

Functional Outcome Post Direct Bypass in Adult Moyamoya Disease: A Local Study

By

DR MAS SYAZANEEZA BINTI SHAB

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School of Medicine



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Abbreviations

CBF	Cerebral Blood Flow
CBV	Cerebral Blood Volume
CRV	Cerebrovascular Reserve
CTP	Computed Tomography Perfusion
CVR	Cerebrovascular Reactivity
DSA	Digital Subtraction Angiography
ECA	External Carotid Artery
EDAS	Encephaloduroarteriosynangiosis
ICA	Internal Cerebral Artery
MCA	Middle Cerebral Artery
MMD	Moyamoya Disease
MRI	Magnetic Resonance Imaging
MRA	Magnetic Resonance Angiography
mRS	Modified Rankin Scale
MTT	Mean Transit Time
STA	Superficial Temporal Artery
TIA	Transient Ischaemic Attack
TTP	Time To Peak

Abstrak

Latar belakang: Pembedahan pintasan ('bypass') telah menjadi cara rawatan yang utama untuk penyakit Moyamoya untuk populasi kanak-kanak dan dewasa. Teknik pembedahan ini agak baharu dan pelbagai kajian telah dan sedang dijalankan untuk melihat hasil daripada pembedahan ini. Tujuan utama kajian ini adalah untuk melihat perubahan dari segi fungsi untuk pesakit dewasa di dalam populasi tempatan, serta mengkaji perubahan dari segi perfusi otak dan demografik serta persembahan klinikal dalam lokaliti tempatan.

Metodologi: Seramai 13 pesakit dewasa Moyamoya yang telah menjalani pembedahan pintasan di Hospital Kuala Lumpur dari Disember 2017 hingga Disember 2021 telah dikenalpasti melalui rekod dewan pembedahan. Rekod perubatan setiap pesakit kemudian diselidik. Demografi pesakit Moyamoya dikategorikan mengikut umur, bangsa, jantina, penyakit sampingan dan bahagian otak yang terlibat. Persembahan klinikal pesakit juga dikenalpasti. Perubahan sebelum dan selepas pembedahan dari segi fungsi diberi gred mengikut 'Modified Rankin Scale'. Perubahan dari segi radiologi di selidik menggunakan 'Computed Tomography Cerebral Perfusion', dan patensi salur darah yg dipintas. Komplikasi selepas pembedahan juga dikenalpasti.

Keputusan: 53.8% pesakit Moyamoya melibatkan sebelah otak. 23% menunjukkan penambahbaikan dari segi fungsi, manakala baki 77% pesakit yang menjalani pembedahan pintasan tidak menunjukkan peningkatan fungsi. Tetapi, tiada pesakit menunjukkan penurunan dari segi fungsi, dan tiada pesakit mengalami episod strok yang berulang. CT Perfusi menunjukkan peningkatan dari segi parameter, tetapi tidak dapat menunjukkan statistik yang signifikan.

Konklusi: Menurut kajian ini, pesakit dewasa yang menghadapi MMD yang telah menjalani pembedahan ‘direct bypass’ menunjukkan perubahan yang statik atau bertambah baik, dan berjaya mengelakkan episod strok yang baru, dan juga menunjukkan peningkatan dari segi fungsi perfusi otak. Walaubagaimanapun, disarankan supaya kajian lebih lanjut dijalankan dengan menambah durasi kajian supaya lebih ramai pesakit dapat disertakan disebabkan penyakit ini yang sangat jarang dikenalpasti di Malaysia.

Abstract

Background: Bypass surgery has been the mainstay of treatment for Moyamoya Disease in both adult and paediatric populations. This surgery is relatively new and emerging number of studies are being done to established the outcome of this bypass procedure. The aim of this study is to assess the functional outcome of direct bypass surgery in adult populations in local setting, as well as improvement in cerebral perfusion and to analyse the demographic and clinical presentation in local setting.

Methods: 13 adult patients who underwent direct bypass surgery for MMD in Hospital Kuala Lumpur from December 2017 to December 2021 are identified from operation theatre record. Each of patient's medical record was then traced. Patients' demographic data was identified and categorized by age, gender, race, comorbidities and laterality of disease. Clinical presentation for each patient is also determined. Pre and post-operative functional outcome were assigned according to Modified Rankin Scale Score. Radiological outcome post-operative were assessed using Computed Tomography Cerebral Perfusion as well as patency of bypass. Any complication following procedure is also identified.

