TRANSCRANIAL DOPPLER ULTRASOUND
AND
CEREBRAL COMPUTED TOMOGRAPHY PERFUSION
FOR ANEURYSMAL SUBARACHNOID HAEMORRHAGE

HEALTH TECHNOLOGY ASSESSMENT SECTION
MEDICAL DEVELOPMENT DIVISION
MINISTRY OF HEALTH MALAYSIA
017/2013

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DISCLOSURE

The authors of this report have no competing interest in this subject and the preparation of this report is totally funded by the Ministry of Health, Malaysia.

EXECUTIVE SUMMARY

Introduction

Intracranial aneurysm is the leading cause of nontraumatic subarachnoid haemorrhage (SAH) which is a neurological emergency. Aneurysmal SAH (aSAH) is associated with as much as 67% patient fatality and 10 to 20% long term dependence in survivors, with substantial burden on healthcare resources, mainly due to hospitalisation. Misdiagnosis accounts for 50% in patients presenting their first visit in the absence of classic SAH signs and symptoms. Neurologic complications such as symptomatic vasospasm, hydrocephalus and rebleeding are common. Vasospasm represents the leading cause of death and disability with 50% of patients will eventually develop ischaemic stroke. Early recognition and prompt treatment of vasospasm can improve neurologic outcome. Digital-subtraction cerebral angiography (DSA) was the gold standard for the detection of cerebral aneurysm and vasospasm in SAH patients. However, this procedure is invasive, expensive, not always available and has limited ability to quantify cerebral blood flow or the risk of cerebral ischaemia. Transcranial Doppler (TCD) has been implemented by many neurosurgical units due to its non-invasiveness in detecting cerebral vasospasm. Similarly, cerebral Computed Tomography perfusion (CTP) which assesses brain perfusion haemodynamics in these cases is non-invasive. Measurement of brain perfusion has been said to be clinically useful for identifying SAH patient at risk of cerebral ischaemia, guiding further therapeutic decision and monitoring treatment effect. However, the effectiveness and safety of TCD and cerebral CTP in the management of aSAH remained debatable. This review was requested by the Director of Sungai Buloh Hospital, Ministry of Health Malaysia to review the evidence on TCD and cerebral CTP to be used in the management of aSAH.

Aims/Objectives

To assess the effectiveness and safety of TCD and cerebral CTP as a non-invasive diagnostic procedure in the management of aSAH.

Results and conclusion

Transcranial Doppler (TCD) Ultrasound

There was limited retrievable fair level of evidences from the electronic databases on the effectiveness and safety of TCD in the management of aneurysmal SAH whereby four full text articles were included in this systematic review; namely systematic review of comparative trials (1), comparative trial (1) and cross sectional (2) in design.

Evidence demonstrated that TCD appeared beneficial for the detection and monitoring of angiographic vasospasm of the intracranial arteries due to ruptured aneurysms, especially the middle cerebral artery. TCD demonstrated good diagnostic value in the detection of cerebral vasospasm after aneurysmal haemorrhage for middle cerebral arteries with high positive likelihood ratio (17) and high specificity, however its diagnostic value for ACA was low (positive likelihood ratio <5). The sensitivity in detecting MCA vasospasm varies from 64% to 67% with specificity from 78% to 99%; in ACA vasospasm the sensitivity ranges from 42% to 45% with specificity of 76% to 84%; while in ICA vasospasm the sensitivity was between 25% to 80% with specificity ranges

from 77% to 91%. Evidence also showed that these TCD parameters; middle cerebral artery velocity (VMCA) measurements and V_{MCA}/V_{ICA} ratio can increase the accuracy of TCD. This investigational procedure also appeared safe with CE certification and without reported adverse event.

This is in tandem with the Guideline from the American Heart/Stroke Association on the Management of Aneurysmal Subarachnoid Haemorrhage which stated that TCD is reasonable to monitor the development of arterial vasospasm after aneurysmal SAH. Similarly, TCD is stated as useful for the detection and monitoring of angiographic vasospasm in the basal segments of the intracranial arteries, especially the middle cerebral artery and basilar artery after aSAH as documented by the American Academy of Neurology in its assessment.

Computed Tomography Perfusion (CTP)

There was limited retrievable fair level of evidence from the electronic databases on the effectiveness and safety of CTP in the management of aneurysmal SAH, with three full text articles (all cross sectional in design) included in this systematic review specifically in the detection of cerebral vasospasm and secondary cerebral infarction after aneurysmal SAH.

Evidences demonstrated that CTP appeared useful in the detection of vasospasm in suspected patients after aSAH. For the diagnosis of angiographic vasospasm, diagnostic performance of CTP as measured by mean transit time (MTT) with a threshold of 6.4 seconds was the most sensitive parameter.

Evidences also showed that CTP appeared useful in the detection of secondary cerebral infarction after aneurysmal SAH, with CTP derived parameter, time-to-peak was the most sensitive parameter.

Evidence also has demonstrated that CTP seemed beneficial in providing immediately applicable information for diagnosing vasospasm, which could further guide decisions for endovascular treatment in the management of aSAH. In term of CTP use to assist decision for endovascular treatment of angiographic vasospasm, evidence showed that the most accurate CTP parameter was cortical regional cerebral blood flow value (rCBF)(94.8%), with sensitivity and specificity of 61.7% and 98.2% respectively. This procedure appeared safe with no safety issue raised related to its use.

This is in line with the Guideline on the Management of Aneurysmal Subarachnoid Haemorrhage by the American Heart/Stroke Association which documented that perfusion imaging with computed tomography or magnetic resonance can be useful in identifying region of potential brain ischaemia after aneurysmal SAH.

Methods

Literature were searched through electronic databases which included PubMed, Medline, Cochrane Database of Systematic Reviews, Cochrane Database of Controlled Trial, Health Technology Assessment, National Horizon Scanning, other websites; INAHTA, ASERNIP-S, CADTH, FDA, MHRA and general databases such as Google. Additional articles retrieved from reviewing the bibliographies of retrieved articles or contacting the authors. A critical appraisal of all relevant literature was performed using Critical Appraisal Skills Programme (CASP) checklist, diagnostic accuracy evidence were graded according to the NHS Centre for Reviews and Dissemination (CRD) University of York, Report Number 4 (2nd Edition) for diagnostic accuracy studies (Appendix 2a) while effectiveness evidence were graded according to the US/Canadian Preventive Services Task Force Level of Evidence (2001).

