PRE AND POST-OPERATIVE CEREBRAL CIRCULATION ASSESSMENT IN ANTERIOR CIRCULATION INTRACRANIAL ANEURYSM CLIPPING PATIENTS USING CT PERFUSION SCAN

by

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Dissertation Submitted In Partial Fulfillment Of The Requirements For The Degree Of Master Of Surgery

(Neurosurgery)

UNIVERSITI SAINS MALAYSIA

2015

ACKNOWLEDGEMENTS

For this thesis to be completed and to exist in the first place, I would like to thank first and foremost my supervisor; Mr Azmin Kass Rosman, who has been very helpful in guiding me through the whole process of completing this task and also giving me the courage to continue on with this journey despite the challenges and difficulties that arises.

To Professor Jafri Malin Abdullah, Professor Zamzuri Idris, Dato' Dr, Abdul Rahman Izani Ghani and Dr Regunath Kandasamy, Neurosciences lecturers of Universiti Sains Malaysia, I thanked you for being understanding especially in the initial phase of the thesis topic selection when I had to face some difficulties in my life as a first time mother.

To my consultants and specialists both in Hospital Sungai Buloh and in Hospital Kuala Lumpur, Mr Saiful Azli Mat Nayan, Mr Liew Boon Seng, Datuk Dr Saffari Mohammed Haspani, Mr Azmi Alias, Mr Saiful Razman and Mr Mohammed Azman Raffiq who has also given their constant guidance and constructive criticism for this thesis and beyond.

To Dr Nor Zaine Ros, a neuroradiologist in Hospital Kuala Lumpur, she had open my eyes in the diversity in CTP and its advantages.

To all my family members especially my husband; Mr Nur Ayub Md Ali; who has been very supportive and patient with my whims, my adorable son, Nur Aariz, my beloved friends and colleague, Dr Fadzlishah Johanabas and Dr Ng Wei Ping; there would be no words that can describe my gratitude towards all of you.

For those who has contributed but no names mentioned; I thanked you all.

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Introduction: Intracranial aneurysm is an abnormal dilatation of blood vessel that may rupture causing intracranial bleed; commonly subarachnoid haemorrhage (SAH). It is associated with high morbidity and mortality commonly due to vasospasm. Fisher grade and Navarro score are among the grading used to predict vasospasm while WFNS grading is used to predict its outcome. Few new modifications of the existing grading are available to obtain a higher sensitivity and specificity to predict the development of vasospasm but still unsuccessful. Once an intracranial aneurysm ruptures, patient's cerebral blood flow may be disturbed during the acute phase of aneurysm rupture resulting in some effect on the patient's cerebral circulation and autoregulation hence their cerebral perfusion even prior to the onset of vasospasm. This may influence the outcome of these patients. CTP is a method to measure the cerebral perfusion status and the values can be compared pre and post-operatively.

Objectives: To determine the relationship between cerebral CTP parameters (CBF, CBV and MTT) with Fisher grade, WFNS grade, Navarro score and modified Rankin score in patients undergoing intracranial aneurysm clipping at 3 and 6 months post-operatively as well as to compare the pre and post-operative CTP parameters in all patients, those with and without hypertension and those with new post-operative infarct.

Patients and Methods: This is a retrospective data collection of 30 patients undergoing anterior intracranial aneurysm clipping between 1st Jan 2013 to 30th June 2014 in Hospital Sungai Buloh. Data collected include the patient's demographic profile, Fisher, WFNS and Navarro score. Both pre and post-operative CTP parameters (CBF, CBV and MTT) are collected to obtain the mean value. The presence of infarcted areas pre and post-operatively are obtained from the CT brain radiology report based on the CT brain done on the day of admission and post-operative day 1. Modified Rankin scale is taken during patients' follow-up visit in clinic at 3 and 6 months.

Results: Out of the 30 patients, majority are males (56.7%) with mean age of 48.9 years old. 85.7% of patients have hypertension and the commonest location for intracranial aneurysm is ACOM aneurysm (56.7%). Most of our patients are WFNS I (33.3%), Fisher grade 3 (50.0%) and Navarro score 6 (20.0%). There is no significant correlation between the mean CBF, CBV and MTT with WFNS, Fisher and Navarro score.