Results: 53.8% of patients has unilateral presentation of MMD. 23% has improvement in functional outcome, while the remaining 77% who underwent direct bypass procedure has static functional outcome. None has deterioration in function, and none developed new episode of stroke. There is improvement in cerebral perfusion parameters post-surgery, however we failed to achieve a statistically significant data.

Conclusion: Based on our study, adult patients with MMD who underwent direct bypass surgery has either static or improvement in functional outcome and manage to prevent future recurrent stroke, with an increment in cerebral perfusion. However in view of our study limitation, a longer duration of study is suggested in order to gain a higher sample size in view of the rarity of disease in Malaysia in order to gain a better understanding of the disease.

Keywords: Moyamoya Disease, Modified Rankin Scale Score, Cerebral Perfusion, Direct Bypass

Introduction

Moyamoya disease (MMD) is a chronic cerebrovascular disorder which is defined by progressive stenosis or occlusion of the intracranial vessels affecting most commonly the intracranial internal carotid arteries and their proximal branches. It was first described by Takeuchi and Shimizu in Japan in 1957.¹

Moyamoya disease has the highest prevalence in East Asian descendants, particularly in Japanese, Koreans, and Chinese. Prevalence in Japan was 10.5 cases per 100,000 people from 2002 to 2006; 18.1 cases per 100,000 people in Korea in 2007, and 3.92 per 100,000 in China.¹ The first documented cases of Moyamoya disease in Malaysia was published in 1995.² Subsequently there is no reported epidemiological data on prevalence and incidence of this disease in Malaysia.

The main aim of surgical intervention in Moyamoya Disease is to improve cerebral perfusion and hence prevent possible future episode of neurological deficit in patients. One of surgical option in Moyamoya Disease is direct bypass surgery, for example Superficial Temporal Artery (STA) - Middle Cerebral Artery (MCA) bypass. The other surgical options in the treatment of MMD is indirect bypass surgery which include for example; encephalo-myo-synangiosis (EMS), encephalo-duro-arterio-myo-synangiosis (EDAMS), encephalo-duro-arterio-synangiosis (EDAS). Direct bypass surgery is the preferred method for surgical intervention in adults, hence adult patients who underwent direct bypass surgery are chosen for this study.

Neurosurgery Department of Hospital Kuala Lumpur has been performing bypass surgery and currently the only government centre offering this direct bypass surgery. Bypass surgery for Moyamoya disease is relatively new and uncommon in Malaysia and there is lack of epidemiological data and outcome of patients who has undergone this bypass surgery. There is by far no such study that has been done in Malaysia for surgical outcome of patients with

Moyamoya disease. Hence, we would like to assess the functional outcomes of this patients who had undergone direct bypass surgery in our centre. Functional outcomes will be graded using Modified Rankin Scale (mRS) score which will grade patients according to symptom and ability to carry out usual duties and activities. Any changes in cerebral perfusion parameters will also be compared pre- and postoperatively to determine if there is any improvement in cerebral perfusion.

This is mainly a descriptive study due to the limited number of sample size where we also described the operative technique.

Methods and Materials

Patient population

Thirteen patients who has been diagnosed with MMD and underwent direct (STA-MCA) bypass in Neurosurgery Department, Hospital Kuala Lumpur from 1st December 2017 until 31st December 2021 are included. Diagnosis of Moyamoya Disease made based on diagnostic guideline proposed by the Research Committee of MMD of the Japanese Ministry of Health, Labour, and Welfare in 2015. Approval for the study was obtained from the National Medical Research Register, NMRR (NMRR ID: RSCH ID-22-00216-ON0) and Medical Research and Ethics Committee (MREC).

Data Collection

Patients who underwent direct bypass (STA-MCA bypass) were identified from neurosurgery operation theatre census. Patient's record were then traced and data such as demographic, presentation, imaging details, as well as functional outcome pre- and post-operative were identified. Functional status were traced from medical record as well as during patient's follow-up in clinic, particularly at 1 month and 3 months follow-up.

The mRS score are further dichotomised into two groups. Patients with mRS score ≤ 2 are patients with good neurological status, and patients with mRS score ≥ 3 are patients with poor neurological status.

Perfusion studies pre- and post-operative are re-analyzed by a single investigator. Perfusion study that is included is CT Brain Perfusion. Post-operative perfusion images are done at approximately 3 months post-operation. Cerebral perfusion parameters obtained are Cerebral Blood Flow (CBF), Cerebral Blood Volume (CBV), Mean Transit Time (MTT), and Time to

Peak (TTP). Standardized elliptical mirrored ROIs drawn manually on basal ganglia section level over the grey cortical grey matter of MCA territory independently.