TRANSCRANIAL DOPPLER ULTRASOUND AND CEREBRAL COMPUTED TOMOGRAPHY PERFUSION FOR ANEURYSMAL SUBARACHNOID HAEMORRHAGE

1. INTRODUCTION

Nontraumatic subarachnoid haemorrhage (SAH) is a neurologic emergency characterized by the extravasation of blood into the subarachnoid space. Rupture of an intracranial aneurysm is the leading cause of nontraumatic SAH which accounts for 80% of cases with high rate of death and complications.[1] In contrast, nonaneurysmal SAH occurs in about 20% of cases and carries a good prognosis with uncommon neurologic complications.[2] Worldwide incidence of SAH is approximately 10.5 cases per 100,000 person-years, affecting people of all ages with the peak around 40 to 60 years. Average SAH case fatality rate is 51%, with approximately one third of survivors need lifelong care. Fourty-six percent of SAH survivors may have long term cognitive impairment affecting functional status and quality of life.[2] Aneurysmal SAH is associated with as much as 67% patient fatality and 10 to 20% long term dependence in survivors.[3] This disorder is also associated with substantial burden on healthcare resources, mainly related to hospitalization.[2]

Typical SAH presentation was sudden onset of severe headache, vomiting, neck pain, photopobia and loss of consciousness. Clinical examination may reveal retinal haemorrhage, meningismus, diminished level of consciousness and localizing neurologic sign. Misdiagnosis accounts for 50% in patients presenting their first visit in the absence of classic signs and symptoms.[2] Neurologic complications are common which include symptomatic vasospasm, hydrocephalus, and rebleeding.[2] Vasospasm represents the leading cause of death and disability[3] with approximately 50% will eventually develop ischaemic stroke.[4] Development of new focal deficit, unexplained by hydrocephalus or rebleeding is the first objective sign of symptomatic vasospasm. Despite early medical and surgical intervention of the ruptured aneurysm, up to 30 to 50% of treated patients developed syndrome of focal neurological deficits and/or cognitive deficits due to cerebral vasospasm between day 3 and 21 after the SAH. Early recognition and prompt treatment of vasospasm can improve neurologic outcome.[5]

Head Computed Tomography (CT) scan should be the first investigation performed in any patient suspected with SAH. A good quality CT scan will reveal SAH in 100% of cases within 12 hours of onset, can predict aneurysm rupture site and reliable to predict cerebral vasospasm. Patients with negative or equivocal CT scan should undergo lumbar puncture. CT angiography (CTA) of the head or cerebral angiography should be the next step in patients with either diagnostic or equivocal lumbar puncture.[2] Digital-subtraction cerebral angiography (DSA) was the gold standard for the detection of cerebral aneurysm and vasospasm in SAH patients.[6] It has the advantage of being accurate and has the capacity to immediately perform endovascular treatment by balloon angioplasty and/or intra-arterial injection of vasodilatory drugs.[2,7] However, this procedure is invasive, expensive, not always

available, has limited ability to quantify cerebral blood flow at the tissue level, and not without risk, in which cerebral embolus, dissection, or rupture of cerebral arteries and haemorrhage have been described.[6,7]

Transcranial Doppler (TCD) has been implemented by many neurosurgical units in detecting cerebral vasospasm due to its non-invasiveness.[7] TCD is used primarily in the evaluation and management of patients with cerebrovascular disease such as sickle cell disease in children, detection of intracranial steno-occlusive disease, haemorrhagic cerebrovascular disease and brain death.[8] Whilst cerebral Computed Tomography Perfusion (CTP) has been used for assessment of cerebrovascular reserve in patient with intracranial vascular stenoses and intracranial neoplasm.[11] CTP which assess brain perfusion haemodynamics is similarly noninvasive and can be easily incorporated into the standard CT/CTA protocol classically performed for SAH patients with suspected vasospasm.[6] Measurement of brain perfusion can be clinically useful for identifying patients with SAH at risk of cerebral ischaemia, guiding subsequent therapeutic decision and monitoring treatment effect.[9] However, the effectiveness and safety of TCD and cerebral CT perfusion in the management of aSAH is debatable.

This review was requested by the Director of Sungai Buloh Hospital, Ministry of Health Malaysia to review the evidence on TCD and cerebral CTP to be used as a non-invasive diagnostic procedure in the management of aSAH.

2. OBJECTIVES

To assess the effectiveness and safety of TCD and cerebral CTP as a non-invasive diagnostic procedure in the management of aSAH.

3. TECHNICAL FEATURES

Transcranial Doppler (TCD) Ultrasound

TCD and the more recent Transcranial Color Doppler (TCCD) are non-invasive tests used to measure blood velocity in the cerebral arterial system. Measurements are usually taken from the middle cerebral artery, although any major branch of the Circle of Willis or the basilar artery can be assessed if an appropriate ‘window’ can be found. It is relatively quick and inexpensive test performed at the bedside and can be repeated as needed or applied for continuous monitoring.[8] Figure 1 showed the TCD device and its application in one of the patients.

The value obtained for a particular artery is the velocity of blood flowing through the vessel, and unless the diameter of that vessel is established by some other means it is not possible to determine the actual blood flow. Thus TCD is primarily a technique for measuring relative changes in flow.[1]

How it works?

Blood flow velocity is recorded by emitting a high-pitched sound wave from the ultrasound probe, which then bounces off of various materials to be measured by the same probe. A specific frequency is used (usually a multiple of 2 MHz), and the speed of the blood in relation to the probe causes a phase shift, wherein the frequency is increased or decreased. This frequency change directly correlates with the speed of the blood, which is then recorded electronically for later analysis. Normally a range of depths and angles must be measured to ascertain the correct velocities, as recording from an angle to the blood vessel yields an artificially low velocity.