There is a significant inverse moderate correlation between pre-operative mean MTT and mRS at 3 months ($r=-0.393$, $p<0.05$). Similarly, there was a significant inverse moderate correlation between pre-operative mean CBV and infarct ($r=-0.366$, $p<0.05$), as well as between pre-operative mean CBF and infarct ($r=-0.456$, $p<0.05$). There is a significant inverse moderate correlation between post-operative mean MTT and mRS at 3 months ($r=-0.401$, $p<0.05$). In contrast, there is a significant moderate correlation between post-operative mean CBF and mRS at 3 months ($r=0.454$, $p<0.05$). Similar significant moderate correlation was found between post-operative mean CBF and mRS at 6 months ($r=0.559$, $p<0.05$).

Comparing between the pre and post-operative mean MTT and mean CBF, all our patients have increase post-operative mean MTT with combination of reduce post-operative mean CBF ($p<0.001$) including those without hypertension. In hypertensive patients, there is only significant increase in the mean MTT. Similar increase in post-operative mean MTT and decrease in post-operative CBF is found in both patients with and without new infarct in their post-operative CT brain.

Conclusion: The conclusion from this study is there is no correlation between CT perfusion parameters with the Fisher grade, WFNS grade and Navarro score. For mRS at 3 months, there is an inverse correlation between the pre-operative mean MTT and post-operative mean MTT. A positive correlation is appreciated between mRS both at 3 months as well at 6 months with post-operative mean CBF. In general, patients undergoing microsurgical intracranial aneurysm clipping are bound to have increased MTT and reduced CBF. Interestingly, patients with no post-operative CT brain infarct also have similar findings of

prolonged MTT with low CBF; indicating the alteration of cerebral perfusion is present even prior surgical intervention.

Dato’ Dr. Abdul Rahman Izani Ghani: Supervisor

Dr Azmin Kass Rosman: Co-Supervisor

Dr Saiful Azli Mat Nayan,: Co-Supervisor

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LIST OF ABBREVIATIONS

ACA anterior cerebral artery

ACOM anterior communicating artery

aSAH aneurysmal subarachnoid haemorrhage

BG basal ganglia

CBF cerebral blood flow

CBV cerebral blood volume

$CMRO_2$ cerebral metabolic rate for oxygen

CT computed tomography

CTA computed tomography-angiography

CTP computed tomography perfusion

DCI delayed cerebral ischaemia

DIND delayed ischaemic neurological deficits

GCS Glasgow Coma Scale

HM-PAO Hexametylpropyleneaminoeoxime

IV intravenous

MCA middle cerebral artery

MRA magnetic resonance angiography

mRS Modified Rankin Scale

MTT mean transit time

$PaCO_2$ arterial carbon dioxide pressure

PCOM posterior communicating artery

PET positron emission tomography

rCBF regional cerebral blood flow

rCBV regional cerebral blood volume

rOEF regional oxygen extraction fraction

ROI region of interest

SAH subarachnoid haemorrhage

SPECT single photon emission computed tomography

TCD Transcranial Doppler

WFNS World Federation of Neurological Surgeons

ABSTRAK

Tajuk

Penilaian perfusi otak pesakit sebelum dan selepas menjalani pembedahan saluran darah otak bengkak menggunakan skan CT Perfusion.

Pengenalan

'Intracranial aneurysm' adalah saluran darah otak yang membengkak dan berupaya untuk pecah sehingga mengakibatkan pendarahan otak; selalunya 'subarachnoid haemorrhage' atau pendarahan di bawah lapisan 'pia' yang menempatkan saluran darah otak manusia. Penyakit ini adalah merbahaya kerana saluran darah otak boleh menjadi sempit disebabkan pengecutan salurannya lalu mengakibatkan bekalan darah untuk kegunaan tisu otak berkurangan dan boleh mengakibatkan strok . 'Fisher grade' dan 'Navarro score' adalah 2 skala yang selalu digunakan untuk menjangkakan risiko untuk seseorang mendapat pengecutan saluran darah otak. Manakala 'WFNS grade' adalah skala yang digunakan untuk menjangkakan prognosis pesakit. Beberapa usaha untuk mencipta skala baru telah dihasilkan kerana skala sedia ada tidak mempunyai kadar sensitiviti dan ketepatan yang tinggi. Bagaimanapun, masih belum menemui kejayaan. Apabila saluran darah otak yang membengkak pecah, pengaliran darah di otak mungkin akan terjejas dan membuatkan perfusi otak menurun. Ini boleh berlaku sebelum pengecutan saluran darah otak terjadi. Apabila ini terjadi, ia boleh mempengaruhi prognosis pesakit. CTP merupakan sejenis skan yang dapat mengukur tahap perfusi otak dan boleh dibandingkan sebelum dan selepas pembedahan.