All the data obtained are inserted into tables. (Appendix B)

Statistical Analysis

Descriptive statistics are reported as the mean $\pm$ standard deviation for continuous variables, and as frequency and percentage for categorical variables. Changes in functional status post-operative will be analyzed using McNemar test. Relative values of surgical side before and after surgery will be compared using paired-T test or Wilcoxon. The association between the variables will be tested using independent T-test or Mann-Whitney test. Data are analyzed using the statistical program, IBM® SPSS® Statistics Version 24. A p-value of <0.05 is considered statistically significant.

Results

Demographic data

A total of 13 patients were involved in this retrospective cohort study, of which 46.2% is Malay, 38.5% is Chinese and the remaining 15.4% Indian, with age ranging from 20 years old to 60 years old, with mean age of presentation of 36.4 years old. There is a slight male predominance (8 to 5). Our patients had an almost equal presentation of unilateral and bilateral presentation, with slightly higher percentage of patients presented with unilateral hemisphere involvement (53.8%), versus bilateral hemispheric involvement (46.2%). (Table 1)

Clinical Presentation

From our cohort, 61.5% (N=8) presented with ischaemic symptoms (completed stroke or recurrent transient ischaemic attack), while 30.8% (N=4) presented with haemorrhage. One patient had an incidental finding from investigation of ophthalmic symptom which has been concluded to be unrelated to MMD. (Table 1)

Table 1: Summary of patients included in the study.

Age (y)/ Sex	Race	Comorbidities	Hemisphere	Presentation	Clinical Event <3mths	Clinical Event >3mths	Outcome	mRS pre-op	mRS 1 month post op	mRS 3 month post op
50/ M	Chinese	HPT, Dyslipidaemia	Left	Haemorrhage	None	None	Improvement	4	4	3
20/ M	Malay	Nil	Right	CS	None	None	Stabilization	3	3	3
60/ M	Chinese	DM, HPT, Dyslipidaemia	Bilateral	Haemorrhage	None	None	Stabilization	1	1	1
31/ F	Chinese	DM, Dyslipidaemia	Right	Incidental	None	None	Stabilization	0	0	0
26/ M	Malay	HPT	Right	TIA	None	None	Improvement	2	2	1
30/ M	Indian	Nil	Left	CS	None	None	Stabilization	2	2	2
43/ F	Indian	Nil	Right	TIA	None	None	Stabilization	1	1	1

41/ M	Malay	CKD	Bilater al	CS,TIA	Seizur e	Seizure	Stabilizat ion	4	4	4
40/ M	Chinese	DM,HP T	Bilater al	Haemorr hage	None	None	Stabilizat ion	2	2	2
39/ F	Malay	DM	Bilater al	Haemorr hage	None	None	Stabilizat ion	2	2	2
38/ F	Chinese	HPT, Dyslipi daemia	Bilater al	TIA	TIA	None	Stabilizat ion	1	1	1
23/ M	Malay	None	Bilater al	CS	None	None	Stabilizat ion	1	1	1
32/ F	Malay	HPT	Left	CS	None	None	Improve ment	4	3	2

DM Diabetes Mellitus; HPT Hypertension; CKD Chronic Kidney Disease; CS Completed Stroke; TIA Transient Ischaemic Attack

Clinical Outcome

The mean period of follow-up after surgery was 21 months, ranging from 3 months to 51 months. One patient developed seizure within 3 months post op which persists until 3 months post operation. One patient who presented with recurrent TIA, continues to have recurrent TIA 3 months post-op, however symptom completely resolved after 3 months. 30.8 % (N=4) patients had poor neurological status (mRS ≥ 3) pre surgery. Following direct bypass surgery, 23% (N=3) shows improvement in mRS score, 77% (N=10) shows stabilization, and none deteriorates over the course of follow-up. One patient showed improvement from poor neurological status (mRS 4) to good neurological status (mRS 2) in 3 months post op. (Table 1,2)

Table 2: Modified Rankin Scale scores preoperatively and at last follow-up in 13 patients undergoing STA-MCA bypass for MMD

Score	No. of Patients	
	Pre-op	Last follow-up
0-1	5	6
2	4	4
3	1	2
4	3	1
5	0	0
6	0	0

There is improvement in cerebral perfusion parameters post-surgery (Table 3), with increment in rCBF (35.96 ± 6.83 vs 39.34 ± 7.01 , $P=0.07$) and rCBV (2.84 ± 0.65 vs 3.44 ± 1.08 , $P=0.15$); and reduction in rMTT(4.69 ± 0.61 vs 4.30 ± 0.44 , $P=0.16$) and rTTP (13.94 ± 2.21 vs 13.03 ± 0.62 , $P=0.18$). However, none of the parameters are significant different between pre- and post-operation. This might be due to our small sample size, in view of rarity of disease, and the unavailability of perfusion studies in six patients (lost imaging or not done in earlier cases).

