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RESEARCH ARTICLE

Risk Factors for Cerebral Hyperperfusion Syndrome After Combined Revascularization in Adult Patients with Moyamoya Disease

Dongxiao Xu[1], Jiaojiao Guo[2], Bingjie Zheng[3], Qiaowei Wu[3], Ilgiz Gareev[4], Ozal Beylerli[4], Aferin Beilerli[5] and Huaizhang Shi[3,*]

[1]*Department of Neurosurgery, The First Affiliated Hospital of Henan University of Science and Technology, Luoyang, China;* [2]*Department of Gynecology, The First Affiliated Hospital of Henan University of Science and Technology, Luoyang, China;* [3]*Department of Neurosurgery, The First Affiliated Hospital of Harbin Medical University, Harbin, China;* [4]*Central Research Laboratory, Bashkir State Medical University, Ufa, Republic of Bashkortostan, 3 Lenin Street, 450008, Russia;* [5]*Department of Obstetrics and Gynecology, Tyumen State Medical University, 54 Odesskaya Street, 625023, Tyumen, Russia*

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Abstract: ***Background*:** Cerebral hyperperfusion syndrome (CHS) is known as a complication after bypass surgery for Moyamoya disease (MMD). However, the incidence of CHS has not been accurately reported, and there is no consensus on the risk factors associated with it.

***Aim*:** The aim of this study was to determine the risk factors associated with postoperative CHS after surgical combined revascularization used to treat adult patients with MMD.

***Objective*:** To assess the frequency and characteristics of CHS in patients with MMD after revascularization operations.

***Methods*:** Patients who received combined revascularization from Jan 2021 to Nov 2022 were retrospectively reviewed. Preoperative clinical characteristics and radiographic features were recorded. Postoperative CHS after surgery were examined. Multivariate logistic regression analyses were performed to identify the risk factors for CHS.

***Results*:** A total of 133 patients (141 hemispheres) were included in this study. Postoperative CHS were observed in 28 hemispheres (19.8%), including focal cerebral hyperperfusion syndrome (FCHS) in 20 hemispheres (14.2%), hemorrhage in 4 (2.8%) hemispheres, seizures in 4 (2.8%) hemispheres. The results of multivariate logistic regression analysis indicated that preoperative hypertension (OR 4.705, 95% CI 1.323 ~ 12.554, $p = 0.014$), cerebral hemorrhage onset (OR 5.390, 95% CI 1.408 ~ 20.642, $p = 0.014$) and higher Hct level (OR 1.171, 95% CI 1.051 ~ 1.305, $p = 0.004$) were significantly associated with CHS after combined revascularization.

***Conclusions*:** Preoperative hypertension, cerebral hemorrhage onset, and higher Hct level were independent risk factors for CHS after combined revascularization.

Keywords: Moyamoya disease, combined revascularization, Preoperative hypertension, cerebral hyperperfusion syndrome, cerebral hemorrhage onset, Hct level.

1. INTRODUCTION

Moyamoya disease (MMD) is characterized by chronic and progressive stenosis or occlusion in the arteries centered on the end of the internal carotid artery (ICA), accompanied by the formation of the abnormal blood vessel network which showed a smoke-like change at the base of the brain [1]. It is one of the main causes of ischemic and hemorrhagic stroke. Although there is currently no specific treatment to prevent or reverse the progression of MMD, recent studies have found that surgical revascularization can reduce the occurrence of stroke by increasing cerebral blood flow (CBF) and reducing hemodynamic pressure and produces more favorable clinical outcomes than conservative treatment. And in recent years, a large number of scholars believe that combined revascularization has advantages over direct revascularization and indirect revascularization [2-6]. However, MMD has complex pathophysiological characteristics, fragile MMD vessels and unstable hemodynamics lead to high postoperative complications, for example, cerebral hyperperfusion syndrome (CHS), which results in poor prognosis of patients and affect the surgical effect.

