THE KNOWLEDGE OF ACUTE STROKE MANAGEMENT AND ITS ASSOCIATED FACTORS AMONG HEALTHCARE PROVIDERS IN EMERGENCY DEPARTMENT, HOSPITAL USM

by

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ABSTRAK

Pengenalan:

Bukti terkini menunjukkan jurang yang besar antara bukti dan amalan rawatan strok akut, yang kemudiannya diterjemahkan ke dalam kadar penggunaan IV rtPA yang rendah. Sebagai penyaring maklumat dalam pengurusan awal untuk pesakit strok iskemia akut, petugas kesihatan di jabatan kecemasan perlu mempunyai pengetahuan yang mencukupi untuk meningkatkan kadar trombolisis intravena pada pesakit strok iskemia akut. Kajian ini bertujuan untuk mengenalpasti tahap pengetahuan pengurusan strok iskemia akut di Jabatan Kecemasan Hospital Universiti Sains Malaysia (HUSM). Seterusnya cuba untuk mengenal pasti faktor-faktor yang mempengaruhi pengetahuan.

Kaedah:

Kajian ini merupakan kajian rentas dari Februari 2018 hingga April 2018 di Jabatan Kecemasan Hospital Universiti Sains Malaysia (HUSM). Soal selidik yang telah divalidasi telah diedarkan kepada petugas kesihatan sepanjang tempoh waktu tersebut. Soal selidik ini mengandungi data sosiodemografik responden, pengetahuan asas dan pengalaman mereka terhadap pengurusan strok akut.

Keputusan:

Seramai 120 peserta terlibat dalam kajian ini. Terdapat lebih ramai wanita berbanding lelaki, (67 (55.8%)), dengan purata usia 31.2 (3.82) tahun. Kebanyakan peserta terdiri

daripada jururawat, (46 (38.3%)) atau doktor perubatan pascasiswazah, (45 (37.5%)). Skor purata untuk pengetahuan keseluruhan adalah tertinggi dalam kalangan pegawai perkhidmatan perubatan, dengan min skor 25.5 (5.19). Doktor perubatan pasca siswazah merupakan kumpulan kedua tertinggi dengan markah purata hampir sama iaitu 25.4 (4.22). Hanya 26.7% peserta tidak berpengalaman dalam penggunaan rTPA dalam trombolisis strok intravena. Petugas kesihatan yang pengalaman bekerja lebih lama (purata skor = 20.22 (6.71)) mendapat skor pengetahuan yang lebih tinggi berbanding mereka yang bekerja kurang dari 5 tahun (purata skor = 16.17 (8.2)) dengan -4.05 purata perbezaan (95% CI: 6.96, -1.14). Perbezaan yang signifikan dapat dilihat dengan faktor pekerjaan di mana doktor adalah lebih berpengetahuan.

Kesimpulan:

Kebanyakan petugas kesihatan mempunyai tahap pengetahuan yang lebih baik untuk pengetahuan pre-hospital dan pengurusan strok di jabatan kecemasan berbanding dengan pengetahuan untuk kriteria eligibiliti untuk trombolisis intravena. Ramai di antara mereka mempunyai minat dalam pengurusan pesakit strok dan berpengalaman dalam penggunaan rTPA dalam trombolisis strok. Pekerjaan sebagai doktor dan tempoh pengalaman bekerja mempunyai kaitan dengan skor pengetahuan yang lebih tinggi dan berpotensi untuk memperbaiki mutu pengurusan pesakit strok iskemik akut.

Kata Kunci:

Strok, jabatan kecemasan, pengetahuan, amalan, trombolisisis intravena

ABSTRACT

Introduction

Current evidence showed a huge gap between evidences and practice on acute stroke treatment, which subsequently translated into the low rate of intravenous (IV) thrombolysis usage. As a gatekeeper in initial management for acute ischemic stroke (AIS) patients, healthcare provider at emergency department (ED) need to have sufficient knowledge in order to improve the rate of IV thrombolysis. The aims of the study were to explore the level of knowledge on AIS management, as well as its associated factors for better usage of IV thrombolysis in the future.

Materials and Methods

This study was a cross-sectional study from February 2018 until April 2018 at ED Hospital Universiti Sains Malaysia (HUSM). A validated questionnaire was distributed among the healthcare providers during the study period. The questionnaire included respondent's sociodemographic data, experience and knowledge on acute stroke management.

Results

A total of 120 participants included in the study. There were more females than males, (67 (55.8%)), with a mean age of 31.2 (3.82) years old. Most of the participants were either staff nurses, (46 (38.3%)) or postgraduate medical doctors, (45 (37.5%)). The mean

score for the knowledge was highest among the service medical officers with mean score of 25.5 (5.19), followed by postgraduate medical doctors' group with mean score of 25.4 (4.22). Only 26.7% of participants have no experience in usage of rTPA in stroke thrombolysis. Participants who had more years of clinical working experience (mean=20.22 (6.71)) have higher score in knowledge compared to those who had clinical experience less than 5 years (mean=16.17 (8.2)) with -4.05 mean difference (95%CI: -6.96, -1.14). There were significant mean difference compared by occupations where doctors are more knowledgeable.

