HAEMORRHAGIC TRANSFORMATION IN ACUTE ISCHAEMIC STROKE AND ITS IMPACT ON FUNCTIONAL DISABILITY AND MORTALITY

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ABSTRACT

Background: Haemorrhagic Transformation (HT) is a common and potentially serious occurrence following acute ischaemic stroke with significant impact on patients’ outcome. Determining the predictors and its outcome will assist the management of acute stroke patients.

Materials and Methods: This was a prospective observational study, involving all acute ischaemic stroke patients admitted to University Kebangsaan Malaysia Medical Centre (UKMMC) from June 2008 to February 2009 (n = 73). A single observer, using pre-defined diagnostic criteria recorded information on demography, assessment of stroke severity on admission and at day 30 based on National Institute of Health Stroke Scale (NIHSS) score and functional disability at day 30 based on Modified Rankin Score (MRS). Computer tomography (CT) of the brain was performed within 24 hours of presentation and followed by MRI T2*2 weighted GRE (Gradient Echo Contrast) within 7 days of the onset of stroke. Earlier imaging was done if the clinical condition suggested HT. A neuroradiologist blinded to clinical information evaluated each scan for the presence of HT.

Result: Seventy three patients with acute ischaemic stroke were enrolled in the study and 19 (26%) of them developed HT. Using Multivariate analysis, the independent predictors of HT was NIHSS > 5 (OR 0.27; 95% CI 1.021-12.704; p=0.046). In multivariate analysis, independent predictors for poor functional outcome at 30 days was severe NIHSS score on admission (OR 2.958; 95% CI 1.713–5.108; p <0.001) and severe Glasgow Coma Scale on admission (OR 0.132; 95% CI 0.021-0.821; p < 0.001). The presence of severe NIHSS score on admission increased 30-day mortality (OR 1.528; 95% CI 1.03-7.217; p = 0.026).

Conclusion: HT was not significant associated with poor functional outcome and mortality at 30 days. Stroke severity on admission predicts the HT development, poor functional outcome and mortality at 30-days. HT does not affect the outcome and mortality after an acute ischaemic stroke.

Keywords: acute ischaemic stroke, haemorrhagic transformation, functional disability, mortality
1.0 Introduction

Stroke is consistently the top three cause of death and the leading cause of disability in elderly adults in Malaysia (1). Haemorrhagic Transformation (HT) after cerebral infarction is common and potentially serious occurrence following acute ischaemic stroke. The pathogenesis of HT is not well established, though ischaemic and reperfusion have been proposed to cause disruption of blood-brain barrier leading to extravasations of blood. Various autopsy and experimental studied on stroke patients have documented HT prevalence rate of 1.5% to 43% (2,3). Bayramoglu et al (4) documented HT on CT scan in 32.2% of their patients. A systemic review study by Richard et al (5) according to the Cochrane Collaboration methods of published reports of HT, showed that MRI appeared to detect more HTs (30-80%) than conventional CT brain imaging (0-60%). In a comparison study of CT brain imaging and three MR sequence (FSE-FLAIR, EPI-SE T2* weighted and EPI-GRE T2* weighted), the EPI-GRE T2* weighted sequence demonstrated highest sensitivity in detecting HTs (6). Several studies have reported the parameters such as advance age, hypertension, poor neurological status at onset, cardio-embolic stroke, large infarct size and MCA infarct, diabetes mellitus and clinical laboratory and radiographic characteristic increased the tendency to HT (7-9). The relationship between the predictors of HT, functional outcome and mortality has not been systematically examined and explored especially in our local setting. The prognostic implications of HT still remain uncertain despite increased understanding of its prevalence and pathogenesis. The purpose of this study was to describe the occurrence of HT after an acute ischaemic stroke detected by MRI GRE-T2* weighted sequence and to investigate the potential predictors for HT development and its impact on functional disability and mortality.