To date, the risk factors for CHS after combined revascularization are unclear. Therefore, we conducted this study to

*Address correspondence to this author at the Department of Neurosurgery, The First Affiliated Hospital of Harbin Medical University, Harbin, China; E-mail: shihuaizhang@hrbmu.edu.cn

explore the risk factors for postoperative CHS complications in adult patients with MMD.

2. METHODS

This report was a retrospective study, and all patients who underwent combined revascularization at the First Affiliated Hospital of Harbin Medical University and at the First Affiliated Hospital of Henan University of Science and Technology from Jan 2021 to Nov 2022 were eligible for the study. This study was authorized by the ethics committee of the First Affiliated Hospital of Harbin Medical University and the First Affiliated Hospital of Henan University of Science and Technology, and informed consent was obtained from all patients or their legal representatives.

2.1. Data Collection

Demographic, clinical, and radiological information was collected from the hospitals electronic health records, including age, sex, the side of operation, onset type of MMD, and comorbidity. Suzuki stage between 4 and 6 were advanced Suzuki stage.

We defined CHS as one of the following: (a) radiological local CHS, which is contributed to focal neurological deficits, including aphasia, hemiplegia, and headaches [7], or (b) cerebral hemorrhage and/or subarachnoid hemorrhage were demonstrated by CT or magnetic resonance imaging (MRI), or (c) computed tomography (CT) perfusion was performed focal hyperperfusion at anastomosis sites, and (d) in addition to the above factors, cerebral infarction must be ruled out by CT or MRI.

Most of the perioperative seizures after combined revascularization were caused by CHS, the biological mechanisms of postoperative seizure and postoperative hyperperfusion syndrome are similar [8, 9]. Therefore, in this study, we classified seizures into CHS and analyzed the related risk factors.

Posterior circulation involvement was defined as vertebrobasilar artery lesions, including: a) stenosis or occlusion of the vertebrobasilar artery system, with or without smoke vessels; b) congenital morphological abnormalities, including vertebral artery dysplasia and vertebral artery tortuosity.

2.2. Inclusion and Exclusion Criteria

The inclusion and exclusion criteria are essentially same as previously reported [10]. The inclusion: 1) adult patients over 18 years old; 2) MMD was diagnosed by digital subtraction angiography (DSA); 3) The first hemisphere to be operated on was the one that caused the symptoms of MMD, and it was also the first surgery; and 4) The surgical procedure was combined revascularization. The exclusion criteria: 1) patients were less than 18 years old; 2) patients with Moyamoya syndrome, caused by Down syndrome, autoimmune disease, or a history of head irradiation; and 3) Patients with incomplete preoperative imaging data.

2.3. Surgical Procedure

All patients underwent superficial temporal artery–middle cerebral artery (STA-MCA) (M4 portion) anastomosis with encephalo-duro-myo-synangiosis (EDMS), or with multiple burr hole (MBH) surgery and dural inversion, or with encephalo-duro-pericranio-synangiosis (EDPS) under general anesthesia by experienced neurosurgeons at the First Affiliated Hospital of Harbin Medical University and at the First Affiliated Hospital of Henan University of Science and Technology according to the previously described procedure.

2.4. Peri-operative Management

In addition to infection prevention and fluid rehydration to ensure blood volume after surgery, changes in patients' vital signs should be strictly monitored, and good hemodynamic control is crucial to prevent postoperative bleeding and infarction [11]. Systolic blood pressure should be controlled at 120 mmHg within one week after surgery, and the blood pressure can be slightly higher for patients with hypertension, but the systolic blood pressure should be controlled below 140 mmHg. Patients who were sensitive to pain were given analgesia in postoperation. The usual drug was dexmedetomidine, which 2 ml (0.2 mg) was added into 50ml 0.9% sodium chloride solution with a concentration of 4ug/ml, which was first slowly injected at 1ug/Kg and then maintained at 0.2-0.7 ug/kg/h. The drug did not continue intravenous injection until the pain is tolerable. For patients with ischemic MMD, head CT was reviewed the next day after surgery, and aspirin 100 mg/d was given to the patients after intracranial hemorrhage was ruled out.

