의학석사 학위논문

모야모야 환자에서 표면 측두 동맥-중뇌 대동맥 동맥 문합 수술 후 과관류 증후군과 높은 수술 전 혈소판 수의 연관성에 대한 연구

High preoperative platelet count is associated with postoperative symptomatic cerebral hyperperfusion syndrome after superficial temporal artery-middle cerebral artery anastomosis in moyamoya patients

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서울대학교 대학원
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ABSTRACT

High preoperative platelet count is associated with postoperative symptomatic cerebral hyperperfusion syndrome after superficial temporal artery–middle cerebral artery anastomosis in moyamoya patients

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Background: Platelets play a critical role in the inflammatory response, accompanied by microvascular endothelial dysfunction, underlying postoperative symptomatic cerebral hyperperfusion syndrome (PSCHS) after superficial temporal artery-middle cerebral artery (STA–MCA) anastomosis in moyamoya patients. We examined whether the preoperative platelet count can predict PSCHS after STA–MCA anastomosis in such patients.
Methods: In 160 adult moyamoya patients undergoing 186 STA–MCA anastomoses, preoperative (demographics, initial clinical manifestation, and Suzuki grade), intraoperative (surgical time, operative side, fluid balance, and maximum and minimum mean blood pressure before and after vessel anastomosis), immediate postoperative (APACHE 2 score), and laboratory

(hemoglobin and C-reactive protein levels and white blood cell and platelet counts) data were collected retrospectively.
Results: 84 patients (90 sides, 48.4%) developed PSCHS with a median (IQR) onset of postoperative day 1 (0-3) and duration of 4 (3-7) days. The preoperative (mean [IQR] 252 [228-280] *vs.* 231 [197-262] $\times 10^3/\mu L$, $p = 0.009$) and immediate postoperative (190 [160-227] *vs.* 174 [148-206] $\times 10^3/\mu L$, $p = 0.037$) platelet counts were significantly higher in patients with PSCHS than in those without. The preoperative platelet count (odds ratio [95% confidence interval], 1.01 [1.00-1.02], $p = 0.002$), operation on the dominant hemisphere (10.38 [4.56-23.64], $p < 0.001$), and negative fluid balance (2.70 [1.10-6.66], $p = 0.031$) were significant independent predictors of PSCHS. The optimal cut-off value for the preoperative platelet count was 227 $\times 10^3/\mu L$. PSCHS developed more frequently in cases with a preoperative platelet count $\geq$ 227 $\times 10^3/\mu L$ (2.90 [1.54-5.45]; $p = 0.001$).
Conclusions: A high preoperative platelet count is associated with the development of PSCHS after STA-MCA anastomosis in adult moyamoya patients.

Keywords: moyamoya disease, platelet, postoperative symptomatic cerebral hyperperfusion syndrome, superficial temporal artery-middle cerebral artery anastomosis
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INTRODUCTION

Moyamoya disease is characterized by chronic cerebrovascular stenosis at the distal portion of the internal carotid artery with abnormal vascular networks.[1] Direct revascularization surgery, including superficial temporal artery-middle cerebral artery (STA-MCA) anastomosis, has been performed in adult moyamoya patients to improve cerebral blood flow (CBF) in the affected area.[2] Postoperative symptomatic cerebral hyperperfusion syndrome (PSCHS), which is defined as a temporary increase in CBF following STA-MCA anastomosis in the brain tissue around the anastomosis site,[3] is a major cause of transient postoperative neurological deficits in moyamoya patients; its reported incidence is 9.8-47%.[4-6] Although the exact pathophysiology of PSCHS remains unclear, cerebral microvascular endothelial dysfunction, inflammation, and oxidative stress injury contribute to the development of PSCHS via multiple, complex cellular and subcellular interactions, which result in breakdown of the blood-brain barrier (BBB).[7-11]

Platelets are a critical mediator linking inflammation and microvascular endothelial dysfunction in various diseases.[12] Oxidative stress injury mediated by free oxygen radicals in cerebral ischemia-reperfusion injury, especially during reperfusion, accompanies inflammation.[13] Such inflammatory reactions produce several characteristic microvasculature responses, called microvascular endothelial dysfunction, which involves the activation of vascular endothelial cells, recruitment and activation of leukocytes and platelets, increased oxidative stress, and barrier dysfunction.[12] Activated platelets contribute to inflammation via increased leukocyte recruitment and migration

into inflamed tissues.[14] Platelets also play an important role in activating the complement pathway, which amplifies both the inflammatory response via leukocyte receptors and activation of the vascular endothelium.[15-17] Platelets are also linked to endothelial cell barrier dysfunction under inflammatory conditions where platelets disrupt the endothelial barrier function via a burst of free oxygen radicals generated by leukocytes.[12, 14] As a result, platelets may play a key role in the pathophysiology of hyperperfusion by provoking an inflammatory response accompanied by cerebral microvascular endothelial dysfunction, which leads to BBB breakdown and vasogenic cerebral edema. However, no study has examined the role of platelets in PSCHS in moyamoya patients undergoing STA-MCA anastomosis.