2.0 Materials and Methods

This is a prospective observational study in single hospital ( UKMMC). A cohort of patients were identified either admitted to general medical ward, high dependency ward or the intensive care unit with clinical diagnosis of acute ischaemic stroke (first ever) from June 2008 to February 2009. A total of 73 patients were enrolled in the study. Acute ischaemic stroke was defined as “rapidly developing clinical signs of focal (or global) disturbance of cerebral function, with symptoms lasting 24 hours or longer or leading to death, with no apparent cause other than of vascular origin” according to the World Health Organisation (WHO) criteria (10). HT was defined as multifocal secondary bleeding into ischaemic tissue of brain infarct, which extends ranging from small petechiae and confluent purpura to parenchymal haematoma. A single observe, using pre-defined diagnostic criteria, determined diagnosis of acute ischaemic stroke, and confirmed diagnosis with brain CT before being admitted to ward. The parameters on admission, which included glucose level, blood pressure, heart rate, Glasgow coma score (GCS), the stroke severity clinically by NIHSS score and radiologically by ASPECTS score were also recorded. The ASPECTS score was used for assessing the infarct size on CT imaging. All patients were subjected to brain MR within 7 days from acute onset of stroke symptoms. Earlier imaging was done if the patient symptomatic. ECASS I and II (European Co-Operative Acute Stroke Study) definition, based on brain MR finding was used to predict the outcome and functional disability and mortality in HT group. The neuroradiologist, blinded to clinical information and presentation, evaluated each scan for the presence of HT. MRI T2* weighted GRE echo imaging was used in this study. T2* weighted gradient echo sequence with TR of 800 ms, echo time (TE) of 26 ms, flip angle of 20⁰, thickness of 5mm, 20 axial slices, distance factor f 0.20, asymmetric matrix of n
x 25, 2 excitations acquisition time of 6 minutes and a field view of 250mm were used. HT was classified as HT from MRI T2* weighted GRE into 2 subgroups; HI Type I-II (defined as small petechiae to more confluent petechiae within infarcted area without space occupying effect) and PH Type I-II (defined as haematoma infarcted area with or without space occupying effect). The NIHSS is used to assess the level of neurological deficit that stroke patients have at the time of presentation. In this study, we chose NIHSS > 5 as unfavourable outcome and considered the patient have a severe stroke outcome. For the purpose of this study, therefore, 30-days favourable outcome and functional status were measured based on Modified Rankin score (MRS) = 0 - 5. A patient with MRS of 0 to 1 or 2 was considered to have a positive outcome score. Negative outcome scores were, therefore, 3 to 5 with 6 occasionally being used for death (independent factor). We chose day 30 as our prognosis predictor assessment as 50% of stroke survivor remain disabled and many need permanent help with activities of daily living at day 30 (7). The patient assessment on day 30 was performed via telephone interview (MRS is validated using via telephone interview).

**Statistical analysis:** All data was analysed based on the distribution of parametric and non-parametric tests. Two separate analyses were conducted. In the first analysis, the presence of HT was determined to be dependent variable. The independent variables were demographic characteristics, admission parameter, stroke severity, size of infarction and type of cerebral infarcts. Variables which were found to have a significant relationship (p<0.05) with presence of HT were included in a multiple logistic regression model. In the second analysis, similar steps were followed except that HT was now considered as independent variable and functional outcome and mortality were made the dependent variable. In both univariate and multivariate analyses, odd ratios with 95% confidence intervals (CI) were used to estimate the effects of each factor. The primary objective was to determine the prevalence of HT detected on brain MRI after acute ischaemic stroke. Secondly, we wanted to determine the potential predictors for HT and whether HT had an effect on functional disabilities and mortality in stroke survivors.

### 3.0 Result

#### 3.1 Demographic results:

During the seven months study period, 73 ischaemic strokes were identified. The mean age of study population was 64.3 years (36 to 92 years) and nearly equal numbers of gender (male 39, female 34) in this study. There were 25 (34%) Malay patients, 42 (57.2%) Chinese patients, 4 (5.5%) Indian patients and 2 (2.7%) patients were from other racial denomination. Based on the TOAST classification of stroke subtype, there were 24 (32.9%) patients in the Large Artery Artherosclerosis group, 38 (52.1%) patients in the small vessel ischaemia group, 5 (6.8%) patients in the cardioembolic group, 1 (1.4%) patient in the stroke of determined aetiology and 5 (6.8%) patients in the stroke of undetermined aetiology. Based on the ASPECTS score, there were 22 (30.1%) patients having an ASPECTS score of less than 8 and 51 (69.9%) patients having an ASPECTS score of more than 8 in this study. On admission, the mean systolic blood pressure was 164.0 mmHg (110 – 253 mmHg) and diastolic blood pressure 87.5 mmHg (51 – 126 mmHg). The median random blood glucose on admission was 7.1 mmol/l (IQR 6.2 - 10.4) ranging 3.4 to 24.1 mmol/L, Glasgow Coma Scale GCS 15 (IQR 2.0 - 15.0) ranging 9 to 15, NIHSS on admission was 6 (IQR 2.0-8.5) ranging 0 to 22 and Modified Rankin Score on day 30 was 3 (IQR 1.0-4.0) ranging from 0 to 6. HT was observed in 19 (26%) of all cases with acute ischaemic stroke. Among those developed HT, 12 (16%)
were male and 7 (9.5%) were female. There were 12 (63%) Chinese patients, 6 (31.5%) Malay patients and 1 (5%) from other races developed HT. No HT was seen in the Indian group. (Figure I). Based on ECASS I and II classification of HT subtype, there were 11 (57%) patients in HT I-II and 8 (42.1%) patients in PH I-II. Seven (9.6%) patients were dead 30days after the acute ischaemic stroke while 66 (90.4%) were still alive at day 30. Among those who developed HT, 2 (10.5%) died before 30 days and 17 (89.5%) of them were alive at the follow-up.