Seizures is one of common complications after combined revascularization, so, valproate sodium was routinely used for 2 to 3 weeks after surgery to prevent it, if there was a seizure, then continue to take anti-epileptic drugs for 3 to 4 weeks.

2.5. Statistical Analysis

All data were analyzed using SPSS 22 (Statistical Package for the Social Sciences Software, IBM) for Windows. Kolmogorov-Smirnov method was used to test the normality of measurement data. The measurement data of normal distribution are showed as $\bar{x} \pm s$, and t test was used for comparison between groups. The categorical variables are represented by the number of cases. Asymmetrically distributed data are represented by the median (m) and the upper and lower quartiles (P25, P75), and the Wilcoxon rank sum test was used for comparisons between groups. The count data were represented by the number of cases and component ratio (n, %), and x2 test was used for comparison between groups. Univariate analysis and multivariate logistic regression analysis were used to analyze the related factors of CHS after combined revascularization, $p < 0.05$ was considered statistically significant.

3. RESULTS

3.1. Clinical Presentation

One hundred and thirty-three patients (141 hemispheres) underwent combined revascularization, including 89 (63.1%) males and 52 (36.9%) females, with a mean age of 52.1 ± 7.4 years old (range, 33-67 years old). There were 9 (6.4%) hemispheres presented with headache, 16 (11.4%) hemispheres with cerebral hemorrhage and 116 (82.2%) hemispheres

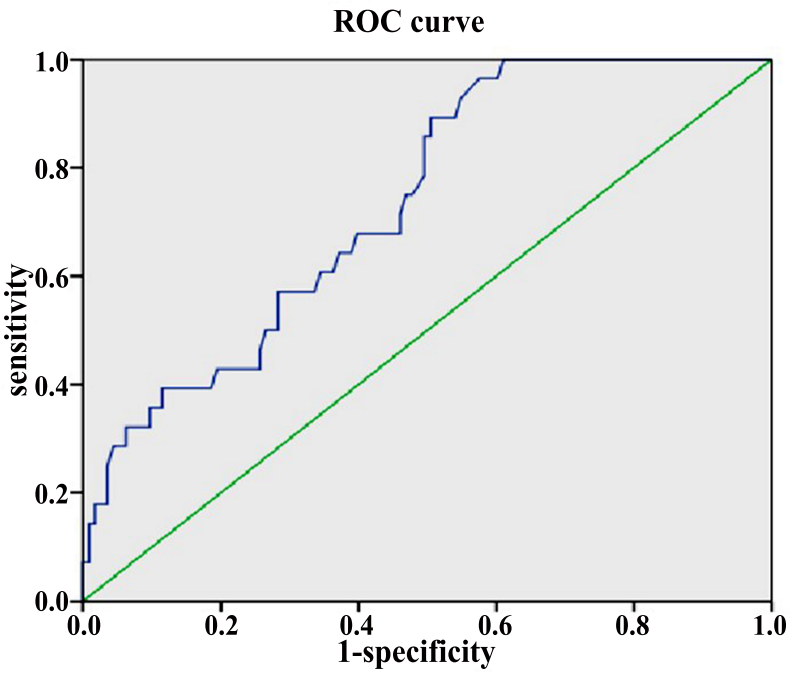

Fig. (1). The value of preoperative Hct in predicting CHS after combined revascularization for Moyamoya disease: ROC curve analysis showed that the area under the curve was 0.731, the optimal preoperative hemimetric cutoff value was 39.05%, and the sensitivity and specificity of its prediction were 96.4% and 42.5%, respectively.