In this study, we postulated that a high platelet count would increase the incidence of PSCHS in moyamoya patients undergoing direct revascularization surgery by increasing the inflammatory response accompanied by cerebral microvascular endothelial dysfunction. We examined whether the preoperative platelet count can predict PSCHS after STA-MCA anastomosis in moyamoya patients.

METHODS

This retrospective study was approved by the Institutional Review Board of Seoul National University Hospital and the need for written informed consent was waived. Adult moyamoya patients undergoing STA-MCA revascularization surgery at Seoul National University Hospital from March 2011 through December 2016 were enrolled. Patients who did not undergo the planned STA-MCA anastomosis because there was no appropriate intracranial vessel for vascular anastomosis or who had unanticipated intraoperative events were excluded. Patients who received additional intraoperative anesthetics (dexmedetomidine and sevoflurane postconditioning) were also excluded from analysis because both agents can affect the development of PSCHS.

Perioperative patient management

No premedication was given to any patient. Anesthesia was induced and maintained with total intravenous anesthesia with propofol and remifentanil by continuous infusion (effect site concentration 3-6 □g/mL for propofol and 3-6 ng/mL for remifentanil) using a target-controlled infusion pump. Blood pressure was monitored with an arterial catheter placed at the radial or dorsalis pedis artery. The intraoperative mean arterial pressure (MAP) was strictly maintained at 20% above the preoperative MAP until the STA-MCA anastomosis was completed. Intravenous phenylephrine was administered intermittently (20-30 μg) or continuously (200-600 μg/h) if necessary. After anastomosis, the MAP was maintained at 10% below the preoperative MAP. Hyperventilation and

hypoventilation were avoided to maintain normocapnia. The intraoperative hemoglobin concentration was maintained at a minimum level of 10 g/dL. All surgical procedures were performed by two neurosurgeons, who both used similar surgical techniques, including craniotomy size, STA preparation, and the site (fourth branch of the MCA) and size of the anastomosis, during the study period.

In all patients, brain computed tomography (CT) was obtained routinely in the immediate postoperative period to detect surgery-related complications, including hematoma and infarction. All patients underwent a complete neurological examination by the neurosurgeons when they became fully awake. MAP was strictly maintained at the preoperative MAP ± 20 mmHg until about postoperative day (POD) 3 or 4. If necessary, intravenous nicardipine was administered intermittently (0.5-1 mg) or continuously at a rate of 5-15 mg/h. If the patients developed neurological symptoms or signs postoperatively, brain CT or diffusion magnetic resonance imaging (MRI) with arterial spin labeling was done to rule out intracranial hematoma and cerebral infarction and to evaluate postoperative changes in cerebral perfusion. If necessary, brain single-photon emission CT (SPECT) was performed to confirm the diagnosis of PSCHS.

Definition of PSCHS

PSCHS was considered if the following four conditions were met: 1) new postoperative focal neurological deficits (*i.e.*, hand motor dysfunction, dysphasia, and dysarthria), seizures, and symptomatic subarachnoid hemorrhage; 2) postoperative reversible neurological deficit symptoms and signs that resolved

completely within 15 POD; 3) no definite hematomas or acute infarction on brain CT or diffusion MRI; and 4) a significant focal increase in CBF around the anastomosis site on postoperative arterial spin labeling MRI or brain SPECT. Finally, the presence of PSCHS was confirmed by two neurosurgeons blinded to the study.[18]

Data collection

The patients' electronic medical records were reviewed retrospectively by one anesthesiologist to collect data, which were roughly categorized into five areas: 1) preoperative factors, including demographics, initial clinical manifestations, Suzuki grade on cerebral angiography,[19] co-morbidity, brain SPECT findings, maximum and minimum mean blood pressures (MBPs) on a general ward, and laboratory findings such as hemoglobin, platelet count and functional platelet parameters, white blood cell (WBC) count with differential, neutrophil/lymphocyte ratio (NLR), and C-reactive protein (CRP); 2) intraoperative factors, including surgical and anesthetic times, the operative side, fluid balance, transfusion, range of MBP before and after vessel anastomosis, range of arterial oxygen and carbon dioxide tensions before and after vessel anastomosis, occlusion time, total amounts of remifentanil and propofol, and nadir hemoglobin; 3) immediate postoperative factors, including the APACHE 2 score and laboratory findings (immediate postoperative hemoglobin, platelet count, WBC count with differential, NLR , and CRP); 4) postoperative laboratory findings, including nadir hemoglobin concentrations, peak platelet counts and functional platelet parameters, peak WBC counts with differential, peak

NLR, and peak CRP on both POD 1-2 and 3-7; and 5) clinical outcome data, including postoperative complications and the lengths of the intensive care unit (ICU) and hospital stays.

