# PRELIMINARY STUDY OF CT PERFUSION OF PENUMBRA IN PATIENTS WITH HYPERTENSIVE INTRACRANIAL HAEMORRHAGE.

By

**DR ZULKIFLI ZAKI ABDUL GHANI**

**Dissertation Submitted In Partial Fulfilment Of The Requirement for the Degree Of Master Of Medicine (Radiology)**

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**2006**

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**To**

**My beloved wife, *Noraziana Abdul Aziz***

**Her loved, understanding and moral support enables me**

**to complete this project and my master program**

**My daughters, *Noraina Amalin, Noraina Aishah, Noraina Amalia.***

**Their cheers and smiles relief my stress**

**Their understanding make all this possible.**

**My parents and my in-laws**

**Thanks for their loves, constant full moral support and**

**enlighten my day and my daily duties**

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## ABBREVIATIONS

| | |
|---|---|
| **CBF** | Cerebral Blood Flow |
| **CBV** | Cerebral Blood Volume |
| **CT** | Computed Tomography |
| **CTP** | Computed Tomography Perfusion |
| **GE** | General Electric company |
| **HU** | Hounsfield Unit |
| **HUSM** | Hospital Universiti Sains Malaysia |
| **ICH** | Intracerebral Haemorrhage |
| **MBI** | Modified Barthel Index |
| **MRI** | Magnetic Resonance Imaging |
| **MTT** | Mean Transit Time |
| **NECT** | Nonenhanced Computed Tomography |
| **PET** | Positron Emission Tomography |
| **ROI** | Region Of Interest |
| **SPECT** | Single Positron Emission Computed Tomography |
| **STICH** | International Surgical Trial in Intracerebral Haemorrhage |

# ABSTRACT (MALAY)


**TAJUK**

Kajian preliminari imbasan perfusi tomografi berkomputer di kawasan penumbra bagi pesakit hipertensi dengan pendarahan di otak.

**PENGENALAN**

Hipertensi adalah masalah kesihatan utama di Malaysia dengan prevalen sebanyak 24% (Zaher et al., 1998) dan pendarahan otak (ICH) adalah komplikasi yang boleh menyebabkan kematian atau ketidakupayaan besar berbanding penyakit infaksi otak (Broderick et al., 1993).

Imbasan tomografi berkomputer tanpa menggunakan contras (NECT) adalah modaliti pengimejan utama untuk mendíagnos ICH. Terdapat percanggahan pendapat samada rawatan medikal atau pembedahan memberi kebaikan kepada pesakit. Imbasan perfusi tomografi berkomputer (CTP) membolehkan perfusi otak dikaji. Ini secara teorinya boleh diguna untuk pemilihan rawatan medikal atau pembedahan.

Barthel index yang diubah (MBI) adalah skala ketidakupayaan yang boleh dipercayai (Sulter et al., 1999) dan diguna sebagai penilai hasil.

**OBJEKTIF**

Kajian preliminari ini bertujuan mengenalpasti corak perfusi sekeliling darah beku and hubungkait dengan hasil klinikal. Ini akan diguna sebagai menjangka hasil akhir samada rawatan secara medikal atau pembedahan memberi kebaikan kepada pesakit. Kajian ini juga untuk mengenalpasti faktor penyebab ketidaknormalan perfusi di keliling darah beku dalam

ICH dan untuk mengenalpasti faktor penyumbang kepada hasil klinikal dalam pesakit ICH hipertensi.

**BAHAN DAN KAEDAH**

Dari Julai 2004 hingga November 2005, 10 pesakit telah dianalisa apabila kriteria peryertaan dipenuhi dan persetujuan bertulis diberi.

Imbasan NECT dijalankan untuk memastikan diagnosis ICH kemudian CTP dijalankan. Data dianalisa di 'CT workstasion'. Isipadu dan jarak darah beku dari tempurung kepala dikira di dalam imbasan NECT. Kawasan keliling darah beku dibahagi kepada 4 bahagian berdasarkan jarak dari tempurung kepala. Kawasan yang ingin dikaji di lukis berdasarkan peta warna CTP. Setiap parameter perfusi dihasilkan oleh perisian perfusi dan dianalisa samada kawasan tersebut mempunyai perfusi yang normal, penumbra atau umbra.

MBI di nilai sewaktu presentasi dan pada minggu keempat.

**KEPUTUSAN**

Perhubungan Spearman di antara umur dengan MBI sewaktu presentasi dan di antara isipadu darah beku dengan jarak dari tempurung kepala adalah ketara pada tahap 0.05 (2-tailed). Perhubungan Pearson antara isipadu darah beku dengan kecederaan iskemia adalah ketara pada tahap 0.01 (2-tailed). Terdapat kecederaan iskemia di kawasan keliling darah beku tetapi tiada hubungan secara statistik dengan keadaan klinikal.

**KESIMPULAN**

CTP adalah kaedah yang berguna, mudah dan praktikal bagi menilai perfusi keliling darah beku. Ketiadaan hubungan secara klinikal di dalam kajian ini berkemungkinan besar disebabkan jumlah kajian yang kecil.

