Original Article

Assessment of Pre- and Post-Operative Cerebral Perfusion in Anterior Circulation Intracranial Aneurysm Clipping Patients at Hospital Sungai Buloh Using CT Perfusion Scan and Correlations to Fisher, Navarro and WFNS Scores

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Abstract

Background: **Intracranial aneurysms may rupture and are typically associated with high morbidity and mortality, commonly due to vasospasm after rupture. Once the aneurysm ruptures, the patient's cerebral blood flow may be disturbed during the acute phase, affecting cerebral circulation and thus cerebral perfusion prior to the onset of vasospasm. Fisher and Navarro scores are used to predict vasospasm, while World Federation of Neurosurgical Societies (WFNS) scores are used to predict patient outcomes. Several score modifications are available to obtain higher sensitivity and specificity for the prediction of vasospasm development, but these scores are still unsuccessful. Alternatively, cerebral CT perfusion scan (CTP) is a non-invasive method for measuring cerebral blood flow (CBF), cerebral blood volume (CBV) and mean transit time (MTT) in regions of interests (ROI) to obtain the cerebral perfusion status as well as detecting vasospasm.**

Methods: **A total of 30 patients' data with clipped anterior circulation intracranial aneurysms admitted to the hospital between 1 January 2013 and 30 June 2014, were collected from the hospital's electronic database. The data collected included patients' admissions demographic profiles, Fisher, Navarro and WFNS scores; and their immediate pre- and post-operative CTP parameters.**

Results: **This study found a significant increase in post-operative MTT (pre- and post-operative MTT) were 9.75 (SD = 1.31) and 10.44 (SD = 1.56) respectively, ($P < 0.001$)) as well as a significant reduction in post-operative CBF (pre- and post-operative mean CBF were 195.29 (SD = 24.92) and 179.49 (SD = 31.17) respectively ($P < 0.001$)). There were no significant differences in CBV. There were no significant correlations between the pre- and post-operative CTP parameters and Fisher, Navarro or WFNS scores.**

Conclusion: **Despite the interest in using Fisher, Navarro and WFNS scores to predict vasospasm and patient outcomes for ruptured intracranial aneurysms, this study found no significant correlations between these scores in either pre- or post-operative CTP parameters.**

These results explain the disagreement in the field regarding the multiple proposed grading systems for vasospasm prediction. CTP measures more than just anatomical structures; therefore, it is more sensitive towards minor changes in cerebral perfusion that would not be detected by WFNS, Fisher or Navarro scores.

Keywords: *intracranial aneurysm, cerebral vasospasm, brain ischemia, brain infarction, cerebrovascular circulation*

Introduction

Intracranial aneurysm is an abnormal dilatation of a blood vessel that may rupture, causing intracranial bleeding. It is associated with high morbidity and mortality, commonly ascribed to vasospasm after all other diagnoses have been excluded. Ecker, a neurosurgeon, alongside with Riemenschneider, a radiologist, were the first to describe angiographic vasospasm in 1951 (1). They concluded at the time that vasospasm is usually seen within several weeks of subarachnoid hemorrhage (SAH) and plays an important role in determining the outcome of patients. Fisher and Navarro scores are among the grading scales used to predict vasospasm, while the World Federation of Neurosurgical Societies (WFNS) score is used to predict patient outcomes. A few modifications of these grading scales are available and are thought to yield higher sensitivity and specificity for the prediction of vasospasm, but these modifications are still unsuccessful. Once an intracranial aneurysm ruptures, cerebral blood flow may be disturbed during the acute phase of aneurysm rupture, resulting in disrupted cerebral circulation and autoregulation. The disturbed cerebral perfusion is thus present prior to the onset of vasospasm and may influence patient outcomes. Cerebral computed tomography perfusion (CTP) is a non-invasive method for measuring cerebral blood flow (CBF), cerebral blood volume (CBV) and mean transit time (MTT) in any region of interest (ROI). Together, these parameters characterise overall cerebral perfusion status, and their values can be compared pre- and post-operatively. Hospital Sungai Buloh is home to Malaysia's first brain suite, which has an integrated CT scanner in its operating theater, and it is one of the principle neurosurgical referral centers in Malaysia. Refer Figure 1. The CT scanner is routinely used for all patients with aneurysm clipping, either for cerebral CT angiogram or CTP as demonstrated in Figure 2.

