Neurosurgical Management and Outcomes of Cerebrovascular Disease in Pediatric Patients with Heart Disease

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Abstract

Antithrombotic treatment has substantial risks, even in pediatric patients. We retrospectively evaluated the management and outcomes of consecutive pediatric patients who underwent neurosurgical treatment for cerebrovascular disease with cardiovascular disease between 1998 and 2017. Patients were divided into patients with comorbid cardiovascular disease (group I); and patients with cardiovascular disease as a primary disease of intracranial complication, without (group IIa) or with (group IIb) extracorporeal circulations. Postoperative resumption of antithrombotic agents was generally initiated within 48 h. Our study included 26 patients; five were categorized as group I, 15 as group IIa, and six as group IIb. All intracranial diseases in groups IIa and IIb were exclusively hemorrhagic. Preoperative anticoagulation therapy was used in one patient (20%) in group I, 13 patients (86.7%) in group IIa, and six patients (100%) in group IIb. Postoperative intracranial hemorrhagic events were observed in one patient (20%) in group I, three patients (20%) in group IIa, and four patients (66.7%) in group IIb. Re-operations were conducted in two (13.3%) and three patients (50%) in groups IIa and IIb, respectively. Death occurred in five (33.3%) and four patients (66.7%) in groups IIa and IIb, respectively. The remaining two patients in group IIb returned to candidate status for implantation. Emergent surgery for patients with intracranial hemorrhage associated with cardiovascular disease has a high risk of postoperative hemorrhagic events and high rate of re-operations with poor vital outcomes, especially in patients with extracorporeal circulations. We should consider maximum neurosurgical treatment achievable with optimal management of antithrombotic treatment.

Key words: cerebrovascular diseases, pediatrics, heart diseases, neurosurgery

Introduction

Intracranial hemorrhagic complications occur each year in 0.6% of Japanese adults who are undergoing antithrombotic treatment using either warfarin or aspirin; this incidence doubles in patients undergoing treatment with multiple antithrombotic agents.[1] In children, a few studies have reported that the incidence of intracranial hemorrhagic complication with anticoagulation ranges from 0.6 to 1.4% per year.[2–4] Thus, there is substantial risk during antithrombotic treatment in children, who usually do not exhibit atherosclerotic changes.

Child heart disease presents as an array of entities, such as congenital heart disease, Kawasaki disease, arrhythmia, and cardiomyopathy. Importantly, all of these manifestations may be treated with antithrombotic therapy, especially in patients with congenital heart disease. As there is a wide variation in patient age, body weight, cardiopulmonary deficit type, and hemodynamic status, no uniform medical management is included in any current guidelines.[5] However, anticoagulation is essential when extracorporeal circulation is conducted. Left ventricular assist devices (LVAD), comprising a surgically implanted mechanical pump that is attached to the heart, have evolved into a standard for patients, both as a bridge to cardiac transplantation and as a destination therapy.[6] Extracorporeal membrane oxygenation (ECMO) is a form of cardiopulmonary life support where blood is drained from the vascular system, circulated outside the body by

means of a mechanical pump, and then reinfused into the circulation.[7] ECMO was initially used for postoperative support in patients following cardiac surgery; later, it began to serve as a bridge to cardiac transplant, through long-term extracorporeal support that focused on the function of oxygenation.

A serious challenge is involved in the management of hemostasis and thromboembolic events in patients who have experienced neurosurgically treated hemorrhagic events; unfortunately, there is no apparent consensus algorithm. In this study, we aimed to evaluate the management and outcomes of neurosurgical treatment for cerebrovascular disease in pediatric patients with concurrent cardiovascular disease.

Materials and Methods

Study population

This was a single-center, retrospective cohort study. Patients with cardiovascular disease were enrolled from among consecutive patients under 18 years old who underwent neurosurgical treatment in our institute with a diagnosis of cerebrovascular disease between January 1998 and April 2017. Only the first neurosurgical procedures for each patient were included. All endovascular procedures, such as mechanical thrombectomy for acute cardiogenic embolism, were outside the scope of this study's investigation. Intracranial non-cerebrovascular diseases, such as brain abscess, brain tumors, or congenital anomalies, were excluded from this study. Intracranial hemorrhagic disease was diagnosed using computed tomography (CT) imaging.