Statistics

The Kolmogorov-Smirnov test was used to evaluate the normality of the distributions of all continuous variables. The Student's *t*-test and Mann-Whitney U test were used to compare normally distributed and skewed variables, respectively. Categorical variables were analyzed using the chi-square or Fisher's exact test. To determine predictors of PSCHS, univariate analyses of preoperative, intraoperative, and immediate postoperative data were performed. Only variables with a p-value < 0.15 in the univariate analysis were entered into a binary logistic regression with the forward stepwise conditional method. A p-value < 0.05 was considered statistically significant.

The incidence of PSCHS was 47% in our previous study.[18] To reproduce this incidence with a confidence interval of 95% and total width of 0.15, the current study needed a minimum of 181 patients.

RESULTS

During the study period, 212 patients underwent 274 surgeries (62 bilateral operations). In total, 7 patients who underwent indirect extracranial-intracranial revascularization surgery and 1 patient who underwent external ventricular drainage due to unexpected intraoperative intraventricular hemorrhage were excluded. Also, 48 and 32 patients who received intraoperative dexmedetomidine and sevoflurane postconditioning at the end of surgery, were excluded respectively. The final data analysis included 160 patients with 186 surgeries.

PSCHS developed in 84 patients (90 sides, 48.4%) with a median (IQR) onset of POD 1 (0-3) and duration of 4 (3-7) days. The major clinical presentations, including dysarthria and motor/sensory dysphasia, were matched to dysfunction near the anastomosis site in the perisylvian area.

Tables 1-3 compare the preoperative, intraoperative, and immediate postoperative variables in patients with and without PSCHS, respectively. Preoperative neurological status, as defined as modified Rankin Score (mRS), did not show any differences between patients with PSCHS and those not. Decreased perfusion status in SPECT findings, including basal perfusion and vascular reserve, did not differ between the groups. The preoperative platelet count (252 [228-280] *vs.* 231 [197-262] $\times 10^3/\mu L$, p = 0.009), preoperative monocyte ratio (6.7 [1.9] *vs.* 7.4 [2.3] %, p = 0.045), and incidence of operations on the dominant hemisphere (60 [66.7] *vs.* 31 [32.3] %, $p < 0.001$) were significantly higher in patients with PSCHS compared to those without PSCHS. The immediate postoperative platelet count (190 [160-227] *vs.* 174 [148-206] $\times 10^3/\mu L$, p = 0.037) was also

higher in patients with PSCHS. In terms of transfusion, red blood cell as well as fresh frozen product transfusion does not show any differences between the groups.

On binary multivariable logistic regression, the preoperative platelet count (odds ratio [95% confidence interval], 1.01 [1.00-1.02], p = 0.002), operation on the dominant hemisphere (10.38 [4.56-23.64], p < 0.001), and negative fluid balance (2.70 [1.10-6.66], p = 0.031) were significant independent predictors of PSCHS (Table 4). In the receiver operating characteristic curve analysis, the preoperative platelet count as a single factor had an area under the curve of 0.61. The optimal cut-off value for the preoperative platelet count was 227 $\times 10^3/\mu$L, and PSCHS developed more frequently in cases with a preoperative platelet count $\geq$ 227 $\times 10^3/\mu$L (2.90 [1.54-5.45]; p = 0.001).

Considering the postoperative laboratory findings and clinical outcomes (Table 5), the peak platelet count and peak plateletcrit (PCT) were significantly higher and the peak mean platelet volume/platelet count (MPV/PTC) ratio was lower in patients with PSCHS on POD 1-2 and 3-7. The peak WBC count and peak segmental neutrophil ratio were higher in patients with PSCHS on POD 1-2 and 3-7. The incidences of postoperative complications, including transient ischemic attack, resolved cerebral infarction, and cerebral infarction with sequelae, did not differ significantly between the two groups. However, the hospital length of stay was significantly longer in patients with PSCHS (11 [9-12] *vs.* 9 [8-11], p = 0.010).