Methods

Data were retrospectively collected from patients diagnosed with anterior circulation aneurysms with aneurysm clipping admitted between 1 January 2013 and 30 June 2014 in Hospital Sungai Buloh. All data were collected from the hospital's electronic database. Data collected included patients' admissions demographic profiles, as well as Fisher, Navarro and WFNS scores. Both pre- and postoperative CTP parameters were collected. Three ROIs were defined in each hemisphere, for a total of six ROIs, to measure the mean CBF, CBV and MTT. The ROIs were defined as the anterior cerebral artery, middle cerebral artery and the internal carotid artery regions (Figure 3).

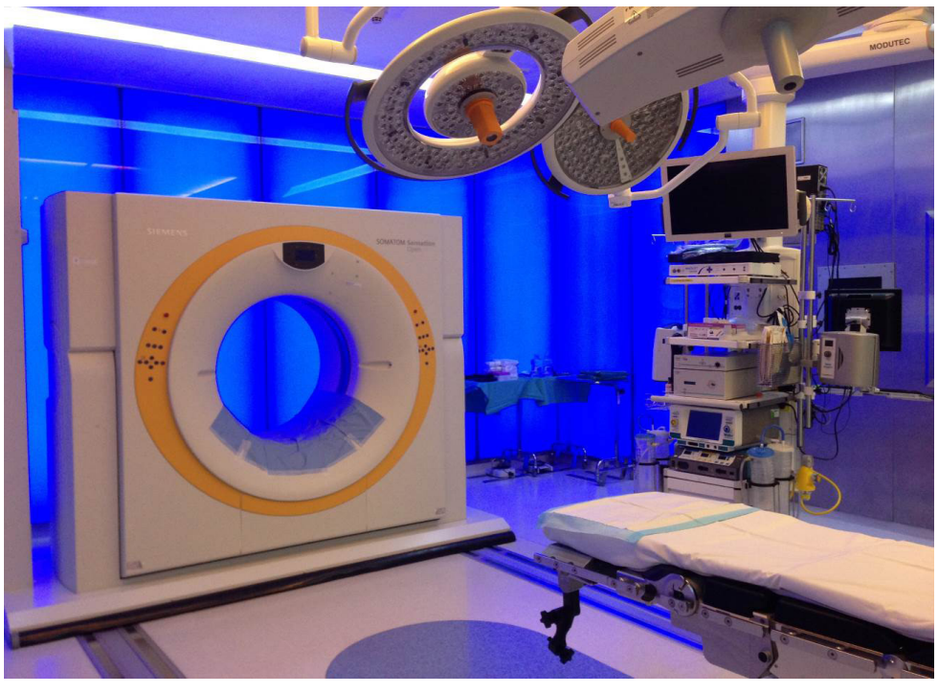

Figure 1. Brainsuite is complete with a floor-mounted sliding CT gantry and radiolucent operating table