Because the bones of the skull block the transmission of ultrasound, regions with thinner walls; insonation windows, must be used for analyzing. For this reason, recording is performed in the temporal region above the cheekbone/zygomatic arch, through the eyes, below the jaw, and from the back of the head. Patient's age, gender, race and other factors do affect bone thickness, making some examinations difficult or even impossible. However, acceptable responses can be obtained using alternate sites to view the vessels.

The Lindegaard ratio is the flow velocity of the middle cerebral artery divided by the velocity measured in the extracranial internal carotid artery. A high flow velocity (>120 cm s1) in association with a Lindegaard ratio of <3 implies cerebral hyperaemia, whereas a Lindegaard ratio >3 is likely to imply cerebral vasospasm.[10] Understanding normal TCD velocities is vital to understand TCD findings of vasospasm, and it is recognized that each major cerebral artery has its own range of normal values.

Figure 1: Transcranial Doppler machine (left) and the machine in used to a patient (right)

Cerebral Computed Tomography (CT) Perfusion

Cerebral Computed Tomography Perfusion (CTP) or also known as Perfusion CT (PCT) is a noninvasive technique used to assess brain perfusion haemodynamics. It uses standard CT equipment and requires only dedicated processing software that

can generate perfusion maps of the brain, within 5 minutes of data acquisition. It can assess blood flow throughout the whole territory perfused by a cerebral artery.[6]

This technique is fast and available for most standard spiral CT scanners equipped with the appropriate software. (Refer Figure 2). Observed area dimension depends on instrument possibilities, amount of contrast medium and radiation dose.[11]

How it works?

Current method of brain perfusion examination using CT is based on dynamic observation of contrast medium bolus flowing through brain bloodstream at a pre-selected brain layer. [12]

CTP is a relatively new technique that allows rapid qualitative and quantitative evaluation of cerebral perfusion by generating maps of cerebral blood flow (CBF), cerebral blood volume (CBV), and mean transit time (MTT).

The technique is based on the central volume principle (CBF = CBV/MTT) and requires the use of commercially available software employing complex deconvolution algorithms to produce the perfusion maps.(Refer Figure 3).

CTP was introduced as a means to rapidly and easily evaluate cerebral perfusion in patients presenting with acute stroke symptoms, most of whom would already undergo unenhanced head CT to exclude acute haemorrhage. CTP can be performed quickly with any standard spiral CT scanner, where CT perfusion data are analyzed and the perfusion maps can be generated in a short time at a workstation equipped with the appropriate software.[11]

It is most commonly carried out for neuroimaging using dynamic sequential scanning of a pre-selected region of the brain during injection of a bolus of iodinated contrast material as it travels through the vasculature. Various mathematical models can then be used to process the raw temporal data to ascertain quantitative information such as rate of CBF following an ischaemic stroke or aneurysmal SAH. PCT has been found to be useful for non-invasive diagnosis of cerebral ischaemia and infarction. [11]

Figure 2: The Cerebral Computed Tomography Perfusion with its workstation equipped with the appropriate software.

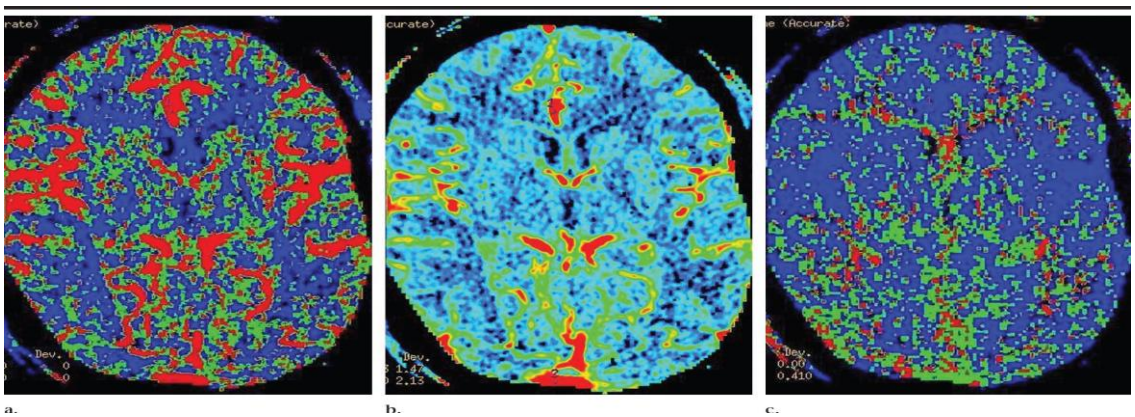

Figure 3: Perfusion maps (transverse CT) in a healthy adult volunteer show normal perfusion. Various colour ramps, selected according to user preference, are used to display the (a) CBF, (b) CBV, and (c) MTT maps

4. METHODOLOGY

4.1 SEARCHING METHODS

Electronic databases searched through the Ovid interface:

- MEDLINE(R) In-process and other Non-Indexed Citations and Ovid MEDLINE(R) 1948 to present
- EBM Reviews - Cochrane Central Register of Controlled Trials – July 2013
- EBM Reviews - Database of Abstracts of Review of Effects (2nd Quarter 2013)
- EBM Reviews - Cochrane Database of Systematic Reviews - 2005 to July 2013
- EBM Reviews - Health Technology Assessment – 3rd Quarter 2013
- NHS economic evaluation database – 3rd Quarter 2013

Other databases:

- PubMed
- Horizon Scanning database (National Horizon Scanning Centre, Australia and New Zealand Horizon Scanning Network, National Horizon Scanning Birmingham)
- Other websites; INAHTA, ASERNIP-S, CADTH, FDA and MHRA.

General databases such as Google and Yahoo were used to search for additional web-based materials and information. Additional articles retrieved from reviewing the bibliographies of retrieved articles or contacting the authors. The search was limited to articles on human. There was no language limitation in the search. Appendix 1 showed the detailed search strategies. The last search was conducted

on 15 July 2013. The search was re-run in August 2013. The search strategy used search terms as in criteria of study inclusion/exclusion below.