#  ABSTRACT (ENGLISH)

**TOPICS**

Preliminary study of CT perfusion of penumbra in patient with hypertensive intracranial haemorrhage

**INTRODUCTION**

Hypertension is a major illness in Malaysia with a prevalence of 24% (Zaher et al., 1998) and haemorrhagic stroke is its complications which much more likely to result in death or major disability than cerebral infarction(Broderick et al., 1993).

Nonenhanced Computed Tomography (NECT) scan is the most common imaging modality used to diagnose intracranial haemorrhage (ICH). There were controversial issues whether medical or surgical treatment benefits these patients. CT perfusion (CTP) allowed the study of cerebral perfusion. Theoretically it is useful in selecting for treatment option.

Modified Barthel index (MBI) was a reliable disability scale (Sulter et al., 1999) and used as outcome assessment.

**OBJECTIVE**

This preliminary study was aimed to determine perfusion characteristics of perihaematoma region and correlation with clinical outcome. These will be used as predictor of the outcome whether medical or surgical treatment benefits the patients. This study also aimed to find contributing factors of abnormal perfusion in perihaematoma of hypertensive ICH and factors affecting its clinical outcome.

## MATERIAL AND METHOD

From July 2004 till November 2005, 10 patients were enrolled as they fulfilled the inclusion criteria and written informed consent obtained.

NECT scan was done to confirm ICH then CTP was performed. The data were analyzed at the CT workstation. Haematoma volume and distance from skull were measured in NECT scan. Perihaematoma regions were divided into four sections in relation to distance from the skull. The regions of interest were drawn based on CTP colour mapping. Each parameters of perfusion were produced by the perfusion software and were analyzed whether selected region were normal, penumbra or umbra perfusion status. MBI was scored at presentation and 4 weeks.

## RESULT

Significant statistical Spearman correlation at the 0.05 level (2-tailed) noted between ages and initial MBI, and haematoma volumes with haematoma distances to skull. Significant Pearson correlation of haematoma volume and ischaemic injury sizes at the 0.01 level (2-tailed) noted.

Perfusion ischaemic injury were found in perihaematoma region however no statistical correlation of the perihaematoma area with clinical outcome.

## CONCLUSION

CTP is a useful, easy and practical method in assessing intracranial perihaematoma perfusion however no correlation with clinical outcome. A bigger sample size may reverse these findings.

# SECTION ONE

## INTRODUCTION

# 1. INTRODUCTION

Hypertension is one of major chronic illness in developed and developing country. This disease causes several complications including hemorrhagic stroke. Currently, stroke imaging requirement has been increased tremendously due to new and more advance treatment. Previously, the managements of stroke were mainly conservative; therefore, conventional plain CT scan of the brain was the primary imaging modality. This is true especially in the ischaemic stroke when hemorrhagic stroke is needed to be excluded before starting thrombolytic agents.

In hemorrhagic stroke, plain conventional CT scan of the brain is adequate for the diagnosis. The examination is fast, reliable and available 24 hours a day in our hospital. At present, there is no consensus among the neurosurgical community regarding its optimal treatment (Tan et al., 2001).

The main treatment for hemorrhagic stroke is surgical removal of the blood clot; however, surgical intervention is not without a risk. This includes the effect of the anesthetic drugs and surgical techniques. Furthermore there are haemodynamic changes within the brain due to irritation and compression by the blood product within the brain parenchyma. Post-operatively, patient also has a risk of rebleeding. About 3.9% of patient had medium or large rebleeding after surgery (Fukamachi et al., 1985). It is undecided whether surgical evacuation of the haematoma or conservative management would result in better outcome (Tan et al., 2001). The international surgical treatment of intracerebral haemorrhage (ISTICH) multi-centre trial study noted that no benefit in early surgery compare with conservative treatment (Mendelow *et al.*, 2005)

Special Writing Group of the Stroke Council, American Heart Association (Broderick et al., 1999) have recommend indicator for surgical treatment of Intracranial Hemorrhage such as:

1. Patients with cerebellar hemorrhage >3mls who are neurologically deteriorating or who have brain stem compression and hydrocephalus from ventricular obstruction should have surgical removal of the hemorrhage as soon as possible.
2. ICH associated with a structural lesion such as an aneurysm, arteriovenous malformation, or cavernous angioma is treated if a patient has a chance for a good outcome and the structural vascular lesion is surgically or endovascularly accessible.
3. Young patients with a moderate or large lobar hemorrhage who are clinically deteriorating.

Blood clot within the brain parenchyma will cause compression, irritation and chemical changes of surrounding the brain tissue which might cause impairment of perilesional blood perfusion.

The more advance technique of CT scan such as CT perfusion, allows detection of cerebral ischaemia; identification of penumbra area and provides valuable information on the extent of perfusion disturbance (Koenig et al., 1998). In comparison with other imaging modalities such as xenon CT, SPECT, PET or MR Perfusion, CT perfusion has lower cost and more practical. It can be performed immediately after plain CT scan without repositioning of the patient with fast acquisition time (Eastwood et al., 2002). Perfusion CT studies of CBF achieved with adequate acquisition parameters and processing lead to accurate and reliable results (Wintermark et al., 2001).

Perihemorrhagic ischaemia may be a potential surrogate indicator to identify patients who will benefit from surgical removal of blood clot (Bullock et al., 1984). This will reduce patient's morbidity and mortality. This is an art of imaging; CT perfusion is currently applicable with our spiral high speed GE CT scan machine and GE CT perfusion software.

