Original Contribution

Long-Term Outcomes of Indirect Bypass for 629 Children With Moyamoya Disease

Longitudinal and Cross-Sectional Analysis

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Background and Purpose—In pediatric moyamoya disease, there are few reports on the efficacy of surgical intervention for stroke prevention. We evaluated the long-term outcomes of indirect bypass surgery on a relatively large number of children with moyamoya disease in a single center.

Methods—From August 1988 to December 2012, 772 children underwent indirect bypass surgery. This study included 629 patients who were followed up for >5 years, excluding patients with moyamoya syndrome. The mean clinical follow-up duration was 12 years (range, 5–29 years). Cross-sectional analysis was performed based on either Karnofsky Performance Scale or Lansky Play Performance Scale to evaluate overall clinical outcomes and factors associated with unfavorable outcomes. To analyze the longitudinal effect of surgery, the annual risk of symptomatic infarction or hemorrhage on the operated hemisphere after indirect bypass surgery was calculated with a person-year method, and the event-free survival rate was evaluated using the Kaplan-Meier method.

Results—The overall clinical outcome was favorable in 95% of the patients. The annual risks of symptomatic infarction and hemorrhage on the operated hemispheres were 0.08% and 0.04%, respectively. Furthermore, the 10-year event-free survival rates for symptomatic infarction and hemorrhage were 99.2% and 99.8%.

Conclusions—Indirect bypass surgery could provide satisfactory long-term improvement in overall clinical outcome and prevention of recurrent stroke in children with moyamoya disease. **(*Stroke*. 2019;50:00-00. DOI: 10.1161/STROKEAHA.119.025609.)**

Key Words: assessment, outcome ■ cerebral revascularization surgery ■ child ■ moyamoya disease ■ stroke

Moyamoya disease (MMD) is a cerebrovascular disorder characterized by progressive occlusion of both the internal carotid artery, including the proximal anterior cerebral artery and the middle cerebral artery, and the arterial collateral vessels at the base of the brain.[1] The clinical presentation of MMD usually includes repeated transient ischemic attacks or infarctions in children and intracranial hemorrhages in adults.[2] The benefit of surgery for the ischemic type of MMD has been well established.[3–8] However, only a few studies have been conducted on postoperative stroke events in pediatric MMD patients after a considerable period of time in a large population. Therefore, it remains necessary to investigate the preventive effect of indirect bypass surgery for late-onset stroke. We previously reported surgical outcomes of MMD in 410 children.[3] Here, we report our assessment of the long-term outcomes in a larger group of children with MMD who underwent similar presurgical evaluation and relatively uniform surgical procedures at a single institute.

We conducted multivariate analysis to provide more details of the clinical characteristics and the independent prognostic factors for overall clinical outcome following indirect bypass surgery and survival analysis to evaluate its longitudinal stroke prevention effect.

Materials and Methods

Patient Population

We reviewed all medical records of children who were operated on using indirect bypass surgery between August 1988 and December 2012. During the study period, we performed 1548 indirect bypass surgeries on 772 patients. MMD was confirmed through cerebral

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angiography. Patients <18 years of age at the time of surgery and who were followed up for >5 years postoperatively were enrolled. Patients associated with other conditions such as Down syndrome, systemic vasculitis, neurofibromatosis, or prior skull-base radiation therapy (moyamoya syndrome) were excluded from this study (15 patients). Finally, a total of 629 patients were included, with 1283 surgeries performed. Overall clinical outcome and stroke event were analyzed based on the records of the most recent outpatient visits, imaging studies, and telephone interview. Of the 629 patients, 219 patients visited the outpatient clinic since January 2018 and 173 patients responded telephone interview. Therefore, we confirmed the current status of 392 patients. In the remaining patients, the clinical status and stroke event of the patients were analyzed based on the records of the last visits. The mean follow-up duration was 12 years (range, 5–29 years). Patient consent was omitted under institutional review board approval (No. 1808-050-964) for this minimal risk study.

The data that support the findings of this study are available from the corresponding author on reasonable request.

Operative Technique

Surgery was performed in 2 stages (n=556 patients), except for patients with unilateral MMD (n=73 patients), which is usually in the symptomatic and the more hemodynamically affected hemisphere first, followed by the other side. Encephaloduroarteriosynangiosis using the superficial temporal artery was performed to obtain collateral formation of the middle cerebral artery area, in most cases. For anterior cerebral artery territories (n=522 patients), bifrontal encephalogaleo(periosteal)synangiosis or multiple burr hole surgery was performed and combined with superficial temporal artery encephaloduroarteriosynangiosis.[9–11] To obtain the collateral formation in the posterior cerebral artery (PCA) territory (n=unilateral, 109 operations; bilateral, 49 operations), encephaloduroarteriosynangiosis using the occipital artery or multiple burr hole surgery was performed.