Conclusion

Most healthcare provider have better level of knowledge in pre-hospital and ED stroke management compare to the knowledge of eligibility criteria for IV thrombolysis. Many of them have interest in stroke management and had experienced in the use of rTPA in stroke thrombolysis. Occupation of doctors and clinical working experience are associated with higher level of knowledge and may improve the management of AIS patients.

Key Words

Acute stroke, emergency department, knowledge, practice, intravenous thrombolysis

CHAPTER 1: INTRODUCTION

1.1 Overview of Acute Ischemic Stroke

Acute ischemic stroke (AIS) according to American Heart Association (AHA) definition is a sudden loss of brain function due to disturbance in the cerebral blood supply with symptoms lasting at least 24 hours or leading to death (Kopyta and Zimny, 2015). The location, size and number of infarcts at presentation mainly accounts for clinical features of stroke patients. Due to the time-sensitive nature of reperfusion treatment, it is very crucial for patients readily have an idea regarding ischemic stroke symptoms, thus they seek medical attention acutely, and that they be diagnosed immediately (Meschia and Brott, 2018).

Reperfusion treatment that is FDA-approved from year 1996 is Alteplase. It is a recombinant tissue-type plasminogen activator (rtPA) that continues to be the only medication proven to improve outcomes when given in the hyperacute time frame after the onset of AIS (NINDS, 1995). However since the approval, its usage is persistently to be significantly underutilized (Fonarow et al., 2011; Go et al., 2013).

1.2 Dilemma in Acute Ischemic Stroke Management

Current evidences showed a huge gap between evidences and practice on acute stroke treatment, which subsequently translated into the low rate of intravenous (IV) rtPA use. As for instance, IV rtPA utilization rate is as low as 7% in Australia, 5% in United Kingdom and 7% in United States (Party and I.S.W, 2011; Foundation et al., 2013; Schwamm et al., 2013). A study by Grol R in Nijmegen, Netherlands estimated that 30-40% of eligible patients do not receive the treatment (Grol, 2001). Multiple obstacles and facilitators to implementation of best-practice care have been recognized at multiple levels, comprising the individual healthcare provider level, and the institutional and healthcare system level (Grol and Wensing, 2005; Carey et al., 2008). In Malaysia, a single centre experience regarding IV thrombolysis in AIS was published in 2017 showed that the utilization rate and its' related complications and outcome was comparable with other findings throughout the world (Keng et al., 2017).

Emergency Department (ED) healthcare providers have a cardinal role in the management of stroke patients (Grady et al., 2014). 7Ds' in stroke care has highlighted the important of their services. Detection, dispatch, delivery by the emergency medical services, door, data, decision and drugs involve the ED healthcare providers, either paramedic, nurses or medical officers. Priority dispatch, similar with acute myocardial infarction and trauma should be emphasize for acute stroke patients (Jauch et al., 2010; Baharuddin et al., 2016). Activation of stroke team also starts from the ED (Jauch et al., 2013).

A number of explanations may attribute to the low usage of IV rtPA, which includes the paucity of public education about recognition and actions taken following AIS symptoms and signs, the slow acceptance of the medication in the medical community, and the

complicatedness of the large system adjustments at the hospital level that is needed for this medication to be served in a safe and timely manner (Schwamm et al., 2009).

A study conducted by Stecksen et.al in 2014 found that the perceived barriers in low usage were paucity of knowledge, lack of recognition, scarcity in experience and stressful working condition. Many participants stated that despite an abundance of new evidence and advanced in stroke care, physicians and paramedics outside stroke care did not always acknowledge the treatment possibilities that were obtainable (Stecksen et al., 2014). Another study showed that even they have adequate knowledge about stroke sign and symptoms, yet they have low awareness of thrombolytic therapy (Mellon et al., 2015). Another commonly cited barrier was an experience deficit with thrombolytic among physicians on duty (Somerfield et al., 2006).

However, stroke research in Malaysia were focusing more on epidemiology, stroke-related risk factors, management and prevention strategies and outcomes for stroke survivors (Kooi et al., 2016). Until now, no similar study has been done in Malaysia assessing healthcare providers' knowledge of acute stroke management.

1.3 Justification of the study

In order for IV rTPA treatment to be extensively practice in emergency settings, knowledge towards the urgency of the treatment need to be in line with clinical practice guidelines. Looking at the worldwide issues on the low utilization of IV rtPA among eligible AIS patients and paucity of related data in Malaysia, we aim to assess the knowledge on acute stroke management among healthcare providers at ED, Hospital Universiti Sains Malaysia (USM). The association between possible factors like age, gender, occupation, working experience and experience attending stroke course are also assessed towards the knowledge. The study was carried out among staff nurses, medical assistants, service medical officers and postgraduate medical doctors.

