

Anticoagulation in Childhood-Onset Arterial Ischemic Stroke With Nonmoyamoya Arteriopathy

Findings From the Colorado and German (COAG) Collaboration

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Background and Purpose—Childhood arterial ischemic stroke treatment guidelines recommend extended anticoagulation in cardioembolism and dissection. We sought to investigate the safety of extended anticoagulation in childhood arterial ischemic stroke with nonmoyamoya arteriopathy, for which the risk of recurrent stroke is high.

Methods—Thirty-seven patients with childhood-onset arterial ischemic stroke with acute arteriopathy (excluding moyamoya) were diagnosed between 1999 and 2007 and treated with anticoagulation for at least 4 weeks. Patients were followed in hospital-based cohort studies at 2 centers and systematically assessed for bleeding episodes and recurrent events.

Results—Over a cumulative anticoagulation duration of 1329 patient-months, there were no major bleeding episodes and 2 clinically relevant bleeding episodes. Cumulative probability of recurrent arterial ischemic stroke at 1 year was 14%.

Conclusions—Anticoagulation can be used safely for secondary arterial ischemic stroke prevention in children with acute nonmoyamoya arteriopathy. Anticoagulation is worthy of evaluation in future randomized, controlled treatment trials in this disease. (*Stroke*. 2009;40:2869-2871.)

Key Words: anticoagulation ■ arteriopathy ■ childhood stroke

Arterial ischemic stroke (AIS) occurs in one to 2/100 000 children per year with acute¹ and long-term^{2,3} neurological sequelae in approximately 70%. Recurrent stroke is a major cause of morbidity, occurring in 15% within 1 year postevent.³ Risk of recurrent AIS is markedly increased among childhood patients with AIS with arteriopathy, a common subtype of childhood AIS involving cerebral/cervical arterial stenosis.³ This includes patients with moyamoya arteriopathy, in whom risk of brain hemorrhage is also elevated.

Currently, anticoagulation is recommended for secondary prevention of childhood AIS in cardioembolism or dissection, in which the risk of recurrence is increased.⁴ Given the high prevalence of thrombophilia in childhood AIS,⁵ children with arteriopathy might also be candidates for anticoagulation if bleeding risk were shown to be low. The objective of the present work, therefore, was to investigate bleeding complications and recurrent AIS in children anticoagulated for AIS with nonmoyamoya arteriopathy.

Materials and Methods

Data on demographic characteristics, risk factors, neuroimaging findings, antithrombotic treatments, clinically significant bleeding

episodes, and recurrent cerebrovascular events were systematically collected in children with acute AIS diagnosed between January 1, 1999, and December 31, 2007, at The Children's Hospital, Colorado and University Children's Hospital, Münster, Germany. In this combined retrospective-prospective hospital-based cohort study, all patients with AIS were followed prospectively from stroke onset with the exception of 5 patients diagnosed with acute AIS before February 28, 2006, in Colorado (for whom data were retrospectively collected before this date and prospectively thereafter). Written informed consent was uniformly obtained for study participation. Inclusion criteria were: (1) age 29 days through 18 years; (2) sudden-onset focal neurological deficit; (3) acute neuroimaging (CT, MRI) demonstrating recent ischemia/infarct of arterial distribution; (4) cerebral/cervical arterial stenosis demonstrated on MR angiography using a 1.5- or 3-T magnet, CT angiography, or conventional angiography; and (5) treatment with anticoagulation for a minimum duration of 4 weeks. Patients with moyamoya, as previously defined,⁶ were excluded.

Neurovascular imaging findings were characterized at each center into one of 4 arteriopathy subtypes (Table 1) confirmed by an independent rater. Anticoagulant therapy used one of several regimens (Table 2). All decisions regarding type, intensity, and duration of anticoagulation were made on clinical grounds and were not protocol-driven. Typical reasons for administration of anticoagulation in arteriopathy included dissection, thrombophilia, concomitant cardioembolism, or development of recurrent AIS/transient ischemic attack on antiplatelet therapy.