Patients were divided into three groups; group I comprised patients with cardiovascular disease that appeared to exist independently from the cerebrovascular disease (comorbidity). Group II (composed of two subgroups) comprised patients with cardiovascular disease that appeared to be associated with occurrence or development of intracranial disease (complication), without extracorporeal circulations (group IIa) or with extracorporeal circulations (group IIb).

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Outcomes and follow-up

The patients' baseline characteristics were obtained through review of medical records. All neurosurgical procedures and peri-surgical management of antithrombotic agents were recorded. Postoperative intracranial events were defined as any intracranial hemorrhagic or ischemic lesion that was confirmed by CT imaging within 1 month postoperatively. Re-operation was defined as unexpected neurosurgical procedures for postoperative intracranial events. A postoperative cardiac event was defined as any cardiac operation, including exchange of extracorporeal circulations, or cardiopulmonary resuscitation. Any deaths were recorded at the time of the last follow-up. The follow-up period began on the day of the first surgery.

Therapeutic procedures

After confirmation of intracranial hemorrhagic events on CT scan, general efforts were initially conducted to stabilize the patients, including optimizing respiratory effort, controlling systemic hypertension, preventing epileptic seizures, and medically managing increased intracranial pressure.[8] Any ongoing antithrombotic treatments were evaluated to determine whether cessation was feasible. For patients who were previously prescribed warfarin, medical reversal was considered using prothrombin complex concentrate (PCC), Vitamin K, or fresh frozen plasma (FFP). For patients who were previously prescribed heparin, protamine was used to normalize their activated partial thromboplastin time (APTT). Under local or general anesthesia, burr hole surgery or craniotomy was performed, according to each patient's intracranial and/or general conditions. Intraoperatively, FFP or platelet concentrate was administered as required. Postoperative resumption of antithrombotic agents was generally begun within 48 h if hemostasis was confirmed by CT.

Statistical analysis

Continuous variables are presented as mean ± standard deviation. Categorical data are reported as frequencies (percentages). Categorical variables were compared by Fisher's exact test. Statistical tests for trends were performed for study groups that were segregated using age, the serum platelet count, and C-reactive protein (CRP) values. Statistical significance was defined as a *P*-value < 0.05. Analyses were performed with the IBM SPSS Statistics (version 21.0; IBM Corp., Armonk, NY).

Results

From January 1998 to April 2017, 431 neurosurgical procedures were performed in our institute for 233 patients who were <18 years old. Among them, 30 patients (12.9%) exhibited cardiovascular disease. Four patients were excluded because of brain abscess (*n* = 2), brain tumor (*n* = 1), or congenital anomaly (*n* = 1). Finally, 26 patients (11.2%) were included

in this study. Five patients were categorized as group I, 15 patients as group IIa, and six patients as group IIb (Fig. 1).

The patients' baseline characteristics are presented in Table 1. The mean age was 8.8 ± 3.2 years in group I, 5.8 ± 7.3 years in group IIa, and 2.8 ± 6.4 years in group IIb (*P* for trend = 0.11). Categorized age distribution is presented in Fig. 2. There were four women (80%) in group I, 10 (66.7%) in group IIa, and three (50%) in group IIb (*P* = 0.57). All patients in groups I and IIa had been treated for congenital heart disease. Three patients in group IIb had been treated for dilated cardiomyopathy using LVAD, whereas the remaining three had been treated postoperatively for congenital heart disease using ECMO. Two patients in group IIa had been diagnosed as having infective endocarditis before intracranial events.

Cerebrovascular diseases are listed in Table 2. In group I, all neurosurgical procedures were elective surgeries with craniotomy for steno-occlusive disease, unruptured aneurysm, or unruptured arteriovenous malformation. All intracranial events in group IIa and IIb were hemorrhagic disease. Intracerebral hemorrhage (ICH) occurred in three patients (20%) in group IIa and two (33%) in group IIb. Neurosurgical procedures with craniotomy were conducted in seven patients (47%) in group IIa and three (50%) in group IIb. No patient with cerebral infarction underwent decompressive craniotomy in this study cohort.