Objektif

Objektif kajian ini adalah untuk mengkaji hubungan antara CT perfusi otak (MTT , CBV dan CBF) dengan ‘Fisher grade’, ‘WFNS grade’, ‘Navarro score’ dan ‘modified Rankin scale’ pada 3 dan 6 bulan selepas pembedahan saluran darah otak yang bengkak dan pecah. Kajian ini juga bertujuan untuk membandingkan CTP semua pesakit yang menjalani pembedahan termasuk yang mempunyai darah tinggi and pesakit yang mempunyai strok pada CT otak selepas pembedahan.

Kaedah

Data pesakit yang menjalani pembedahan saluran darah otak yang bengkak dan pecah di antara 1 Januari 2013 sehingga 30 Jun 2014 dikumpulkan dari pangkalan data elektronik di Hospital Sungai Buloh. Data seramai 30 pesakit dikumpulkan termasuk umur, jantina, bangsa, ‘Fisher grade’, ‘WFNS grade’, dan ‘Navarro score’. Kedua-dua keputusan CTP yang dilakukan sebelum dan selepas pembedahan dicampurkan untuk mendapatkan purata. Kehadiran strok pada CT otak pesakit pada hari kemasukan ke wad dan selepas 1 hari pembedahan adalah berdasarkan laporan bahagian radiologi. ‘Modified Rankin scale’ adalah berdasarkan kunjugan pesakit ke klinik pada 3 dan 6 bulan setelah pembedahan.

Keputusan

Data seramai 30 pesakit telah dikaji untuk kajian ini. Majoriti pesakit adalah lelaki (56.7%) dengan purata umur kesemua pesakit 48.9 tahun. 85.7% pesakit mempunyai tekanan darah tinggi dan lokasi paling kerap untuk pesakit kami mendapat saluran darah bengkak dan pecah ialah di ‘Anterior Communicating artery’ (56.7%). 33.3% pesakit mendapat gred I

berdasarkan ‘WFNS grade’, 50.0% mendapat gred 3 berdasarkan ‘ Fisher grade’ dan 20.0% mendapat skor 6 denagan ‘Navarro score’. Didapati tiada korelasi di antara jumlah purata CBF, CBV dan MTT dengan ‘WFNS’, ‘Fisher’ dan ‘Navarro score’.

Terdapat hubungkait yang sonsang melibatkan purata MTT sebelum pembedahan dengan mRS di 3 bulan ($r=-0.393$, $p<0.05$). Begitu juga dengan purata CBV sebelum pembedahan dengan strok ($r=-0.366$, $p<0.05$) dan purata CBF sebelum pembedahan dengan strok ($r=-0.456$, $p<0.05$). Di antara purata MTT selepas pembedahan dan mRS di 3 bulan, terdapat hubungkait yang songsang juga ($r=-0.401$, $p<0.05$).

Ini berlainan dengan purata CBF selepas pembedahan dan mRS di 3 bulan di mana mempunyai hubungkait yang positif ($r=0.454$, $p<0.05$). Purata CBF selepas pembedahan dan juga mRS di 6 bulan juga mempunyai hubungkait yang memberangsangkan ($r=0.559$, $p<0.05$).

Jika dibandingkan di antara purata MTT dan purata CBF sebelum dan selepas pembedahan, kesemua pesakit mempunyai peningkatan purata MTT selepas pembedahan dan penurunan purata CBF selepas pembedahan ($p<0.001$); termasuklah pesakit yang tidak mempunyai darah tinggi. Untuk pesakit yang menghidapi penyakit darah tinggi, mereka hanya mempunyai peningkatan purata MTT selepas pembedahan. Kedua-dua pesakit yang mempunyai strok dan tidak mempunyai strok juga mempunyai keputusan yang serupa.