Tables

Table 1. Comparisons of preoperative variables in moyamoya patients undergoing superficial temporal artery–middle cerebral artery anastomosis with versus without postoperative symptomatic cerebral hyperperfusion syndrome (PSCHS)

	PSCHS (n = 90)	No PSCHS (n = 96)	P value
Age (yr)	38 (28–45)	40 (28–48)	0.312
Sex (M:F)	36:54	28:68	0.162
Body mass index (kg/m^2)	24.3 (21.5–27.3)	24.1 (21.6–26.1)	0.841
Initial clinical manifestation			
Transient ischemic attack	45 (50.0%)	42 (43.8%)	0.480
Infarction	30 (33.3%)	27 (28.1%)	0.541
Hemorrhage	13 (14.4%)	22 (22.9%)	0.197
Radiologic progression	2 (2.2%)	5 (5.2%)	0.446
Preoperative neurological deficits (mRS)			0.108
0	17 (18.9%)	22 (22.9%)	
1	62 (68.9%)	52 (54.2%)	
2	10 (11.1%)	17 (17.7%)	
3	1 (1.1%)	5 (5.2%)	
Suzuki grade			
2	10 (11.1%)	9 (9.4%)	0.882
3	44 (48.9%)	46 (47.9%)	1.000
4	19 (21.1%)	26 (27.1%)	0.436
5	17 (18.9%)	15 (15.6%)	0.693

Co-morbidity			
Hypertension	27 (30.0%)	21 (21.9%)	0.272
Hyperlipidemia	9 (10.0%)	4 (4.2%)	0.154
Diabetes	7 (7.8%)	7 (7.3%)	1.000
Chronic kidney disease	1 (1.1%)	0 (0.0%)	0.484
Thyroid disease	8 (8.9%)	9 (9.4%)	1.000
Heart disease	3 (3.3%)	2 (2.1%)	0.674
SPECT findings			0.389
No basal hypoperfusion and preserved vascular reserve	13 (14.4%)	19 (19.8%)	
Only decreased vascular reserve	23 (25.6%)	16 (16.7%)	
Only basal hypoperfusion	9 (10.0%)	13 (13.5%)	
Basal hypoperfusion and decreased vascular reserve	45 (50.0%)	48 (50.0%)	
Maximal MBP at ward (mmHg)	103 (10)	101 (11)	0.105
Minimal MBP at ward (mmHg)	82 (10)	81 (9)	0.492
Preoperative Hb (g/dl)	13.4 (12.6-14.5)	13.1 (12.1-14.2)	0.142
Preoperative platelet ($x10^3$/ul)	252 (228-280)	231 (197-262)	0.009
Preoperative PCT	0.26 (0.23-0.29)	0.25 (0.20-0.28)	0.217
Preoperative MPV	10.1 (9.6-10.9)	10.1 (9.6-10.8)	0.780
Preoperative MPV/PCT ratio	39.2 (34.9-44.0)	41.7 (35.2-47.7)	0.100
Preoperative PDW	11.9 (10.8-13.2)	11.7 (10.7-13.3)	0.923
Preoperative WBC ($x10^3$/ul)	6.4 (5.3-7.4)	6.1 (5.2-7.2)	0.361

Preoperative segmental neutrophil (%)	58.3 (8.4)	57.2 (8.5)	0.381
Preoperative lymphocyte (%)	31.4 (7.1)	31.9 (7.8)	0.654
Preoperative monocyte (%)	6.7 (1.9)	7.4 (2.3)	0.045
Preoperative eosinophil (%)	2.3 (1.2-3.7)	2.0 (1.4-3.1)	0.878
Preoperative basophil (%)	0.6 (0.4-0.8)	0.5 (0.4-0.7)	0.951
Preoperative NLR	1.8 (1.5-2.3)	1.7 (1.4-2.4)	0.436
Preoperative CRP (mg/dL)	0.04 (0.01-0.12)	0.04 (0.01-0.12)	0.460

Data are presented as number (%), mean (SD), or median (IQR). SPECT, MBP, mean blood pressure; Hb, haemoglobin; PCT, plateletcrit; MPV, mean platelet volume; PDW, platelet distribution width; WBC, white blood cell; NLR, neutrophil to lymphocyte count ratio; CRP, C-reactive protein

Table 2. Comparisons of intraoperative variables in moyamoya patients undergoing superficial temporal artery–middle cerebral artery anastomosis with versus without postoperative symptomatic cerebral hyperperfusion syndrome (PSCHS).

	PSCHS (n = 90)	No PSCHS (n = 96)	P-value
Anesthesia time (min)	360 (335–391)	355 (335–415)	0.781
Surgical time (min)	292 (272–320)	290 (271–330)	0.812
Dominant site operation	60 (66.7%)	31 (32.3%)	<0.001
Fluid balance (ml)	520 (–155–1000)	595 (173–1195)	0.125
Negative fluid balance	25 (27.8%)	17 (17.7%)	0.143
Transfusion	22 (24.4%)	31 (32.3%)	0.307
Red blood cell	18 (20.0%)	29 (30.2%)	0.152
Fresh frozen plasma	2 (2.2%)	3 (3.1%)	1.000
Others	3 (3.3%)	0 (0.0%)	0.111
Maximal MBP B–A (mmHg)	115 (108–125)	112 (104–122)	0.079
Minimal MBP B–A (mmHg)	86 (60–92)	86 (81–90)	0.331
Maximal MBP A–A (mmHg)	100 (92–108)	98 (92–104)	0.651
Minimal MBP A–A (mmHg)	67 (11)	70 (10)	0.064
Maximal PaO_2 B–A(mmHg)	262 (232–288)	261 (234–299)	0.622
Minimal PaO_2 B–A(mmHg)	238 (206–267)	241 (196–269)	0.959
Maximal PaO_2 A–A(mmHg)	243 (223–267)	248 (224–273)	0.561
Minimal PaO_2 A–A(mmHg)	239 (219–266)	247 (218–270)	0.605
Maximal $PaCO_2$ B–A(mmHg)	40 (38–42)	39 (37–41)	0.161
Minimal $PaCO_2$ B–A(mmHg)	36 (34–38)	36 (34–38)	0.815