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CHAPTER 2: STUDY PROTOCOL

2.1 Introduction

Cerebrovascular accident (CVA), also known as stroke, had been diagnosed increasingly not in Malaysia but globally as well. Worldwide, CVA are the second leading cause of death and third leading cause of disability-adjusted life-years (DALYs) from the Global Burden of Diseases, Injuries and Risk Factors Study (GBD) in 2010 (Lozano et al.,2012, Murray et al., 2012). It also one of the leading cause of dementia and depression (Owolabi et al., 2015). As a more daunting facts; there were nearly 25.7 million survivors of stroke (71% with ischemic stroke) and 6.5 million deaths from stroke (51% died from ischaemic stroke), 113 million DALYs due to stroke (58% due to ischaemic stroke) and 10.3 million new strokes (67% ischaemic stroke) in 2013 (Feigin et al., 2015). According to epidemiological projections, this figure will ascend to 77 million by 2030 (Béjot et al., 2016). Furthermore, there were an estimated 7.2 million cases of ischemic stroke among younger adults (Krishnamurthi et al., 2015), indicating the need for specific arbitrations in that age group. This is especially true for people living in low- and middle- income countries, as stroke occurs 15 years earlier- and causes more deaths, when compared to those in high income countries (Owolabi et al., 2015). Even though primary prevention has contributed to a reduction in stroke incidence in high income countries, the so-called 'epidemiological transition' has led to a rise in incidence in middle- to low-income countries as well (Béjot et al., 2016).

Whereas in Malaysia, stroke was reported as the third leading cause of mortality for males, in 2009, after ischaemic heart disease and pneumonia, whilst it ranked second for

females after ischaemic heart disease (Loo et al., 2012). The incidence and prevalence of stroke in Malaysia has shown an increased pattern for the 2010-2014 (Aziz et al., 2015).

The first stroke incidence study in Malaysia was administered in the South West District of Penang Island between April 2010 and March 2011 (Neelamegam et al., 2013). The overall age-standardized stroke incidence in the study region was 67 per 100,000 persons. Greater than half (53.1%) were males and nearly a quarter (23.7%) were recurrent strokes. Stroke patients in Malaysia were basically younger. The mean age of stroke onset in Malaysia was between 54.5 and 62.6 years (Jaya et al., 2002, Ong et al., 2002, Hamidon et al., 2003, Loo et al., 2012, Nazifah et al, 2012, Grover et al., 2014), yet it proves the global statistics that I have mentioned earlier.

Our Malaysian population study regarding acute ischemic stroke also have a comparable findings with other countries as well, as evidence by a comparison of Malaysian and Australian stroke registries on young adults aged between 18 and 49 years. The study showed a similar age of onset as well as gender ratio for ischemic stroke (Tan et al., 2010). The median age was 41.5 ±8.8 years for Malaysia and 40.1 ±8.8 years for Australia with a sex ratio of male to female 1.4:1 and 1.54:1 in collaboration.

There are two types of stroke, the ischemic and the haemorrhagic type. About two-third of reported stroke cases in Malaysia were of ischaemic type, while the rest one-third being haemorrhagic (intracerebral and subarachnoid haemorrhages) (Jaya et al., 2002, Ong et al., 2002, Hamidon et al., 2003, Loo et al., 2012, Nazifah et al, 2012, Neelamegam et al., 2013, Grover et al., 2014). In a single centre prospective study, by the whole of stroke patients admitted to Penang Hospital over one-year period, 74.8% were ischaemic and 25.2% haemorrhagic type (Ong et al., 2002). The other two studies across the country also showed similarity where ischemic stroke was recorded in the range of 73.3% to

79.9% (Nazifah et al., 2012, Neelamegam et al., 2013). In comparison with higher income countries, Malaysia had a higher percentage of haemorrhagic strokes (Neelamegam et al., 2013, Hamidon et al., 2003). The patients who miss their antihypertensive treatment reported to get more haemorrhagic stroke compared to ischaemic stroke (Grover et al., 2014).

Among all patients whom presented with acute ischaemic stroke; between 2009 and 2010, the Malaysian National Stroke Registry involving two tertiary hospitals in Terengganu and Penang recorded that 43.4% of ischaemic stroke patients had partial anterior circulation infarct (PACI), 27.4% had lacunar infarct (LACI), 16% had total anterior circulation infarct (TACI), 7% had posterior circulation infarct (POCI) whereas 6.2% were unclassified or uncertain (Nazifah et al., 2012). This classification are based on the Oxfordshire Community Stroke Project (OCSP) classification.

The intravenous recombinant Tissue Plasminogen Activator (rtPA) had been approved by the United State Food and Drug Administration (US FDA) as thrombolytic therapy for acute ischemic stroke (AIS) since 1995 (The National Institute of Neurological Disorders and Stroke (NINDS) tPA Study Group, 1995). It has been now 23 years elapsed since the publication of this randomized controlled trial, which commence a fundamental change in the management of acute ischemic stroke. One of the ticket to success of the NINDS rtPA study was the incredible numbers of patients who were suitable to be treated within 90 minutes of stroke symptom onset, a major logistic attainment that remains arduous for routine practice at many centres even until now (Campbell et al., 2015).

