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EFFECTS OF CEREBRAL COLLATERAL (DSA CEREBRAL ANGIOGRAM) ON CLINICAL PRESENTATION AND NEUROLOGICAL IMPROVEMENT IN ISCHAEMIC STROKE

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ABSTRACT:

Background:
DSA (digital subtraction angiography) remains the gold standard in assessing the status of cerebral collaterals. Several studies have shown that the presence of good collateral circulation in ischemic stroke patients is associated with better functional outcomes with reduction of morbidity and mortality. Therefore, in this study, we aimed to assess the correlation between the collateral status seen on DSA cerebral angiogram with the clinical presentation of stroke and patients' functional outcomes.
Method:
We recruited a cohort of ischemic stroke patients who underwent DSA and collected demographic data, stroke risk factors and clinical data, which includes the National Institutes of Health Stroke Scale (NIHSS) scores, at time of admission. We assessed the collateral status and its grading using DSA and categorized based on established criteria. Subsequently we followed up the patients up at 3 months post stroke event to assess their functional outcomes using the modified Rankin Scale (mRS).
Results:
There was a significant association between good collateral status and favourable outcome in ischaemic stroke patients ($p < 0.05$).
We also found that, there is correlation between the NIHSS (upon discharge) and neurological outcome (MRS at 90 day) with Spearman correlation coefficient of 0.849.
Conclusion:
In conclusion, cerebral collateral status has the ability to prognosticate the functional outcome of ischemic stroke patients.
Keywords:
angiography, digital subtraction, clinical outcome, ischaemic stroke, modified Rankin scale

INTRODUCTION:

'Time is brain' is a very well-known phrase is stroke management strategy emphasizing early management of stroke in term of recanalization of the blocked vessel and to restoring blood flow to the ischemic brain but not yet infarcted. This can be established by means of thrombolytic agents or endovascular thrombectomy. In recent years, another new concept has emerged where 'time is brain', but collateral set the pace'. In other words, the presence of good cerebral collateral will help to sustained blood flow and the brain perfusion immediately after the event of ischaemic stroke, even before the treatment commenced. With further additional help of medical recanalization (intravascular thrombolysis or endovascular thrombectomy) the final core infarcted area will even further reduce. Subsequently, this will further limit the brain damage and subsequently result in fewer and less severe long-term morbidity for the patient [1].

Opposing to the traditional assumption that collateral vessels only develop over time in chronic stenotic condition, there is an observable phenomenon that collateral network develops immediately in acute arterial stenosis or occlusion. This is activated by fluid shear stress, which occurs between the territories of stenotic/occluded arteries and those fed by surrounding intact arteries [2]. Besides that, good collateral status primes to higher recanalization rate, smaller infarction volume and better neurological outcome[1,13.] In their later study, they also found that a well-developed collateral flow can lower the rate of haemorrhagic transformation after thrombolytic and/or endovascular therapies [3].

METHODS:

Written ethical approval and permission were obtained from The Ethics Committee for Research involving Human Subjects of University Putra Malaysia (JKEUPM). We recruited a cohort of ischemic stroke patients who underwent DSA in Hospital Sultan Abdul Aziz Shah, UPM (HSAAS) from 1st January 2021 until December 2022. Acute ischaemic stroke patients who do not have DSA cerebral angiogram performed, stroke patient of other causes and incomplete data were excluded. We collected demographic data, stroke risk factors and clinical data, which includes the National Institutes of Health Stroke Scale (NIHSS) scores, at time of admission. We assess the collateral status and its grading using DSA and categorized patients into good or poor collateral status groups based on established criteria. Subsequently we followed up the patients up at 3 months post stroke event to assess their functional outcomes using the modified Rankin Scale (mRS). We compared between the NIHSS scores (upon discharge) and 3-month mRS scores with the cerebral collateral grades using appropriate statistical tests.

Design

The patient's demographic data and clinical outcome are taken from the hospital database (Shivam and PutraHis). Data regarding the patient age, gender, underlying co-morbid, NIHSS and MRS information were collected. The DSA images were retrieved from the Picture Archiving and Communication System (PACs) Radiology Department in HSAAS. The scoring and grading of DSA cerebral was done by a radiologist who was blindfolded to the patient's clinical presentation information as well as the outcome at 90 days.