Perioperative infarctions included an obviously increased extent of a previous infarction or a new-onset infarction accompanying new neurological symptoms. Perioperative adverse events were defined as infarctions or hemorrhages that occurred within 2 weeks after the operation.

Cross-Sectional Analysis: Overall Clinical Outcome

Karnofsky Performance Scale (KPS) or Lansky Play Performance Scale (LPS) for young age patients (under the age of 10 years) were used for evaluating functional outcome. These scales allow patients to be classified as to their functional impairment. This can be used to compare effectiveness of different therapies and to assess the prognosis in individual patients. They score range from 0 to 100. The lower the score, the worse their functional status. It is also known that both scales have the same score rule and correlate well with each other. The favorable outcome was defined that KPS or LPS is ≥80. The definition of KPS of 80 is that the patients can do normal activity with efforts. LPS of 80 means that the patients have restriction of strenuous play and tire more easily, otherwise active.

Cross-Sectional Analysis: Factors Associated With Unfavorable Outcome

We analyzed whether there was a difference between the unfavorable outcome group and favorable outcome group in the ratio of girl, the mean age at operation, the rate of initial stroke, the mean preoperative KPS or LPS, the mean incidence of perioperative complications, Suzuki stage, and preoperative perfusion status. Among the factors that represent a significant difference between the 2 groups, a univariate and multivariate logistic regression was performed to identify the factors associated with the unfavorable outcome.

Longitudinal Analysis: Newly Developed Stroke Event and Stroke-Free Survival Rate

A newly developed stroke event was defined as all ischemic and hemorrhagic strokes with neurological symptoms occurring >30 days after surgery. This is the same definition used in previous large studies.[12,13]

Statistical Analysis

Continuous variables were presented as the mean±SD. Paired *t* tests were performed to compare clinical states in patients who had consecutive follow-ups preoperatively and postoperatively. Pearson correlation tests were used to identify correlations between clinical features and poor functional outcomes. The annual risk of symptomatic infarction or hemorrhage on the operated hemispheres after indirect bypass surgery was calculated with a person-year method, and the event-free survival rate was evaluated using the Kaplan-Meier method. The end points were the occurrence of stroke and last follow-up (censored). A value of $P<0.05$ was considered statistically significant. All statistical analyses were performed using SPSS 23.0 software (IBM SPSS, Inc, Chicago, IL).

Results

Demographics and Clinical Presentation

A total of 629 pediatric patients were included, consisting of 326 girls and 303 boys (Table 1). The ratio of girls to boys was 1.1:1. The mean age at operation was 7.7 (0.6–17) years. The majority of initial presenting type was ischemia (98%). Among these, 44% patients had infarctions confirmed by preoperative magnetic resonance imaging. Middle cerebral artery, anterior cerebral artery, PCA territorial or larger infarctions beyond the arterial territory occurred in 160 patients (25%). Hemorrhage (2%) was rare.

Table 1. Summary of Demographics, Clinical Presentation, and Perioperative Complication

Baseline Characteristics	No. of Cases or Value
Sex (girls:boys)	326:303 (1.1:1)
Age, y	7.7 (0.6–17, ±3.5)
Initial presentation	
Ischemia	617 (98%)
TIA	338 (54%)
Infarction	279 (44%)
Symptomatic infarction	160 (25%)*
Hemorrhage	12 (2%)
Total operation	1283
Average operation per person	2.0 (1–4, ±0.5)
Perioperative adverse event	104 (8%)
Infarction†	74 (12% per person, 6% per operation)
Intracranial extraaxial hemorrhage	29 (2%)
Intracerebral hemorrhage	2 (0.2%)
Status epilepticus	1 (0.2%)

TIA indicates transient ischemic attack.

*Two with intracranial hemorrhage.

†Infarctions per site were 39 cases in superficial temporal artery encephaloduroarteriosynangiosis, 31 cases in frontal lobe, 3 in occipital lobe, and 1 in contralateral hemisphere.