Maximal $PaCO_2$ A-A(mmHg)	39 (37-41)	39 (37-41)	0.786
Minimal $PaCO_2$ A-A(mmHg)	38 (37-40)	38 (36-40)	0.629
Occlusion time (min)	38 (34-41)	37 (32-40)	0.636
Remifentanil total amount (g)	2900 (2300-3425)	3000 (2345-3600)	0.632
Propofol total amount (mg)	3000 (2655-3625)	3000 (2600-3495)	0.694
Nadir Hct (%)	29 (27-33)	29 (27-32)	0.462

Data are presented as numbers, mean (SD), or median (IQR). MBP, mean blood pressure; B-A, before anastomosis; A-A, after anastomosis; PaO_2, arterial oxygen partial pressure; $PaCO_2$, arterial carbon dioxide partial pressure; Hct, haematocrit.

Table 3. Comparisons of immediate postoperative variables in moyamoya patients undergoing superficial temporal artery–middle cerebral artery anastomosis with versus without postoperative symptomatic cerebral hyperperfusion syndrome (PSCHS).

	PSCHS (n = 90)	No PSCHS (n = 96)	P-value
APACHE II score	16 (14–20)	17 (13–19)	0.871
Immediate postoperative Hb (g/dl)	11.2 (10.2–11.9)	11.3 (10.4–12.0)	0.548
Immediate postoperative platelet (x10^3/ul)	190 (160–227)	174 (148–206)	0.037
Immediate postoperative WBC (x10^3/ul)	7.8 (2.1)	7.8 (2.5)	0.864
Immediate postoperative segmental neutrophil (%)	67.4 (7.1)	68.9 (9.5)	0.234
Immediate postoperative lymphocyte (%)	23.8 (5.8)	22.6 (8.0)	0.252
Immediate postoperative monocyte (%)	5.8 (5.0–7.0)	5.7 (4.5–7.0)	0.386
Immediate postoperative eosinophil(%)	2.1 (1.2–3.0)	1.9 (1.2–2.6)	0.119
Immediate postoperative basophil (%)	0.4 (0.3–0.5)	0.4 (0.2–0.5)	0.780
Immediate postoperative NLR	2.7 (2.4–3.5)	3.1 (2.3–4.5)	0.255
Immediate postoperative CRP (mg/dL)	4.8 (2.8–7.8)	4.6 (2.2–8.0)	0.521

Data are presented as numbers, mean (SD), or median (IQR). APACHE, acute physiology and chronic health evaluation; Hb, haemoglobin; WBC, white blood cell; NLR, neutrophil to lymphocyte count ratio; CRP, C-reactive protein.

Table 4. Independent predictors for postoperative symptomatic cerebral hyperperfusion syndrome (PSCHS) after superficial temporal artery–middle cerebral artery anastomosis in patients with moyamoya disease on a forward stepwise binary logistic regression.

	PSCHS*		
	OR	95% CI	P-value
Preoperative platelet count ($x10^3$/ul)	1.01	1.00-1.02	0.002
Operation on the dominant hemisphere	10.38	4.56-23.64	< 0.001
Negative fluid balance	2.70	1.10-6.66	0.031

Nagelkerke R^2 statistic is 0.331 in the step 3. Hosmer and Lemeshow goodness of fit test is not significant at 5% (p = 0.566) in the step 3.

*: adjusted for preoperative maximum mean blood pressure in ward, preoperative hemoglobin concentration, preoperative mean platelet volume to plateletcrit ratio, preoperative monocyte percentage, maximum mean blood pressure before anastomosis, minimal mean blood pressure after anastomosis, immediate postoperative platelet count, immediate postoperative eosinophil percentage, which are factors with a P < 0.15 in univariate analysis.

Table 5. Comparisons of postoperative laboratory findings and clinical outcomes in moyamoya patients undergoing superficial temporal artery–middle cerebral artery anastomosis with versus without postoperative symptomatic cerebral hyperperfusion syndrome (PSCHS).