4.2 SELECTION OF STUDIES

A reviewer screened the titles and abstracts against the inclusion and exclusion criteria and then evaluated the selected full-text articles for final article selection. The inclusion and exclusion criteria were:

Inclusion criteria

Population	Patient with spontaneous subarachnoid haemorrhage (SAH), aneurysmal SAH, non-traumatic SAH
Interventions	• Transcranial Doppler, Transcranial color Doppler • Computed tomography (CT) perfusion, Perfusion CT, cerebral CT perfusion
Comparators	Cerebral Angiography, conventional angiography Digital subtraction angiography (DSA)
Outcomes	Diagnostic performance • Detection of vasospasm after SAH - Angiographic vasospasm and symptomatic vasospasm - Sensitivity and specificity - Positive and negative predictive value • Use for endovascular treatment/therapy decision - Sensitivity and specificity - Positive and negative predictive value
Study design	Systematic reviews, comparative study, cohort study, cross sectional studies
Type of publication	English, full text articles, human studies

Exclusion criteria

Intervention	Other types of SAH: traumatic SAH, non anerurysmal SAH, isolated perimesencephalic SAH
Study design	Anecdotal, Case series/reports, animal and laboratory studies
Type of publication	Non-english

Relevant articles were critically appraised using Critical Appraisal Skills Programme (CASP) and diagnostic accuracy evidence graded according to the NHS Centre for Reviews and Dissemination (CRD) University of York, Report Number 4 (2nd Edition) for diagnostic accuracy studies (Appendix 2a) while effectiveness evidence graded according to the US/Canadian Preventive Services Task Force Level of Evidence

(2001) (Appendix 2b). Abbreviation list used in this report was as in Appendix 3. Data were extracted and summarized in evidence table as in Appendix 4. The data were not pooled and only qualitative analysis was carried out.

5. RESULTS AND DISCUSSION

Seven full text articles on TCD and cerebral CTP in the management of aSAH met the inclusion/exclusion criteria, which were systematic review of comparative trials (1), comparative trial (1), diagnostic studies (5) in design and hence were included in this systematic review.

A technology assessment report from the American Academy of Neurology on TCD ultrasonography and a guideline from the American Heart/Stroke Association on the management of aneurysmal subarachnoid haemorrhage were also included.

5.1 DIAGNOSTIC ACCURACY AND EFFECTIVENESS

Transcranial Doppler (TCD) Ultrasound

Four full text articles on TCD in the management of aSAH met the inclusion/exclusion criteria which were systematic review of comparative trials (1), comparative trial (1) and diagnostic studies (2) in design were included in this systematic review.

i. Detection of cerebral vasospasm (all arteries)

Lysakowski C *et al* conducted a systematic review of comparative trials in 2001 to evaluate the accuracy of Transcranial Doppler (TCD) compared with angiography for the diagnosis of cerebral vasospasm after SAH due to a ruptured aneurysm and its usefulness as a screening method in this setting. Only studies using conventional TCD device were included (color TCD excluded). Angiography was the gold standard diagnostic test in this setting. The review included twenty-six studies comparing TCD with angiography, which were appraised using a modified 10-point validity score for diagnostic tests. Median validity score was 4.5 (range 1 to 8) and 50% of the studies had a score of <5. However, meta analysis could only be performed with data from seven studies. They found that for the middle cerebral artery (MCA) (5 studies, 317 tests), sensitivity of TCD in detecting vasospasm was 67% (95% CI 48% to 87%), specificity was 99% (98% to 100%), positive predictive value (PPV) was 97% (95% to 98%), negative predictive value (NPV) was 78% (65% to 91%), positive likelihood ratio was 17(5-56) and negative likelihood ratio of 0.4(0.2-0.7). Whereas for the anterior cerebral artery (3 studies, 171 tests), sensitivity of TCD in detecting vasospasm was 42% (11% to 72%), specificity was 76% (53% to 100%), PPV was 56% (27% to 84%), and NPV was 69% (43% to 95%). Result summary was as illustrated in Table 1 below. The review demonstrated that data for other arteries was from a single trial each. They were internal carotid

artery, posterior cerebral artery, basilar cerebral artery and vertebral cerebral artery; with their respective sensitivity and specificity of 25% and 91%, 48% and 69%, 77% and 79%, followed by 44% and 88% respectively. They also found the cut off for a positive TCD was defined as a flow velocity in the MCA of 120 cm/sec in five studies, and of 130 cm/sec and 140 cm/sec in one study each. The cut off for a positive angiography was defined as a lumen reduction in any artery of at least 25% in five studies, and of at least 30% in one study. The author concluded that TCD demonstrated high specificity but low sensitivity for MCA, whereas both the sensitivity and specificity were low for ACA. TCD has good diagnostic value in detecting vasospasm for MCA with high positive likelihood ratio (17), whereas diagnostic value was low for ACA (positive likelihood ratio <5). There is no evidence for any usefulness of TCD as a diagnostic tool for spasms of other cerebral arteries. No conclusion could be drawn since data was only available from one study each. [7]
level II-1

Table 1: TCD vs angiography in patient with vasospasm due to ruptured aneurysm: Result of individual trial and meta analysis