Management of antithrombotic treatment

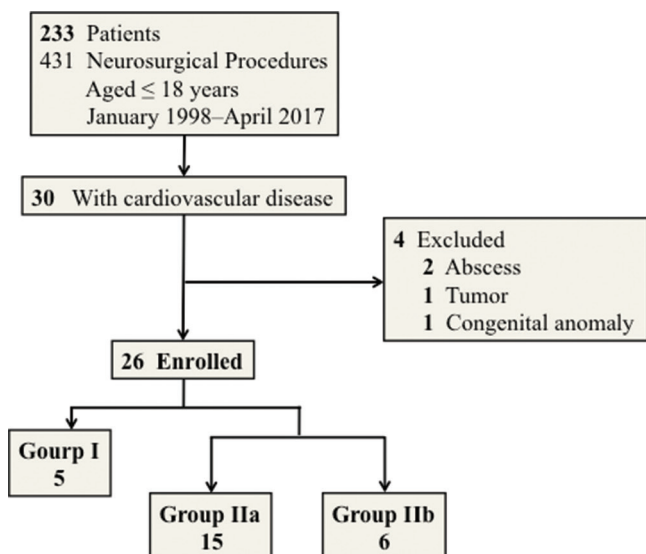Preoperatively, one patient (20%) underwent anticoagulation therapy in group I; 13 patients

Fig. 1 Participant flow chart.

Table 1 Baseline and cardiac characteristics of the patients

	Group I N = 5	Group IIa N = 15	Group IIb N = 6
Age (y)	8.8 ± 3.2	5.8 ± 7.3	2.8 ± 6.4
Female sex	4 (80%)	10 (66.7%)	3 (50%)
Heart disease*			
PDA	2	0	0
ASD	2	0	0
DORV	0	5	0
TOF	0	3	0
DCM	0	0	3
Others	1	7	3
Type of extracorporeal circulation			
LVAD	0	0	3
ECMO	0	0	3
Anticoagulation therapy	1 (20%)	13 (86.7%)	6 (100%)
Anticoagulation agent			
Heparin	0	6	5
Warfarin	1	6	1
Nafamostat	0	1	2
Antiplatelet therapy	3 (60%)	0	1 (16.7%)
Multiple antithrombotic agent	1 (20%)	1 (6.7%)	3 (50%)

ASD: atrial septal defect, DORV: double-outlet right ventricle, DCM: dilated cardiomyopathy, ECMO: extracorporeal membrane oxygenation, LVAD: left ventricular assist device, PDA: patent ductus arteriosus, TOF: tetralogy of Fallot. *Note that all the patients with congenital heart disease exhibited multiple anomalies; the heart diseases listed in this table were representative. "Others" contains common atrio-ventricular canal in group I, mitral valve regurgitation, complete transposition of the great arteries, ventricular septal defect, atrioventricular septal defect, Williams syndrome, and corrected transposition of great arteries in group IIa, and aortic bifurcation malformations, scimitar syndrome, and complete transposition of the great arteries in group IIb.

(86.7%) in group IIa and six patients (100%) in group IIb underwent anticoagulation therapy. Antiplatelet therapy was maintained in three patients (60%) in group I and one patient (16.7%) in group IIb. Multiple antithrombotic agents were used in one patient (20%) in group I, one patient (6.7%) in group IIa, and three patients (50%) in group IIb (Table 1).
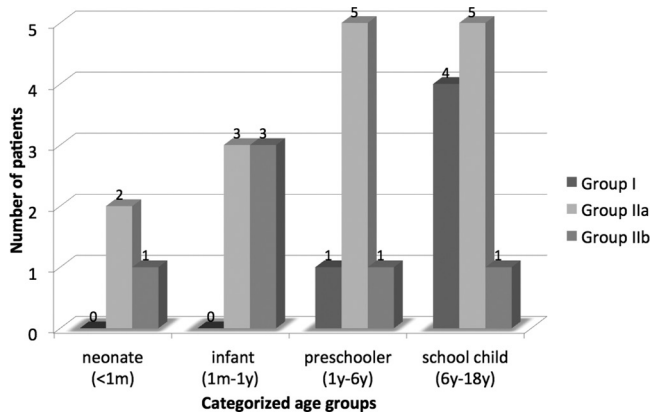
Fig. 2 Bar graphs showing the age distribution in group I, group IIa, and group IIb. Children were categorized as neonate (≤28 d), infant (≤1 y), preschooler (≤6 y), and school child (≤18 y).