Modified Barthel index is functional assessment by assessing daily activity. It is a valid measure of disability (Collin et al., 1988). It measures parameters of personal hygiene, self bathing, feeding, toileting, stair climbing, dressing, bowel control, bladder control, ambulation and chair/bed transfer. Each parameter was scored and cumulative score will indicate dependency level. The higher the score, less dependent is the patient. These score were used in this study as assessment progression after treatment, either surgical or conservative.

Currently not many published data is available in using CT perfusion in assessing intraparenchyma cerebral haemorrhage as an indicator for the choice of treatment or prediction of clinical outcome.

Thus, this dissertation project aims to established pattern of perfusion in hemorrhagic stroke and the correlation with functional ability. Thus the findings will help in objectively measured the patient conditions and whether surgery is indicate.

A significant correlation of CT perfusion and Modified Barthel index will provide valuable prognostic information in management of hypertensive intracranial haemorrhage and improve usage of CT perfusion in evaluation and treatment in these patients.

# SECTION TWO

## LITERATURE REVIEW

# 2. LITERATURE REVIEW

## 2.1. INCIDENCE

The prevalence of hypertension in adult population found at screening ranges from 15-25%. In Malaysia a recent survey (the National Health and Morbidity Survey II) indicate a prevalence of 24% (Zaher et al., 1998)

Stroke is major cause of disability in developing and developed country. In United States of America, about 600,000 people suffer a stroke each year; 85% of them first attacks and 15% recurrent attacks (Dato' Chuah Jui Meng, 2002, Meng, 2002)

Haemorrhagic stroke is one of the complications of hypertensive disease. Control of elevated blood pressure has contributed to reduce in morbidity and mortality from stroke (Zaher et al., 1998). Intracerebral hemorrhage (ICH) is more than twice as common as subarachnoid hemorrhage (SAH) and is much more likely to result in death or major disability than cerebral infarction or SAH (Broderick et al., 1993).

Every year about 2,500 deaths and 12,000 stroke discharges are recorded in government hospitals (Jusoh et al., 2000). In Kuala Lumpur Hospital (KLH) 1,000 stroke cases are seen per year with 30-35% acute mortality (Jusoh et al., 2000). Ischaemic stroke seen in 67% of stroke cases and 33% were due to haemorrhage (Jusoh et al., 2000). Local study of spontaneous ICH conducted at Hospital University Science Malaysia (HUSM) revealed 22% of all stroke were haemorrhagic in origin and hypertension is the most important risk factor for ICH (Muiz et al., 2003). Another study for Malaysian population revealed that 9-31% of stroke was hemorrhagic (Ong and Raymond, 2002).

The worst prognosis in cerebral haemorrhage is acute mortality rate of 60-80% which is higher than seen infarction stroke about 20-40% (Jusoh et al., 2000). A study in HUSM noted, 25% mortality rate by 3 months, 58.9% poor final outcome, and 41.1% had a good outcome (Muiz et al., 2003).

## 2.2. DEFINITIONS

Stroke is a clinical symptom when there is a sudden loss of brain function caused by a blockage or rupture of a blood vessel to the brain, characterized by loss of muscular control, diminution or loss of sensation or consciousness, dizziness, slurred speech, or other symptoms that vary with the extent and severity of the damage to the brain. It is also called cerebral accident, or cerebrovascular accident.

Hypertension is defined when systolic pressure above 140mmHg and diastolic pressure above 90mmHg (Zaher et al., 1998). It can be categorized as mild (systolic 140-159mmHg diastolic 90-99mmHg), moderate (systolic 160-179mmHg diastolic 100-109mmHg), severe (systolic 180-209mmHg diastolic 110-119) and very severe (systolic >210mmHg, diastolic >120mmHg). Hypertension should not be diagnosed on the basis of a single measurement unless there is a target organ damage or systolic blood pressure >210mmHg or diastolic blood pressure >120mmHg (Zaher et al., 1998).

CT perfusion is a functional imaging showing changes in how parts of the brain tissue behave over time, particularly the density of blood product in those tissues. Contrast media is used, injected intravenously. Changes of various perfusion parameters over a short period of time are calculated. The parameters are cerebral blood flow (CBF), cerebral blood volume (CBV) and mean transit time (MTT).

Cerebral Blood Flow (CBF) is defined as the volume flow of blood through vasculature including the large conductance vessels, arteries, arterioles, capillaries, venules, veins and sinuses in a given brain volume in a given time. Units: ml/min/100g. (Cullen et al., 2002)

Cerebral Blood Volume (CBV) is the volume of blood in the vasculature including the large conductance vessels, arteries, arterioles, capillaries, venules, veins and sinuses in a given brain volume. Units: ml/100g (Cullen et al., 2002).

Mean Transit Time (MTT) is blood traverses the vasculature through different path lengths such that there does not exist in a unique transit time from the arterial inlet to venous outlet. Instead there is a distribution of transit times and the mean transit time is the mean time of such a distribution.

Penumbra is the areas adjacent and surrounding the haematoma which has perfusion less than normal but higher than infarction values. It is an area of ischaemic viable tissue. If the tissues become infracted or non-viable, it is called umbra area.