Following that, there have been 6 further randomized trials differentiating rTPA and placebo in different time windows 0 to 6 hours from stroke symptom onset (Figure 1; Table) (Campbell et al., 2015).

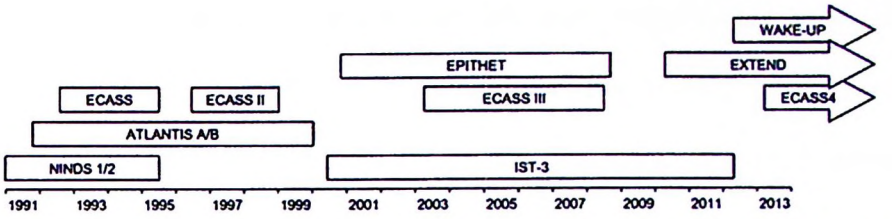

Figure 1. Evolution of the tissue-type plasminogen activator trials and ongoing efforts to extend the time window beyond 4.5 hours. ATLANTIS indicates Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke; ECASS, European Cooperative Acute Stroke Study; and EPITHET, Echoplanar Imaging Thrombolytic Evaluation.

Fig. 1: Evolution of rtPA trials

The latest individual patient meta-analysis published in 2014 highlighted the overall efficacy of rTPA in the 0-to 4.5-hour time window, despite of baseline stroke severity or age, but once more corroborating a prominent relationship with treatment time (Emberson et al., 2014). Even though there is still persistent remote but outspoken opponents of the evidence for rTPA, the treatment is no longer contentious among clinicians whom treating AIS patients. It is a mainstay of every evidence-based acute stroke guideline around the globe (Jauch et al., 2013, Lindsay et al., 2014).

Current class I recommendations from Level -A evidence for best practice showed that intravenous thrombolysis therapy with rtPA is an established treatment in AIS patients presenting within 3 hours after the stroke onset, whereas it is also recommended for patients presenting within 3 and 4.5 hours from AIS symptom onset; as it is graded as Class of recommendation I and level of evidence B-R (Furie et al., 2018). This recommendation is stated in the latest 2018 Guidelines for the Early Management of Patients with Acute Ischemic Stroke, from American Heart Association/ American Stroke Association (Powers et al., 2018).

Meanwhile, this treatment as a standard of care for acute ischemic stroke patients also available in the latest Malaysian Clinical Practice Guidelines (CPG) for Management of Ischemic Stroke that was released in 2012. In the guideline, it was mentioned that intravenous rtPA (0.9mg/kg, maximum 90mg), with 10% of the dose given as a bolus followed by a 60-minute infusion, is recommended within 4.5 hours of onset of ischaemic stroke. It has graded as Level of Evidence I, and Grade of Recommendation A in this CPG (Malaysian Society of Neurosciences, 2012).

Emergency Department Hospital USM readily have had a protocol regarding thrombolytic therapy in acute stroke. It was compiled by Senior Consultant Neurologist; Prof. John Tharakan, from a consensus reached by Neurologists, Neurosurgeons, Emergency Physicians, Radiologist and Anaesthetist. rTPA is available for treatment of acute ischemic stroke in Hospital USM since 2004.

2.2 Problem statement & Study rationale

Despite scientific evidences and increased support for the use of rtPA for acute stroke management, translation into clinical practice is slow (Langhorne et al., 2012; Norrving & Kissela, 2013; Berkowitz et al., 2013). Despite the fact that IV rtPA treatment rates may range as high as 20% to 30% in some hospital and quality registry (Grotta et al., 2001; Rost et al., 2012), national estimation of IV rtPA utilization only ranged 3% to 5% since 2004 (Adeoye et al., 2011; Nasr et al., 2013). However, a good fact is the rate of utilization is slowly improved over time, as evidence by a study done at Netherlands

showing mean national thrombolysis rate was actually increased from 6.4% in 2005 to 14.6% in 2012 (Scherf, 2016).

A lot of obstacles were said to restrict the clinical uptake of IV rTPA, namely the clinically exigent diagnosis, narrow therapeutic window, and the need to outweigh risk of symptomatic intracranial haemorrhage and benefit in patients (Rother et al., 2013). An effort to optimize service coordination mainly on pre- and in-hospital pathways may, nevertheless, increase the uptake up to 20% of patients being suitable using current guidelines (Morris et al., 2000). A lot of hard work is needed, as a study done by Hoffmeister et al. showed, the current rate of IV rtPA use of 2% has only minimal population impact. According to her study, we need to reach a minimum of 12% rate of IV rtPA uptake for us to gain the significant population effect on disability, thus should be a public policy aim (Hoffmeister et al., 2016).

The exact statistics on actual use of this thrombolytic usage in treating AIS was not available in Malaysia but the similar underutilization pattern may exist. This may be due to lack of knowledge or it is not a standard practice of the managing centres.

Thus, a study to assess the utilization of rtPA as part of acute stroke management is necessary. The level of knowledge need to be assessed as utilization is closely related to knowledge. This study findings may help in further plan on education and training to improve the services in managing AIS patients.