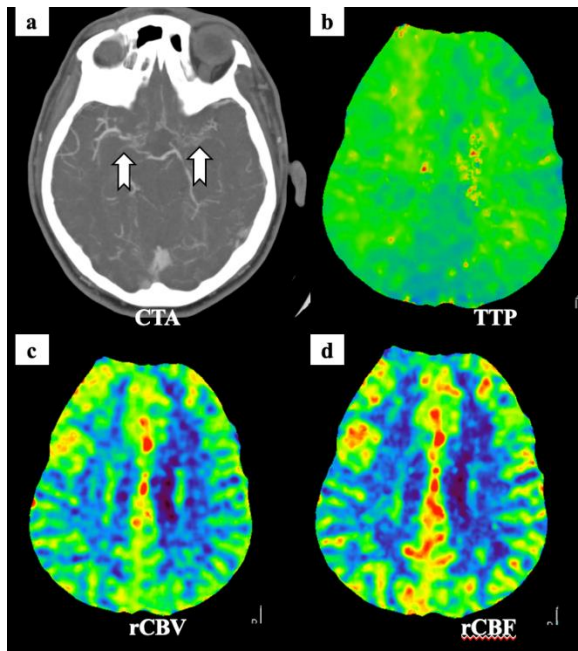


Figure 1a: Pre STA-MCA bypass

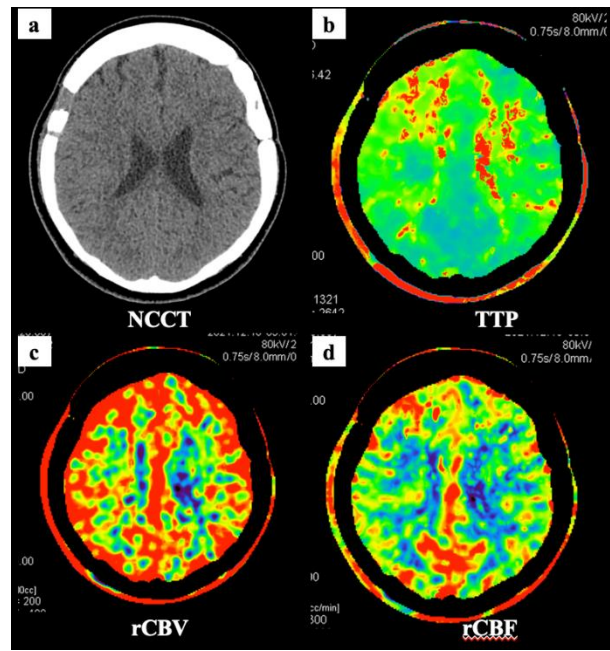


Figure 1b : Post STA-MCA bypass

Figure 1a: Axial CTA (a) shows collateral vessels at the region of basal ganglia indicating moyamoya syndrome. Axial CT perfusion map (b,c and d) show increased TTP at bilateral cerebral hemispheres, reduced rCBF at bilateral cerebral hemispheres and relatively normal rCBV at bilateral cerebral hemispheres.

Figure 1b: NCCT (a) shows normal study. Axial CT perfusion map (b,c and d) show relatively normal TTP at bilateral cerebral hemispheres with increased rCBF and rCBV at bilateral cerebral hemispheres.

Table 3: Comparison of CT perfusion relative parameters pre- and postoperatively (n=7)

Perfusion Parameters	Preoperative (mean $\pm$ SD)	Postoperative (mean $\pm$ SD)	<i>P</i> -value
rCBF(ml/100g/min)	35.96 $\pm$ 6.83	39.34 $\pm$ 7.01	0.07 ^a
rCBV(ml/100g/min)	2.84 $\pm$ 0.65	3.44 $\pm$ 1.08	0.15 ^a
rTTP (sec)	13.94 $\pm$ 2.21	13.03 $\pm$ 0.62	0.18 ^b
rMTT (sec)	4.69 $\pm$ 0.61	4.30 $\pm$ 0.44	0.16 ^a

a: Paired-sample t-test

b: Wilcoxon Signed Rank Test

Surgical Procedure

Here we describe the operative technique for direct bypass (STA-MCA bypass) that was done in our centre. (Figure 2-5)