The cerebral collateral scoring was done based on The American Society of Interventional and Therapeutic Neuroradiology (ASITN/SIR) classification. The grades then further categorized into poor and good collaterals for analyse purposed; Grade <3 is regards as poor whereas >2 is regards as good, shown in Table 1.

Statistical analysis

Data were collected and analysed by using SPSS (Statistical Package for the Social Science, version 20, IBM, and Armonk, New York). Quantitative data were expressed as mean ± standard deviation (SD). Nominal data were given as number (n) and percentage (%). Chi-Square test was implemented on such data. Predictors of functional outcome were determined by logistic regression analysis using Spearman correlation.

Results

A total of 68 samples were analysed in this study and had met both inclusion and exclusion criteria. The calculated mean for age was 62.78 years old. The majority of patients (48(70.6%)) were male. Only 8 patients (11.7%) who presented with AIS have no underlying medical problems whereas the remaining 60 patients (88.3%) have underlying medical problems namely hypertension, diabetes mellitus, dyslipidaemia, IHD and AF. Majority of patient 66.2% has underlying hypertension.

Table 2 shows no significant difference of patient demographic which includes age, gender, co morbidities with the cerebral collateral status. The p value of the age is 0.472 and gender =0.384 which are statistically not significant; $p > 0.05$. For co-morbidities such as history of CVA and atrial fibrillation (p=1.0), hypertension (p=0.430), diabetes mellitus (p=0.951), dyslipidaemia (p=0.102), ischaemic heart disease (p=0.419); there are also found to be statistically not significant; $p > 0.05$.

Based on Chi-Square test, there is correlation between the cerebral collateral and neurological outcome (MRS at 90 day) as shown in Table 3. The association between cerebral collateral and MRS score is statistically significant with p=0.009 which is smaller than the significant value ($p<0.05$). Based on Chi-Square test, there is correlation between the NIHSS (upon discharge) and neurological outcome (MRS at 90 day), as shown in Table 4. The association between cerebral collateral and MRS score is statistically significant with p=0.002.

Table 5 shows correlation between the NIHSS (upon discharge) and neurological outcome (MRS at 90 day). Based on Spearman rank correlation, the Spearman correlation coefficient is 0.849 which indicates a strong positive correlation between the NIHSS and modified Rankin score (mRS) at 90 days.

DISCUSSION:

The current approach in treating acute stroke primarily by restoring cerebral blood flow to prevent patients from experiencing permanent neurological impairments caused by an ischemic event in the affected part of the brain. This can be established by recanalization, be it by medical thrombolysis or mechanical thrombectomy. In the recent years, cerebral collateral has been discussed as key factor to successful reperfusion therapy.

Based on our results, we are able to demonstrate the significant association between cerebral collateral status and the neurological outcome. This further strengthen the previous study [1,4,5,6,7,8,11,15]. We then proceeded with the Spearman correlation to further assess the correlation. Result shows negative correlation between these two parameters; where good collateral score given at presentation will produce lower mRS - good functional outcome.

Another significant correlation that was found in this study is between the NIHSS (upon discharge) and the clinical outcome (p value is <0.02). This means that NIHSS (upon discharge) can predict the neurological outcome. Spearman correlation coefficient of 0.849 indicating high correlation and suggests a strong relationship between these two variables. In simple word, high NIHSS with predict high MRS (poor functional outcome). This is similar to previous records [1,9,10,12,14], where NIHSS score post admission day 7 of at least 6, can anticipates a poor long-term outcome after stroke. Possible explanation

is that those high NIHSS already has larger ischaemic area whereas those with lower NIHSS will have smaller ischaemic area. Larger ischaemic area with subsequently lead to more long-term disability or death. However, we need not to consider this as only dependent factor as there are other multiple additional factors which would determine the outcome. This further emphasize that, those who has higher NIHSS should be handle promptly. The ability to detect early stroke and the early commencement of treatment may cause reperfusion of the brain and prevent further brain injury. According to American Heart Association (Guidelines for the Early Management of Patients with Acute Ischemic Stroke: 2019), a cut off value for NIHSS score in commencing thrombolytic agent and endovascular thrombectomy is when NIHSS > 6. Score > 6 indicates a moderate to severe stroke. As mentioned earlier in the discussion, those with higher NIHSS score are at increased risk of poor outcomes, such as disability or death. Therefore, prompt recanalization therapy is crucial to improve their chances of recovery.