	PSCHS (n = 90)	No PSCHS (n = 96)	P-value
Nadir Hb POD 1–2 (g/dl)	10.5 (9.9–11.6)	10.5 (9.9–11.3)	0.739
Peak platelet POD 1–2 (x10^3/ul)	202 (172–244)	185 (160–220)	0.037
Peak PCT POD 1–2	0.20 (0.18–0.25)	0.19 (0.16–0.23)	0.026
Peak MPV POD 1–2	10.5 (1.1)	10.4 (1.1)	0.609
Peak MPV/PCT ratio POD 1–2	51.8 (13.5)	56.6 (14.9)	0.042
Peak PDW POD 1–2	12.0 (10.8–13.6)	12.1 (10.9–13.6)	0.581
Peak WBC POD 1–2 (x10^3/ul)	14.1 (11.1–16.7)	11.4 (9.6–12.8)	<0.001
Peak segmental neutrophil POD 1–2 (%)	88.0 (81.9–92.2)	86.0 (78.9–90.0)	0.037
Peak lymphocyte POD 1–2 (%)	7.0 (4.7–11.2)	8.3 (5.1–12.4)	0.128
Peak monocyte POD 1–2 (%)	4.2 (2.2–6.1)	5.0 (3.4–6.9)	0.063
Peak eosinophil POD 1–2 (%)	0.1 (0.0–0.4)	0.3 (0.0–1.0)	<0.001
Peak basophil POD 1–2 (%)	0.1 (0.0–0.3)	0.2 (0.1–0.3)	0.052
Peak NLR POD 1–2	12.7 (7.4–19.9)	10.3 (6.3–17.6)	0.126
Peak CRP POD 1–2	4.9 (3.0–7.8)	4.9 (2.5–8.0)	0.974
Nadir Hb POD 3–7 (g/dl)	11.2 (10.4–12.1)	11.3 (10.6–12.2)	0.406
Peak platelet POD 3–7 (x10^3/ul)	266 (226–319)	234 (195–284)	0.011
Peak PCT POD 3–7	0.24 (0.20–0.28)	0.21 (0.18–0.25)	0.008
Peak MPV POD 3–7	10.3 (9.8–11.3)	10.4 (9.8–10.8)	0.504
Peak MPV/PCT ratio POD 3–7	44.0 (36.6–54.3)	48.6 (40.0–58.2)	0.038
Peak PDW POD 3–7	12.0 (10.8–14.0)	12.0 (10.9–13.4)	0.971
Peak WBC POD 3–7 (x10^3/ul)	8.5 (6.5–11.4)	6.4 (5.2–8.2)	<0.001
Peak segmental neutrophil POD 3–7 (%)	73.9 (58.9–87.0)	63.9 (55.1–72.5)	<0.001
Peak lymphocyte POD 3–7 (%)	17.7 (9.0–28.4)	24.2 (16.1–30.7)	0.009

Peak monocyte POD 3−7 (%)	6.7 (3.5−8.4)	8.1 (6.8−9.6)	<0.001
Peak eosinophil POD 3−7 (%)	0.1 (0.0−1.2)	0.3 (0.2−0.5)	<0.001
Peak basophil POD 3−7 (%)	0.1 (0.0−0.3)	0.3 (0.2−0.5)	<0.001
Peak NLR POD 3−7	4.3 (2.1−9.8)	2.6 (1.9−4.5)	0.004
Peak CRP POD 3−7 (mg/dL)	1.06 (0.55−2.87)	2.32 (1.08−3.84)	<0.001
Platelet before discharge (x10^3/ul)	258 (107)	214 (91)	0.001
PCT before discharge	0.25 (0.08)	0.21 (0.07)	<0.001
MPV before discharge	9.9 (9.2−10.8)	10.0 (9.4−10.6)	0.421
MPV/PCT before discharge	39.0 (14.6)	46.7 (18.2)	0.001
PDW before discharge	11.2 (3.4)	11.6 (2.5)	0.281
Postoperative complications (%)			
Transient ischemic attack	2 (2.2%)	8 (8.3%)	0.102
Cerebral infarction (resolve)	2 (2.2%)	9 (9.4%)	0.059
Cerebral infarction (sequelae)	1 (1.1%)	3 (3.1%)	0.622
Hemorrhage	2 (2.2%)	5 (5.2%)	0.446
Seizure	8 (8.9%)	5 (5.2%)	0.395
ICU length of stay (day)	2 (2−3)	2 (2−3)	0.548
Hospital length of stay (day)	11 (9−12)	9 (8−11)	0.010

Data are presented as numbers, mean (SD), or median (IQR). APACHE, acute physiology and chronic health evaluation; Hb, haemoglobin; WBC, white blood cell; NLR, neutrophil to lymphocyte count ratio; CRP, C−reactive protein; POD , postoperative day; PCT, plateletcrit; MPV, mean platelet volume; PDW, platelet distribution width; ICU, intensive care unit.