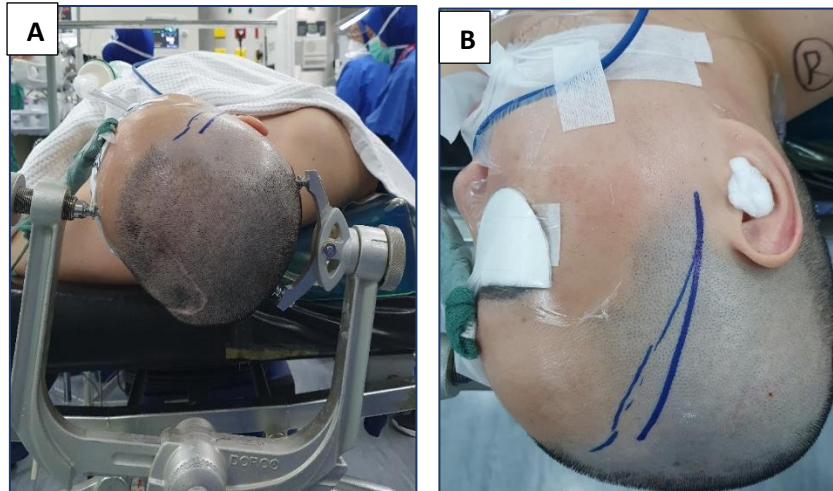


Figure 2 (A, B): Patient positioning and incision. A- Patient was put in supine position, shoulder roll underneath ipsilateral shoulder, and head rotated towards contralateral side. B- Linear incision designed over temporal frontal region. Alternatively, a small ‘question-mark’ incision can be done.