Kesimpulan

Kesimpulan dari kajian ini ialah tiada korelasi didapati di antara jumlah purata CBF, CBV dan MTT dengan ‘WFNS’, ‘Fisher’ dan ‘Navarro score’.

Untuk mRS di 3 bulan, terdapat hubungkait songsang di antara purata MTT sebelum dan juga selepas pembedahan. Korelasi yang positif juga wujud antara mRS di 3 bulan dan 6 bulan dengan purata CBF selepas pembedahan.

Secara umumnya, semua pesakit yang menjalani pembedahan ini, akan mempunyai peningkatan purata MTT dan penurunan purata CBF. Yang menariknya, pesakit yang tidak mempunyai strok juga mempunyai keputusan yang sama. Ini bermaksud, terdapat perubahan di dalam perfusi otak walaupun sebelum pembedahan.

ABSTRACT

Title

Pre and post-operative cerebral circulation assessment in anterior circulation intracranial aneurysm clipping patients using CT Perfusion scan

Authors

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Introduction

Intracranial aneurysm is an abnormal dilatation of blood vessel that may rupture causing intracranial bleed; commonly subarachnoid haemorrhage (SAH). It is associated with high morbidity and mortality commonly due to vasospasm. Fisher grade and Navarro score are among the grading used to predict vasospasm while WFNS grading is used to predict its outcome. Few new modifications of the existing grading are available to obtain a higher sensitivity and specificity to predict the development of vasospasm but still unsuccessful. Once an intracranial aneurysm ruptures, patient's cerebral blood flow may be disturbed during the acute phase of aneurysm rupture resulting in some effect on the patient's cerebral circulation and autoregulation hence their cerebral perfusion even prior to the onset of

vasospasm. This may influence the outcome of these patients. CTP is a method to measure the cerebral perfusion status and the values can be compared pre and post-operatively.

Objectives

To determine the relationship between cerebral CTP parameters (CBF, CBV and MTT) with Fisher grade, WFNS grade, Navarro score and modified Rankin score in patients undergoing intracranial aneurysm clipping at 3 and 6 months post-operatively as well as to compare the pre and post-operative CTP parameters in all patients, those with and without hypertension and those with new post-operative infarct.

Methods

This is a retrospective collection of data obtained from the electronic database for patients undergoing microsurgical clipping of intracranial aneurysm between 1st Jan 2013 to 30th June 2014 in Hospital Sungai Buloh. A total of 30 patients were recruited in this study. Data collected include the patient's demographic profile, Fisher, WFNS and Navarro score. Both pre and post-operative CTP parameters (CBF, CBV and MTT) are collected to obtain the mean value. The presence of infarcted areas pre and post-operatively are obtained from the CT brain radiology report based on the CT brain done on the day of admission and post-operative day 1. Modified Rankin scale is taken during patients' follow-up visit in clinic at 3 and 6 months.

Results

30 patients are recruited for this retrospective study, majority are males (56.7%) with mean age of 48.9 years old. 85.7% of patients have hypertension and the commonest location for intracranial aneurysm is ACOM aneurysm (56.7%). Most of our patients are WFNS I (33.3%), Fisher grade 3 (50.0%) and Navarro score 6 (20.0%). There is no significant correlation between the mean CBF, CBV and MTT with WFNS, Fisher and Navarro score.

There is a significant inverse moderate correlation between pre-operative mean MTT and mRS at 3 months ($r=-0.393$, $p<0.05$). Similarly, there was a significant inverse moderate correlation between pre-operative mean CBV and infarct ($r=-0.366$, $p<0.05$), as well as between pre-operative mean CBF and infarct ($r=-0.456$, $p<0.05$). There is a significant inverse moderate correlation between post-operative mean MTT and mRS at 3 months ($r=-0.401$, $p<0.05$). In contrast, there is a significant moderate correlation between post-operative mean CBF and mRS at 3 months ($r=0.454$, $p<0.05$). Similar significant moderate correlation was found between post-operative mean CBF and mRS at 6 months ($r=0.559$, $p<0.05$).

Comparing between the pre and post-operative mean MTT and mean CBF, all our patients have increase post-operative mean MTT with combination of reduce post-operative mean CBF ($p<0.001$) including those without hypertension. In hypertensive patients, there is only significant increase in the mean MTT. Similar increase in post-operative mean MTT and decrease in post-operative CBF is found in both patients with and without new infarct in their post-operative CT brain.