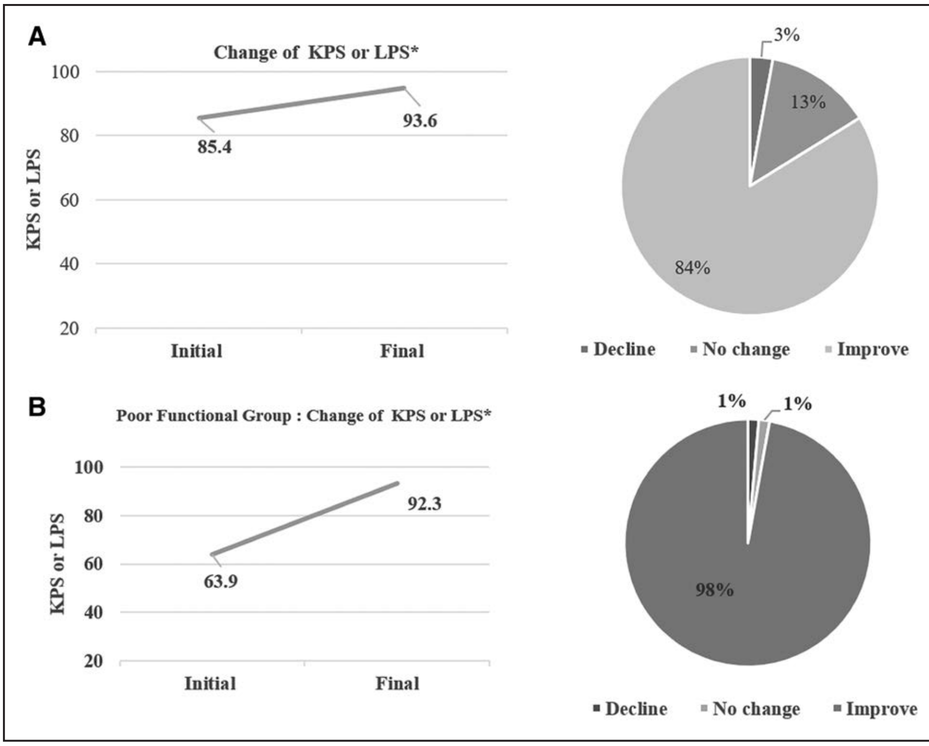

Figure 1. Change of functional status. **A**, Final Karnofsky Performance Scale (KPS) or Lansky Play Performance Scale (LPS) showed significant improvement over its initial KPS or LPS (final KPS or LPS−initial KPS or LPS; mean, 8.2; $P<0.001$), and only 3% of patients showed a decrease in KPS or LPS. **B**, Patients whose KPS or LPS was initially low (<80) also showed significant improvement in their final follow-up (final KPS or LPS−initial KPS or LPS; mean, 28.4; $P<0.001$). Ninety-eight percent of patients showed improvement in KPS or LPS. *KPS and LPS for under the age of 10 y.

Surgical Outcomes

A total of 1283 operations were conducted on 629 patients; average operation per person was 2.0 (1–4, ±0.5; Table 1). The overall perioperative adverse event rate was 8% per operation. Infarctions were the dominating complication, occurring in 74 cases (12% per patient; 6% per operation). Seizures tended to occur in patients preceding the infarction, and status epilepticus occurred in 1 patient (0.2%). The other complications are epidural and subdural hematoma requiring surgical removal (2%) and intracerebral hemorrhage (0.2%). Notably, of 104 patients with perioperative complications, 88 patients recovered normal neurological function during long-term follow-up.

Cross-Sectional Analysis: Overall Clinical Outcome

The overall clinical outcome was favorable in 95% of patients based on their final KPS or LPS (≥80). Final functional status (mean KPS or LPS, 93.6) showed significant improvement over its initial functional status (final KPS or LPS−initial KPS or LPS; mean, 8.2; $P<0.001$; Figure 1A). Even patients whose KPS or LPS was initially low (<80) also showed significant improvement in their final follow-up. The mean of difference between final KPS or LPS and initial KPS or LPS of these patients was 28.4 ($P<0.001$; Figure 1B).

Cross-Sectional Analysis: Factors Associated With Unfavorable Outcome

When comparing the unfavorable outcome group and favorable outcome group, there was a significant difference in the mean age at operation, the presence of initial symptomatic stroke, the mean preoperative KPS or LPS, and the rate of perioperative complications associated with surgery. On the contrary, there were no differences in sex, Suzuki stage, or perfusion status.

Univariate logistic regression analysis showed that age <3 years (odds ratio [OR], 3.7; 95% CI, 1.7–8.3; P=0.001), initial symptomatic stroke (OR, 8.6; 95% CI, 4.4–16.6; $P<0.001$), preoperative poor KPS or LPS (OR, 6.8; 95% CI,

Table 2. Univariate and Multivariate Logistic Regression Analyses of Risk Factors for Unfavorable Outcome (KPS or LPS <80)

Characteristics	Parameters	OR	95% CI	*P* Value
Univariate analysis				
Age at the operation, y	<3	3.7	1.7–8.3	0.001
Initial presentation with symptomatic stroke	Present	8.6	4.4–16.6	<0.001
Preoperative KPS or LPS	<80	6.8	3.6–13.0	<0.001
Perioperative complications	Present	4.3	2.2–8.4	<0.001
Multivariate analysis				
Age at the operation, y	<3	1.1	0.4–2.6	0.972
Initial presentation with symptomatic stroke	Present	4.9	2.2–10.8	<0.001
Preoperative KPS or LPS	<80	2.5	1.1–5.5	0.027
Perioperative complications	Present	3.1	1.5–6.4	0.002

LPS, under the age of 10 y. KPS indicates Karnofsky Performance Scale; LPS, Lansky Play Performance Scale; and OR, odds ratio.