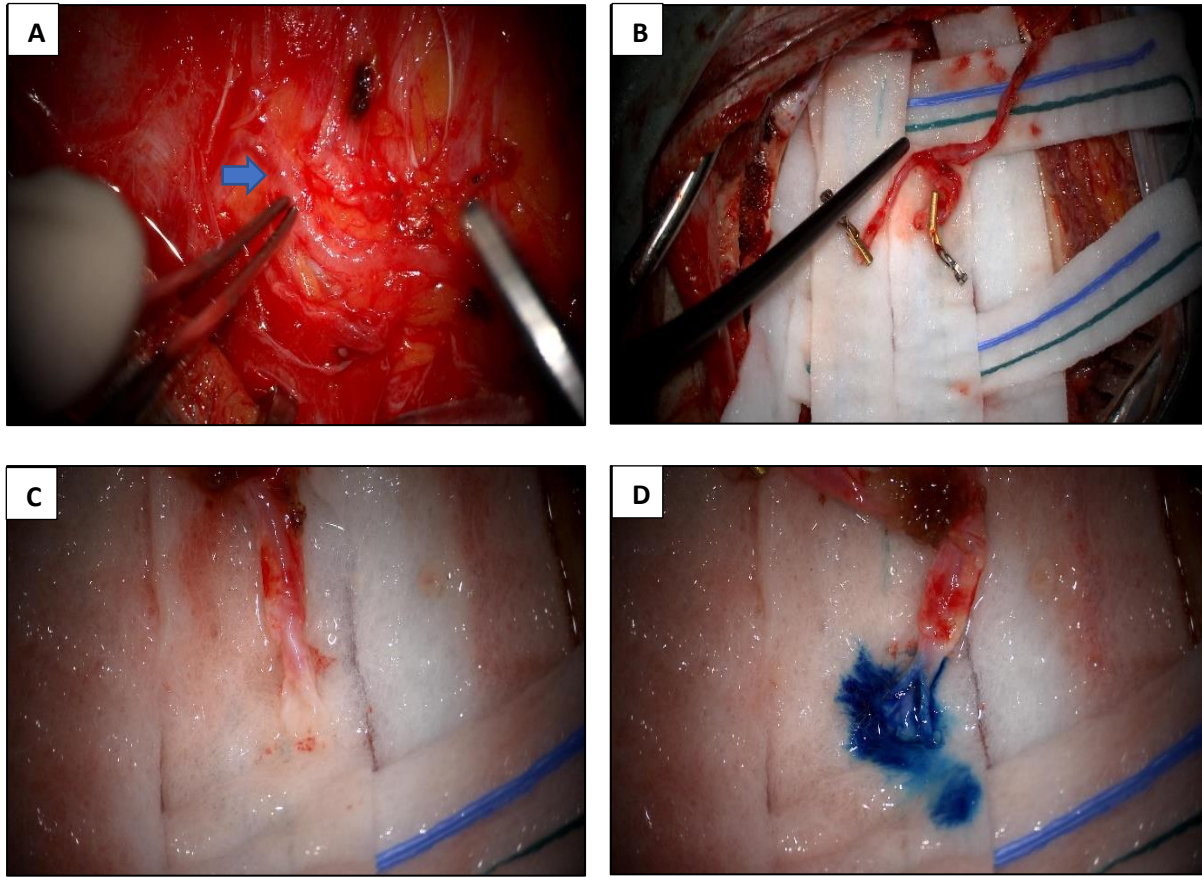


Figure 3 (A-D): Preparation of Superficial Temporal Artery (Donor artery). A-STA identified and carefully dissected and skeletonized. B- Temporary clip applied at a sufficient length of STA and disconnected. C- Fish mouth arteriotomy done over distal end of STA D- Methylene blue applied at planned anastomotic end. (Blue arrow: Superficial Temporal Artery (STA))

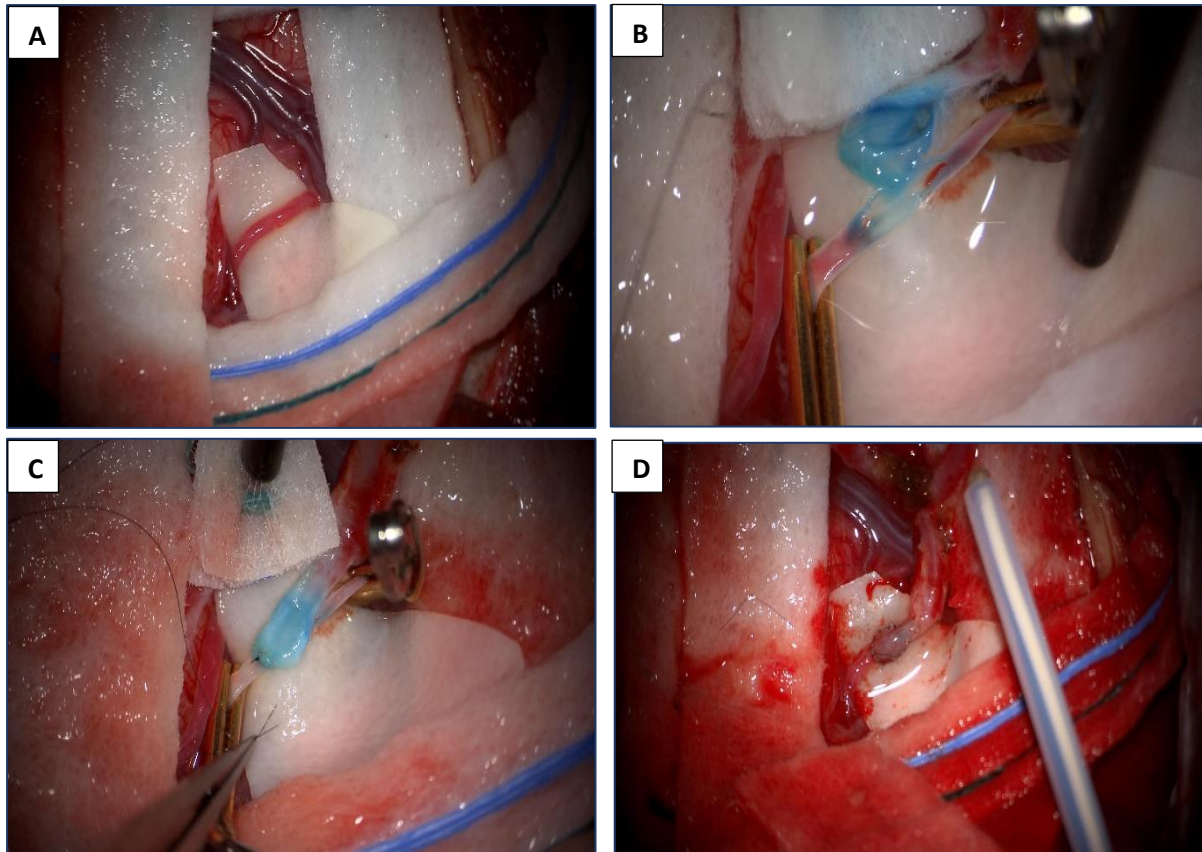


Figure 4 (A-D): Preparation of recipient artery and anastomosis. A- Cortical branch of Middle Cerebral Artery identified, dissected, and skeletonized. B-Arteriotomy done over MCA C-End to side anastomosis done using Prolene 10/0 suture. D-Anastomosis completed and patency checked with intra-operative Doppler