3.2 Predictors for haemorrhagic transformation (HT)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Wald Value</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>1.711</td>
<td>2.214</td>
<td>0.673-7.287</td>
<td>0.191</td>
</tr>
<tr>
<td>NIHSS &gt; 5</td>
<td>3.969</td>
<td>0.278</td>
<td>1.021-12.704</td>
<td>0.046</td>
</tr>
<tr>
<td>ASPECTS &lt; 8</td>
<td>3.475</td>
<td>0.326</td>
<td>0.944 – 9.966</td>
<td>0.062</td>
</tr>
<tr>
<td>Random blood glucose on admission</td>
<td>0.813</td>
<td>1.072</td>
<td>0.921 – 1.248</td>
<td>0.367</td>
</tr>
</tbody>
</table>

Multivariate logistic regression analysis; p < 0.05 is statistically significant

The multivariate analysis showed Stoke Severity NIHSS > 5 as independent predictor for HT development (Table 1). There was no significant increase in risk of HT in other parameter observed, namely gender, advance age, past history of diabetes mellitus, atrial fibrillation, ischaemic heart disease, blood glucose on admission, ASPECT score <8 and GCS on admission.

3.2 Predictors for poor functional outcome

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Wald Value</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>GCS on admission</td>
<td>0.132</td>
<td>0.132</td>
<td>0.021 – 0.823</td>
<td>0.030</td>
</tr>
<tr>
<td>NIHSS on admission</td>
<td>2.958</td>
<td>2.958</td>
<td>1.713 – 5.108</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age</td>
<td>1.094</td>
<td>1.094</td>
<td>0.997 – 1.201</td>
<td>0.059</td>
</tr>
<tr>
<td>Haemorrhagic transformation</td>
<td>0.156</td>
<td>0.156</td>
<td>0.015 – 1.653</td>
<td>0.123</td>
</tr>
</tbody>
</table>

Multivariate logistic regression analysis; p value < 0.05 statistical significant
In this study analysis, four variables (advance age > 75, Large artery atherosclerosis, NIHSS score > 5 on admission, GCS on admission) were associated with unfavourable outcome at day 30 after an acute ischaemic stroke ($p = 0.004$, $p=0.004$, $p < 0.001$, $p<0.001$). Independent predictors of unfavourable outcome at day 30 using multivariate analysis were GCS on admission and NIHSS on admission (OR 0.312 95% CI 0.021 to 0.823 $p = 0.03$; OR 2.958 95% CI 1.713 to 5.108 $p <0.001$) (Table 2).

### 3.3 Predictors of mortality at 30 days after stroke onset

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Wald Value</th>
<th>Odds Ratio</th>
<th>95 % CI</th>
<th>$p$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>GCS on admission</td>
<td>0.802</td>
<td>1.423</td>
<td>0.657-3.080</td>
<td>0.370</td>
</tr>
<tr>
<td>NIHSS on admission</td>
<td>4.980</td>
<td>1.528</td>
<td>1.03-7.217</td>
<td>0.026</td>
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<tr>
<td>Age</td>
<td>0.050</td>
<td>1.013</td>
<td>0.902-1.139</td>
<td>0.824</td>
</tr>
<tr>
<td>Haemorrhagic transformation</td>
<td>0.670</td>
<td>3.412</td>
<td>0.181-64.478</td>
<td>0.413</td>
</tr>
<tr>
<td>Gender ( Female)</td>
<td>2.529</td>
<td>0.077</td>
<td>0.003-1.815</td>
<td>0.112</td>
</tr>
</tbody>
</table>

Multivariate Logistic Regression; $p$ value < 0.05 is statistically significant

Advance age > 75, GCS on admission and NIHSS score > 5 on admission were associated with increased risk of mortality within 30 days of acute ischaemic stroke ($p <0.001$, $p=0.017$ , $p=0.017$). The NIHSS on admission was an independent predictor for mortality within 30 days after an acute ischaemic stroke (OR 0.011 95% CI 0.0 to 0.719 $p = 0.034$) in the multivariate analysis. Presence of HT and other parameter observed, namely blood pressure on admission, Stroke Subtype, size of infarctions and HT subtypes were not significantly increase risk of mortality within 30 days (Table 3).