## 2.3. PATHOLOGY/PATHOGENESIS

Hypertension is among the commonest causes of atraumatic cerebral hemorrhage in adults (Bagley, 1999, Ong and Raymond, 2002). Hypertensive hemorrhages typically occur within the putamen, thalamus (Bagley, 1999, Tan et al., 2001, Hsiang et al., 1996), external capsule, and posterior fossa, particularly pons and cerebellar hemispheres (Bagley., 1999).

In hemorrhagic stroke, haematoma will be formed within brain parenchyma. This causes increase in perilesional pressure gradient and limits the extent of haemorrhage. This pressure gradient will cause compression to the microcirculation. Haematoma also will cause reduction in regional cerebral blood flow (Mendelow et al., 1984, Xi et al., 2001) with production of chemical vasoconstriction (Mendelow et al., 1984). These effects will cause perilesional ischaemic changes and brain cell changes. Acidosis, edema, potassium and calcium ions transit and inhibition of protein synthesis may contribute to cerebral ischaemia (Siesjo., 1992). This is seen as marked swelling of astrocytes particularly perivascular astrocytic foot processes on electron microscope (Bullock et al., 1984).

The time when the surgery is performed is also important. Red blood cells (RBCs) constituents such as hemoglobin and its degradation products (oxyhemoglobin, deoxyhemoglobin or methemoglobin) those appear after delayed lysis, increase blood-brain barrier permeability, contributing edema formation. Oxyhemoglobin is a spaminogen (Xi., 2001) and also can induce apoptosis in cultured endothelial cells and apoptosis has been found in intracerebral haemorrhage (Ogihara et al., 1999, Matsushita et al., 2000, Gong et al., 2001). This can occur when the cerebral blood flow value is 10-15ml/min/100g causing failure of energy dependent sodium pump. This leads to accumulation of intracellular sodium and water shift into the cells causing neuronal swelling leading to cytotoxic oedema. This edema causes leakage from epithelial lining of capillaries leading to vasogenic edema 6 hours after ischaemic event. Cerebral edema increases intracranial pressure and further compromises the blood supply to the brain parenchyma.

Thrombin has been implicated in brain injury and edema formation after intracerebral hemorrhage. Erythrocyte lysis causes marked blood brain barrier disruption and increases blood brain barrier permeability to 11 fold. This causes significant entry of prothrombin into brain (Xi et al., 2001). If activated factor X is present, an efflux of prothrombin results in the generation of thrombin within the brain, leading to edema formation.

Perilesional edema on CT scan images always corresponded topographically with perfusion deficits on SPECT (Mayer et al., 1998).

In hypertensive patients, degenerative changes occurred such as perivascular micro infarcts, lacuna formation, sub adventitial vascular micro hemorrhages, and fibrinoid vessels necrosis(Bullock et al., 1984).This may worsen the ischaemic insult.

Infarction occurs in all of the patients with cerebral blood flow (CBF) reduction of more than 70% and in half of the patients with CBF reduction of 40% to 70% (Mayer et al., 2000). Although vulnerable neurons may undergo selective injury with mild degrees of ischaemia, many cells will survive for significant period of time with reductions in cerebral blood flow of up to 40% of normal (Cullen et al., 2002). At this level of reduced perfusion, neurons have ceased to function normally and become electrically silent, no longer releasing neurotransmitters, but have not undergone cell death (Cullen et al., 2002). This region is called ischaemic penumbra area. Normal autoregulation mechanism will lead to an increase in cerebral blood flow and mean transit time. Restoration of blood flow to penumbra ischaemic area will reverse the ischaemic injury. (Cullen et al., 2002). In umbra area (non-viable ischaemic tissue), the autoregulation mechanism is abolished so that both cerebral blood flow and cerebral blood volume are reduced with a normal mean transit time. To preserve this vulnerable (penumbra) area, surgical intervention might be useful to release the pressure on adjacent blood vessels.

However, surgical evacuation of long standing intracerebral haematoma may establish reperfusion of a large zone of perilesional ischaemic tissue, thus worsening edema and possibility neurological status(Bullock et al., 1988).

## 2.4. CONVENTIONAL CT SCAN IMAGING IN HEMORRHAGIC STROKE

Conventional computed tomography (CT) is the main and primary imaging modality being performed for diagnosis of intracranial and intracerebral haemorrhage (Jager and Saunds, 2001). The acute haematoma will appear as increased radiodensity on CT and reaches around 100 HU (Chang et al., 2004, Jager and Saunds, 2001). The increased density of blood in relation to the surrounding parenchyma of the brain relates to the hemoglobin protein contained in extravasated blood (Chang et al., 2004).

The site of haematoma may give a clue for the causes. The basal ganglia or thalamic bleed in hypertensive patient is suggestive of hypertensive intracranial bleed. No further investigation require unless the cause is not obvious. This may require CT angiogram or reconstruction images. The mass effect, perilesional oedema and intraventricular haemorrhage are the common accompanying features. These may cause further injury to brain parenchyma.

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Its CT density depends on the initial haemoglobin level, dilution by extracellular fluid and partial volume effects. Very rarely haematomas can be isodense to surrounding brain, in severely anaemic patient with haematocrit of 20% or less (Jager and Saunds, 2001).