Table 3. Summary of Longitudinal Surgical Outcome

Parameters	No. of Cases or Percentages
Follow-up period	12 (5–29) y
Newly developed stroke event (≥30 d after operation)	20
Infarction	17
Contralateral to operated hemisphere	3
Operated hemisphere	14
Silent infarction	8
Symptomatic infarction	6
Hemorrhage	3 (9, 16, and 24 y)
Annual symptomatic stroke rate in operated hemisphere	0.12%
Infarction	0.08%
Hemorrhage	0.04%

y indicates years after indirect bypass surgery.

3.6–13.0; $P<0.001$), and perioperative complications (OR, 4.3; 95% CI, 2.2–8.4; $P<0.001$) were associated with unfavorable clinical outcomes (Table 2). Multivariate logistic regression analysis revealed that age (OR, 1.1; 95% CI, 0.4–2.6; $P=0.972$) was not associated with unfavorable outcome. Initial symptomatic stroke (OR, 4.9; 95% CI, 2.2–10.8; $P<0.001$) remained most strongly associated with unfavorable outcome (Table 2).

Longitudinal Analysis: Newly Developed Stroke Events During Follow-Up

During the follow-up period, a total of 17 infarctions occurred (Table 3). There were 3 untreated hemispheric infarctions while waiting for the second-stage surgery. Patient ages were 3, 4, and 6 years. The interval between the first operation and the second operation was longer than that of the other patients by 6 to 11 months because of various reasons. Excluding them, a total of 14 infarctions occurred on the operated hemisphere. There were 8 silent infarctions (ie, infarction on regular follow-up images without neurological symptoms). One was a posterior border zone infarction that occurred after PCA progression. The others (7 patients of 8 silent infarction) were small infarctions within the operated area.

Symptomatic infarction occurred in 6 patients. Of these, 2 were PCA territory infarctions due to progressive occlusion of the PCA (one at 6 years and the other at 17 years). One of these 2 infarctions due to PCA progression occurred 17 years after the surgery. The remaining 4 cases were cerebral infarctions on the operated territory. Of these 4 cases, 3 revealed strokes within 6 months (one at 4 months and two at 6 months) and the latest one at 2 years after surgery. Among new-onset infarcted patients, 2 patients were under 3 years of age. Their infarctions were distant from the previous infarction site. By contrast, the other 2 patients showed increased extent of previous infarctions. On their follow-up imaging, increased tissue defects were documented.

According to initial presentation, all patients who showed symptomatic new-onset infarction after operation were initially presented as ischemic type without exceptions. Among them, 3 patients presented with symptomatic infarctions.

New hemorrhage after surgery was also rare. A total of 3 cases of hemorrhage occurred. However, unlike infarction, they tended to occur after considerable time after surgery. All hemorrhagic events occurred 5 years after surgery. In our cohort, hemorrhage occurred at 9, 16, and 24 years after surgery, respectively. All patients experienced hemorrhage in their 20s and 30s, not during adolescence. One had pure intraventricular hemorrhage of the third and fourth ventricles. Her perfusion images during follow-up showed preserved vascular reserve and improved cerebral blood flow after surgery. Cerebral angiography was performed to evaluate the vascular cause. There were no suspected findings on angiography. The patient had long-term uncontrolled renovascular hypertension. The other 2 cases were intracerebral hemorrhage combined with intraventricular hemorrhage. One