DISCUSSION

Our study shows that the preoperative, immediate postoperative, and postoperative platelet counts were significantly higher in moyamoya patients with PSCHS, compared with those without PSCHS. The preoperative platelet count was a significant independent predictor of PSCHS. In addition to the preoperative platelet count, an operation on the dominant hemisphere and negative fluid balance were associated with the development of PSCHS.

Platelets play an important role in immune and inflammatory reactions, as well as in hemostasis.[12, 20, 21] Platelets are an important target in inflammation accompanied by oxidative stress injury after cerebral ischemia-reperfusion. The oxidative stress that accompanies inflammation results in phospholipase A2 activation and the generation of platelet-activating factor and other arachidonic acid metabolites, which are potent platelet activators. Activated platelets release numerous bioactive molecules, including CD40 ligand, adenosine diphosphate, p-selectin, angiogenic factors, and reactive oxygen species (ROS), which can affect the function of vascular endothelial cells and circulating immune cells. In other words, platelets play a critical role in the development of microvascular endothelial dysfunction (*e.g.*, increased oxidative stress and disruption of the endothelial barrier) and augmentation of inflammation (*e.g.*, increased recruitment, migration, and activation of leukocytes and activation of the alternative and classical complement pathways). Platelets are activated by soluble mediators such as ROS, adenosine diphosphate, platelet activating factor, tumor necrosis factor-alpha, and p-selectin released by activated leukocytes

and endothelial cells. There is a positive feedback loop embedded in the cross-talk among platelets, vascular endothelial cells, and leukocytes via various cellular and subcellular interactions among them directly or indirectly. In this study, based on the fact that platelets are a major mediator in the cross-talk between inflammation and microvascular endothelial dysfunction, we examined whether the platelet count was associated with the development of PSCHS in moyamoya patients undergoing direct revascularization surgery. Indeed, we found that the preoperative platelet count was a significant predictor of PSCHS after STA-MCA anastomosis in moyamoya patients, and patients with a preoperative platelet count $\geq$ 227 $\times 10^3/\mu$L had a 2.9-fold higher risk.

Notably, this study shows that the peak WBC count and segmental neutrophil ratio measured on POD 1-2 and 3-7 were significantly higher in patients with PSCHS compared with those without. The peak NLR on POD 3-7 was also higher in patients with PSCHS. Similar to our findings, we previously demonstrated that an increased postoperative WBC count was associated with postoperative transient neurological deterioration due to cerebral hyperperfusion after STA-MCA anastomosis in adult moyamoya patients.[18] Together, these results imply that inflammation is involved in the development of PSCHS. Moreover, the immediate and postoperative platelet counts were significantly higher in patients with PSCHS. Considering the onset and duration of PSCHS, our results suggest that platelets contribute to the development of PSCHS by increasing the inflammatory response after STA-MCA anastomosis in adult moyamoya patients.

However, caution is required when interpreting our results because we did not prove the role of platelets in the inflammatory reaction in patients with PSCHS directly.

Impaired autoregulation is also thought to be a central mechanism of PSCHS because reduced preoperative CBF and cerebral vascular reserve capacity cause vasodilation of cerebral microvessels in the affected area and lead to a rapid increase in CBF after STA-MCA anastomosis.[22, 23] A possible mediator of impaired autoregulation is nitric oxide, which causes vasodilation and increases the permeability of the cerebral vessels.[23] The nitric oxide level in cerebrospinal fluid is chronically elevated in moyamoya patients.[24] Another study also demonstrated that increased nitric oxide and ROS levels during clamping and declamping of the internal carotid artery were involved in cerebral microvascular endothelial dysfunction and the deterioration of autoregulatory mechanisms.[25]

In this study, to explain the association between PSCHS and platelets, we focused on the role of platelets, which can affect cerebral microvascular permeability by augmenting the inflammatory response accompanied by cerebral microvascular endothelial dysfunction, leading to disruption of the intact BBB and vasogenic cerebral edema around the vascular anastomosis site.