Acute intracerebral clot is usually rounded and homogenously radiodense. Therefore the assessment of the size of haematoma is easily done and reliable in estimating the clot volume.

In deep seated or extensive intracranial haemorrhage, blood frequently leaks into ventricles where it may adhere to the ependyma or to the choroids plexus; alternatively, it can sink to the most dependent part of ventricular system, usually the occipital horn, forming a fluid level within the ventricular fluid (Jager and Saunds, 2001).

The high attenuation of an acute intracranial bleed on CT may persist for approximately 1 week (Chang et al., 2004). Over the course of several days, an untreated haematoma becomes less radiodense, from periphery towards the centre, and appears smaller. After several weeks, the CT density of blood products can be similar to that of the brain or CSF (Jager and Saunds, 2001).

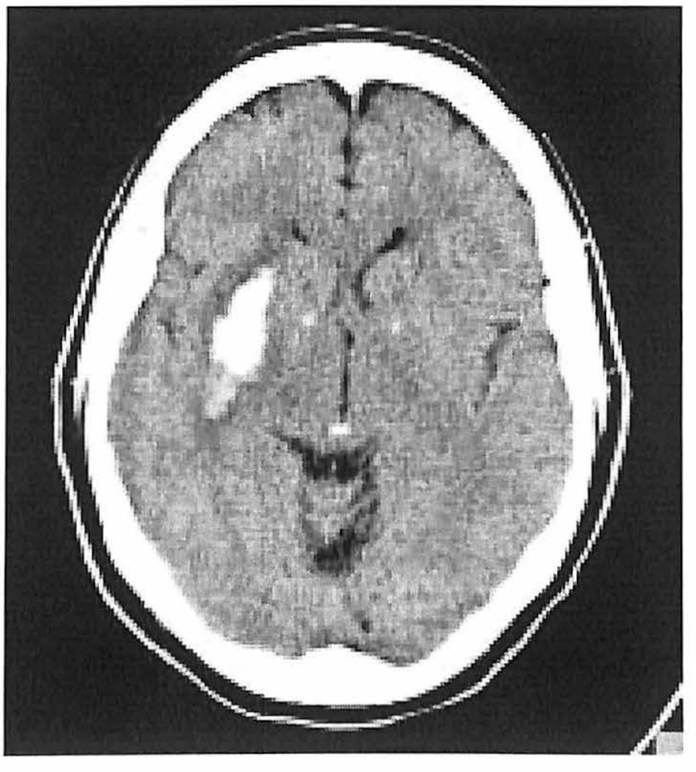

**Figure 2-1: Right putaminal hemorrhage on NECT examination of the head.**

**Tiny hyperdense foci in the basal ganglia and pineal gland represent calcifications.**

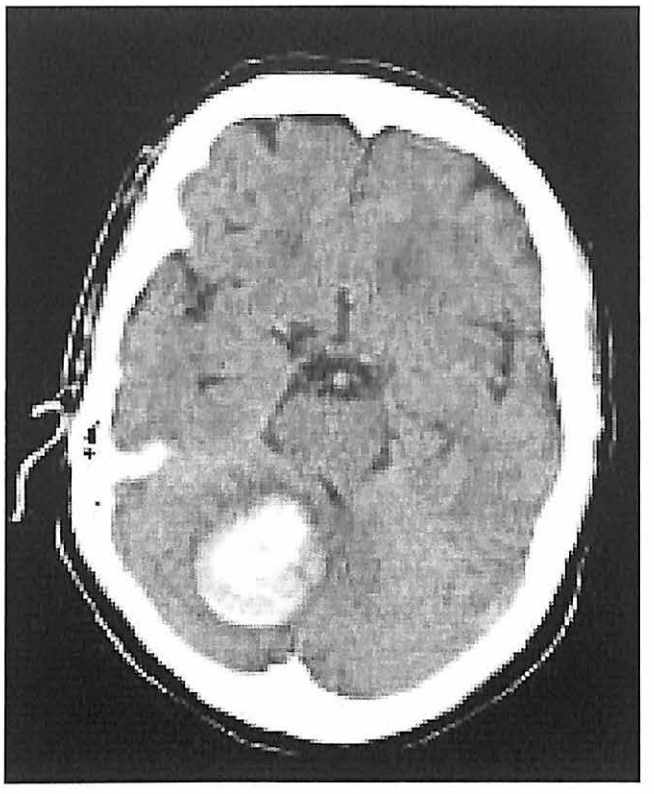

**Figure 2-2: NECT examination of the head showed a large right cerebellar hemorrhage.**

Plain CT scan is also used for reassessment of the post operative bleeding especially when there is reduction in the conscious level or when the expected recovery did not achieve. However, post operative CT scan findings were not used as a predictor factor of the outcome in this study

## 2.5. CT PERFUSION IN CEREBROVASCULAR ACCIDENT

In 1971, Godfrey Hounsfields introduced CT scan. Eight years later, in 1979, Leon Axel first proposed a method for determination tissue perfusion from dynamic contrast enhanced CT data. This needs rapid image acquisition and processing, which was not widely available at that time. This factor limited CT perfusion to only research for renal or myocardial blood flow using electron beam CT system. Nowadays, since advent of spiral CT systems in

1990s, CT perfusion was able to be performed with conventional CT system. The development of the multislice CT systems has increase of the use of CT perfusion with more advance technique from single-slice technique to a volume-based technique. Nowadays, with the availability of more commercial software packages from a range of CT manufactures, the clinical usage of CT perfusion had increased.