2.3 Literature Review

2.3.1 Acute Ischemic Stroke

American Heart Association (AHA) define stroke as a sudden loss of brain function due to disturbance in the cerebral blood supply with symptoms lasting at least 24 hours or leading to death (Kopyta et al., 2015). Whereby an article written by Hossmann K-A also mentioned that stroke occurs as a result of disruption in the blood supply to a brain region, causing death or permanent neurological deficits (Hossmann et al., 2006).

Patients suffering from AIS are predominantly in middle and late years of life. There are many modifiable risk factors which can predisposed patients to get AIS, which include cardiac disease (mainly atrial fibrillation), diabetes, hypertension, hyperlipidaemia, smoking, alcohol intake and oral contraceptive usage. Whereas non-modifiable risk factors also play a role for patients to get AIS, which comprise of age, gender, race, ethnicity and heredity (Shrestha et al., 2014).

Following stroke, a patient suffers a variable neurological deficits including balance problems, hemiplegia, loss of sensory and vibratory sensation, decreased reflexes, numbness, ptosis of the eyelid, aphasia, apraxia and visual field defects (Tsuchiya et al., 1992). These neurological symptoms is solely determined by the location and volume of the lesion, and eventually dictate the functional outcome. The functional outcome is actually the ability of the patients to be independent of him or herself, especially on basic daily living activities, suchlike eating, dressing, using the toilet and grooming, furthermore as the more advanced task, leisure or social activities. Modified Rankin Scale (mRS) score is the scale that usually been used to grade the functional outcome for AIS

patients; which graded between 0 to 6, with 0 suggesting normal functional status and 6 suggesting fatal outcome. mRS score of 0-2 indicates the patient is functionally independence for activities of daily living, and a score of 0-1 is usually categorized as an excellent functional outcome (Mikulik & Wahlgren, 2015).

We can further classify stroke to either ischemic or haemorrhagic subtype, depending on the underlying pathology (Amarenco et al., 2009). While both of them are distressing, ischemic stroke account for 87% of all strokes hence entitled the greatest stroke burden (MEMBERS et al., 2017).

The pathophysiology underlying stroke is complicated. Following ischemic stroke, neurons are divest of oxygen and energy with deleterious effects on energy-dependent processes in neuronal cells (Murphy et al., 2008). Instantly after ischemia, neurons are unable to support their normal transmembrane ionic gradient and homeostasis. This evokes various processes that lead to cell death: excitotoxicity, oxidative and nitrative stress, inflammation and apoptosis. These pathophysiological processes are badly injurious to neurons, glia and endothelial cells (Ouyang et al., 2007; Besancon et al., 2008; Xu et al., 2010; Breton et al., 2012) and are incorporated, triggering each other in a positive feedback loop that ceases in neuronal destruction (Siesjo et al., 1992). Figure 2 showed the details of pathophysiological response resulting in neural injury (Hossman, 2006).