Reference	True Positive Angio+ TCD+	False-Positive Angio− TCD+	True Negative Angio− TCD−	False-Negative Angio+ TCD−	No. Patients/No. Tests	Sensitivity	Specificity	PPV	NPV	Likelihood Ratio	
										Positive Test	Negative Test
Middle cerebral artery											
Burch[21]	15	3	45	24	49/87	38%	94%	83%	65%	6.2	0.7
Kyoi[27]	10	0	7	1	18/18	91%	100%	100%	88%	14.0	0.1
Langlois[28]	11	0	97	4	56/112	73%	100%	100%	96%	140.9	0.3
Lennihan[29]	6	1	58	1	41/66	86%	98%	86%	98%	50.6	0.1
Sloan[34]	17	0	5	12	34/34	59%	100%	100%	29%	7.0	0.4
Random effects (95% CI)						67% (48–87)	99% (99–100)	97% (95–98)	78% (65–91)	17 (5–56)	0.4 (0.2–0.7)
Anterior cerebral artery											
Kyoi Kikuo[27]	9	2	5	2	18/18	82%	71%	82%	71%	2.9	0.3
Lennihan[29]	2	0	51	13	41/66	13%	100%	100%	80%	16.3	0.9
Wozniak[40]	9	13	24	41	49/87	18%	65%	41%	37%	0.5	1.3
Random effects (95% CI)						42% (11–72)	76% (53–100)	56% (27–84)	69% (43–95)	1.7 (0.6–4.9)	0.9 (0.6–1.3)
Internal carotid artery											
Burch[21]	11	4	42	33	84/90	25%	91%	73%	56%	2.9	0.8
Posterior cerebral artery											
Wozniak[40]	11	19	42	12	47/84	48%	69%	37%	78%	1.5	0.8
Basilar cerebral artery											
Sloan[35]	10	6	23	3	42/43	76.9%	79%	63%	88%	3.7	0.3
Vertebral cerebral arteries											
Sloan[35]	7	6	42	9	42/64	43.8%	88%	54%	82%	3.5	0.6

Suarez *et al*. in 2002 conducted a retrospective review to evaluate the reliability of TCD ultrasound in detecting symptomatic vasospasm in post aneurysmal SAH patients and in monitoring response after hypertensive and endovascular treatments. The study involved 199 patients admitted to neurosciences critical care unit, John Hopkins Medical Institution, with the diagnosis of SAH between January 1990 and June 1997. Of the 199 patients, 55 had symptomatic vasospasm whilst 144 have no symptomatic vasospasm. The sensitivity and specificity of TCD for anterior circulation vessels were calculated by using a mean CBF velocity criterion of >120 cm/sec. Clinical diagnosis of symptomatic vasospasm was used as the standard to determine sensitivity and specificity of TCD and cerebral angiography. The result demonstrated that in patients with symptomatic vasospasm, sensitivity of TCD ultrasound for anterior circulation was 73% with a specificity of 80%. The sensitivity of cerebral angiography was 80%. For individual vessels, the sensitivity and specificity of TCD ultrasound were 64% and 78% for middle cerebral artery, 45% and 84% for anterior cerebral artery, and 80% and 77% for internal carotid artery, respectively. The mean times for symptomatic and TCD ultrasound signs of vasospasm presentation were 6.4 ± 2 and 6.1 ± 3 days, respectively. The author concluded that the reliability of TCD ultrasound was better in detecting high mean CBF velocities in patients with symptomatic vasospasm related to MCA and ICA distributions, than for ACA distribution. TCD ultrasound was as sensitive as cerebral angiography in detecting symptomatic vasospasm. TCD signs of vasospasm can be apparent at a mean of 24 hours before the presence of symptomatic vasospasm. They also concluded that daily TCD ultrasound monitoring could provide early identification of patients with aSAH who are at high risk for symptomatic vasospasm.[13] level 3

ii. Detection of cerebral vasospasm (middle cerebral artery)

Krejza *et al* in 2005 conducted a cross sectional study to determine the accuracy of transcranial color-coded duplex (TCCD) ultrasonography used alone, and in conjunction with carotid artery US for the diagnosis of MCA spasm after SAH, with interarterial DSA used as the reference standard. The study involved 120 subjects from Bialystok University Hospital, Poland where 64 of them were female and 56 were male. Their mean ages were 45.5 ±13.6 years. These subjects were routinely referred for DSA after SAH, with US performed two hours or less before angiography. Vasospasm was graded as mild (≤25% reduction in vessel diameter), moderate (>25% to 50% reduction), or severe (>50% reduction). The ratio of flow velocity in the middle cerebral artery (V_{MCA}) to flow velocity in the ipsilateral extracranial internal carotid artery (V_{ICA}) was calculated. Diagnostic accuracy was evaluated by calculating the area under the receiver operating characteristic curve (Az). The result demonstrated that spasm was mild in 17, moderate in 16, and severe in only nine of 222 arteries studied. They found that these TCCD parameters (peak systolic velocity and V_{MCA}/V_{ICA} ratio) has the highest Az value (0.90, 95%CI 0.85 to 0.96 and 0.91, 95%CI 0.87 to 0.94) compared to other velocity parameters; mean time-averaged maximum and end diastolic parameter, with Az value of 0.88 and 0.84 respectively. Difference in Az value between end-diastolic velocity and the

respective V_{MCA}/V_{ICA} ratio (4%) reached statistical significance ($p<0.05$). Az values for peak systolic velocity and V_{MCA}/V_{ICA} ratio in the diagnosis of moderate to severe vasospasm were 0.93 and 0.95 respectively. The stepwise approach using V_{MCA}/V_{ICA} ratio after flow velocity measurement in the MCA resulted in decrease number of false-negative findings in both groups. The author concluded that TCCD US alone, or in conjunction with carotid artery US has excellent accuracy for angiographic detection of vasospasm. The use of these parameters (MCA velocity measurements and V_{MCA}/V_{ICA} ratio) may help to increase the diagnostic accuracy of Doppler US. [14 level 3] Appendix 4 summarize the pertinent diagnostic findings of TCD in patient with aSAH from the above studies.

iii. Detection of microembolic signals

Romano JG *et al* conducted a comparative study to determine the frequency and characteristics of microembolic signals (MES) in aSAH in 2002. The study involved 23 patients (46 vessels with 138 observations) with aSAH admitted to Neuroscience Intensive Care Unit at Jackson Memorial Hospital in Miami and 11 control subjects comprised of those individuals without SAH or other cerebrovascular diseases who (22 vessels) were treated in the same unit. Each patient underwent monitoring of both MCA for the presence of MES and vasospasm using TCD ultrasonography for 30 minutes three times each week, but control subjects underwent assessment of each MCA once. All patients underwent initial cerebral catheter angiography for the diagnosis of aSAH. They found that MES were detected in 16 of 23 patients (70%) at some time during their stays in the intensive care unit and in 2 of 11 control subjects (18%) ($p<0.006$). Monitoring was initiated at a mean of 5.9 days after SAH (range, 1 to 16 days) and lasted at a mean of 6.8 days (range, 1 to15 days). The mean time to detection of the first MES was 6.9 days (range, 2 to18 days) after SAH. Clinical vasospasm was present in 12 cases, MES were observed in 10 of those 12 cases (83%) but in only 6 of 11 cases (54%) without clinical vasospasm ($p = 0.19$). Ultrasonographic vasospasm was observed for 71 of 138 arteries (51.5%); MES were observed for 28% of vessels with vasospasm and 36% of those without vasospasm. The author concluded that MES were common in SAH, occurring in 70% of cases of SAH and one-third of all vessels monitored. Although MES were more frequent among patients with clinical vasospasm, this difference did not reach statistical significance. The author suggested further studies to be conducted to determine the origin and clinical relevance of MES in SAH.[15 level II-1]