Currently the most common clinical applications of CT perfusion are in acute stroke and oncology which stimulating by the development of new therapeutic options such as thrombolysis in acute stroke and anti-angiogenesis therapy for tumour (Miles and Griffiths, 2003). In evaluating ischaemic stroke tissue, perfusion values must be related to known ischaemic threshold, and hence absolute quantification in terms of volume of blood flowing per unit of tissue is essential. This is different in setting for tumour perfusion, which exploits the increase in perfusion that result from tumour neovascularization. However, the perfusion in a tumour vascular bed is also affected by the cardiac output and thus perfusion parameters that correct for cardiac output may reflect the density of vascular bed more directly than absolute perfusion value.

Conventional CT is used widely in assessing patient with acute stroke, which classically is to exclude intracerebral haemorrhage. However, 85% of stroke patients were ischaemic in origin and majority of the patients were scanned within first 6 hours. These cases revealed normal or subtle abnormalities that are easily undetected. The usage of CT perfusion had increased the detection of ischemic area which only required 50mL of contrast media and CT perfusion scan was completed in less than 5 minutes time. This reduces the time delay for further investigation with additional modalities in diagnosing acute stroke therefore necessary treatment can be given immediately.

Neuronal function is critically dependent upon blood flow and the brain has an autoregulation system of controls for maintenance of cerebral perfusion. This autoregulation is reflected in the perfusion CT findings in patient with cerebral ischemia. Slight reduction of cerebral blood flow of ischaemic brain parenchyma will be compensated by increase in blood volume to respective region. The mean transit time also will be increased. When the ischemic injury is prolonged, the autoregulation will be impaired causing reduction of both cerebral blood flow and cerebral blood volume with or without prolong mean transit time. This causes ischemic brain tissue to be infracted.

**Table 2-1 : Summary of perfusion parameters in ischaemic injury (Miles and Griffiths, 2003)**

| | CBF | CBV | MTT |
|---|---|---|---|
| Autoregulatory range | N | + | + |
| Oligemia (misery perfusion) | - | ++ | ++ |
| Ischaemia (metabolic impairment) | - | + | ++ |
| Irreversible damage(necrosis) | -- | - | -/+ |
| N:normal, +:raised, -:decreased | | | |

In most cases of hemorrhagic stroke, there will be reduction of hounsfields unit in perihaematoma area in comparison to the surrounding brain parenchyma. This area was considered as area of cerebral oedema secondary to injury by the haematoma. It also considered as area of hypoperfusion since the oedema can cause compression on the vasculature bed leading to ischaemic injury. Rosand et al. (2002) reported that there was most pronounce reduction of cerebral blood flow immediately adjacent to the haematoma. The ischaemic injury is as seen in thrombosis stroke. In patients with hypertensive intracerebral haemorrhage, the reduction of blood pressure may aggravate the hypoperfusion injury of perihaematoma area in spite of limiting haematoma expansion (Rosand et al., 2002).

Perfusion CT is also used in other than systems such as oncology. The basis for CT perfusion in oncology is that the micro vascular changes in angiogenesis (process of neovascularization) are reflected by increased tumour perfusion in vivo and this is essential for the tumoural growth and determined the ability of tumours to metastasis. Current CT protocols for tumours with CT perfusion provide information of incremental benefit in diagnosis, staging, assessment of tumour grade and prognosis, and therapy monitoring.

The determination of tissue perfusion using CT is based on examining the relationships between the arterial, tissue and potentially the venous enhancement after the introduction of a bolus of contrast material. Repeated rapid CT scans are acquired at the same location to allow determination of time-attenuation curves (TAC). Several methods have been developed to obtain perfusion values and been made commercially available by the major CT vendors together with CT scan machine such as in our hospital which we have it from General Electric company. All the techniques are based on the intravenous administration of iodine based CT contrast material and the change in attenuation due to this contrast material is directly proportional to the enhancement, expressed as a CT number or Hounsfields Unit (HU), can be directly used in tracer based techniques. The series of images obtained as the bolus of contrast material washes into and out of the tissue must contain at least one non contrast-enhanced image to act as a baseline. The baseline image is subtracted either on a pixel by pixel or regional basis, from the remaining image set to obtain time enhancement data. The use of regions of interest allows the generation of organ, regional or pixel time enhancement curves.

Few factors may degrade CT perfusion images, thus perfusion values. The major limitation is the limited sample volume. This leads to only limited section of organ of interest can be studied. Patient movement during repeating scanning of the same tissue volume over extended periods of time will cause error in perfusion values. Breathing movement will be a continuing problems in spite of instruction to patients especially perfusion involving respiration region such as lung nodule. Beam hardening artifact can affect the perfusion values. The typical tissue enhancement in CT perfusion is of the order of 10HU.