### 4.0 Discussion

HT has been a recognised complication after an acute ischaemic stroke. The pathogenesis of HT has been investigated in experimental and clinical studies. One famous theory by Fisher and Adam [31] in 1951, postulated that HT occurs due to thromboembolus fragmentation with subsequent reperfusion of the ischaemic territory. Using the MRI, the rate of HT is expected to be high. A review by Richard et al. [32] published reports of HT showed the frequency of any HT using brain CT and MRI and in the absence of any treatment was 8.5% (95% CI 7%-10%). Based on this systemic review, the MRI detected more HT in comparison with CT (39%-85% versus 0%-60%). In our study, we focused on acute ischaemic stroke patients who were identified by using the WHO definition of stroke and its clinical and radiological features based on TOAST stroke subtype and ASPECTS score. We concentrated on events of HT in non-thrombolysed patients who were either symptomatic or asymptomatic. In this
study, HT developed in 19 (26%) of all cases with acute ischaemic stroke and mainly involved the large artery atherosclerosis subtype. This ranged between 13 and 71% in the literature. High rates have been reported in studies in which autopsy and advanced neuro-imaging tools were used. In our study, the rate of HT is lower than expected possibly due to the small number of subjects and the fact that some patients died before repeat MR images could be performed. In a study by Okada et al. [8] the rate of HT development in thrombolysed patients was reported as 6.2%, 27.5% and 40.6% on 4th, 5th and 30th day, respectively. Since HT development on only the first 14 days was considered in our study, the rate of 26% is higher in comparison with previous studies in non-thrombolysed patients. We expected a higher percentage as we used GRE T2* weighted MR images which is sensitive in detecting haemorrhage.

This study identified stroke severity NIHSS > 5 could help predict HT. Severe stroke severity has been shown to be a risk factor and associated with HT [4,6,8]. Stroke severity has been demonstrated to be a predictor for symptomatic HT in the NINDS trial and ECASS I/II study. In our multivariate analysis, NIHSS > 5 supported our finding and showed significant association with HT development. This finding supports the theory that stroke severity is an independent risk factor for HT. We analysed whether cardioembolism or atrial fibrillation were associated with HT. Autopsy studies [16,18] have demonstrated that haemorrhagic events occur in 51-71% of embolic stroke and thus significantly more frequent than non-embolic stroke (2-20% occurrence). In our study, there was no statistically significant association found between cases with atrial fibrillation or cardioembolic stroke (p = 0.750) and HT. This finding is consistent with the ECASS II secondary analysis which found that atrial fibrillation on admission or history of atrial fibrillation was not associated with an increased risk of HT. Blood glucose value of diabetic patients at the time of admission or in the acute period facilitates HT according to several reports [5-7]. Our data suggested an association between random blood glucose in the acute period and HT, although it did not reach a level of significance (p 0.077). Interestingly, in this study, we found that non diabetics and non ischaemic heart disease patient were associated with non HT ( p = 0.028 , p= 0.031). Perhaps they play protective roles in the development of HT and should be explored further. Older age group was reported as a parameter affecting HT and was shown to increase the tendency for HT in the ECASS I study. In a systemic analysis of 6 studies of intravenous thrombolysis with r-tPA, Engelter et al. [33] reported a higher 3-month mortality for patients aged 80 years and older to those younger than 80 years, but the rates of symptomatic HT were similar in both groups. There was no statistically significant association between age group and HT in our study. Hypertension (when blood pressure > 160/95 mmHg) has a three-fold overall increase in incidence of stroke. One interesting finding in a study done by Bayramoglu et al. [4] is that a higher rate of HT was found in non hypertensive patients compared to patients with preexisting hypertension and based on their study, hypertension alone cannot be identified as a contributing factor in HT. In our study, blood pressure during hospitalisation or history of hypertension was not related to the incidence of HT. We used the Aspects score-10 points quantitative topographic CT scan and TOAST classification of stroke subtype in evaluation of size of infarction and clinically in correlation with risk of HT development. In a study by Okada et al. [8], HT was more common in patients with large infarcts or midline shift of the brain. In their autopsy, Lodder et al. [16] emphasized that HT was related more to infarct size than to stroke mechanism. Therefore HT may indicate large infarcts and may predict ischaemic stroke prognosis. The Mast-E trial showed a threefold increase in the risk of symptomatic HT was noted in patients with early infarct size of less than a third of the MCA
territory, and the risk increased by six fold in those with changes affecting more than a third [19]. Similar results were obtained in the ECASS I study.