Conclusion

The conclusion from this study is there is no correlation between CT perfusion parameters with the Fisher grade, WFNS grade and Navarro score. For mRS at 3 months, there is an inverse correlation between the pre-operative mean MTT and post-operative mean MTT. A positive correlation is appreciated between mRS both at 3 months as well at 6 months with post-operative mean CBF. In general, patients undergoing microsurgical intracranial aneurysm clipping are bound to have increased MTT and reduced CBF. Interestingly, patients with no post-operative CT brain infarct also have similar findings of prolonged MTT with low CBF; indicating the alteration of cerebral perfusion is present even prior surgical intervention.

Keywords: intracranial aneurysm, clipping, vasospasm, delayed cerebral ischaemia, delayed neurological deficits, cerebral autoregulation, CTP

INTRODUCTION

Intracranial aneurysm is an abnormal dilatation of blood vessel that may rupture causing intracranial bleed; most commonly subarachnoid haemorrhage (SAH). SAH is defined as bleeding within the subarachnoid space situated in between the pia and the arachnoid membrane. It is mainly due to trauma but may be spontaneous secondary to other lesions such as arteriovenous malformations , cavernous malformations, idiopathic and iatrogenic coagulopathy, vessel dissections, central nervous system infections or even drug misuse (Lauren F. Schwartz, 2004). However, spontaneous SAH in adults are most commonly due to rupture of intracranial aneurysm.

Ruptured intracranial aneurysm is associated with high morbidity and mortality associated directly with SAH burden or secondary causes due to the systemic changes that are associated with intracranial aneurysm rupture. However, the frequent cause associated with poor outcome is usually vasospasm. The risk of patients having vasospasm can be predicted by Fisher grade based on their admission CT brain (Fisher CM, 1980). However, several recommendations arose to modify Fisher grade with the objective of having a higher sensitivity and specificity; but as for now still unsuccessful. Although it may be multifactorial, the possibility of acute insult occurring in the initial phase after the haemorrhage causes cerebral autoregulation disturbances and vasospasm may further aggravate this.

Autoregulation in the brain is crucial to maintain the normal cerebral blood flow and cerebral perfusion. Normal cerebral circulation can only be auto regulated when the cerebral perfusion pressure is between 60 mmHg to 160 mmHg (Phillips and Whisnant, 1992). When an intracranial aneurysm ruptures, cerebral autoregulation may be affected and in turn affect the patient's cerebral circulation and perfusion. This subsequently will affect the patient's outcome. However, the disturbances in patient's cerebral blood flow may have occurred during the acute phase of aneurysm rupture resulting in some effect on the patient's cerebral circulation even prior to the onset of vasospasm. This may also influence the outcome of patients (Hayashi *et al.*, 2000; Budohoski *et al.*, 2012).

CHAPTER 1: INTRACRANIAL ANEURYSM

1.1: PATHOLOGY

Aneurysm is derived from the Greek words of *ana* (up) and *euros* (widen). When combined, it means to stretch. This derivation gave rise to the Greek word *aneurynein* to dilate and subsequently the word aneurysma (Michael L. DiLuna, 2004).

Intracranial arteries are comprised of the outer layer of adventitia, the muscular media which maintain most of the vessel wall integrity and the inner layer of intima. They are different from other vessels in the body as it does not possess external elastic lamina therefore less elasticity of the media in addition to the thinner adventitia as compared to extracranial artery wall. These vessels are also situated in the subarachnoid space which has no surrounding connective tissue to support the vessels (Vini G. Khurana, 2004). These factors make intracranial arteries susceptible to saccular aneurysm formation.

Aneurysms occur due to the stress exerted by the flowing blood to the arterial wall mainly at the arterial bifurcation and when there is a bend in the parent artery where the flow and turbulence is at its highest. The starting point is usually due to a defect or point of weakness

in the media causing an outpouching through the vessel wall which further expand in size due to the hydrostatic pressure coming from the blood flow.