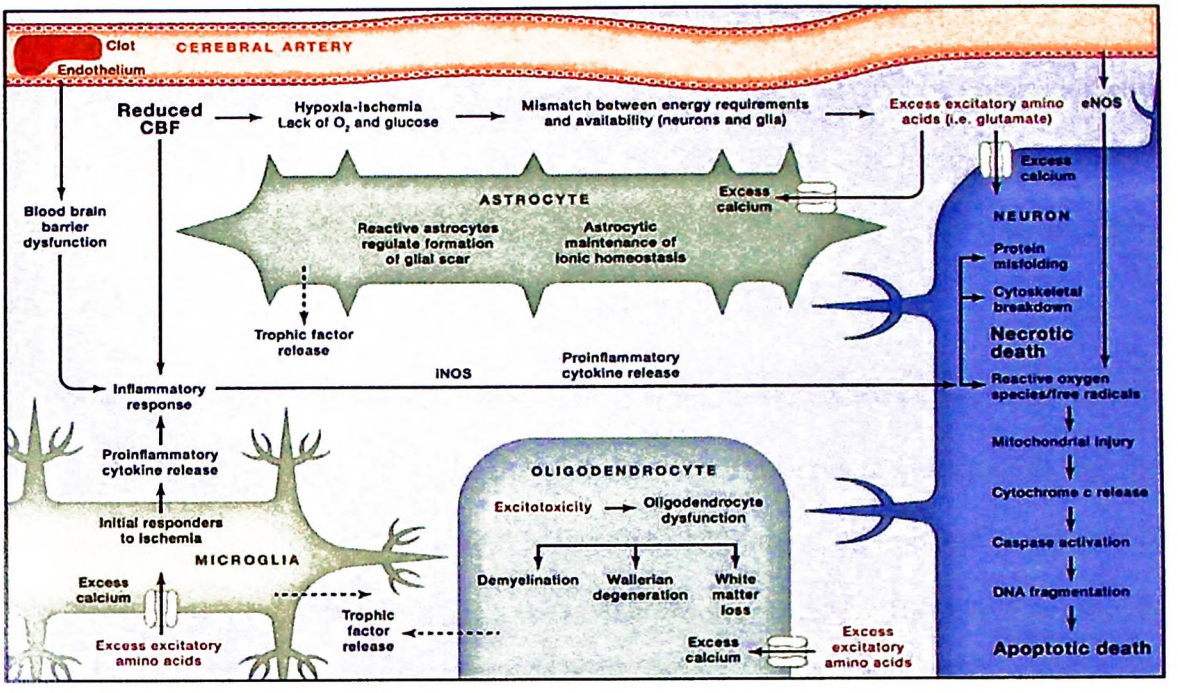

Figure 1. Pathophysiology of Stroke

Fig. 2: Pathophysiology of stroke

Ischemic stroke can be further classified depending on various aetiologies; either thrombotic stroke (large vessel and small vessel types); embolic stroke (with/without known cardiac and/or arterial factor); systemic hypoperfusion (Watershed or Border Zone stroke); or venous thrombosis. Regardless of the cause, the key event in majority (85-90%) of acute strokes is compromised vascular supply to the brain. Furthermore, brain tissue particularly endangered to effects of ischemia due to its low respiratory reserve and complete dependence on aerobic metabolism. A wide range of severity is generally seen in the affected region of the brain, due to the presence of collateral circulation. Consequently, part of the brain parenchyma (core) subjected to immediate death, meanwhile others may only partly injured with likely to recover (*penumbra*).

Cerebrovascular tissue undergoing ischemia has two layers: (a) inner core of severe ischemia with blood flow less than 10-25%, showing necrosis of both neuronal plus supporting glial elements; and (b) outer layer of less severe ischemia (*penumbra*), supplied by collaterals. This *penumbra* is the target for therapeutic agents, as it can be salvaged by timely therapeutic intervention (Deb et al., 2010).

Subsequently after an ischemic event, the centre of the core is perfused at 10-12ml/100g/min or less, meanwhile the ischemic area around it (surrounded by the *penumbra*) is desperately hypoperfused at less than 18-20ml/100g/min and is vulnerable of dying within hours. In contradiction, the *penumbra* is perfused at less likely at roughly 60ml/100g/min and is less likely to die (Heuschmann et al., 2003). Neurons in the penumbra is largely dysfunctional, but may salvage if reperfused in time. This is the foundation of current protocols which support early pharmacologic intervention for re-canalization of occluded vessel, because it will not only retrieve neuronal and glial cells from penumbra, but also glial cells from the central ischemic core zone as well, hence markedly limiting the size of infarcted tissue (Turner et al., 2007).

As mentioned by Saver in his article, for every minute an artery is occluded in an acute ischemic stroke event, an estimated of 2 million neurons die, in which over 10 hours is correspond to the anticipated neuronal loss happening with 26 years of normal aging process (Saver, 2006).

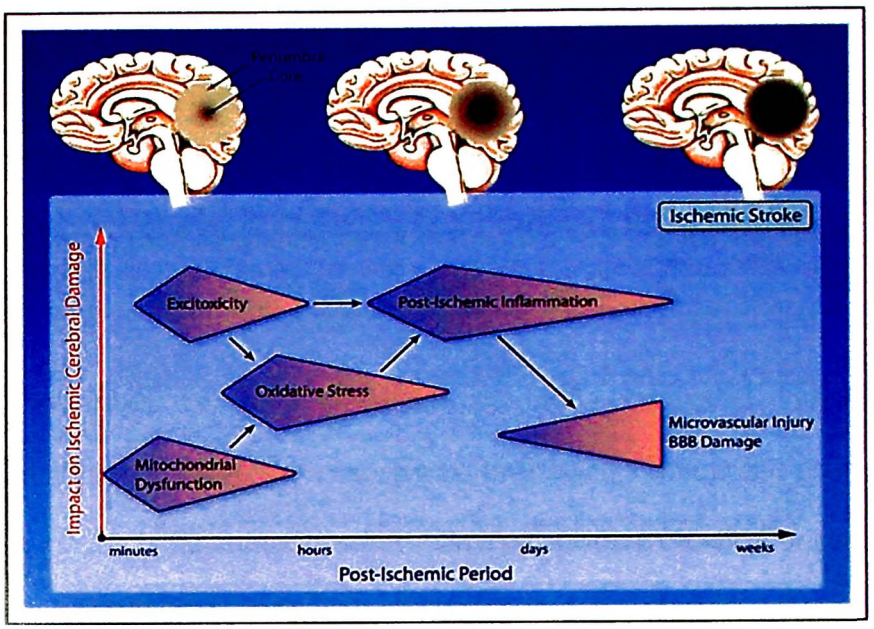

Fig. 3: Schematic presentation of the cascade of injury over time.