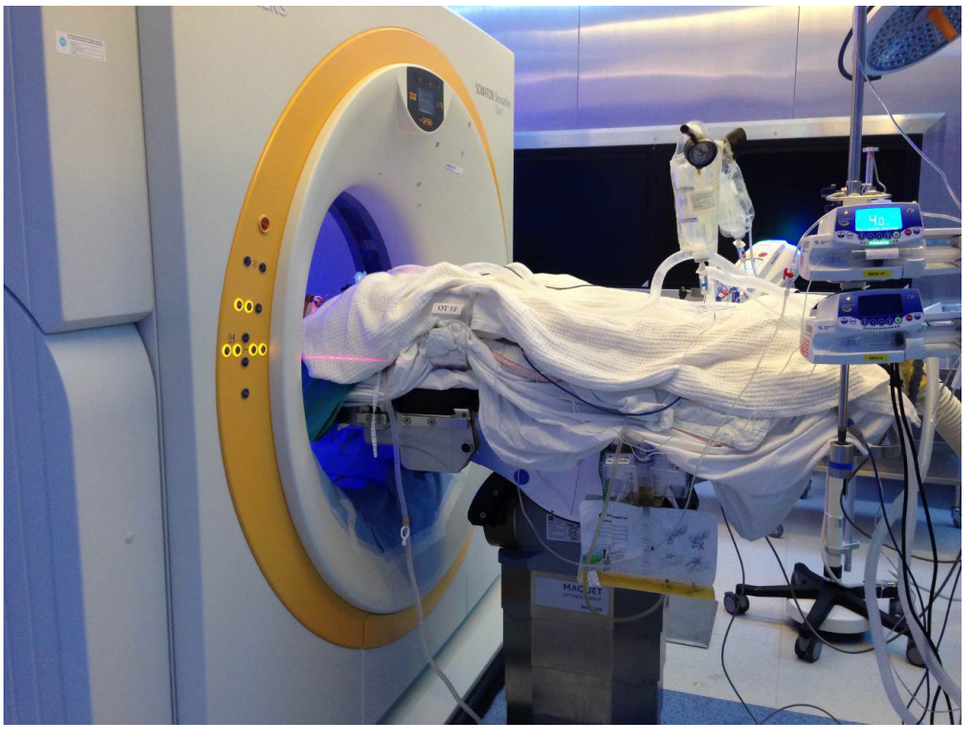

Figure 2. A patient undergoing CTP scan

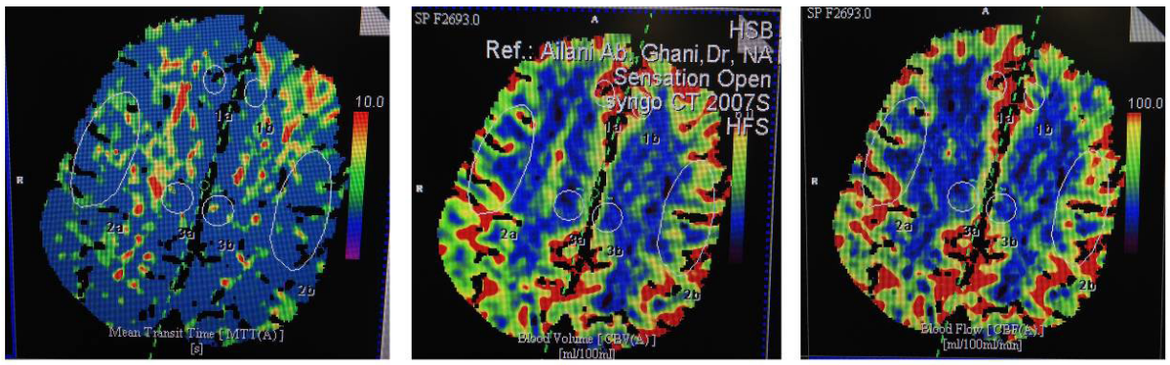

Figure 3. The region of interest (ROI) selected to obtain the mean CTP parameters

Results

The characteristics of study participants are in Table 1 (2). The mean age of patients was 48.9 years old with majority of them (46.7%) were 40 to 49 years old and more than half were male (56.7%) and of Malay ethnicity (63.3%). There were almost equal numbers of patients with (46.7%) and without (53.3%) co-morbidities as tabulated in Table 2 (2). Among the 14 patients with co-morbidities, 12 of them had hypertension, six with diabetes and remaining three had asthma and ischaemic heart disease. While the presenting Fisher, Navarro and WFNS grade are shown in Table 3 (2).

As tabulated in Table 4, pre- and post-operative mean MTTs were 9.75 (SD = 1.31) and 10.44 (SD = 1.56), respectively. This difference between pre- and post-operative mean MTTs was significant ($P < 0.001$) with a higher post-operative mean MTT.

Pre- and post-operative mean CBVs were 10.85 (SD = 2.84) and 11.36 (SD = 2.75), respectively. However, the difference between pre- and post-operative mean CBVs was not significant ($P = 0.128$).

The pre-operative mean CBF was 195.29 (SD = 24.92), and the post-operative mean CBF was 179.49 (SD = 31.17). The CBF mean decreased significantly post-operatively ($P < 0.001$).