All antithrombotic treatment was discontinued until the day of surgery in group I. Anticoagulation was medically reversed preoperatively in six of 13 patients (46.2%) in group IIa and four of six patients (66.7%) in group IIb. In the post-neurosurgical period, three of four patients in group I restarted antiplatelet treatment with aspirin. In groups IIa and IIb, nine of 13 (69.2%) and five of six (83.3%) patients, respectively, restarted anticoagulation with heparin, warfarin, or nafamostat. Four of 10 patients who underwent burr hole surgery and one of six patients who underwent craniotomy restarted anticoagulation immediately postoperatively. Overall, three of four patients (75%) with preoperative antiplatelet treatment and 13 of 20 patients (65%) with preoperative anticoagulation restarted antithrombotic treatment. Antithrombotic treatment by anticoagulant was restarted within 48 hours postoperatively in seven of nine patients (77.8%) in group IIa and in all five patients in group IIb (Table 2).

Neurosurgical results and outcomes

Table 3 shows the neurosurgical results. Postoperative intracranial hemorrhagic events were observed in one patient (20%) in group I, three patients (20%) in group IIa, and four patients (66.7%) in group IIb. An intracranial ischemic event was only observed in one patient (6.7%) in group IIa. No cardiac events were observed. Re-operations were conducted in two patients (13.3%) in group IIa and three patients (50%) in group IIb. Among patients who restarted their anticoagulation within 48 h postoperatively, three of 12 patients (25%), all in group IIb, experienced intracranial hemorrhagic events; two of them underwent re-operation.

The mean follow-up periods were 39.4 ± 29.3 months in group I, 83.1 ± 84.3 months in group IIa, and 4.6 ± 7.3 months in group IIb; during the follow-up period, death occurred in five patients (33.3%) in group IIa and four patients (66.7%) in group IIb. Cardiovascular disease was considered the main cause of death in four patients in group IIa and three patients in group IIb. Two surviving patients in group IIb who underwent LVAD returned to candidate status for implantation; one of these patients underwent implantation abroad, 8 months after neurosurgical procedures.

Laboratory data analysis

In patients undergoing anticoagulation with heparin, the pre-reversal mean APTT was 69.5 ± 27.5 (range 49–110) and post-reversal mean APTT was 45.8 ± 11.1 (range 37–65). In patients with warfarin, pre-reversal mean international normalized ratio (INR) was 4.2 ± 3.4 (range 1.9–8.1), and post-reversal mean INR was 1.5 ± 0.5 (range 1.1–2.1). Comparing pre-neurosurgical laboratory data of all patients, the mean CRP level was higher (group I: 0.21 ± 0.19 mg/dl vs. group IIa: 3.41 ± 6.1 mg/dl vs. group IIb: 10.8 ± 7.3 mg/dl, P for trend = 0.006) and mean platelet count was lower (group I: 27.2 ± 11.3 × 10^4/µl vs. group IIa: 23.5 ± 14.4 × 10^4/µl vs. group IIb: 12.9 ± 7.3 × 10^4/µl, P for trend = 0.06) in patients of group IIb than in those of the other groups.

Discussion

This study aimed to evaluate the management and outcomes of neurosurgical treatment for cerebrovascular disease in pediatric patients with cardiovascular disease. This study demonstrated that among 233 neurosurgically treated pediatric patients over 19 years, (1) the rate of cardiovascular disease in patients with concurrent cerebrovascular disease was 11%; (2) in patients with cardiovascular disease as a comorbidity (group I), the results and outcomes of neurosurgical procedures were favorable; (3) in patients with cardiovascular disease as a primary disease associated with complications of intracranial hemorrhagic events (group IIa and IIb), most patients received anticoagulation therapy—74% of them restarted anticoagulation therapy within 48 h postoperatively; (4) in patients with extracorporeal circulations (group IIb), the rates of postsurgical intracranial hemorrhagic complication and re-operation were both high (67 and 50%, respectively), and the vital prognosis at the last follow-up was poor; and (5) in contrast, two surviving patients in group IIb returned to candidate status for implantation.