The American Academy of Neurology in its assessment on TCD ultrasonography has stated that TCD is useful in monitoring the temporal course of angiographic vasospasm after aSAH. TCD is useful for the detection and monitoring of angiographic vasospasm in the basal segments of the intracranial arteries, especially the middle cerebral artery and basilar artery. [8 level III]

Guideline on the Management of Aneurysmal Subarachnoid Haemorrhage from the American Heart/Stroke Association stated that TCD is reasonable to monitor the development of arterial vasospasm in the management of cerebral vasospasm and

delayed cerebral ischaemia after aSAH. It was also stated that perfusion imaging with computed tomography (CT) or magnetic resonance can be useful to identify region of potential brain ischaemia.[16 level III]

Computed Tomography Perfusion (CTP)

Three full text articles on CTP in the management of aSAH met the inclusion/exclusion criteria were included in this systematic review which were all diagnostic studies.

i. Detection of vasospasm

Wintermark M *et al* conducted a retrospective review to evaluate the utility of CTP combined with CTA for the diagnosis and management of vasospasm, using DSA as the gold standard. The study consisted of 27 patients admitted at University of California Hospital with acute SAH between January and September 2003 who had undergone CT Angiography (CTA)/CTP, DSA, and TCD ultrasonography within a time interval of 12 hours of one another. The patients' charts were reviewed for treatment of vasospasm. CTA, CTP, TCD, and DSA examinations were independently reviewed and quantified for vasospasm. CTP thresholds, CTA findings, noncontrast CT (NCT) hypodensities, and TCD thresholds were evaluated for accuracy, sensitivity and specificity, as well as for negative (NPV) and positive predictive values (PPV) in the prediction of angiographic vasospasm and endovascular treatment, considering DSA as the gold standard. They found that a total of 123 arterial territories in 11 patients demonstrated angiographic vasospasm, and six patients underwent endovascular therapy. The evidence demonstrated that for the diagnosis of vasospasm, diagnostic performance of CTP as measured by mean transit time (MTT) with a threshold of 6.4 seconds was the most sensitive parameter (95.1%), with NPV of 98.7%, compared to other parameters; CTP relative cerebral blood volume, CTP relative cerebral blood flow, and CTP time to peak with respective sensitivity and specificity; 27.6% and 74.6%, 80.5% and 94.1%, and 87.0% and 89.2%.The accuracy, sensitivity, specificity, NPV, and PPV of the MTT/CTA combination were 93.0%, 72.4%, 98.0%, 93.6, and 89.9%, respectively. Whereas MTT considered alone represented the most sensitive parameter (NPV, 98.7%). For endovascular treatment, they found that cortical regional cerebral blood flow value (rCBF) of <39.3 (mL x 100 g^{-1} x min^{-1}) represented the most accurate (94.8%) CTP parameter with sensitivity and specificity of 61.7% and 98.2% respectively. MTT has the highest NPV, but this time at a threshold of 7.6 seconds. PCT had significantly higher PPV (89.9%) than TCD (62.9%). The author concluded that a CT survey combining CTA and CTP represents an accurate screening test in patients with suspected vasospasm.[6 level 3]

Nabavi DG *et al* conducted a diagnostic prospective study to assess the feasibility and diagnostic relevance of repetitive dynamic (contrast enhanced) CT measurement of CBF, CBV and MTT in the first three weeks after aSAH. The study involved 15 patients with aSAH (within 48 hours) mean age of 56 years from the University of Western Ontario. All patients underwent standard treatment.

Occurrence and severity of vasospasm were assessed by post-operative DSA and TCD at regular intervals. Routine diagnostic CT was performed before each dynamic CT study by interventional radiologists. The results were correlated with the clinical course and time after the event and the occurrence of vasospasm. They found that five patients had no sign of vasospasm, while four had mild and six moderate to severe vasospasm. A total of 70 dynamic CT studies were performed, however 59 dynamic CT studies including 944 region of interest were analyzed. For Cerebral Perfusion and Cerebral Infarct, they found that patients with early infarct had higher overall CBV than those with delayed infarct ($p<0.001$) indicating cerebral autoregulation. For cerebral perfusion after SAH, they found that minimal CBF and CBV values occurred 1 to 3 and 10 to 17 days after SAH, respectively. Mean CBF and CBV were significantly lower in patients with moderate to severe vasospasm, compared to none in mild vasospasm. The study could not define a clear-cut threshold for cerebral infarct using perfusion CT, attributed by relatively large region of interest which resulted in volume averaging with normal and ischaemic tissue. Further investigation may lead to definition of a CTP ischaemic threshold in patient with aSAH. Ability to assess CBV and MTT may help in understanding the impairment of autoregulation believed to occur in some patients after SAH[9 level 3]