In this study, there were no significant correlations between the CTP parameters and Fisher, Navarro or WFNS scores, either pre- or post-operatively; as shown in Table 5.

Table 1. Description of study participants

Characteristics		
Age	Mean (SD)	48.90 (12.26)
	30–39	6 (20.0)
	40–49	14 (46.7)
	50–59	4 (13.3)
	60	6 (20.0)
Gender	Male	17 (56.7)
	Female	13 (43.3)
Ethnicity	Malay	19 (63.3)
	Chinese	8 (26.7)
	Indian	1 (3.3)
	Others	2 (6.7)

Data presented as *n* (%) unless indicated.
Table adapted from Ailani AG, Saiful Azli MN, Regunath K, Azmin Kass R, Abdul Rahman Izani G. Characteristics and outcomes of patients with anterior circulation intracranial aneurysm managed with clipping in Hospital Sungai Buloh. *Malays J Med Sci.* 2016;**23(6)**:113–117. http://dx.doi.org/10.21315/mjms2016.23.6.12.

Table 2. Presence of co-morbidities in study participants

		n (%)
Co-morbidities	Yes	14 (46.7)
	No	16 (53.3)
Hypertension[a]	Yes	12 (85.7)
	No	2 (14.3)
Diabetes[a]	Yes	6 (42.9)
	No	8 (51.7)
Other co-morbidities[a,b]	Yes	3 (21.4)
	No	11 (78.6)

[a]Presented as per within group of patients with co-morbidities
[b]Asthma and IHD
Table adapted from Ailani AG, Saiful Azli MN, Regunath K, Azmin Kass R, Abdul Rahman Izani G. Characteristics and outcomes of patients with anterior circulation intracranial aneurysm managed with clipping in Hospital Sungai Buloh. *Malays J Med Sci*. 2016;**23(6)**:113–117. http://dx.doi.org/10.21315/mjms2016.23.6.12.

Table 3. Fisher, Navarro and WFNS score of study participants

	Scores	*n* (%)
Fisher	0	1 (3.3)
	3	15 (50.0)
	4	14 (46.7)
Navarro	1	2 (6.7)
	2	1 (3.3)
	3	1 (3.3)
	4	0 (0)
	5	5 (16.7)
	6	2 (6.7)
	7	5 (16.7)
	8	1 (3.3)
	9	3 (10)
	10	6(20)
	11	4 (13.3)
WFNS	I	10 (33.3)
	II	5 (16.7)
	III	1 (3.3)
	IV	6 (20.0)
	V	8 (26.7)

Table adapted from Ailani AG, Saiful Azli MN, Regunath K, Azmin Kass R, Abdul Rahman Izani G. Characteristics and outcomes of patients with anterior circulation intracranial aneurysm managed with clipping in Hospital Sungai Buloh. *Malays J Med Sci*. 2016;**23(6)**:113–117. http://dx.doi.org/10.21315/mjms2016.23.6.12.

Table 4. Comparison of pre and post-operative mean MTT, CBV and CBF in all patients undergoing microsurgical clipping

Mean score[a]	Pre-operative	Post-operative	*t*-test[b]	Wilcoxon Signed Rank Test[c]	*P*
MTT (s)	9.75 (1.31)	10.44 (1.56)		4.001	< 0.001**
CBV (ml/100ml)	10.85 (2.84)	11.36 (2.75)		1.522	0.128
CBF (ml/100g/min)	195.29 (24.92)	179.49 (31.17)	3.954		< 0.001**

[a]Sum of average ACA, MCA and BG scores
[b]Data is normally distributed, presented as mean (SD) and analysed with paired *t*-test
[c]Data is skewed, presented as median (IQR) and analysed with Wilcoxon Signed Rank Test
**significant at $P < 0.001$

Table 5. Correlation between mean CTP parameters with Fisher, Navarro and WFNS score

	Mean score[a]					
	Pre-operative			Post-operative		
	MTT[c]	CBV[c]	CBF[b]	MTT[c]	CBV[b]	CBF[b]
Fisher	0.214	-0.132	0.086	0.297	-0.257	-0.352
Navarro	0.012	-0.237	-0.168	0.012	-0.225	-0.168
WFNS	-0.052	-0.250	-0.236	-0.052	-0.333	-0.236

[a]Sum of average ACA, MCA and BG scores
[b]Data is normally distributed and analysed with Pearson's *r*
[c]Data is skewed and analysed with Spearman's rho
*significant at $P < 0.05$

Discussion

This paper retrospectively studied cerebral circulation in the pre- and post-operative periods of patients with intracranial aneurysms undergoing microsurgical clipping by observing the effects of surgery on cerebral perfusion and correlating CTP parameters with Fisher, Navarro and WFNS scores.