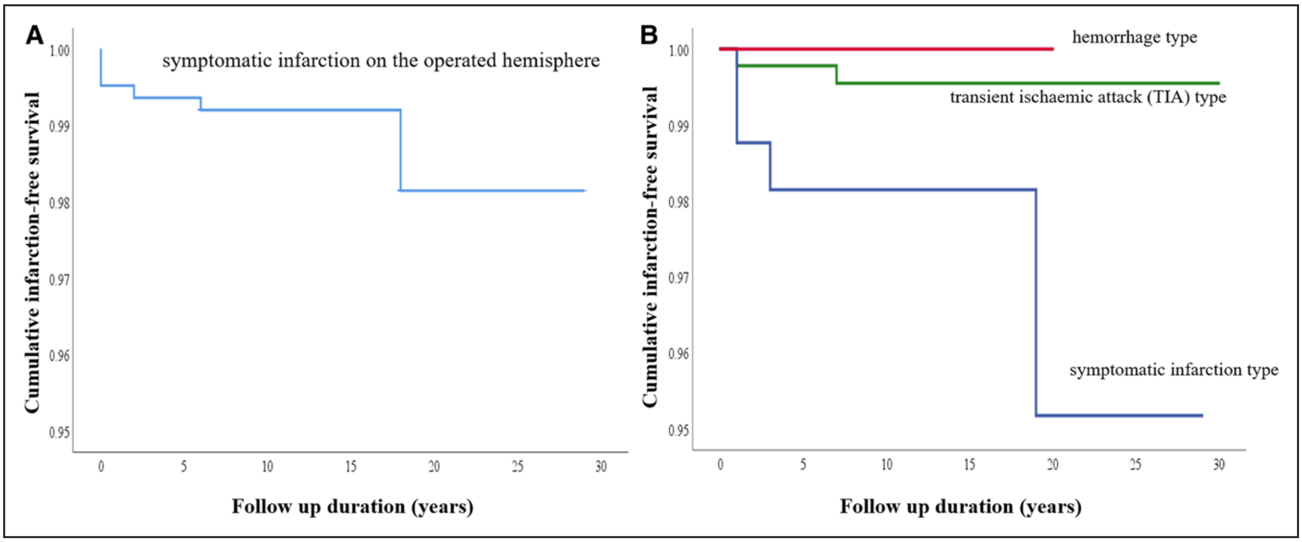

Figure 2. Kaplan-Meier survival curves of symptomatic infarction. **A**, Symptomatic infarction on the operated hemisphere. **B**, Symptomatic infarction on the operated hemisphere, according to the initial presentation, symptomatic infarction type (blue line), transient ischemic attack (TIA) type (green line), hemorrhage (red line, log-rank test, $P=0.959$).

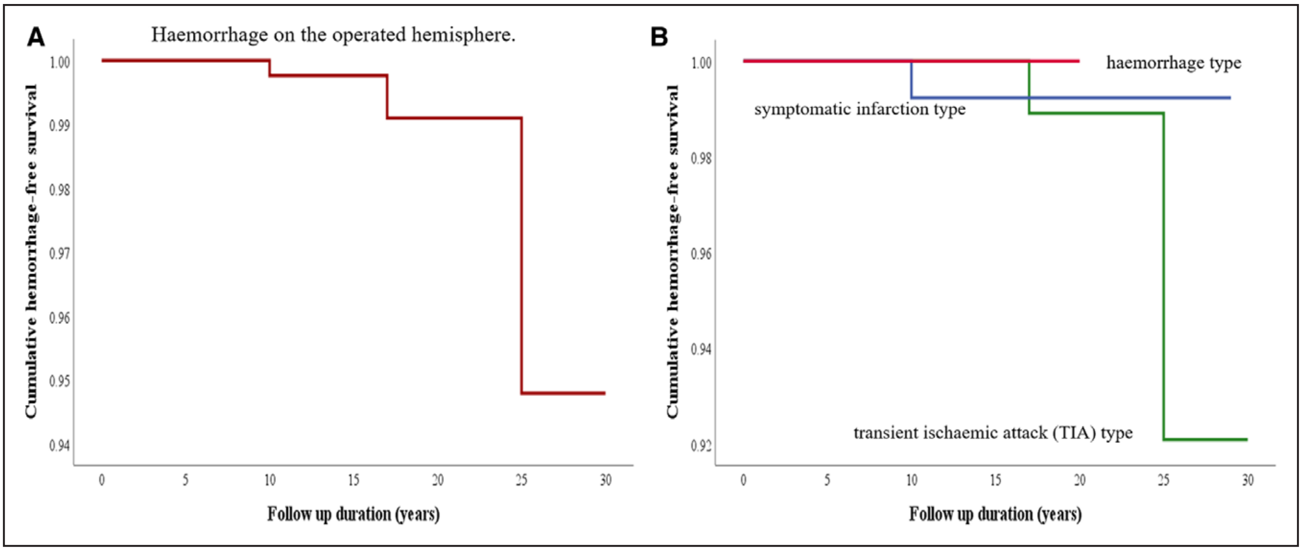

Figure 3. Kaplan-Meier survival curves of hemorrhage. **A**, Hemorrhage on the operated hemisphere. **B**, Hemorrhage according to the initial presentation, symptomatic infarction type (blue line), transient ischemic type (TIA; green line), hemorrhage (red line, log-rank test, *P*=0.959).

intracerebral hemorrhage was located in the splenium, classified as posterior hemorrhage.[14,15] On angiography, there were no demonstrable collaterals causing such as hemorrhage. The patient had been diagnosed with hypertension in her adolescence. The other intracerebral hemorrhage was in the frontal lobe and putamen, which was called anterior hemorrhage.[15] She does not have any comorbidity.