2.3.2 Burden of AIS

Stroke disseminate an abundant socio-economic burden to individuals, family and community. A study done by Aznida FAA et al. investigating the cost of treating an acute ischemic stroke from admission to the out-patient follow-up at a teaching hospital (Aznida et al., 2012). The mean in-hospital length of stay was 9.8 days for major strokes and 3.6 days for minor strokes. Roughly every stroke patient have to attend two outpatient clinic visits in three months period. An average, minor and major stroke engaged in 10 and 15 sessions of outpatient rehabilitation, respectively over six months. Collectively, the anticipated cost for hospital admission were MYR 9000 and MYR 3353 for a major and minor stroke mutually. Meanwhile in outpatient setting, the cost were quantified to be MYR 103 for each specialist clinic visit and MYR 43 for one rehabilitation therapy session per patient, irrespective of stroke severity (Aznida et al., 2012). The other case analysis study done by Nordin et al. described the mean cost of care per patient in a

teaching hospital is equal to MYR 3696.40 or 16% of per capita gross domestic product (GDP) per country. The cost was derivable mainly to human resource equivalent to MYR 1343.90 (36.4% of total direct medical cost), subsequently by medications (MYR 867.30 or 23.5%) and laboratory services (MYR 337.90 or 9.2%). The most severe stroke use up higher cost than mild stroke, by MYR 1598.10 (Nordin et al., 2012).

Apart from the financial burden, morbidity associated with stroke poses significant liability to patients, their caregivers, healthcare systems and providers. The main input to morbidity is functional disability. In a prospective observational study done by Rameezan et al. in 2005, at discharge, only 13% of post-stroke patients were able to ambulate with aids and 87% need assistance for ambulation of variable degree. After 3 months, 82% of them showed improvement in overall function, with 60% were ambulating independently while another 40% still required assistance (Rameezan et al., 2005).

2.3.3 Management of AIS

2.3.3.1 Intravenous thrombolysis (IVT)

Acute ischemic stroke is a neurological emergency, thus, rapid assessment and treatment are essential to improve neurological outcome. It can be treated with time sensitive interventions, including intravenous thrombolysis and endovascular approaches (Gross, Guilliams & Sung, 2015).

Thrombolysis is an application of thrombolytic agents to lyse a thrombus and subsequent re-establishment of cerebral blood flow by cerebrovascular recanalization and consecutive brain reperfusion (Schellinger et al., 2001b). Alteplase (recombinant tissue plasminogen activator or rTPA) commences local fibrinolysis by binding to fibrin in a thrombus (clot) and transforming entrapped plasminogen to plasmin. Sequentially, plasmin disperse the thrombus into fibrin degradation products.

There are in general two available AIS reperfusion strategies, a local (intra-arterial) approach or also known as endovascular therapy (EVT), and a systemic (intravenous) application of the thrombolytic agent.

US FDA approved the use of intravenous recombinant tissue plasminogen activator (rTPA) for acute ischemic stroke in 1996. It was a year after the publication of the landmark National Institute of Neurological Disorders and Stroke (NINDS) rTPA study (including Parts I and II), demonstrating effectiveness between 0 and 3 hours from stroke onset by disclosing a 30% relative risk reduction (absolute risk reduction of 11%-15%) compared with placebo at 90 days in the likelihood of having minimal or no disability. The number needed to treat was 8 to 9, for rtPA <3 hours. In other words, 31% to 50% of

the patients whom be given IV rTPA (depending on the scale used) had a good outcome at 3 months, in contrast with 20% to 38% of patients given placebo. The good outcome was found despite of ischemic stroke subtype and maintained 1 year after therapy. The trial showed a significant increased risk of spontaneous intracerebral hemorrhage in the rTPA group during the first 36 hours (rTPA 6% versus placebo 0.6%); though the overall mortality rate at 3 months between the groups was not statistically significant (rtPA 17% versus placebo 21%; P=0.30), and the proportion of patients left severely disabled was lower among those receiving rTPA (The National Institute of Neurological Disorders and Stroke rTPA Stroke Study Group, 1995). The NINDS trial was entitled as the pioneer placebo-controlled trial that showed efficacy of rTPA in AIS. The existing trials using different thrombolytic agents, dissimilar dosing, or different time windows were failed to show neither benefit nor harm.

Subsequent trials performed were concentrated on expanding the limits of the IV rtPA time window. ATLANTIS trial (Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke) Part A and B (Clark et al., 1999), EPITHET (Echoplanar Imaging Thrombolysis Evaluation Trial) (Davis et al., 2008), and ECASS trials (European Cooperative Acute Stroke Studies) 1 (Hacke et al., 1995) and 2 (Hacke et al., 1998) were unsuccessful.

A pooled analysis of the ATLANTIS, ECASS and NINDS rTPA studies in 2004 established the strong association between rapid treatment and favourable outcomes and proposed a potential benefit of rTPA infusion $\leq$4.5 hours after stroke onset, with an OR of 1.40 (CI 1.05-1.85) (Hacke et al., 2004).