Cerebral CTP imaging is a non-invasive technique that provides perfusion parametric information (the measurement of CBF, CBV and time to peak) in specific regions of the brain. The total volume of blood flowing in a given brain volume is defined as the CBV, the total volume of blood passing through a given volume of brain per unit time is defined as the CBF, and the average time taken for blood to pass through a given brain region is defined as the MTT (3). CBF and MTT maps describe the extent of hypoperfusion areas, and the most profoundly affected regions show as a decrease in CBV. Cerebral autoregulation is intact if there is an increase in CBF and MTT but no difference in CBV (4).

The significant increase in the post-operative mean MTTs [pre-operative 9.75 (SD = 1.31), post-operative 10.44 (SD = 1.56)] indicates that the brain is trying to maximise its oxygen retrieval by prolonging the passage of blood flow through a particular region of brain tissue. When cerebral perfusion pressure is low, cerebral autoregulation will cause precapillary resistance vessels to dilate, increasing the cerebral blood volume. This change maintains the cerebral perfusion pressure (5). Unfortunately, prolonged MTT is also associated with high mortality, especially when cerebral autoregulation fails (6, 7). This happens when prolonged MTT is accompanied by increased CBF and decreased CBV.

This study demonstrated that mean MTT scores in all patients were significantly higher post-operatively which may also indicate mild to moderate vasospasm, as suggested by Binaghi et al. (40), while prolonged MTT with CBF and/or CBV abnormalities indicates severe vasospasm. Since prolonged MTT occurred post-operatively in all patients undergoing microsurgical clipping, this stasis of blood flow could be due to brain

retraction intraoperatively or even to the vessel manipulation that occurs during surgery.

The advantage of measuring MTT is its value is not affected by sedative drugs which will normally affect the brain perfusion. In healthy volunteers, sedative drugs have been reported to decrease CBV and CBF and to increase CBF responsiveness to CO_2. However, midazolam does not affect the CBF/CBV ratio. Since MTT is defined as the CBV/CBF, mean MTT is independent of any sedative effect (8).

When an intracranial aneurysm ruptures, it causes intracranial changes mainly due to increased intracranial pressure, which leads to a reduction of cerebral blood flow and corresponding reduction in oxygen supply, impaired autoregulation, altered metabolism and reduction in systemic blood volume (9–16). This vicious cycle starts after an aneurysm ruptures, though the disturbances in a patient's cerebral blood flow may have already occurred during the acute phase of aneurysm rupture, resulting in alterations in cerebral circulation prior to the onset of vasospasm (17, 18).

Reduction in cerebral blood flow is associated with a reduction in cerebral metabolism (11, 15). This reduction in cerebral metabolism, measured by $CMRO_2$, occurs in the early stage after an intracranial aneurysm ruptures, prior to the onset of vasospasm (19). During the initial stage following a ruptured intracranial aneurysm, subarachnoid hemorrhage already shows a direct adverse effect on the cerebral vessels, causing a reduction in $CMRO_2$ followed by a reduction in cerebral blood flow.

Conversely, cerebral blood volume (CBV) was increased in all patients after intracranial aneurysm rupture (20). The exact mechanism for this increase is still a mystery, though it is thought to be caused by compensation of the distal microcirculation in response to vasospasm of the proximal vessel (21). Distal vasodilatation causes a decrease in cerebral compliance and autoregulation. Findings from cerebral CTP suggest that dysfunction of cerebral autoregulation may result in an inability to increase CBV in the event of reduced cerebral blood flow (4).