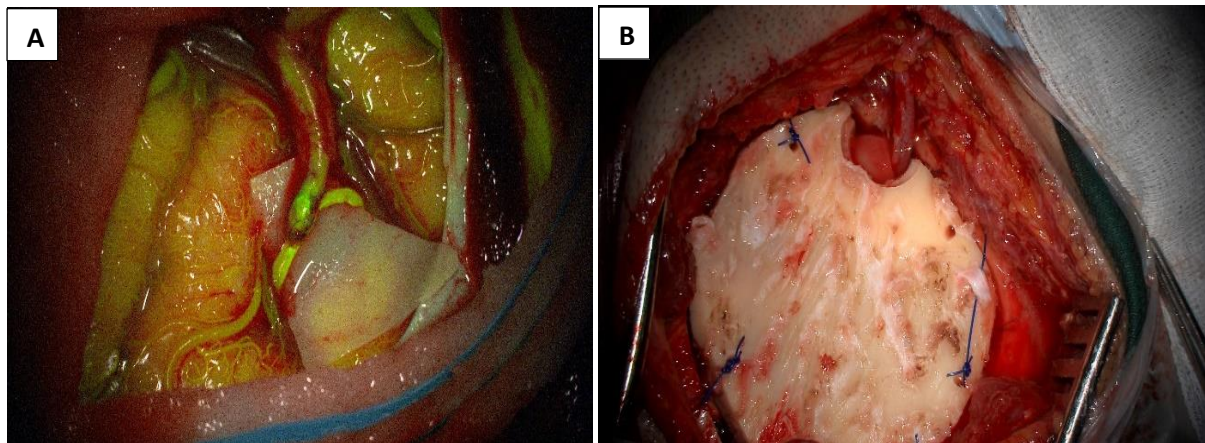


Figure 5 (A-B): Checking for bypass patency and closure. A-Fluorescein dye used to check for bypass patency intra-operative. B-Bone flap replaced making sure that burr hole was placed at side of STA, ensuring no compression over STA.

Discussion

MMD has been increasingly diagnosed throughout the world, but the prevalence remains to be higher in East Asian countries particularly in Japan, Korea, and China.^{1,3} The high prevalence of MMD in East Asia compared to other countries might be attributable by a mutation in RNF213 gene which is lacking in patients in western or other population.^{4,5}

MMD is relatively rare in Malaysia, and possibly undiagnosed. From our limited sample size population, those of Malay descendant has a slightly higher incidence compared to those of Chinese descendant (46.2% vs 38.5%). It has been postulated that adult patients diagnosed with MMD predominantly presented with intracranial bleed as opposed to ischaemic symptoms⁶. However in our study, majority of patients presented with ischaemic symptoms (61.5% vs 30.8%). This coincides with a US study in which they observed a predominance of ischaemic rather than haemorrhagic stroke in adult cases (66% vs 17%).^{7,8} Out of the four patients that presented with haemorrhagic stroke, two patients had basal ganglia bleed, one with pure intraventricular haemorrhage, and one with lobar bleed. MMD haemorrhage location in one study reported pure intraventricular haemorrhage, as the commonest location, followed by lobar and putaminal bleed.^{2,9} The tendency to bleed into ventricle might be due to the prominent anterior choroidal artery, and patients have the tendency to have recurrent bleed and infarction.^{9,29} A wide range of neurocognitive impairment has also been reported in adult patients with MMD, with disruption in functions, particularly those mediated by subcortical and frontal regions. This dysexecutive cognitive syndrome is possibly related to frontal perfusion impairment with a reduction in rCVR (-13.5 ± 13.2 vs 20.2 ± 21.3 , $P=0.019$) in frontal lobe.^{22,23,24}

Functional and Clinical Outcome Post Direct Bypass

Surgical options for MMD includes direct bypass, indirect bypass or combined revascularization surgery. Regardless of mode of surgery chosen, the primary aim of revascularisation surgery for MMD is to restore blood supply to stabilise cerebrovascular hemodynamic causing the fragile Moyamoya vessels to regress and prevent bleeding; and subsequently result in secondary stroke prevention resulting in improved neurological/neurocognitive outcome, as well as improvement in long term functional outcome status.^{10,11}

Majority of our patients achieved a stabilisation of disease, with similar functional status (77%), and none recorded a reduction in functional outcome. There is also a resolution of TIA symptom in which patient reported to have reduction of episode of transient weakness as early as 3 months, and completely symptom free after 3 months.