Nevertheless, it's important to note that the decision to treat a patient with stroke is based on a variety of factors, not just the NIHSS score. Other factors such as the time since symptom onset, the patient's age and medical history, and imaging findings are also taken into consideration when determining the appropriate treatment approach. For an effective stroke management approach, it is crucial to begin with a comprehensive strategy that includes early recognition and accurate diagnosis in the out-of-hospital setting, followed by continued care in the emergency department and throughout the inpatient admission process. As such, it is imperative for personnel such as Emergency Medicine and Trauma Service (EMTS) professionals, Medical Emergency Coordination Centre (MECC) or Ambulance Dispatch Centre (ADC) staff, pre-hospital care responders, and emergency department (ED) personnel to be well-equipped with the necessary skills and knowledge to promptly identify stroke cases and provide appropriate care. In term of hospital management, a dedicated stroke team in essential in making sure that the flow of patient treatment is smooth and effective in order to salvage the brain tissue (CPG Management of Stroke 2020).

Based on our result, we can see that some of the result shows discrepancies from some of the previous study. This may be attributed to a small sample size due to selection bias as this study is conducted in a new tertiary referral centre. Furthermore, a small sample size may not be sufficient to analyse the subtle differences among various factors that being studies and further contribute to inconsistent result with no significant outcome.

CONCLUSION:

Our study has shown that good collateral status is associated with good functional outcome supporting the previous established study. Therefore, identifying cerebral collateral need to be highlight in the management of acute ischaemic stoke. Also, in this study, NIHSS is one of the significant indications of neurological outcome. Hence, accurate assessment of NIHSS is mandatory during the initial presentation of stroke. The ability to triage the patient accordingly based on NIHSS can helps the physician to initiate treatment in the correct group, hoping that this will helps to improve the functional outcome of stroke patient.

DATA AVAILABILITY:

Further information regarding the data used for this work can be obtained from the corresponding author upon reasonable request.

FUNDING:

This work received no external funding.

CONFLICT OF INTEREST:

The authors have no conflicts of interest to declare and are in agreement with the contents of the manuscript.

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TABLE LEGEND:

Table 1: Cerebral collateral scoring and grade

Grade	Angiographic collaterals (Digital subtraction angiography)	Category
0	No collateral visible to the ischaemic site	Poor
1	Slow collaterals to the periphery ischaemic site with persistence	
2	Rapid collaterals to the periphery of ischaemic site with persistence some of the defect and to only a portion of the ischaemic territory	
3	Collaterals with slow but complete angiographic blood flow of the ischaemic bed by late venous phase	Good
4	Complete and rapid collateral blood flow to the vascular bed in the entire ischaemic territory by retrograde perfusion	

Table 2: Patient demographic according to collateral status.

Demographic	**Good collateral status (n= 22)**	**Poor collateral status (n=46)**	**P value**
Age	60.91±17.38	63.67±13.36	0.472
Sex			
Male	14 (63.6)	34 (73.9)	0.384
Female	8 (36.4)	12 (26.1)	
Co-morbidities			
CVA-HX	0 (0.0)	1 (100.0)	1.000
HPT	16 (72.7)	29 (63.0)	0.430
DM	10 (45.5)	19 (41.3)	0.951
Dyslipidemia	14 (63.6)	18 (39.1)	0.102
IHD	7 (31.8)	9 (19.6)	0.419
AF	2 (9.1)	(10.9)	1.000

Table 3: Association between the CC category with neurological outcome (MRS 90 days).