In a healthy brain, cerebral circulation is maintained with normal cerebral blood flow despite variations in cerebral perfusion pressure, commonly known as autoregulation. In intact cerebral autoregulation, arterial smooth muscle cells will react to intravascular pressure or changes in brain metabolism to maintain the oxygen demand. However, in ruptured intracranial aneurysm with subarachnoid hemorrhage, autoregulation is impaired and the graph is shifted to the right. Autoregulation is thought to be significantly lost in patients with heavy subarachnoid hemorrhage burden (22). As a result, minimal reductions in blood pressure may cause cerebral edema and an increase in intracranial pressure (23).

Vasospasm, which may occur later, will eventually exacerbate ischemia and explain delayed neurological deficits if it is not treated (24). An understanding of this pathophysiology leads to treatments for vasospasm, including arterial dilatation, either directly or indirectly. By increasing the vessel diameter, more blood flow is available to the region and the risk of ischemia or infarct is reduced. Poor outcomes in patients with ruptured intracranial aneurysms are usually related to vasospasm and are commonly predicted from Fisher or Navarro scores (25, 26). However, cerebral autoregulation, which is frequently overlooked, is already impaired at the moment of aneurysm rupture, and in such cases, vasospasm can only worsen the damage that has occurred.

Vasospasm is due to decreases in brain perfusion that lead to irreversible cell death and eventually structural damage, explaining losses in neurological functioning. The challenge is to detect vasospasm early and to treat it before it becomes irreversible. Vasospasm prolongs patient hospital stays and is also associated with poor outcomes at three months (27). In addition, vasospasm is significant considering its neurological sequelae of cerebral ischemia, which can lead to disability and even death. Vasospasm is also potentially the most treatable factor (28).

Symptomatic vasospasm occurs because of arterial narrowing, causing cerebral ischemia and explaining corresponding symptoms and signs. Vasospasm is also known to cause delayed cerebral ischemia (DCI) or delayed ischemic neurological deficits (DIND). However, not all instances of vasospasm cause cerebral infarction and not all instances of severe vasospasm cause cerebral ischemia (29). The outcome depends upon the length and severity of arterial narrowing, as well as other factors that may influence cerebral blood flow, including the circulating blood volume, arterial blood pressure, collateral and anastomotic blood supply and the brain's metabolic demand (30, 31). These factors may explain why not all cases of radiological vasospasm will present with symptomatic vasospasm.

Vasospasm is a diagnosis of exclusion traditionally thought to be attributed to DIND, as stated above; however, cerebral circulation post-SAH is now known to also be affected by other factors such as disturbances in cerebral autoregulation. Unfortunately, cerebral circulation and its mechanisms of disturbance are still poorly understood.

As initially demonstrated by Fisher et al. in 1980, vasospasm can be predicted based on the volume, density and presence of SAH in the CT brain scan (25). Another study by Claassen et al. found that bilateral intraventricular hemorrhage and SAH in any cistern or fissure are significant factors associated with delayed cerebral ischemia (27). However, Frontera et al. (41) proposed a modified grading, as indicated in the Table 6, in which the probability of having vasospasm increases with the grading. Another alternative grading is the Barrow Neurological Institute grading scale, which is based on the thickness of the cisternal clot (32). A study by Navarro (26) considers five predictive factors, which includes WFNS score, pre-existing hypertension, thickness of blood clot, presence of intraventricular hemorrhage and hydrocephalus in CT brain scan, to correlate with positive angiographic vasospasm. Low Navarro scores show a 100% sensitivity but only 8% specificity (Refer Table 7). Higher scores show lower sensitivity but are more specific.

Generally, the total probability of vasospasm depends on the subarachnoid clot volume and its location. Clot volume may also predict the outcome of patients with SAH as this group of patients will develop delayed cerebral ischemia more often and earlier (33). A study by Schmieder et al. showed there is increased impairment in autoregulation with higher Fisher scores, although the risk of vasospasm is higher in grade 3 (22). Other risk factors that may contribute to vasospasm besides thick subarachnoid clots on CT scans include poor neurological condition at admission, age younger than 35 years old or older than 65 years old, cigarette smoking and pre-existing hypertension (34–36).