All late-onset hemorrhages occurred in patients who had not initially presented with hemorrhage at disease onset. Two presented with ischemic symptoms without symptomatic infarction; 1 had presented with large infarctions at the middle cerebral artery territory and anterior, posterior border zone.

During the entire follow-up period, overall newly developed stroke occurred in 20 cases (3.2%) including 17 cases of infarctions (8 silent, 6 symptomatic infarctions on the operated hemisphere, 3 contralateral side to operated hemisphere) and 3 hemorrhagic cases (0.47%).

The annual symptomatic stroke rate on the operated hemisphere was 0.12%. The annual symptomatic infarction and hemorrhage rates were 0.08% and 0.04% per person-year, respectively. The 10-year event-free survival rates for symptomatic infarction on the operated hemispheres were 99.2% (Figure 2). The 10-year event-free survival rates for symptomatic hemorrhage were 99.8%, higher than that of infarction, although it decreased to 99.2% for 20-year and 95.8% for 25-year rates (Figure 3).

Discussion

Overall Clinical Outcome

Most of our patients showed favorable functional outcome (95%). Postoperative KPS or LPS improved in 84% of patients compared with preoperative KPS or LPS. As children grow, scores can naturally improve. Therefore, the improvement of score is not purely the effect of surgery. However, considering the natural history of the conservatively treated group, it would have been difficult to catch up with functional status if they were exposed to repeated stroke without surgery.

Factors Associated With Unfavorable Outcome

Initial symptomatic strokes (OR, 4.9) were found to be the most powerful factors associated with adverse results, and age had no effect. Preoperative poor KPS or LPS may be the result of a symptomatic infarction before surgery. Moreover, it is known that the probability of surgical complications is high when preoperative infarction is present.[3] Therefore, current findings strongly suggest that early diagnosis and intervention before symptomatic infarction can reduce stroke rates and improve clinical results.

Among perioperative complications, surgery-related infarctions were the most common complications, and they were closely related to an unfavorable outcome. Therefore, careful attention should be paid to maintaining adequate hemodynamic status during the perioperative period.[16]

Stroke-Preventive Effect of Indirect Bypass Surgery

Whether direct or indirect, the benefits of surgery have been well established in pediatric MMD with ischemic symptoms. The natural history of untreated MMD varies from intermittent slow progression to rapid neurological and cognitive decline, with an overall mortality rate of 4.3% in the Japanese literature.[12] The long-term outcome of the disease is not good because this decline is inevitable in most patients, and symptoms progress up to 66% after 5 years of diagnosis.[17] In postoperative follow-up studies of pediatric MMD, recurrence of ischemic stroke was also rare; only a small proportion (0%–0.8%) of patients experienced late ischemic str oke.[4,5,7,8,12,13,18,19]

The incidence of late-onset ischemic stroke in our cohort was as low as 0.08% per year. After 6 months of surgery, there were few symptomatic infarctions on the operated hemisphere. After stabilization of indirect bypass, it appears that a patient can live without fear of infarction. The exceptionally late infarction on the operated territory, which occurred 2 years after surgery, was related to 14 days of high fever and dehydration. These results suggest that indirect bypass surgery might be an effective long-term safeguard against cerebral infarction in children with MMD.

However, if PCA stenosis progresses, a late-onset symptomatic infarction can occur.

In many cases, additional surgery for PCA territory (occipital artery encephaloduroarteriosynangiosis or occipital artery multiple burr hole) is required. Early detection of PCA insufficiency through periodic follow-up and active surgical prevention is important to prevent infarction. On the contrary, the surgical preventive effect for hemorrhage is controversial. There has been too little experience with hemorrhagic cases of pediatric MMD to form any conclusion regarding the efficacy of bypass surgery. Our group has previously reported the implicit effect of indirect surgery on hemorrhage.[20] However, another group insisted that indirect bypass was insufficient to prevent recurrence of hemorrhage based on their retrospective data.[21] In 2014, a Japan group published the results of the only randomized clinical trial to evaluate the preventive effect of direct bypass surgery for rebleeding in adult patients with MMD presenting with hemorrhage (JAM trial [Japan Adult Moyamoya]).[22] They concluded that bilateral direct surgery prevents rebleeding. Among our patients, recurrent bleeding was not observed in patients with hemorrhagic MMD after surgery. In addition, the incidence of new-onset hemorrhage was estimated at 0.04% per year after surgery. This is low compared with the hemorrhage rate in asymptomatic adult patients (2%–3% per year).[21,23] Indirect surgery in childhood is probably beneficial for primary prevention of hemorrhage. Nevertheless, the possibility of new-onset hemorrhage should not be overlooked. Sudden bleeding can occur even though the patient had been without symptoms for a considerable time. Some retrospective reports agree with our findings. New-onset hemorrhage might increase at 20 years of age or later, even >10 years after bypass surgery.[6,13,24]