presented with ischemic symptoms in preoperation, including transient ischemic attack (TIA) in 25 (17.7%) hemispheres, frequent TIA in 13 (9.2%) hemispheres and cerebral infarction in 78 (55.3%) hemispheres. Among the cerebral hemispheres that underwent surgery, 74(52.5%) hemispheres were accompanied by hypertension, 33 (23.4%) hemispheres were accompanied by diabetes, 29 (20.6%) hemispheres were accompanied by hyperlipidemia, 58 (41.1%) hemispheres had a history of smoking, and 53 (37.6%) hemispheres had a history of drinking. The posterior circulation involved was 24 (17.0%) hemispheres. Among these hemispheres, with mRS score of 0–2 and with mRS score of 3 were 130 (92.2%) and 11 (7.8%), respectively. In the 141 hemispheres undergoing surgical treatment, according to preoperative DSA and Suzuki staging system, the hemispheres were divided into stages 1-6. Specific data are presented in Table **1**.

3.2. CHS Complication after Combined Revascularization

In this study, CHS occurred in 28 (19.8%) cerebral hemispheres after operation, including cerebral hemorrhage in 4 (2.8%) hemispheres, seizures in 4 (2.8%) hemispheres, and focal CHS in 20 (14.2%) hemispheres. The main manifestations were aphasia, immobility of limbs, and headache. Specific data are presented in Table **2**.

3.3. Factors Associated with CHS

3.3.1. Univariate Analysis

The results of univariate analysis indicated that cerebral hemorrhage onset (p =0.011), preoperative hypertension (p =0.002), higher haematocrit (Hct) level (p <0.001) and left cerebral hemisphere surgery (p =0.037) were different between the CHS group and the non-CHS group. Specific data are presented in Table **3**.

Table 1. Clinical features.

Clinical Features	Number (%)
No. of patients	133
No. of hemispheres	141
Age, years ($\bar{x}$ ±s)	52.1±7.4
Sex	
Male	89(63.1)
Female	52 (36.9)
Left hemispheres	61（43.3%）
Onset Symptoms	
Hemorrhage	16（11.4）
Cerebral infarction	78(55.3)
TIA	25(17.7)
Frequent TIA	13(9.2)
Headache	9(6.4)
Comorbidity	
Diabetes	33（23.4）
Hypertension	74 （52.5）
Hyperlipidemia	29（20.6）
Smoking	58（41.1）
Drinking	53（37.6）
Posterior circulation involved	24（17.0）
Baseline mRS	
0	14（9.9）
1	91（64.5）
2	25（17.8）
3	11（7.8）
Suzuki Stage	
2-3	87（61.7）
4-6	54（38.3）

Table 2. Cerebral hyperperfusion syndrome (CHS) complication.

Complication	Number of Patients (%)
Focal cerebral hyperperfusion syndrome	20 (14.2)
Hemorrhage	4 (2.8)
Seizures	4 (2.8)

Table 3. Univariate analysis of potential related factors for cerebral hyperperfusion syndrome (CHS).

Clinical Presents		CHS (n=28)	Non-CHS (n=113)	χ^2 /Z	*p*
Female（n，%）		13（46.4%）	39（34.5%）	1.369	0.242
Age (years): M(P25,P75)		51.0(46.5,55.7)	52(48.0,58.0)	-0.890	0.373
Hct (%): M(P25,P75)		43.3(40.5,47.7)	40.0(35.0,44.1)	-3.778	<0.001
Smoking（n，%）		9（32.1）	49（43.4）	1.167	0.280
Drinking（n，%）		10（35.7）	43（38.1）	0.052	0.819
Hypertension（n，%）		22（78.6）	52（46.0）	9.536	0.002
Diabetes（n，%）		6（21.4）	27（23.9）	0.076	0.783
Hyperlipidemia（n，%）		7（25.0）	22（19.5）	0.420	0.517
Headache（n，%）		2（10.7）	7（6.2）	0.034	0.854
TIA onset（n，%）		4（14.3）	21（18.6）	0.304	0.581
Frequent TIA（n，%）		3（10.7）	10（8.8）	0.093	0.760
Cerebral infarction（n，%）		17（60.7）	61（54.0）	0.411	0.521
Hemorrhage（n，%）		7（25.0）	9（8.0）	6.473	0.011
Posterior circulation involved（n，%）		8（28.6）	16（14.2）	3.300	0.069
Left hemispheres（n，%）		17（60.7）	44（38.9）	4.335	0.037
Advanced Suzuki stage（n，%）		12（42.9）	42（37.2）	0.307	0.579
Baseline mRS (n, %)	0	6（21.4）	8（7.1）	5.751	0.124
	1	16（57.1）	75（66.4）		
	2	5（17.9）	20（17.7）		
	3	1（3.6）	10（8.8）		
Receptor vascular site（n，%）	Frontal lobe	7（25.0）	10（8.8）	5.523	0.063
	Temporal lobe	14（50.0）	68（60.2）		
	Parietal lobe	7（25.0）	35（31.0）		