Rosen et al. found that the volume of the subarachnoid clot is typically larger in elderly patients, which may be explained by brain atrophy with larger cistern spaces, and in hypertensive patients and patients presenting with higher WFNS grade (37). A larger subarachnoid clot may explain poor outcomes in these groups of patients.

Multiple scales have been developed purporting to predict patient outcomes after aneurysmal SAH, including the well-known World Federation of Neurological Societies grading (WFNS) (38). However, these scores are usually obtained during initial hospital admission. A study by Aulmann et al. found that scores taken on the operation day itself show higher prognostic value compared to the scores taken during admission (39).

Although there are many scales suggested to predict vasospasm and hence the outcomes of patients with intracranial aneurysms, there is no single score that is both highly sensitive and highly specific. Even if patients are confirmed to have radiological vasospasm, their risk of developing neurological deficits is still uncertain, as there is much more to this risk than simply the existence of pure vasospasm. More importantly, brain changes occur mainly at the cellular level, which can be detected by CTP.

Further study of cerebral perfusion and its measurements are needed to understand the pathology of intracranial aneurysm at the microcirculation level and to characterise changes in cerebral perfusion after intracranial aneurysm for better patient management in the future. If pre-operative cerebral autoregulation is impaired, the risk of patients developing infarction is high. Hence, the development of vasospasm may further worsen the patient's condition. This possibility should cause physicians to be more careful with this population of patients. CTP also provides details about the crucial penumbra area that may yet be salvageable for better prognosis of patients with intracranial aneurysm.

Table 6. Comparison between Fisher and other grading to predict risk of vasospasm

Proposed Grading	(Fisher CM, 1980) Fisher Grading	(Claassen et al., 2001)	(Frontera et al., 2006)
Grade	Blood on CT		
0		No SAH or IVH	No SAH or IVH
1	No SAH (very low risk of vasospasm)	Minimal/thin SAH, no IVH in both lateral ventricles	No thick clot or bilateral IVH present
2	Thin layers of clot, less than 1mm thick (low risk)	Minimal/thin SAH, *with* IVH in both lateral ventricles	Bilateral IVH present
3	Thick clots greater than 1mm (moderate to high risk)	Thick SAH, no IVH in both lateral ventricles	Thick cisternal clot present
4	Intracerebral or intraventricular clot with no or little subarachnoid blood	Thick SAH, *with* IVH in both lateral ventricles	Both IVH and thick cisternal clot present

Table 7. Navarro score is a proposed screening for vasospasm in aSAH (26)

Risk factors		Score
Hypertension	No	0
	Yes	1
Admission WFNS grade	I	
	II	1
	III	2
	IV	3
	V	4
*Clot thickness	Local thin	1
	Local thick	2
	Diffuse thin	3
	Diffuse thick	4
Intraventricular haemorrhage	Yes	0
	No	1
Hydrocephalus	No	0
	Yes	1

*Clot thickness
Local thin: confined to one cistern < 1 mm
Local thick: confined to one cistern > 3 mm
Diffuse thin: layer of SAH < 1 mm
Diffuse thick: layer of SAH > 3mm

Conclusion

Despite current hype about the value of Fisher, Navarro and WFNS scores for predicting vasospasm and outcomes of ruptured intracranial aneurysm patients, this study found no significant correlations between these scores and either pre- or post-operative CTP parameters. This may explain the disagreement in the field regarding the multiple proposed grading scales for prediction of vasospasm. CTP measures more than just anatomical structures; therefore, it is more sensitive towards minor changes in cerebral perfusion that would not be detected by WFNS, Fisher or Navarro scores.

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Authors' Contributions

Conception and design: AAG, SAMN, RK, ARIG, AKR
Analysis and interpretation of the data: AAG, SAMN, RK, ARIG, AKR
Drafting of the article: AAG, SAMN, RK, ARIG, AKR
Critical revision of the article for important intellectual content: AAG, SAMN, RK, ARIG, AKR
Final approval of the article: AAG, SAMN, RK, ARIG, AKR
Provision of study materials or patients: AAG, SAMN, AKR
Statistical expertise: AAG, SAMN, RK, ARIG, AKR
Administrative, technical, or logistic support: AAG, SAMN, RK, ARIG, AKR
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