ii. Detection of secondary cerebral infarction

Pham M *et al* conducted a cross sectional study to assess the diagnostic accuracy of CT perfusion (CTP) and Transcranial Doppler (TCD) sonography for the prediction of secondary cerebral infarction (SCI) after aSAH. This study involved 38 patients with aSAH Hunt and Hess grades I to IV admitted to Hospital University of Wurzburg, Germany. During two weeks after SAH, 38 consecutive patients completed an average of 3.5 CT/CTP and 10.7 TCD examinations at regular intervals as required by the study protocol, which were daily neurologic examination and TCD over 2 weeks were performed. SCI was defined as delayed infarction on native CT between 3 and 14 days after SAH. Measures of diagnostic accuracy were calculated for qualitative CTP (visual color-map ratings from two blinded observers) and TCD assessments (mean flow velocity >120 cm/s in anterior, middle, and posterior cerebral artery territories). The result demonstrated that 14 patients (36.9%) develop SCI. Median interval between the predictive CTP sessions before complete SCI on native CT was 3 days (range 2 to 5 days). Table 2 demonstrated prediction of SCI by different CTP parameter. Time-to-peak (TTP) color maps predicted SCI with high sensitivity (0.93), whereas CBF and CBV predicted SCI with high specificity (0.96 and 0.96) respectively. Any combination of CTP measures did not improve diagnostic performance. They also found that for TCD, daily TCD before manifestation and all TCD examination over 14 days of observation predicted SCI with low sensitivity (0.58,0.77) and specificity (0.50,0.38) respectively (Table 3). Figure 4 below displays the sensitivity plot of qualitative CTP and TCD ratings in the time course before and after SCI which showed marked difference in sensitivity for the two noninvasive modalities early before infarction.

Table 2: Prediction of SCI by different CTP parameter

CTP Parameter	Sensitivity	Specificity	NPV	PPV
TTP	0.93	0.67	0.94	0.62
CBF	0.29	0.96	0.70	0.67
CBV	0.21	0.96	0.68	0.75

Table 3: Prediction of SCI by TCD

TCD	Sensitivity	Specificity	NPV	PPV
Daily TCD before manifestation	0.58	0.50	0.71	0.37
All TCD examination over 14days of observation	0.77	0.38	0.75	0.40

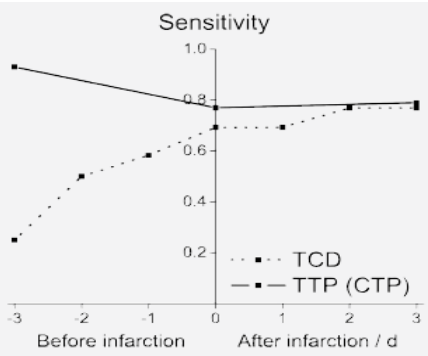

Figure 4: Sensitivity plots of TCD and TTP derived from CTP for the prediction of SCI

The author concluded that TTP as indicated by CTP is a sensitive and early predictor of secondary cerebral infarction in patient with aneurysmal SAH. [17] level 2

5.2 SAFETY

There was no retrievable evidence from the electronic databases on the safety of TCD and cerebral CTP in the management of aSAH.

An unrelated adverse event such as headache and disturbed vision post procedure has been reported by FDA.[18]

TCD has CE mark and was classified under Class II Medical Device by the USFDA.[18] However, the registration of CTP with USFDA could not be retrieved.[18]

5.3 COST EFFECTIVENESS

There is no evidence retrieved on TCD & CTP cost effectiveness. Estimated price per item were RM[redacted] to RM[redacted] per set of TCD US (as it requires a high end ultrasound system), while a CT Perfusion costs approximately RM5million (as it requires at least 64 slice CT scanner).

5.4 ORGANISATIONAL ASPECT

TCD is an operator dependant procedure which requires training and is depending on the operator level of experience to perform and interpret result. It is performed by technologists, sonographers and physicians and interpreted by neurologist and other specialist.[6,9] TCD limiting factors such as limitations of insonation secondary to adequate acoustic windowing restrict its use in about 8% of patients. [19]

Software to analyze the perfusion CT data is commercially available and relatively easy to use, although training is required. CTP requires radiologist specialising in neuroradiology. The amount of training necessary to create reliable perfusion maps is not known. Results of an initial investigation indicate that the findings are reproducible between different operators. This study used experienced radiologist investigators to create the perfusion maps. The reproducibility between experienced and inexperienced radiologists, between radiologists and technologists, or between the same radiologist or technologist on different days has not been evaluated.[20]

In order for both TCD and CTP to be performed and interpreted effectively on patients, specialized individual training is required. In addition, other requirement that is needed to be ready in place before CTP can be performed is the availability of spiral CT scanners equipped with the appropriate software.

5.4 LIMITATION

Our study has several limitations. The selection of studies was done by one reviewer. Although there was no restriction in language during the search, only English full text articles were included in this report. Any abstracts without full text articles were also excluded. Furthermore, some of the studies included have small sample size.

6. CONCLUSION

Based on the above review, there was limited retrievable fair level of evidences from the electronic databases on the effectiveness and safety of TCD and CTP in the management of aneurysmal SAH.

Transcranial Doppler (TCD) Ultrasound

There was limited retrievable fair level of evidences from the electronic databases on the effectiveness and safety of TCD in the management of aneurysmal SAH whereby four full text articles were included in this systematic review; namely systematic review of comparative trials (1), comparative trial (1) and cross sectional (2) in design.

Evidence demonstrated that TCD appeared beneficial for the detection and monitoring of angiographic vasospasm of the intracranial arteries due to ruptured aneurysms, especially the middle cerebral artery. TCD demonstrated good diagnostic value in the detection of cerebral vasospasm after aneurysmal haemorrhage for middle cerebral arteries with high positive likelihood ratio (17) and high specificity, however its diagnostic value for ACA was low (positive likelihood ratio <5). The sensitivity in detecting MCA vasospasm varies from 64% to 67% with specificity from 78% to 99%; in ACA vasospasm the sensitivity ranges from 42% to 45% with specificity of 76% to 84%; while in ICA vasospasm the sensitivity was between 25% to 80% with specificity ranges from 77% to 91%. Evidence also showed that these TCD parameters; middle cerebral artery velocity (VMCA) measurements and V_{MCA}/V_{ICA} ratio can increase the accuracy of TCD. This investigational procedure also appeared safe with CE certification and without reported adverse event.

This is in tandem with the Guideline from the American Heart/Stroke Association on the Management of Aneurysmal Subarachnoid Haemorrhage which stated that TCD is reasonable to monitor the development of arterial vasospasm after aneurysmal SAH. Similarly, TCD is stated as useful for the detection and monitoring of angiographic vasospasm in the basal segments of the intracranial arteries, especially the middle cerebral artery and basilar artery after aSAH as documented by the American Academy of Neurology in its assessment.