The findings of the pooled analysis triggered the ECASS III study, which was drafted to assess the effectiveness and safety of rTPA in AIS between 3 and 4.5 hours. The study

exerted additional exlusion criteria in accordance with the European Medicines Evaluation Agency, including history of diabetes and prior stroke, age >80 years old, and NIHSS >25. The primary results showed a sparse yet significantly greater rate of functional independence at 3 months, in favour of rTPA groups compared with placebo within 4.5 hours of symptom onset (rtPA 52.4% versus placebo 45.2%; OR 1.34 (CI 1.02-1.76); P=0.04). The number needed to treat for benefit was 14 (Hacke et al., 2008). Remarkable differences in ECASS III in contrast with the NINDS study were lower recruitment stroke severity in both groups, a greater percentage of the placebo arm with a history of prior stroke, and the further exclusions limiting generality for older patients with more severe strokes. Even so, the AHA/ASA updated guidelines to support the use of rTPA in this extended time window for vigilantly selected patients (Powers et al., 2018).

The third International Stroke Trial (IST-3) was published in 2012, randomized the largest cohort of AIS patients (3035) to date. The standard dose of IV rTPA was given to the patients in the treatment group, up to 6 hours after stroke onset, with 72% of them was given rtPA after 3 hours. The investigators loosened the exclusion criteria, inclusive of eliminating any upper age limit and increasing the acceptable blood pressure range before rtPA treatment (systolic 90 to 220 mmHg; diastolic 40 to 130 mmHg) (Group, 2012). It showed that regardless of early hazards from a higher risk of ICH, thrombolysis within 6 hours' time window improved functional outcomes even in patients age >80 years, and the treatment benefit in the particular age group was at least as great as in younger patients. As a consequence, there is no more reason to exclude otherwise healthy elderly patients from thrombolysis.

The latest individual patient meta-analysis published in 2014 also revealed similar generalized efficacy across age and severity spectrum (Emberson et al., 2014). The meta-analysis in which included 6756 AIS patients, consistently showed benefits across different ischemic stroke subtypes (Mustanoja et al., 2011). As commented by Campbell in his topical review regarding the meta-analysis, he said that the available data found a neutral effect on mortality at 3 months since the ≈2% increase in fatal sICH in the first week was equilibrated by subsequent deaths in the placebo group due to complications of severe stroke. Among the overall 3 months mortality of ≈17%, most deaths in rTPA-treated patients corresponded to severe stroke rather than treatment-related issues. It is crucial to account that the risks of sICH equal to stroke severity and so the risk-benefit of treatment remains in proportion across the severity spectrum (Campbell et al., 2015).

2.3.3.2 Other approaches to IVT

There are several limitations of rTPA, including a short half-life (4-8 minutes), low recanalization rate of 30% to 40%, particularly for proximal occlusions and of <5% for distal ICA occlusions (Bhatia et al., 2010), adverse effects on the blood-brain barrier and neurotoxicity, ICH risks, time-sensitive administration, and extended list of absolute contraindications. The flaws of rTPA have encouraged investigators to evaluate other thrombolytic agents.

The promising results in the acute myocardial infarction ASSENT-2 trial (Anglo-Scandinavian Study of Early Thrombolysis) (Van De Werf et al., 1999) have initiated the series of clinical trials of tenecteplase in 1999. Tenecteplase safety for the treatment of AIS within 3 hours, at smaller doses compared with the dose reported in cardiology, was reported in the early phase IIB (Haley et al., 2010; Parsons et al., 2012) and a pilot studies

(Parsons et al., 2009) data, in addition with its benefit of higher early reperfusion rates as measured by perfusion/diffusion scans, and better functional outcome (NIHSS at 24 hours) when compared with rTPA. The results gave on to the ongoing phase III trials, TASTE (Tenecteplase versus Alteplase for Stroke Thrombolysis Evaluation Trial) (Demeestere et al., 2016), whereas the recently published NOR-TEST (The Norwegian Tenecteplase Stroke Trial) showed almost similar primary outcomes (354 (64%) versus 345 (63%), mortality rate at 3 months (29 (5%) versus 26 (5%), and serious adverse events (145 [26%] in the tenecteplase group vs 141 [26%] in the alteplase group; p=0.74) among the two treatment group. This showed that tenecteplase was not superior to alteplase and showed a similar safety profile. Since most patients enrolled in this study had mild stroke, further trials are needed to establish the safety and efficacy in patients with severe stroke and whether tenecteplase is non-inferior to alteplase (Logallo et al., 2017).

The other type of thrombolytic agent that have been studied was Desmoteplase, a fibrin-spesific thrombolytic drug with a longer half-life and less neurotoxicity than rTPA. Initial 2 trials; phase II trials (DIAS [Desmoteplase in Acute Ischemic Stroke] (Hacke et al., 2005), and DEDAS [Dose Escalation of Desmoteplase in Acute Ischemic Stroke] (Furlan et al., 2006) showed reperfusion efficacy within 9-hour window and safety at lower doses. Unluckily, the subsequent phase III studies (DIAS-3 (Albers et al., 2015) and DIAS-4 (von Kummer et al., 2016)) failed to show benefit.

Eventually, the integration of rTPA with other treatment options such as hypothermia, epifibatide, activated protein C, and consideration to extend the therapeutic time window of alteplase to $\leq$9 hours using novel imaging modalities are being investigated with the expect of improving IV thrombolytic therapy in this time sensitive, complicated disease process.