The mechanism of new-onset hemorrhage remains obscure. In our cases, the patients had lived well with good performance status before hemorrhagic events occurred. There were no characteristic angiographic findings such as pseudoaneurysm and prominent collaterals. Hypertension may have contributed to new-onset hemorrhage. Even though they were in their 20s and 30s, 2 of the 3 patients were diagnosed with hypertension. Patients with MMD may have high blood pressure at a young age. As with one of our patients, 5% to 8% of moyamoya patients have renal artery stenosis.[25] Therefore, life-long regular follow-up and risk factor control is requested even for the patients with excellent long-term surgical outcome.

Limitations

This study has limitations as a retrospective study. It is a long-term follow-up study, but it might be insufficient when we consider the patient's overall life expectancy. More long-term tracking data need to be accumulated to clarify the clinical course of surgically treated children with MMD.

Conclusions

Our long-term survey revealed that indirect bypass surgery for children with MMD could achieve favorable clinical outcomes. Surgical management is expected to provide excellent protection for both ischemic and hemorrhagic stroke. Nevertheless, a few new-onset hemorrhagic events and ischemic events due to PCA progression were observed a considerable time after the initial surgery. Therefore, careful and long traces should be made for the remainder of life, even though the course has been good for several years after surgery.

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Disclosures

None.

References

1. Suzuki J, Kodama N. Moyamoya disease–a review. *Stroke*. 1983;14:104–109. doi: 10.1161/01.str.14.1.104
2. Kim T, Oh CW, Bang JS, Kim JE, Cho WS. Moyamoya disease: treatment and outcomes. *J Stroke*. 2016;18:21–30. doi: 10.5853/jos.2015.01739
3. Kim SK, Cho BK, Phi JH, Lee JY, Chae JH, Kim KJ, et al. Pediatric moyamoya disease: an analysis of 410 consecutive cases. *Ann Neurol*. 2010;68:92–101. doi: 10.1002/ana.21981
4. Bao XY, Duan L, Yang WZ, Li DS, Sun WJ, Zhang ZS, et al. Clinical features, surgical treatment, and long-term outcome in pediatric patients with moyamoya disease in China. *Cerebrovasc Dis*. 2015;39:75–81. doi: 10.1159/000369524
5. Karasawa J, Touho H, Ohnishi H, Miyamoto S, Kikuchi H. Long-term follow-up study after extracranial-intracranial bypass surgery for anterior circulation ischemia in childhood moyamoya disease. *J Neurosurg*. 1992;77:84–89. doi: 10.3171/jns.1992.77.1.0084
6. Mukawa M, Nariai T, Matsushima Y, Tanaka Y, Inaji M, Maehara T, et al. Long-term follow-up of surgically treated juvenile patients with moyamoya disease. *J Neurosurg Pediatr*. 2012;10:451–456. doi: 10.3171/2012.8.PEDS11539
7. Goda M, Isono M, Ishii K, Kamida T, Abe T, Kobayashi H. Long-term effects of indirect bypass surgery on collateral vessel formation in pediatric moyamoya disease. *J Neurosurg*. 2004;100(2 suppl Pediatrics):156–162. doi: 10.3171/ped.2004.100.2.0156
8. Imai H, Miyawaki S, Ono H, Nakatomi H, Yoshimoto Y, Saito N. The importance of encephalo-myo-synangiosis in surgical revascularization strategies for moyamoya disease in children and adults. *World Neurosurg*. 2015;83:691–699. doi: 10.1016/j.wneu.2015.01.016
9. Kim SK, Wang KC, Kim IO, Lee DS, Cho BK. Combined encephaloduroarteriosynangiosis and bifrontal encephalogaleo(periosteal)synangiosis in pediatric moyamoya disease. *Neurosurgery*. 2002;50:88–96. doi: 10.1097/00006123-200201000-00016
10. Matsushima Y, Inaba Y. Moyamoya disease in children and its surgical treatment. Introduction of a new surgical procedure and its follow-up angiograms. *Childs Brain*. 1984;11:155–170.
11. Kawamoto H, Kiya K, Mizoue T, Ohbayashi N. A modified burr-hole method 'galeoduroencephalosynangiosis' in a young child with moyamoya disease. A preliminary report and surgical technique. *Pediatr Neurosurg*. 2000;32:272–275. doi: 10.1159/000028950
12. Scott RM, Smith JL, Robertson RL, Madsen JR, Soriano SG, Rockoff MA. Long-term outcome in children with moyamoya syndrome after cranial revascularization by pial synangiosis. *J Neurosurg*. 2004;100(2 suppl Pediatrics):142–149. doi: 10.3171/ped.2004.100.2.0142
13. Funaki T, Takahashi JC, Takagi Y, Yoshida K, Araki Y, Kikuchi T, et al. Incidence of late cerebrovascular events after direct bypass among children with moyamoya disease: a descriptive longitudinal study at a single center. *Acta Neurochir (Wien)*. 2014;156:551–559; discussion 559. doi: 10.1007/s00701-013-1975-7
14. Funaki T, Takahashi JC, Houkin K, Kuroda S, Takeuchi S, Fujimura M, et al. Angiographic features of hemorrhagic moyamoya disease with

