemic stroke.
Table 1: Demographic and Clinical Presentation of the Stroke Patients in ED HKL

<table>
<thead>
<tr>
<th></th>
<th>Haemorrhagic Stroke n(%)/mean(SD)</th>
<th>Ischaemic Stroke n(%)/mean(SD)</th>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>Male 33 (23.1%)/51.1 (14.9)</td>
<td>55 (38.4%)/56.8 (9.7)</td>
<td>0.014</td>
</tr>
<tr>
<td></td>
<td>Female 10 (7%)/17(11.9)</td>
<td>45 (31.5%)/82 (57.3%)</td>
<td>0.007</td>
</tr>
<tr>
<td>Age (years)</td>
<td>51.1 (14.9)/12.3 (2.4)</td>
<td>56.8 (9.7)/166.6 (21.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ethnic</td>
<td>Malay 22 (15.4%)/9.5 (2.8)</td>
<td>56 (39.2%)/12.3 (2.4)</td>
<td>0.802</td>
</tr>
<tr>
<td></td>
<td>Chinese 13 (9.1%)/174.8(22.5)</td>
<td>25 (17.5%)/166.6(21.1)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Indian 8 (5.6%)/97.5(12.6)</td>
<td>19 (13.3%)/96.6 (11.8)</td>
<td></td>
</tr>
<tr>
<td>LOC</td>
<td>Yes 33(23.1%)/14(9.8%)</td>
<td>25(17.5%)/7(4.9%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>No 10(7.0%)/29(20.3%)</td>
<td>75(52.4%)/93(65%)</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>Yes 26(18.2%)/12.3 (2.4)</td>
<td>18(12.6%)/7(4.9%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>No 17(11.9%)/29(20.3%)</td>
<td>82(57.3%)/93(65%)</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>Yes 14(9.8%)/14(9.8%)</td>
<td>7(4.9%)/7(4.9%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>No 29(20.3%)/29(20.3%)</td>
<td>93(65%)/93(65%)</td>
<td></td>
</tr>
<tr>
<td>GCS</td>
<td>9.5 (2.8)/9.5 (2.8)</td>
<td>12.3(2.4)/12.3(2.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SBP</td>
<td>174.8(22.5)/174.8(22.5)</td>
<td>166.6(21.1)/166.6(21.1)</td>
<td>0.039</td>
</tr>
<tr>
<td>DBP</td>
<td>97.5(12.6)/97.5(12.6)</td>
<td>96.6(11.8)/96.6(11.8)</td>
<td>0.681</td>
</tr>
</tbody>
</table>

* - Pearson Chi-Square
- Independent t-test

Table 2 derived from multivariate analysis shows the adjusted ORs for ischaemic versus haemorrhagic stroke. Five clinical characteristics were predictive for types of stroke: a) age, b) GCS, c) sex, d) headache and e) LOC. Our results show that for every one-year increase in the age and every unit increase in the GCS, the odds for ischaemic stroke became 6% and 44% higher, respectively. Conversely, being male (adj. OR 0.18, 95% CI 0.05-0.59, p<0.05), having headache (adj.OR 0.16, 95% CI 0.06-0.47, p< 0.05) and had LOC (adj.OR 0.20, 95% CI 0.06-0.66, p <0.05) were all related to having lower odds for ischaemic stroke, hence higher odds for haemorrhagic stroke. Only 7 (4.9%) patients presented less than 3 hours and number of patients with haemorrhagic and ischaemic stroke were 2 (4.7%) and 5 (5%) respectively. Most of the patients (64.3%) presented more than 6 hours (Table 3). None of the ischaemic stroke patients presented less than 3 hours received thrombolytic therapy due to delay in imaging and decision in the treatment.
Table 2: Adjusted odds to have ischaemic vs haemorrhagic strokes