Cerebral collateral	**MRS (n, %)**		χ^2	**P value**
	Poor	Good		
Poor (n, %)	32, 69.6%	14, 30.4%	6.773	0.009*
Good (n, %)	8, 36.4%	14, 63.6%		

*Significant at $p<0.05$ (Chi-square)
-Percentage within CC category.

Table 4: Association between the neurological outcome with NIHSS.

MRS	**NIHSS (n, %)**		χ^2	**P value**
	Low	High		
Poor (n, %) Good (n, %)	5 (26.3) 14 (73.7)	35 (71.4) 14 (28.6)	11.504	0.002*

*Significant at p<0.05 (Chi-square)
-Percentage within NIHSS category.

Table 5: Spearman rank NIHSS and modified Rankin score (mRS).

			NIHSS	**Modified rankin score test person**
Spearman's rho	**NIHSS**	Correlation coefficient	1.000	0.849**
		Sig. (2-tailed)	.	0.000
		N	64	64
	Modified Rankin score test person	Correlation coefficient	0.849**	1.000
		Sig. (2-tailed)	0.000	.
		N	64	68

** Correlation is significant at the 0.01 level (2-tailed).

ANTIPLATELETS GUIDELINES IN ENDOVASCULAR TREATMENT OF INTRACRANIAL ANEURYSMS: RECOMMENDATIONS FROM MALAYSIAN NEUROINTERVENTIONAL SOCIETY (MyNIS)

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INTRODUCTION

The landscape of periprocedural antiplatelet therapy has witnessed significant evolution alongside advancements in the endovascular management of intracranial aneurysms. This includes the introduction of flow-diverting stents, intracranial stents, intrasaccular devices, and stent-assisted coiling. Traditionally, a dual antiplatelet therapy (DAPT) regimen involving Aspirin and Clopidogrel has been widely adopted due to its established safety and efficacy. However, recent studies have identified alternative antiplatelet agents such as Ticagrelor, Tirofiban, or Prasugrel, which have demonstrated comparable efficacy and safety profiles. Endorsed by the Malaysian Society of Interventional Neuroradiology (MYNIS), this guideline aims to assist Interventional Neuroradiologists (INRs) and other physicians involved in treatment in selecting the most appropriate antiplatelet therapy for patients undergoing interventional procedures.

COX-1 INHIBITORS

Aspirin

Aspirin, also known as acetylsalicylic acid (ASA), functions as an irreversible inhibitor of cyclooxygenase-1 (COX-1), thereby impeding the production of thromboxane A2. Even with daily doses as low as 75 mg, Aspirin achieves complete inactivation of COX-1 within platelets due to its irreversible binding and the fact that platelets do not synthesize new proteins during their 7- to 10-day lifespan. This characteristic renders Aspirin an ideal antiplatelet agent, characterized by a stable half-life and predictable therapeutic response, particularly in preventing thromboembolism in the treatment of unruptured intracranial aneurysms. Its onset of action typically occurs within 15–30 minutes, and the plasma half-life of Aspirin is approximately 15–20 minutes.

Original trials involving intracranial flow diverters utilized daily maintenance doses ranging from 100 mg to 325 mg of Aspirin, while a standard dosage of 325 mg per day is commonly employed for intracranial stents and flow-diverting devices. Research suggests that Aspirin may contribute to the reduction of aneurysmal degradation and inflammation of the aneurysmal wall, in addition to promoting endothelial progenitor cell mobilization. Common side effects of Aspirin administration include gastritis and ulceration attributed to its non-selective COX blockade.

$P2Y_{12}$ INHIBITORS

Clopidogrel

Clopidogrel, a thienopyridine compound, functions by irreversibly inhibiting the platelet P2Y12 adenosine diphosphate receptor, thereby reducing platelet aggregation. Additionally, it impedes platelet aggregation by other platelet agonists such as thromboxane A2 and thrombin by diminishing the amplification effect of ADP released from platelet-dense granules. With a half-life spanning 7–8 hours and an onset of action typically ranging from 2 to 4 hours, Clopidogrel is commonly administered in a loading dose of 300 to 600 mg, complemented by a daily dosage of 75 mg.