In our study, we found a significant relationship between clinical and radiological classification with HT development. From our data, we detected HT occurred more frequently in large artery atherosclerosis subtype. An ASPECTs score < 8 showed trend towards risk of developing HT, although it did not reach a level of significance. We investigated functional disability and mortality outcome in our stroke survivors and HT patients and found there was little difference between patients who did and did not develop HT. There are a few possible reasons for this. The patients who develop acute stroke and HT were referred early to our rehabilitation unit (i.e. physiotherapist and occupational therapist) to minimise complications and this early rehabilitation is associated with better stroke outcome. Secondly, it may be the case that HT has no negative effect on functional outcome and mortality in patients. Our univariate analysis showed a possible association between age and poor functional outcome of stroke survivors ($p <0.001$) with a mean age of 69.54 (SD 11.943) years. We believe that multiple factors such as multiple co-morbidities with advanced age had a role in poor functional outcome. Unfortunately, we did not look and explore further into that aspect. In our study, when we classified HT into 2 subtypes HI I–II and PH I–II, we found there were little differences in haemorrhagic subtype and functional outcome and mortality within 30 days. Our findings, therefore, are consistent with those from the ECASS study where, most haemorrhagic events (whether defined clinically or radiologically) do not lead to a poorer long term outcome. In this study, we detected small vessel ischaemia and small infarct areas were not statistically associated with poor outcome ($p < 0.046$). This supports the finding that small infarct size has better outcome and prognosis. Many previous studies have shown the importance of NIHSS in predicting the outcome of the patient [40]. In our data, we detected poor neurological status and GCS at the onset has worse functional outcome and mortality than the other group. We found that NIHSS on admission as the most important and independent predictor of HT, poor functional outcome and mortality compared to other variables. There are many factors contributing to mortality and morbidity of acute ischaemic stroke outcome within 30 days. In this study, we focused on the mortality within 30 days and several predictors that had been identified. Our study showed a 9.6 % mortality of acute ischaemic stroke over the 30-day follow-up. Among those who developed HT, about 10.5% died before 30 days. Univariate analysis showed age and stroke severity were predictors for 30-day mortality and with significantly increased risk for disability and death after stroke onset. Thus, they appear as confounding factors for influence of HT. Overall 30-day mortality and disability were not influenced by HT. In a recent paper, investigators reported the superiority of MR images in detecting intracerebral haemorrhages using a special MR sequence called gradient recall echo (GRE). Based upon the results from Kidwell CS et al. [39], MRI should be used instead of CT scan in the assessment of acute stroke due to its ability to better identify cerebral haemorrhage. In our study, we found that MR images of the brain in 19 patients with HT examined within 3 to 14 days of onset clearly demonstrated the sensitivity of GRE T2* weighted MR sequence for fresh intracranial blood. Based on our study, there is no significant prognostic value of MR images in detecting asymptomatic haemorrhage after an acute ischaemic patient as it does not affect the functional outcome and mortality of the stroke survivor. Thus, to repeat brain imaging after an acute ischaemic stroke is not necessary unless in symptomatic patients. In most institutions, CT scan is more readily available than MR. While MR may provide more information than CT in a hyperacute or subacute setting where the essential requirement is to exclude overt haemorrhage, CT may still be the preferred method. Our study has limitations. Our sample size was relatively small.
and the sample size for sub analysis for HT in this group was small (n=19). This raises the possibility that the predictors of HT and long term outcome and mortality could have been missed because of lack of power. The targeted number could possibly be achieved if this study involved multiple centers and was extended over a longer period. The small number of patients with HT could probably be due to a more severe stroke and patients died before repeat MR could be performed. Despite these limitations, our results have implications for the general concept in HT in acute ischaemic stroke, particularly in non-thrombolyzed patients.

5.0 Conclusion and recommendation

Stroke severity independently predicts the development of haemorrhagic transformation. However, we do not recommend that all MCA infarcts or all severe stroke patients be subjected for brain imaging unless they are symptomatic. This is because the occurrence of HT does not predict the outcome of the stroke patients (for both functional disability and mortality). However, larger studies need to be done to ascertain this. Stroke severity remains the strongest predictor for stroke outcome.

References