<table>
<thead>
<tr>
<th>Variables</th>
<th>wald(df)</th>
<th>adj.OR(95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>6.05(1)</td>
<td>1.06(1.01-1.11)</td>
<td>0.014</td>
</tr>
<tr>
<td>GCS</td>
<td>9.22(1)</td>
<td>1.44(1.14-1.82)</td>
<td>0.002</td>
</tr>
<tr>
<td>Sex</td>
<td>Female</td>
<td>8.02(1)</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td></td>
<td>0.18(0.05-0.59)</td>
</tr>
<tr>
<td>Headache</td>
<td>No</td>
<td>11.33(1)</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>6.96(1)</td>
<td>0.16(0.06-0.47)</td>
</tr>
<tr>
<td>LOC</td>
<td>No</td>
<td>6.96(1)</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>0.20(0.06-0.66)</td>
<td></td>
</tr>
</tbody>
</table>

*Binary logistic regression
Haemorrhagic - 0
Ischaemic - 1

Table 3: Time of presentation in relation to the type of strokes

<table>
<thead>
<tr>
<th>Time of presentation</th>
<th>Haemorrhagic n(%)</th>
<th>Ischaemic n(%)</th>
<th>Total n(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than 3 hours</td>
<td>2(1.4%)</td>
<td>5(3.5%)</td>
<td>7(4.9%)</td>
</tr>
<tr>
<td>3-6 hours</td>
<td>25(17.5%)</td>
<td>19(13.3%)</td>
<td>44(30.8%)</td>
</tr>
<tr>
<td>More than 6 hours</td>
<td>16(11.2%)</td>
<td>76(53.1%)</td>
<td>92(64.3%)</td>
</tr>
</tbody>
</table>

Pearson Chi-Square : 22.01
P value : <0.001

**DISCUSSION:**

The majority of patients in this study were Malays, followed by Chinese and Indian. This is in keeping with the distribution of Malaysian population. Male patients were the majority and almost 40% of patients were female. This gender distribution was quite similar in previous studies done in Hospital Universiti Sains Malaysia (HUSM), Kelantan and Penang Hospital (12,13,14). Acute Stroke Registry Malaysia, 2010-2014 showed 55% of the patients were male with the mean age of 62.7 (±12.5) years old2. In this study, the mean age of patients with stroke was in 50’s compared to previous studies that showed mean age was 62.5 (±11.2) and 65 (±11) years old respectively12,13. This higher incidence in the relatively young population is yet to be determined.

Clinical characteristic to differentiate ischaemic and haemorrhagic stroke seems to be least important since the invention of CT scan. CT brain has been used widely to confirm and differentiate the diagnosis of either ischaemic or haemorrhagic stroke and has become paramount importance if reperfusion therapy is applicable15. However, in Malaysia, with limited facilities and availability of neurosciences services, clinical characteristic may be helpful to physicians to make sound decision in managing the patients’ blood pressure and starting the aspirin. From our
experiences, most patients from remote areas with minor stroke refused for tertiary referral because of the long journey and they think that their symptoms and signs are not serious.

Male patients, having LOC and headache and lower GCS are all characteristics associated with higher odds to have haemorrhagic stroke. This result is comparable with Siriraj score which include the altered level of consciousness, vomiting and headache as part of the clinical characteristics for haemorrhagic stroke\(^4\). However, our result is slightly different from the SCAN rule study that involves 4 symptoms - severe hypertension (S), confusion (C), anticoagulation (A), and nausea and vomiting (N) - as clinical characteristics\(^5\). The differences are possibly due to demographic, ethnic differences and severity of stroke as many patients in the SCAN rule study presented to outpatient clinic rather than hospital\(^8\). We reported that a single year increase in the age, would increase the odds for being diagnosed with ischaemic stroke by 6% (p-value=0.014) and 1 unit increase in GCS increased the odds for being diagnosed with ischaemic stroke by 44% (p-value=0.002).