There was a variation in cardiac output in every individual. This caused variation of perfusion in individual people. Therefore the suitable method to detect perfusion defect was by comparing between perfusion parameters in left and right cerebral hemisphere at the same anatomical area. However, a variation in size of right and left intracerebral arteries (ICA) in different individual also present thus might cause a variation in blood volume arrived to both cerebral hemispheres. This might cause slight different of perfusion in left or right cerebral hemisphere. Presuming good cross supply through communication arteries, therefore the perfusion between both cerebral hemispheres won't be affected.

## 2.6. CURRENT MANAGEMENT IN HEMORRHAGIC STROKE.

The most important step is to make a correct diagnosis of the hemorrhagic stoke. Several other causes may appear as hypertensive intracerebral hemorrhagic stoke. This is due to physiological effect of the intracranial vascular channels to maintain the blood flow to the brain parenchyma leading to increase in blood pressure. Vascular malformation such as aneurysm or arteriovenous malformation may present classically with subarachnoid haemorrhage. Intraparenchyma bleed at unusual site for hypertensive bleed such as perisylvian haemorrhage, abnormal intracranial calcification, prominent vascular structures are other presentations of vascular malformation (Broderick et al., 1999). Haemorrhage into cerebral infarction area is also common. This can be differentiating by detail clinical history and plain CT scan findings. Intracranial haemorrhage usually presented by severe headache (Broderick et al., 1999) before unconscious associated with vomiting (Broderick et al., 1999) and the weakness usually global. Plain CT scan will revealed predominant hyperdense area as a bleeding area. Another cause mimicking hypertensive intracerebral haemorrhage is tumour bleeding, however the usual history is chronic headache with early morning vomiting and CT will revealed heterogeneous hyperdense area with tumour tissue in the outer layer. Contrast enhanced CT scans will be helpful. Sometimes there is an associated skull vault change.

The hypertensive intracerebral haemorrhage management is either medical or surgical management. Medical management includes initial acute management of airway, breathing and circulation, and detection of focal neurological deficits(Broderick et al., 1999). Patient who decreased in conscious level are candidates for aggressive airway management including intubation. Blood pressure was recommended to maintained below 130mmHg(Broderick et al., 1999) . Patient who has intracranial pressure (ICP) monitoring, cerebral perfusion pressure which was the product of mean arterial pressure (MAP) minus ICP (MAP-ICP) should be kept >70mmHg. Mean arterial blood pressure >100mmHg should be avoided immediately postoperative. Elevated ICP is defined as intracranial pressure more or equal to 20mmHg for >5minutes. The therapeutic goal for all treatment of elevated ICP is ICP <20mmHg and cerebral perfusion pressure (CPP) >70mmHg. Fluid management is also mandatory and central venous pressure (CVP) should be maintained between 5-12 mmHg and pulmonary wedge pressure about 10-14mmHg. Electrolytes must be in optimum level. Seizures are common and must be treated aggressively. Antiepileptic drugs should be used and doses are titrated accordingly. Body temperature should be maintained at normal levels. Acetaminophen 650mg or cooling blankets should be used to treat hyperthermia >38.5°C. Other medical treatments are including psychological support to patient and family. Depending on patients' clinical state, physical therapy, speech therapy, and occupational therapy should be initiated as soon as possible.

The ideal goal for surgical treatment is to remove as much as blood clots as possible and as quickly as possible with the least amount of brain trauma from the surgery itself. It also should prevent complications such as hydrocephalus and mass effect of the blood clot. Craniotomy is the standard approach for removal of intracerebral haemorrhage. Its major advantage is adequate exposure to remove the clot. The major disadvantage is the more extensive surgical approach may lead to further brain damage, particularly patient with deep seated clot. Endoscopy aspiration of haemorrhage is another technique for clot removal and patient with haematoma <50cm$^3$ had better quality of life compare to those treated medically(Broderick et al., 1999).

## 2.7. MODIFIED BARTHEL INDEX

The Barthel Index (BI) is commonly used scales to assess outcome and the most commonly used scale for assessing activities of daily living and a reliable disability scale for stroke patients (Sulter et al., 1999). The maximum patient scoring for modified Barthel index is 100 (Carroll et al., 1965).

The items can be divided into group that is related to self-care(feeding, grooming, bathing, dressing, bowel and bladder care, and toilet use) and a group related to mobility(ambulation, transfers, and stair climbing). The final score will be categorized as favorable or poor outcome. This is the drawback of the Barthel index as it is an ordinary (noncontiguous) scale. Therefore, parametric statistical method cannot be used (Sulter et al., 1999).

A different in category of disability on BI may allow assessment of a global shift toward independence in subsequent categories of scores rather reliance on a single score that dichotomizes outcome into favorable or poor. The Modified Barthel Index is a score that can give continuous scale and it is also a functional assessment by assessing daily activity. It is a valid measure of disability (Collin C et al., 1988).

The items in Modified Barthel Index includes personal hygiene, bathing self, feeding, toilet, stair climbing, dressing, bowel control, bladder control, ambulation or wheelchair and chair/bed transfer. Each of the items is scored on basis of the best ability to perform the task. It is divided into unable to perform task, substantial help required, moderate help required, minimal help required or fully independent and each is given a number values.

The Modified Barthel Index Total Scores is calculated by the sum of all the items scored. The categorization of Modified Barthel Index is based on total scores and categorize into 1,2,3,4 and 5. If patient is dead, he/she is categorized as 0.