Computed Tomography Perfusion (CTP)

There was limited retrievable fair level of evidence from the electronic databases on the effectiveness and safety of CTP in the management of aneurysmal SAH, with three full text articles (all cross sectional in design) included in this systematic review specifically in the detection of cerebral vasospasm and secondary cerebral infarction after aneurysmal SAH.

Evidences demonstrated that CTP appeared useful in the detection of vasospasm in suspected patients after aSAH. For the diagnosis of angiographic vasospasm, diagnostic performance of CTP as measured by mean transit time (MTT) with a threshold of 6.4 seconds was the most sensitive parameter.

Evidences also showed that CTP appeared useful in the detection of secondary cerebral infarction after aneurysmal SAH, with CTP derived parameter, time-to-peak was the most sensitive parameter.

Evidence also has demonstrated that CTP seemed beneficial in providing immediately applicable information for diagnosing vasospasm, which could further guide decisions for endovascular treatment in the management of aSAH. In term of CTP use to assist decision for endovascular treatment of angiographic vasospasm, evidence showed that the most accurate CTP parameter was cortical regional cerebral blood flow value (rCBF)(94.8%), with sensitivity and specificity of 61.7% and 98.2% respectively. This procedure appeared safe with no safety issue raised related to its use.

This is in line with the Guideline on the Management of Aneurysmal Subarachnoid Haemorrhage by the American Heart/Stroke Association which documented that perfusion imaging with computed tomography or magnetic resonance can be useful in identifying region of potential brain ischaemia after aneurysmal SAH.

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9. APPENDIX

9.1. Appendix 1: LITERATURE SEARCH STRATEGY

Ovid MEDLINE® In-process & other Non-Indexed citations and OvidMEDLINE® 1948 to present

1 Transcranial doppler ultrasound {Including Related Terms}

2 Ultrasonography, Doppler, Transcranial/ or exp Cerebrovascular Circulation/

3 1 and 2

4 Perfusion Imaging/ or Tomography, X-Ray Computed/

5 Brain/ and Perfusion Imaging/ and Tomography, X-Ray Computed/

6 Subarachnoid Haemorrhage/bl, co, di, ec, ep, mo, pa, pp, ra, ri, rh, su, th, us [Blood, Complications, Diagnosis, Economics, Epidemiology, Mortality, Pathology, Physiopathology, Radiography, Radionuclide Imaging, Rehabilitation, Surgery, Therapy, Ultrasonography]

7 3 and 6

8 4 or 5

9 6 and 8

OTHER DATABASES

EBM Reviews - Cochrane Central Register of Controlled Trials	Similar MeSH, keywords, limits used as per MEDLINE search
EBM Reviews - Database of Abstracts of Review of Effects	
EBM Reviews - Cochrane database of systematic reviews	
EBM Reviews - Health Technology Assessment	
PubMed	
NHS economic evaluation database	
INAHTA	Transcranial Doppler, computed tomography perfusion, cerebral perfusion scanning, subarachnoid haemorrhage
FDA	Transcranial Doppler, computed tomography perfusion, cerebral perfusion scanning, subarachnoid haemorrhage

9.2 Appendix 2a

HIERARCHY OF EVIDENCE FOR TEST ACCURACY STUDIES

Level	Description	
1.	A blind comparison with reference standard among an appropriate sample of consecutive patients	
2.	Any one of the following	Narrow population spectrum
3.	Any two of the following	Differential use of reference standard
4.	Any three or more of the following	Reference standard not blind
		Case control study
5.	Expert opinion with no explicit critical appraisal, based on physiology, bench research or first principles.	

SOURCE: NHS Centre for Reviews and Dissemination (CRD) University of York, Report Number 4 (2nd Edition)

9.2 Appendix 2b

HIERARCHY OF EVIDENCE FOR EFFECTIVENESS STUDIES

DESIGNATION OF LEVELS OF EVIDENCE

I Evidence obtained from at least one properly designed randomized controlled trial.

II-I Evidence obtained from well-designed controlled trials without randomization.

II-2 Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one centre or research group.

II-3 Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence.

III Opinions or respected authorities, based on clinical experience; descriptive studies and case reports; or reports of expert committees.

SOURCE : US/CANADIAN PREVENTIVE SERVICES TASK FORCE (Harris 2001)

9.3 Appendix 3

LIST OF ABBREVIATION

aSAH	Aneurysmal subarachnoid haemorrhage
CBF	Cerebral blood flow
CBV	Cerebral blood volume
CE	European Conformity
CT	Computed tomography
CTA	Computed tomography angiography
CTP	Computed Tomography Perfusion
DSA	Digital subtraction angiography
MCA	Middle cerebral artery
MES	Micro emboli signal
MTT	Mean transit time
NPV	Negative predictive value
PCT	Perfusion Computed Tomography
PET	Positron Emission Tomography
PPV	Positive predictive value
rCBF	Relative cortical blood flow
TTP	Time to peak
SAH	subarachnoid haemorrhage
SPECT	Single-Photon Emission Computed Tomography
TCD	Transcranial Doppler
TCCD	Transcranial Color Doppler
US	Ultrasound
USFDA	US Food and Drug Administration

9.4 Appendix 5

Summary: Diagnostic value of TCD in patient with vasospasm

Study author	Type of TCD	Gold-standard	Reference /Parameter	Sensitivity %	Specificity %	Area under ROC (Az value)
Lysakowski et al. 2001	TCD	Angiography	MCA	67	99	-
			ACA	42	76	-
			ICA	25	91	-
			PCA	48	69	-
Suarez et al 2002	TCD	Clinical symptomatic vasospasm	ACA	45	84	-
			MCA	64	78	-
			ICA	80	77	-
Krejza et al 2005	TCCD	Intraarterial DSA	Peak systolic value	-	-	0.90
			VMCA/VICA	-	-	0.91
			Mean time averaged	-	-	0.88
			End diastolic	-	-	0.84