Table 2 Neurosurgical and antithrombotic therapy management

	Group I N = 5	Group IIa N = 15	Group IIb N = 6
Cerebrovascular disease			
Comorbidity			
Middle cerebral artery stenosis	2	0	0
Moyamoya disease	1	0	0
Unruptured aneurysm	1	0	0
Arteriovenous malformation	1	0	0
Complication			
Chronic subdural hematoma	0	5	1
Acute subdural hematoma	0	3	2
Intracerebral hemorrhage	0	3	2
Intraventricular hemorrhage	0	2	0
Acute epidural hematoma	0	1	1
Subarachnoid hemorrhage	0	1	0
Neurosurgical procedure			
Craniotomy	5 (100%)	7 (46.7%)	3 (50%)
Burr hole surgery	0	8 (53.3%)	3 (50%)
Medical reverse	0	6/13 (46.2%)	4/6 (66.7%)
Medical reverse agent			
PCC	0	3	0
Protamine	0	0	3
Vitamin K	0	2	0
FFP	0	2	1
Resume of antithrombotic treatment	3/4 (75%)	9/13 (69.2%)	5/6 (83.3%)
Restarted antithrombotic agent			
Aspirin	3	0	0
Heparin	0	6	2
Warfarin	0	2	0
Nafamostat	0	1	2
Antithrombotic therapy restarting time (d)	6.3 ± 6.7	1.8 ± 1.6	0.8 ± 1.1
Antithrombotic restarted ≤48 h postoperatively	0	7/9 (77.8%)	5/5 (100%)

FFP: fresh frozen plasma, PCC: prothrombin complex concentrate.

Table 3 Neurosurgical results and outcomes

	Group I N = 5	Group IIa N = 15	Group IIb N = 6
Postoperative events			
Intracranial hemorrhage	1 (20%)	3 (20%)	4 (66.7%)
Intracranial ischemia	0	1 (6.7%)	0
Cardiac event	0	0	0
Re-operation	0	2 (13.3%)	3 (50%)
Mean follow-up period (m)	39.4 ± 29.3	83.1 ± 84.3	4.6 ± 7.3
Final mRS score 6	0	5 (33.3%)	4 (66.7%)
Main cause of death			
Cardiac condition	0	4	3
Neurological condition	0	1	1

mRS: modified Rankin scale.

In this study, all intracranial diseases in groups IIa and IIb were exclusively hemorrhagic. No patient with cerebral infarction due to cardio-embolism underwent decompressive craniotomy. It is difficult to determine the incidence of hemorrhagic transformation after cerebral infarction among patients with ICH. However, cerebral ischemic complications without hemorrhagic change in pediatric patients with cardiovascular disease might not have been malignant enough to require neurosurgical intervention in this study population. Further investigation is needed to examine this assumption with data of patients with cerebral infarction who were conservatively managed.

In addition to the wide variety of hemodynamic cardiovascular statuses, low bodyweight and functionally undeveloped organs make it difficult to establish a uniform treatment strategy for child heart disease, especially in cases of congenital heart disease. There is