Every patient is assessed using Modified Barthel Index at presentation to hospital and at four weeks after presentation and categorized accordingly. This is to assess whether there is improvement or worsening in daily living activity after four weeks.

# SECTION THREE

## AIM AND OBJECTIVES

# 3. AIM AND OBJECTIVES

## 3.1. GENERAL OBJECTIVE

The general objective for this study is;

1. To establish pattern of perfusion in haemorrhagic stroke patients.

## 3.2. SPECIFIC OBJECTIVES

The specific objectives for this study are;

1. To determine perfusion characteristics of perihaematoma region whether penumbra present or not.
2. To determine correlation between CT perfusion parameters with short term clinical outcome at 4 weeks period (This is as a prognostic prediction).
3. To find contributing factors of abnormal perfusion in perihaematoma of hypertensive intracerebral haemorrhage.
4. To find factors affecting the outcome of the hypertensive intracerebral haemorrhage patients.

## 3.3. HYPOTHESIS

### 3.3.1. Null hypothesis

1. There is no change of perfusion in perihaematoma area in hypertensive hemorrhagic stroke.
2. Penumbra perfusion cannot be used as a prognostic factor.

### 3.3.2. Alternative hypothesis

1. There are changes of perfusion in perihaematoma area in hypertensive hemorrhagic stroke
2. The penumbra perfusion can be used as a prognostic predictor.

# SECTION FOUR

## RESEARCH DESIGN AND METHODOLOGY

# 4. RESEARCH DESIGN AND METHODOLOGY.

This cross-sectional study obtained its ethical clearance from the School of Medical Sciences Ethical Committee, Universiti Sains Malaysia in March 2004. The study was conducted in Hospital Universiti Sains Malaysia in Kubang Kerian, Kelantan after had clearance from hospital director in June 2004. Data were collected from July 2004 till November 2005.

The initial calculation sample size (n) for this study was 50 patients. This was obtained by sample size calculation, with precision $(\Delta) = 28\%$ of SD.

$$n = Z^2\left(\frac{S}{\Delta}\right)^2 = 1.96^2 \times \left(\frac{1}{0.28}\right)^2 = 50$$

Sample size has been determined as 50. Although the optimal sample size should be more than 50, it is limited by availability of cases during the study period (less than 2 years). With this sample size (50), the obtained precision not worse than 28% of the population Standard deviations (SD) in calculating 95% confidence intervals (CI) means (If the population SD is 10, the precision will be 2.8).

Although a detail sample size calculation could not be done for the objective determining the relationship between perfusion and the clinical outcomes, probably the detectable alternative that the study could detect with the 80% power and the level of significance at 0.05, would be rather large with above sample size.

However, this study hopefully will give a preliminary or exploratory result rather than a reasonably conclusive result with above sample size. By the end of the study periods, there were ten patients involved in this study.

## 4.1. PATIENT SELECTIONS

This study was conducted in Hospital Universiti Sains Malaysia (HUSM), Kubang Kerian, Kelantan.

## 4.2. INCLUSION CRITERIAS

The inclusion criteria for this study were;

1. All patients with age of 15 years old and above who admitted to our hospital (HUSM).
2. Diagnosed to have hypertensive intracranial haemorrhage. This was confirmed by a plain CT scan of the brain which was performed in HUSM.
3. Patient or legal next-of-kin will give a written informed consent before proceed with the study.

## 4.3. EXCLUSION CRITERIAS

Exclusion criteria for this study were;

1. Patients (or legal next-of-kin) who do not give consent for the study.
2. Patients who have contraindication for contrasted study (such as allergy to sea-food/drug/asthma/pregnant etc.).
3. Patients who were diagnosed to have subarachnoid haemorrhage, intracerebral hemorrhage resulted from underlying vascular malformation, hemorrhagic transformation of an ischaemic stroke, vasculitis, tumour or trauma.
4. Patient who have previous stroke within 6 weeks of presentation.

When patient fulfilled the inclusion criteria and do not have exclusion criteria, CT perfusion of the brain will be followed at same setting. This is done by following CT perfusion protocol.

## 4.4. TECHNIQUE

Data acquisition was done using a multi detector CT scanner (Light speed; General Electric Medical Systems).

Patient was position with the radiographic baseline perpendicular to the table. A scanogram was acquired. Helical plain CT scan of 3.75mm thick basal sections and 7.5mm thick supratentorial axial section was obtained. The images were reviewed by senior medical officer for present of haematoma and determine the slice location at the level of largest bleeding site. Using the angiographic power injector, 50ml of 320mgI/ml strength iodinated contrast media (Visipaque) was introduced into the peripheral vein through an 18G catheter at 4ml/s. Scan was delayed for 4s and total scan time was 45s.

Four sections in one second with the thickness of 5mm and image matrix of 512 x 512 were obtained immediately after plain CT scan. The kilovolt was set at 80 with mA of 190-200. Total 180-200 images were obtained and were sent to workstation for review and post processing.

## 4.5. MODIFIED BARTHEL INDEX

A baseline Modified Barthel index scoring was done by attending doctor at the same setting of CT Perfusion according to Modified Barthel Index guideline. A cumulative score was determined for each patient at the end of the assessment.