Abbreviations: Advanced Suzuki stage: Suzuki stage between 4 and 6 stage; TIA: transient ischemic attack; mRS: modified Rankin Scale; Hct: haematocrit.

3.4. Multivariate Logistic Regression Analysis

Variables with $p < 0.05$ were included in multivariate logistic regression analysis. The results of multivariate logistic regression analysis indicated that preoperative hypertension, cerebral hemorrhage onset, and higher Hct level were significantly associated with CHS after combined revascularization. The odds ratio (OR) is: 4.075[95% confidence interval (95% CI): 1.323 ~ 12.554, $p = 0.014$], 5.390[95% confidence interval (95% CI): 1.408 ~ 20.642, $p = 0.014$], 1.171[95% confidence interval (95% CI): 1.051 ~ 1.305, $p = 0.004$], respectively. Specific data are presented in Table **4**.

Table 4. Multivariate analysis of potential related factors for CHS.

Clinical Presents	B	SE	OR (95%CI)	*p*
Left hemispheres	0.809	0.488	0.864 ~ 5.845	0.097
Hypertension	1.405	0.574	1.323 ~ 12.554	0.014
Hemorrhage onset	1.685	0.685	1.408 ~ 20.642	0.014
Hct	0.158	0.055	1.051 ~ 1.305	0.004

Note: Hct: haematocrit; OR (95%CI): odds ratio (95% confident interval); B: beta; SE: standard error.

4. DISCUSSION

CHS is one of the common complications after combined revascularization. According to previous studies, the incidence of CHS was 7.9% ~ 50% [7, 12-15], and the incidence of CHS in this study was 19.8%, which was basically consistent with previous reports [10]. In this study, multivariate logistic regression analysis was used to analyze and find that the cerebral hemorrhage onset, preoperative hypertension and higher Hct level were independent risk factors for CHS complications after combined revascularization.

The association between a higher pre-operative hematocrit level and CHP syndrome in this study is confirmed. ROC curve analysis results showed that the optimal preoperative Hct cut off value was 39.05%, which may be due to the fact that higher Hct level could increase blood viscosity and lead to venous thrombosis [16], thus causing internal microcirculation venous congestion including the STA-MCA anastomosis site, which can result in temporary increased cerebral blood volume (CBV) and local congestion. Katsuki *et al.* found that local congestion around the anastomosis site and early filling of cortical veins were observed in patients with moyamoya disease with higher Hct level after combined revascularization [7], and Machida *et al* reported that intraoperative congestive vein redness may be a sign of CHS in adult MMD patients who accepted STA-MCA anastomosis [17]. Similarly, Fujimura *et al*., reported that there was a significant correlation between increased local CBV and CHS, and higher Hct level may lead to proper venous congestion and CBV increase subsequent at STA-MCA anastomoses, thus promoting the development of CHS [18]. Therefore, appropriately reducing higher Hct level before surgery may reduce the risk of CHS (Fig. **1**).