neither a consensus guideline for antithrombotic treatment for congenital heart disease,[5] nor a management guideline concerning peri-neurosurgical antithrombotic management for intracranial hemorrhagic complications. Kuramatsu et al.[9] reported that among patients with oral anticoagulant (OAC)-associated ICH, medical reversal of anticoagulation and lowering of systolic blood pressure for 4 h were associated with lower rates of hematoma enlargement. The occurrence of hematoma enlargement is an established risk factor for poor outcome in both primary and OAC-associated ICHs.[10–12] Moreover, resumption of anticoagulant therapy was associated with lower risk of ischemic events without risk of increased bleeding complications.[9] In the Kurumatsu report, oral anticoagulation was restarted in 23.9% of cases with median time until OAC resumption of 31 days (interquartile range, 18–65). In European Stroke Organization guidelines, there are no firm recommendations regarding whether and when to resume antithrombotic drugs after ICH.[13] In American Heart Association/American Stroke Association guidelines, avoidance of OAC for at least 4 weeks might decrease the risk of ICH recurrence in patients without mechanical heart valves.[14] Romualdi et al.[15] systematically reviewed six observational cohorts with 120 cases regarding OAC therapy in patients with mechanical heart valves and ICH. All were adult cases including 20 neurosurgical procedures; however, details of the surgeries were not shown. Anticoagulation was restarted within a broad range of time (2 days to 3 months); overall incidences of cerebral ischemic and hemorrhagic events were 0.8 and 3.3%, respectively. Compared with those results, the current results revealed more surgical complications. However, the reports reviewed by Romualdi et al.[15] primarily utilized conservative treatments. Based on the report by Yasaka et al.[16] that an INR value < 2.0 at admission (or for 24 h after immediate INR correction with PCC) prevented ICH enlargement, hemostasis may be achieved after 24 h even in patients undergoing anticoagulation therapy. Our strategy, which involves resuming anticoagulation at 48 h in cases of high thromboembolic risk, is thought to have a double-fold safety margin. In this study, among patients restarting anticoagulation within 48 h postoperatively, no intracranial hemorrhagic event was observed in group IIa patients, whereas three of five group IIb patients experienced ICH. Although no cardiac events and a low ischemic event rate were confirmed in our current protocol, the optimal timing and therapeutic agent for patients with extracorporeal circulation should be examined in a future study.

There is a paucity of literature regarding neurological complications following LVAD implantation in

pediatric patients.[17–19] Mayer et al.[20] reported that the overall incidence of ICH was 6.5% of a total cohort of 46 patients, with two of three patients who presented with ICH requiring operative treatment. One of two surgically treated patients had recurrent subdural hematoma; ultimately, two patients died. The rates of neurological complications and, in particular, hemorrhage, were similar in children when compared with that in adults (2.5–10%). Moreover, Mayer et al.[20] concluded that although the surgical risk is substantial, neurosurgical evacuation of hemorrhage plays an important life-saving role that can yield successful and acceptable outcomes. In our current study, two patients returned to implantation status. Owing to the greater brain plasticity in children,[21] we should consider the maximum neurosurgical treatment possible with optimal management of antithrombotic treatment. Further studies are also needed to clarify appropriate patient selection in such a limited condition.

In laboratory data, mean APTT and INR were effectively corrected to a normal range using reversal agents. Kuramatsu et al.[9] noted a significant relationship between timing (within 4 h after admission) and extent of INR reversal (below 1.3), associated with frequency and relative risk of hematoma enlargement. In this study, we did not assess the relationship between preoperative and postoperative laboratory data and intracranial events because there were biases in the timing of examinations, as well as a wide variation in the continued usage of blood derivatives intraoperatively and postoperatively. The evidence of a low pre-surgical platelet count and high pre-surgical CRP level in group IIb may have resulted from chronic consumption or inflammation related to the extracorporeal circulation, and contributed to its hemorrhagic tendency.

This study has several limitations. First, selection bias may exist because of the nonrandom choice of treatment and the retrospective nature of the study. The long duration of the study period may have also influenced selection bias. However, a wide variation in patient age, bodyweight, cardiopulmonary deficit type, and hemodynamic status makes it difficult to conduct a randomized, controlled study for child heart disease. Second, the study population was small, and data on conservatively treated patients were absent. A further prospective, multicenter cohort study will resolve such issues.

In conclusion, elective surgery for pediatric cerebrovascular disease patients, with cardiovascular disease as a comorbidity, seems relatively safe with favorable outcomes. Conversely, emergent surgery for patients with intracranial hemorrhagic disease, associated with cardiovascular disease, has a high risk of postoperative intracranial hemorrhagic

events and a high rate of re-operations with poor vital outcomes, especially in patients with extracorporeal circulations. Although there are difficulties in perioperative management, owing to the greater brain plasticity in children, we should consider the maximum neurosurgical treatment with optimal management of antithrombotic treatment.

Conflicts of Interest Disclosure

The authors declare that they have no conflicts of interest.

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