However, platelet activation generates vascular thrombosis via platelet aggregation in various diseases associated with ischemia. In this study, the incidence of transient ischemic attack after revascularization was 5.4%, which is similar with that (7%) shown in other study.[29] Moreover, the incidence of postoperative transient ischemic attacks was lower than that of PSCHS after

STA-MCA anastomosis in moyamoya patients. This suggests that platelets are involved in the increased inflammatory response accompanied by microvascular endothelial dysfunction rather than vascular thrombosis in the early postoperative period in these patients. An *in vitro* study demonstrated that nitric oxide released from activated platelets modestly inhibited platelet activation but markedly inhibited additional platelet recruitment.[26]

In this study, the operation site was an independent risk factor for PSCHS. Patients undergoing STA-MCA anastomosis on the dominant hemisphere had a 10.4-fold higher risk of PSCHS. Similarly, many studies have demonstrated that an operation on the dominant hemisphere predicted PSCHS in moyamoya patients undergoing STA-MCA anastomosis.[6, 18] The intraoperative fluid balance was also a risk factor for PSCHS in this study. Patients with a negative fluid balance had a 2.7-fold higher risk of PSCHS. In contrast to our result, dehydration is known to precipitate postoperative ischemic symptoms (*i.e.*, transient ischemic attacks) in moyamoya patients.[27] A possible explanation for this is that dehydration may be associated with impaired autoregulation. A study demonstrated that dehydration impaired cerebrovascular autoregulatory capacity following heavy exercise in healthy patients.[28] Because moyamoya patients have impaired cerebral autoregulation, it is possible that a negative intraoperative balance at least contributes to PSCHS by augmenting impaired cerebral autoregulation.

Our study has some limitations. First, because it was a retrospective study, inevitable selection and recall biases existed. Because this study was conducted at a tertiary teaching hospital, our results have limited generalizability. Although STA-MCA

anastomosis has been accepted as a surgical treatment in adult moyamoya patients, the indications for and proficiency with the surgical procedure may differ from hospital to hospital. Second, platelet function and aggregation tests were not done. So we could not explain the role of platelet activation in the pathophysiology of PSCHS. We also did not check serum markers indicating inflammation, oxidative stress, cerebral microvascular endothelial dysfunction, or impaired autoregulation. Third, the power to explain predictors of PSCHS in the binary logistic regression model was low, suggesting that important parameters were omitted from the data analysis.

In conclusion, a high preoperative platelet count is associated with PSCHS in adult moyamoya patients undergoing direct revascularization surgery. A large-scale prospective study is needed to verify the association between platelet count and PSCHS in these patients and to explain the pathophysiological role of platelets in the development of PSCHS.

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초록

모야모야 환자에서 표면 측두 동맥-중뇌 대동맥 동맥 문합 수술 후 과관류 증후군과 높은 수술 전 혈소판 수의 연관성에 대한 연구

배경: 혈소판은 모야모야 환자에서 표면 측두 동맥-중뇌 동맥 (STA-MCA) 문합 수술 후 발생하는 과관류 증후군의 원인으로 알려진 미세 혈관 내피 기능 장애와 그에 동반되는 염증 반응에서 결정적인 역할을 한다. 우리는 이러한 환자에서 수술전 혈소판 수가 표면 측두 동맥-중뇌 뇌동맥 문합 수술 후 과관류 증후군 발생의 잠재적 예측 인자가 될 수 있는지 여부를 확인하고자 하였다.

방법: 총 186건의 표면 측두 동맥-중뇌 뇌동맥 문합 수술을 받은 160명의 성인 모야 모야 환자에서 수술 전 (인구 통계, 초기 임상 증상, 스즈키 등급), 수술 중 (수술시간, 수술 부위, 체액 균형, 혈관 문합 전후의 최대 및 최소 평균 혈압), 수술 직후 (APACHE2 점수), 혈액 검사 (헤모글로빈 및 C-반응성 단백질, 백혈구, 혈소판 수) 데이터를 후향적으로 수집하였다.

결과: 84명의 환자 (90건, 48.4%)는 과관류 증후군이 평균 (IQR) 첫 발생 (술후 1 [0-3]일) 및 지속 기간 (4 [3-7] 일)로 나타났다. 수술 전 혈소판 수 (252 [228-280] vs 231 [197-262] $x10^3$/ul, p = 0.009) 및 수술 후 혈소판 수 (190 [160-227] vs 174 [148-206] $x10^3$/ul, p = 0.037) 는 과관류 증후군이 발생한 환자에서 유의하게 더 높았다. 수술전 혈소판 수치의 최적 절단값은 $227x10^3$/ul (2.90 [1.54-5.45]; p = 0.001) 이다. 수술 전 혈소판 수 (교차비 [95% 신

뢰 구간], 1.01 [1.00-1.02], p = 0.002), 우성대뇌반구의 수술 (10.38 [4.56-23.64], p <0.001) 및 음성 체액 균형 (2.70 [1.10-6.66], p = 0.031)은 과관류 증후군에 대해 중요한 독립적인 요인이었다.

결론: 수술 전 높은 혈소판 수는 성인 모야모야 환자에서 표면 측두 동맥-중뇌 뇌동맥 문합 수술 후 과관류 증후군 발생과 관련이 있다.

주요어: 모야모야 병, 혈소판, 수술후 과관류 증후군, 표면 측두 동맥-중뇌 뇌동맥 문합 수술

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