The combination of Clopidogrel with Aspirin as part of dual antiplatelet therapy (DAPT) is a widely adopted practice in endovascular aneurysm treatment. However, a major concern with Clopidogrel is its nature as a prodrug, necessitating enzymatic conversion to active metabolites for its antiplatelet effects to manifest. Consequently, loading doses are often required to achieve rapid efficacy. Various factors, including drug interactions, polymorphisms within the CYP450 enzyme family, and smoking status, can contribute to a significant proportion of individuals showing an inadequate response to Clopidogrel treatment.

Prasugrel

Prasugrel is a newer generation thienopyridine, functions by inhibiting the P2Y12 receptor and has a half-life ranging from 2 to 15 hours. In comparison to Clopidogrel, it offers a faster onset of action and increased efficacy. Prasugrel undergoes more efficient conversion to its active metabolites and exhibits reduced dependence on CYP enzymes compared to Clopidogrel. Prasugrel is primarily used for patients undergoing intracranial flow diversion, especially when Clopidogrel fails to produce an adequate response due to altered hepatic metabolism. The duration of action of Prasugrel is similar to other thienopyridines, involving irreversible binding to ADP receptors. The standard dosing regimen is a 60 mg loading dose followed by a once-daily maintenance dose of 10 mg (or 5 mg if the patient weighs less than 60 kg). Prasugrel is associated with an increased risk of major bleeding and is contraindicated in patients with acute stroke due to the increased risk of hemorrhagic transformation.

Ticagrelor

Ticagrelor is a reversible inhibitor of P2Y12 receptors, belonging to the thienopyridine class, similar to Clopidogrel and Prasugrel. It has a median onset of action of 1.3–2 hours, a half-life of 4.6–6.3 hours, and becomes undetectable in plasma after 20 hours. Unlike Clopidogrel, Ticagrelor does not require hepatic metabolism for activation, making it effective for patients with genetic resistance to Clopidogrel due to CYP2C19 enzyme alterations. Ticagrelor is considered a safe and efficacious alternative to Clopidogrel, typically administered with a loading dose of 180 mg and a maintenance dose of 90 mg twice daily for 3–6 months.

GLYCOPROTEIN IIB/IIIA AGENTS

Tirofiban

Tirofiban, a glycoprotein IIb/IIIa receptor antagonist, binds reversibly to the GPIIb/IIIa receptor and has a plasma half-life of 2.5 hours. It is helpful in preventing platelet aggregation and thrombosis, particularly in acute ischemic stroke and during endovascular treatments. Administered intravenously, Tirofiban achieves more than 90% inhibition of ADP-induced platelet aggregation within 10–40 minutes with a 0.4 μg/kg loading infusion, followed by a maintenance infusion of 0.1 μg/kg/min. Platelet function returns to near baseline in 90% of patients within 4–8 hours after discontinuing the infusion. Similar to Eptifibatide, Tirofiban is renally cleared and requires dose adjustment in patients with impaired renal function; however, it can be effectively cleared by hemodialysis.

Eptifibatide

Eptifibatide, a cyclic heptapeptide derived from rattlesnake venom, reversibly binds to the GPIIb/IIIa receptor and has a plasma half-life of 1.5–2.5 hours. A bolus dose of 180 μg/kg achieves over 80% inhibition of platelet function within 15 minutes. An infusion of 0.5–0.75 μg/kg/min decreases platelet function after 4–6 hours, the time required to reach a steady state. This delay can be mitigated by administering a second 180 μg/kg bolus within 10 minutes after the first. Less than 50% of platelet aggregation inhibition remains 4 hours after stopping the infusion. Eptifibatide is renally cleared and requires dosage adjustment in patients with a creatinine clearance of less than 50 ml/min. It is particularly useful for proximal thrombus or in-stent occlusions during aneurysm coil embolization, with no reported hemorrhagic complications or worsening of pre-existing subarachnoid hemorrhage, although it may be less effective for distal thrombi.