In our centre, direct bypass procedure is done to adult patients with MMD, whereas indirect bypass is done for paediatric patients. The optimal surgical modality for MMD still is up for debate, but it has been found that adult patients with MMD who underwent direct bypass has a longer stroke free time as compared to patients who underwent indirect bypass surgery (mean 72.1 months vs 61.0 months, $P=0.045$), however there is no significant difference between groups in term of good neurological status (91.4% vs 94.3%, $P=0.512$).^{12,19} Direct bypass has been favoured in several studies, with current study indicates that revascularisation technique which includes a direct bypass should be applied to patients regardless of age, if technically feasible,^{10,21} and combined revascularisation technique can achieve a satisfactory long-term outcomes in clinical, angiographic, and haemodynamic states.^{13,14} However, if direct bypass is

not feasible, indirect bypass surgery also showed to have satisfactory improvement in mRS score post op.^{15,19,26}

Cerebral Perfusion Post Direct Bypass

CT Perfusion is chosen as post-operative imaging to assess radiological outcome post-surgery, and is done at least 3 months post-surgery. CT is chosen as imaging modality due to the feasibility, lower cost and non-invasive as compared to MRI or cerebral DSA.¹⁶

Our study showed that there is improvement in cerebral perfusion post direct bypass surgery, however we failed to come to a statistically significant result. This might be due to the very small sample size. A similar study investigating perfusion parameters post direct bypass surgery managed to come to a statistically significant result which shows reduction in rMTT and rTTP values ($P<0.05$) and improvement in rCBF ($P<0.05$) in patients with bypass patency.^{17,20,28}

Cerebral Perfusion and Clinical Outcome

Cerebrovascular reactivity (CVR) is defined as an increase in cerebral blood flow (CBF) in response to a given vasodilatory stimulus. In a study done to evaluate the effect of surgical revascularisation on CVR, it was postulated that no patient with CVR improvements exhibited new clinical symptom, but failure of CVR improvement corresponded to a poorer long-term prognosis ($P<0.001$).¹⁸ Improvement in perfusion has also been shown to improve cognitive function in adults post revascularisation surgery.^{25,27,30}

Even though our study failed to prove a statistically significant improvement in cerebral perfusion, none of our patients deteriorated and none developed recurrent symptom post op. A

larger sample and longer follow-up is needed to have a better overview on correlation between cerebral perfusion and outcome post-surgery.

Study Limitation

There are limitations in this study that possibly lead to the non-significant result of pre and post-operative perfusion study. First, the overall sample size is small due to the rarity of disease, and an even smaller perfusion data is available. To compensate for the small sample size and rarity of disease, a longer duration of study should be employed. Due to limitation of time, the follow-up period is limited to only 3 months post-op for the recent cases. A longer follow-up period can be done should this study be repeated with a longer period of study. Overall, to improve this study in the future, a larger sample size, and longer duration of study should be done to achieve a possible significant result.

Conclusion

In conclusion, direct revascularisation surgery prevent deterioration of functional status and recurrent neurological symptom. Although this study is unable to show a statistically significant result for changes in cerebral perfusion post-surgery, clinically patients did not developed new symptom during follow-up. Majority of patients had stabilisation of functional status which may indicate a significant correlation should the sample size be larger. Overall, this study would offer insight to the diagnosis of Moyamoya disease in Malaysia, and possible surgical intervention that can be offered.

REFERENCES

1. Kim, J. S. (2016). Moyamoya disease: epidemiology, clinical features, and diagnosis. *Journal of Stroke*, 18(1), 2.
2. Ng, W. K., Tan, C. T., George, J., Lee, M. K., & Loh, T. G. (1995). Moyamoya disease in Malaysia: two documented cases. *The Medical journal of Malaysia*, 50(2), 186-188.
3. Shang, S., Zhou, D., Ya, J., Li, S., Yang, Q., Ding, Y., ... Meng, R. (2020). Progress in moyamoya disease. *Neurosurgical Review*, **43**(2), 371–382. doi:10.1007/s10143-018-0994-5
4. Kamada, F., Aoki, Y., Narisawa, A., Abe, Y., Komatsuzaki, S., Kikuchi, A., ... Kure, S. (2011). A genome-wide association study identifies RNF213 as the first Moyamoya disease gene. *Journal of Human Genetics*. doi:10.1038/jhg.2010.132
5. Fujimura M, Sonobe S, Nishijima Y, Niizuma K, Sakata H, Kure S, T. T. (1996). Genetics and Biomarkers of Moyamoya Disease: Significance of RNF213 as a Susceptibility Gene Genetics and Biomarkers of Moyamoya Disease Basic pathology of MMD Histo-pathological characteristics. *The Lancet*, 347(9011), 1304–1305. doi:10.1016/S0140-6736(96)90944-7