1.2: EPIDEMIOLOGY AND DEMOGRAPHIC

In the United Kingdom, the incidence of spontaneous SAH ranges between 8-12 per 100,000 while in Malaysia, the annual incidence is estimated to be 1.1- 1.7 per 100,000 in year 1998. 2.3% of adults without risk factors are found to have intracranial aneurysm and it increases with age (Rinkel *et al.*, 1998). Intracranial aneurysm rupture is commonly occurring in patients in their 50's. It is commoner in female gender (1.5 times greater than male), in Blacks, Japanese and Finnish (Chee, 1998; Kirkpatrick, 2002; Samandouras, 2010).

1.3: RISK FACTORS FOR INTRACRANIAL ANEURYSM

Because of the above reasons stated in section 1.1, this make aneurysms fairly common in hypertensive patients and in patients with congenital condition which predispose them for having defects in the muscular layer of the arterial wall such as autosomal dominant polycystic kidney disease, fibromuscular dysplasia, Ehler-Danlos and Marfan syndrome (Rinkel *et al.*, 1998; H Hunt Batjer, 2005). Other factors include cigarette smoking, oral

contraceptive use, alcohol consumption, diurnal variation in blood pressure, pregnancy and parturition.

The vessels involved for aneurysm formation are usually the large cerebral arteries of the anterior part of the circle of Willis. There is a 20% chance of a patient to have multiple aneurysms at one time.

1.4: NATURAL HISTORY OF RUPTURED INTRACRANIAL ANEURYSM

Nearly 50% of patients may have warning signs 6 to 20 days prior to the major bleed (Okawara, 1973). 10% of patients will die before reaching hospital while those who did reach hospital; another 10% will die due to the progressive deterioration owing to the initial bleed. 15-20% may die within 2 weeks due to rebleeding from the aneurysm and 7% is due to vasospasm.

Once ruptured, an intracranial aneurysm may re-rupture as long as the aneurysm is still not obliterated from the parent artery. Risk of rebleeding within 24 hours is 4% and may reach 50% within 6 months (Richardson *et al.*, 1964; Winn *et al.*, 1983). The risk of rebleeding is highest within the first 6 hours post-ictal. After the initial 24 hours, the risk of rebleeding decreases to 1-2% per day. After 6 months, the risk of rebleeding reduces back to 3% per

year. Each time a patient bleeds, it is associated with a poorer outcome where 78% of rebleed patients will eventually die (Nishioka *et al.*, 1984).

The overall mortality may reach 46% in 30 days (Greenberg, 2010).

1.5: NATURAL HISTORY OF UNRUPTURED INTRACRANIAL ANEURYSM

Unruptured intracranial aneurysms are aneurysms that do not produce any symptoms due to haemorrhage and are found incidentally (e.g. compression of the 3rd cranial nerve causing pupillary dilatation). Prevalence of incidental intracranial aneurysms is 5-10% of the general population (FP., 1986). 90% of unruptured intracranial aneurysms are in the anterior circulation (Wiebers, 2003).

The presentation of unruptured intracranial aneurysm depends on its location. It can cause brainstem compression producing hemiparesis and cranial neuropathies. Compression of oculomotor nerve can cause third nerve palsy. Visual loss can occur with ophthalmic artery aneurysm compressing on the optic nerve. Intra or suprasellar aneurysm may cause endocrine disturbance due pituitary gland or stalk compression. Other symptoms include headache and seizures (Greenberg, 2010).

According to International Study Group of Unruptured Intracranial Aneurysm (ISUIA 2003), the risk of rupture for an unruptured intracranial aneurysm depends on several factors including aneurysm size and its location (Wiebers, 2003).

1.6: DIAGNOSTIC EVALUATION FOR INTRACRANIAL ANEURYSM

When a patient is admitted with a history suggestive of ruptured intracranial aneurysm, a non-contrast enhanced computed tomography (CT) brain is the initial imaging. The diagnosis of intracranial aneurysm is then confirmed with cerebral CT angiogram (CTA) or cerebral angiogram before patient is subjected for clipping or coiling of the intracranial aneurysm.

1.6.1: Non-contrast enhanced computed tomography (CT) brain

A non-contrast enhanced CT brain is the initial imaging to detect subarachnoid haemorrhage (SAH). It is the first line investigation that is readily available and fast to perform especially for the critically ill patients. It is 95% sensitive in detecting SAH within 24 hours post ictus (van der Wee *et al.*, 1995). If performed within 6 hours post headache; sensitivity and specificity is 100% (Perry *et al.*, 2011).