high recurrence risk: a supplementary analysis of the Japan Adult Moyamoya trial. *J Neurosurg*. 2018;128:777–784. doi: 10.3171/2016.11.JNS161650
15. Fujimura M, Funaki T, Houkin K, Takahashi JC, Kuroda S, Tomata Y, et al. Intrinsic development of choroidal and thalamic collaterals in hemorrhagic-onset moyamoya disease: case-control study of the Japan Adult Moyamoya trial. *J Neurosurg*. 2019;130:1453–1459.
16. Wang KC, Phi JH, Lee JY, Kim SK, Cho BK. Indirect revascularization surgery for moyamoya disease in children and its special considerations. *Korean J Pediatr*. 2012;55:408–413. doi: 10.3345/kjp.2012.55.11.408
17. Ibrahimi DM, Tamargo RJ, Ahn ES. Moyamoya disease in children. *Childs Nerv Syst*. 2010;26:1297–1308. doi: 10.1007/s00381-010-1209-8
18. Kuroda S, Houkin K, Ishikawa T, Nakayama N, Iwasaki Y. Novel bypass surgery for moyamoya disease using pericranial flap: its impacts on cerebral hemodynamics and long-term outcome. *Neurosurgery*. 2010;66:1093–1101; discussion 1101. doi: 10.1227/01.NEU.0000369606.00861.91
19. Rashad S, Fujimura M, Niizuma K, Endo H, Tominaga T. Long-term follow-up of pediatric moyamoya disease treated by combined direct-indirect revascularization surgery: single institute experience with surgical and perioperative management. *Neurosurg Rev*. 2016;39:615–623. doi: 10.1007/s10143-016-0734-7
20. Ahn JH, Wang KC, Phi JH, Lee JY, Cho BK, Kim IO, et al. Hemorrhagic moyamoya disease in children: clinical features and surgical outcome. *Childs Nerv Syst*. 2012;28:237–245. doi: 10.1007/s00381-011-1535-5
21. Kobayashi E, Saeki N, Oishi H, Hirai S, Yamaura A. Long-term natural history of hemorrhagic moyamoya disease in 42 patients. *J Neurosurg*. 2000;93:976–980. doi: 10.3171/jns.2000.93.6.0976
22. Miyamoto S, Yoshimoto T, Hashimoto N, Okada Y, Tsuji I, Tominaga T, et al; JAM Trial Investigators. Effects of extracranial-intracranial bypass for patients with hemorrhagic moyamoya disease: results of the Japan Adult Moyamoya trial. *Stroke*. 2014;45:1415–1421. doi: 10.1161/STROKEAHA.113.004386
23. Yoshida Y, Yoshimoto T, Shirane R, Sakurai Y. Clinical course, surgical management, and long-term outcome of moyamoya patients with rebleeding after an episode of intracerebral hemorrhage: an extensive follow-Up study. *Stroke*. 1999;30:2272–2276. doi: 10.1161/01.str.30.11.2272
24. Funaki T, Takahashi JC, Miyamoto S. Late cerebrovascular events and social outcome after adolescence: long-term outcome of pediatric moyamoya disease. *Neurol Med Chir (Tokyo)*. 2018;58:240–246. doi: 10.2176/nmc.ra.2018-0026
25. Togao O, Mihara F, Yoshiura T, Tanaka A, Kuwabara Y, Morioka T, et al. Prevalence of stenoocclusive lesions in the renal and abdominal arteries in moyamoya disease. *AJR Am J Roentgenol*. 2004;183:119–122. doi: 10.2214/ajr.183.1.1830119