Previous studies have shown that preoperative hypertension is closely related to postoperative CHS complications [12, 19], which is consistent with this study. The reason may be that hypertension can cause the deterioration of vascular self-regulation ability and the increase of vascular permeability fragility, which leads to postoperative CHS. In addition, patients with MMD have fragile smoke-like blood vessels at the base of the brain and the basal ganglia, where the pressure will be suddenly increased after combined revascularization, and hypertension may lead to a more significant increase in hemodynamic pressure, then resulting in the smoke-like blood vessels rupture and intracranial hemorrhage. Fujimura *et al.* found that preventive blood pressure control (systolic blood pressure was controlled bellow 130mmHg) immediately after STA-MCA anastomosis in MMD patients can significantly reduce the occurrence of postoperative CHS, which proves that hypertension is directly related to CHS [19]. Meanwhile, a study showed that the incidence of CHS in hypertension group was significantly higher than the control group, and cerebral perfusion pressure was directly related to mean arterial pressure after carotid endarterectomy [20]. Therefore, the most direct method for CHS treatment is to control blood pressure, but too low blood pressure will lead to cerebral hypoperfusion and infarction, therefore, the best postoperative systolic blood pressure is maintained in the range of 120-140 mmHg.

In this study, we found that cerebral hemorrhage onset was a risk factor for CHS complications after combined revascularization. Fujimura *et al.* believed that the destruction of blood-brain barrier after cerebral hemorrhage in MMD patients is more likely to cause CHS after revascularization [13]. A number of studies have shown that MMD patients with cerebral hemorrhage onset were often accompanied by the expansion and branch extension of AChA and PcomA [2, 21-26], and with the progression of the disease, the collateral vessels from the anterior cerebral artery and the middle cerebral artery will be narrowed along with the narrow of the end of the internal carotid artery [26], then, the hemodynamic pressure was transferred to the collateral branches of AChA and PcomA, thus causing arterial rupture and bleeding. Although the pressure of collateral vessels of AChA and PcomA could be improved after revascularization to reduce the risk of rebleeding, the uneven distribution of postoperative blood flow and the increased fragility of the blood vessels themselves might lead to rebleeding [24, 27].

5. LIMITATIONS

The study has several limitations: first, this study was retrospectively carried out, and selection bias may exist. Second, more detailed information on operational details and techniques cannot be collected. Perhaps more detailed observational measures should be taken in the future research design to obtain more detailed conclusions.

CONCLUSION

Our study showed that preoperative hypertension, cerebral hemorrhage onset and higher Hct level were independent risk factors for CHS after combined revascularization.

AUTHORS' CONTRIBUTIONS

All authors made a significant contribution to the study and manuscript preparation. DX, BZ and HS contributed to study conception and design, DX, JG, OB, AB and QW contributed to data acquisition, data interpretation and analysis. DX drafted the manuscript. BZ contributed to the major revision of the manuscript. HS, BZ, QW and JG contributed significant intellectual content. IG, BZ and HS contributed to the revision of the paper. All authors contributed to the article and approved the submitted version.

LIST OF ABBREVIATIONS

CHS	=	Cerebral Hyperperfusion Syndrome
CT	=	Computed Tomography
DSA	=	Digital Subtraction Angiography
MMD	=	Moyamoya Disease
TIA	=	Transient Ischemic Attack

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The institutional review board of the First Affiliated Hospital of Harbin Medical University and the First Affiliated Hospital of Henan University of Science and Technology approved this retrospective study.

HUMAN AND ANIMAL RIGHTS

All procedures performed in studies involving human participants were in accordance with the ethical standards of institutional and/or research committee and with the 1975 Declaration of Helsinki, as revised in 2013.

CONSENT FOR PUBLICATION

Written informed consent was obtained from all the patients before the procedure. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AVAILABILITY OF DATA AND MATERIALS

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

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CONFLICT OF INTEREST

The authors declare no conflict of interest financial or otherwise.

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