Since this study was conducted prior to ECASS 3 trial, we took 3 hours as the cut point for time of presentation. Majority (95.1%) of our patients presented more than 3 hours to hospital from the onset of the symptom. Only 7 (4.9%) patients presented less than 3 hours. Presentation between 3-6 hours was seen in 30.8% of patients and 64.3% of them presented after 6 hours. Late presentation to the hospital was also observed in Penang Hospital which showed about 48% of the patients was brought to the hospital on the next day after the onset\(^14\). Other studies done in HUSM showed the mean time of presentation were 10.5 hours and 17.2 hours respectively\(^12,13\). Developed countries showed only 17–38% of stroke patients had arrived to hospitals within 2 to 3 h after onset of their strokes\(^16\). To date, late presentation is still happening and seems to have no change for the past 10 years. Out of 4762 first-ever ischemic stroke patients admitted to 13 government hospitals in Malaysia from July 2009 to June 2015, only 31 (0.65%) patients were treated with thrombolysis\(^17\).

In this study, ischaemic stroke constituted 69.9% and haemorrhagic stroke was 29.1% of all patients. This composition is almost similar with the study done by Ong and Raymond\(^14\). However Acute Stroke Registry Malaysia had a higher incidence of ischaemic stroke that accounts 79.4% of the cases\(^2\). From 7 patients who presented less than 3 hours, 2 (1.4%) of them had haemorrhagic stroke and 5 (3.5%) patients had ischaemic stroke that were eligible for the thrombolytic therapy. However, none of them received thrombolytic therapy as the diagnosis could only be confirmed after 3 hours. These patients may be benefitted under the ECASS 3 trial as the treatment can be administered within 4.5 hours\(^11\). Health promotion strategies to improve community awareness of early symptoms of stroke, education of local physicians about the importance of early referrals to the stroke centers and wider availability and use of ambulance services are promising methods to improve time of presentation to hospital\(^18\).
To improve the management of stroke patients with thrombolytic therapy, the ‘7 Ds’ of Stroke Care (detection, dispatch, delivery, door, data, decision and drug administration) must be strictly adhered to. This concept emphasizes the importance of pre-hospital and emergency care. Stroke should be given a priority dispatch similar to that for acute myocardial infarction or trauma to ensure early diagnosis and treatment. Blood pressure management is also important to improve the outcome of stroke patients. Outcomes are generally worse in those who present with either low or severely high blood pressure. With the loss of normal cerebral autoregulation, high BP can lead to cerebral oedema, haematoma expansion or haemorrhagic transformation whereas low BP can lead to increased cerebral infarction or perihaematomal ischaemia. Recent large, high-quality, randomised trials improve our understanding in managing BP in acute phase of stroke. For patient with acute ischaemic stroke, CATIS trial showed that no benefit of blood pressure reduction unless a patient's SBP is ≥ 220 mmHg or DBP is ≥ 120 mmHg. However this trial also showed that lowering the BP is not harmful for ischaemic stroke patient and can be considered safe.

As for haemorrhagic stroke, The Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial (INTERACT-2) showed early intensive lowering of SBP around 140mmHg is safe and associated with improved functional outcome. As such, we propose that BP of any patients with clinical characteristic of higher odds for haemorrhagic stroke should be treated intensively with a target of SBP ≥ 140mmHg. This practice may be considered as a standard practice in primary or secondary healthcare centre while enroute patient to tertiary centre for CT scan investigation and further management. If the CT scan result shows ischaemic stroke instead of hemorrhagic stroke, this practice is still safe and causes no harmful effect based on the CATIS trial.

**CONCLUSIONS:**

Our logistic model contained five important variables predictive of the type of stroke – age, GCS, sex, headache and LOC. Increasing age and GCS were associated with higher odds of being diagnosed with ischaemic stroke. Conversely, male patients, having headache and having LOC increased the odds to have haemorrhagic stroke. There was significant delayed of presentation for stroke patients. Many factors need to be improved to reduce the time of presentation. BP in clinically stroke patients that have higher odds for haemorrhagic stroke should be lowered with a target of SBP ≥ 140mmHg to improve the outcome.
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