CLINICAL SCENARIO

CASE 1
Elective procedure with no intra-operative complication, e.g unruptured intracranial aneurysm for flow diverter stent placement

Pre-procedure:
Oral Aspirin 300-325mg and Clopidogrel 300-600mg given 5-7 days prior to the procedure

Post-procedure:
Oral Aspirin 75-100mg daily for 12 months and Clopidogrel 75mg daily for 3-6 months; *or*
Oral Aspirin 75-100mg daily for 12 months and Ticagrelor 90mg BD for 3-6 months

CASE 2
Emergency procedure with no intra-operative complication, e.g ruptured intracranial aneurysm for flow diverter stent or stent and coiling placement

Pre-procedure:
Oral Aspirin 300-325mg or IV Aspirin 500mg, and Clopidogrel 300-600mg prior to the procedure

Post-procedure:
Oral Aspirin 75-100mg daily for 12 months and Clopidogrel 75mg daily for 3-6 months; *or*
Oral Aspirin 75-100mg daily for 12 months and Ticagrelor 90mg BD for 3-6 months

CASE 3
Elective procedure with intra-operative thrombosis, e.g placement of flow diverter in unruptured intracranial aneurysm complicated with thrombosis.

Pre-procedure:
Oral Aspirin 300-325mg and Clopidogrel 300-600mg given 5-7 days prior to the procedure

Intra-procedure:
Tirofiban 12µg/kg loading infusion over 30 minutes

Post-procedure:
IV infusion of Tirofiban 0.1µg/kg/min for 12-24 hours; *and*
Oral Aspirin 75-100mg daily for 12 months and Clopidogrel 75mg daily for 3-6 months; *or*
Oral Aspirin 75-100mg daily for 12 months and Ticagrelor 90mg BD for 3-6 months

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TABLE LEGEND:

Table 1: Summary of pharmacokinetic and pharmacodynamics of commonly used antiplatelet agents

Antiplatelet Agents	Mechanism of action	Half-life	Onset of action	Consideration	Side effects
Aspirin	COX-1 inhibitor	15–20min in plasma	15-30min	Effect on platelets 8–10 days given irreversibility of COX inhibition	Bleeding. Gastrointestinal upset
Clopidogrel	Irreversible P2Y12 inhibitor	7-8h	2-4h	Requires hepatic metabolism, potential genetic resistance (CYP2C19 variations)	Bleeding. Marrow suppression. Thrombotic thrombocytopenic purpura
Prasugrel	Irreversible P2Y12 inhibitor	2-15h	30min	Effects last 8–10 days. Rapid onset of action due to fast conversion to active metabolites	Bleeding
Ticagrelor	Reversible P2Y12 inhibitor	4.6-6.3h	1.3-2h	Not affected by CYP polymorphisms	Bleeding. Respiratory discomfort
Tirofiban	Reversible GPIIb/IIIa receptor antagonist	2.5h	10-40min	Given IV or IA. Needs renal adjustment	Bleeding. Thrombocytopenia
Eptifibatide	Reversible GPIIb/IIIa receptor antagonist	1.5-2.5h	15min	Given IV or IA. Needs renal adjustment	Bleeding. Thrombocytopenia

Table 2: Recommended antiplatelet regimes and dosage

Antiplatelet Agents	Dosage		Duration
	Loading	Maintenance	
Elective			
Aspirin	300-325mg	75-100mg daily	5-7 days prior, then continue minimum for 12 months
Clopidogrel	300-600mg	75mg daily	5-7 days prior, then continue for 3-6 months
Prasugrel	30-60mg	5-10mg daily	3-6 months
Ticagrelor	180mg	90mg twice daily	3-6 months
Emergency			
Aspirin	Oral: 75-325mg IV: 500mg Rectal: 120-300mg	75-100mg daily	STAT, then continue minimum for 12 months
Clopidogrel	300-600mg	75mg daily	STAT, then continue for 3-6 months
Prasugrel	30-60mg	5-10mg daily	3-6 months
Ticagrelor	180mg	90mg twice daily	3-6 months
Rescue Therapy			
Tirofiban	12μg/kg for 30 min	0.1μg/kg/min	IV or IA bolus, followed by infusion 12-24 hours
Eptifibatide	180μg/kg for 1-2 min	1-2μg/kg/min	IV or IA bolus, followed by infusion 12-24 hours