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Table 1. Age, Stroke Characteristics, Arteriopathy Subtypes, and Thrombophilia Findings

	Prophylactic Group	Therapeutic Group	Total
N	21	16	37
Age at diagnosis (median and range)	5 years (7 months to 14 years)	6 years (6 weeks to 17 years)	5 years (6 weeks to 17 years)
Stroke characteristics			
Intracranial hemorrhage at presentation	0 (0%)	2 (13%)	2 (5%)
Anterior circulation only	14 (67%)	13 (81%)	27 (73%)
Posterior circulation only	3 (14%)	2 (13%)	5 (14%)
Anterior and posterior	4 (19%)	1 (6%)	5 (14%)
Arteriopathy subtypes			
Intracranial large vessel stenosis	13 (62%)	8 (50%)	21 (57%)
Dissection	6 (29%)	5 (31%)	11 (30%)
Vasculitis	1 (5%)	2 (13%)	3 (8%)
Other arterial abnormality	1 (5%)	1 (6%)	2 (5%)
Thrombophilia findings*			
Mild thrombophilia only	14 (67%)	6 (38%)	20 (54%)
Potent thrombophilia†	0 (0%)	7 (44%)	7 (19%)
Total (any thrombophilia)	14 (67%)	13 (82%)	27 (73%)

*Comprehensive thrombophilia testing was performed at each site in accordance with international recommendations from the Subcommittee for Perinatal and Pediatric Thrombosis of the Scientific and Standardization Committee of the International Society of Thrombosis and Haemostasis.

†"Potent thrombophilia" was defined by any one of the following: (1) severe anticoagulant deficiency (<30% antithrombin; <20% protein C or protein S); (2) homozygosity for the factor V Leiden or prothrombin G20210A polymorphisms; (3) antiphospholipid antibody syndrome; or (4) multitrait thrombophilia. All other single-trait thrombophilia states were characterized as "mild thrombophilia only." In addition to testing noted here, thrombophilia assessment included plasma factor VIII activity, serum homocysteine concentration, and plasma lipoprotein(a) level.

Descriptive analyses involved proportions for categorical data and median values with ranges for continuous data. Proportions were compared between groups using χ^2 or Fisher exact testing, as appropriate. Cumulative duration of anticoagulation was expressed in patient-months (total months of exposure across all patients). Kaplan-Meier survival functions were used to calculate cumulative probability of recurrent AIS over time. All statistical analyses used SAS 9.1 (SAS Institute, Cary, NC).

Results

Among 102 childhood patients with AIS with arteriopathy seen at the 2 centers during the study period, 37 met eligibility criteria of receiving anticoagulation for at least 4 weeks. Arteriopathy subtypes and overall thrombophilia findings are shown in Table 1.

Table 3 summarizes treatment and outcomes data. Therapeutic anticoagulation was administered in 43% of patients and prophylactic anticoagulation in 57%. Median duration of anticoagulation was 6 months (range, 1 month to 4 years). Over the cumulative treatment duration of 1329 patient-months of anticoagulation for the study population, there

were no major bleeding episodes (including no intracranial hemorrhages) and 2 nonmajor clinically relevant bleeding episodes (one outpatient evaluation each for menorrhagia and soft tissue hematoma). Kaplan-Meier analysis revealed a cumulative probability of recurrent AIS of 14% at 1 year among all children.

Discussion

Previous studies in adult AIS have reported intracranial hemorrhage in 8% of patients with atherosclerotic intracranial arterial stenosis in whom anticoagulation was administered.⁷ To what extent these observations may apply to intracranial large vessel stenosis in childhood AIS remains unclear. To date, knowledge of the safety of anticoagulation in childhood AIS remains limited, particularly in the common subtype of childhood AIS with acute arteriopathy.

Although not derived from a clinical trial, the present findings suggest that anticoagulation, whether administered by therapeutic or prophylactic regimen, may be a safe

Table 2. Anticoagulant Therapy Regimens

	Prophylactic Regimen		Therapeutic Regimen	
	Frequency	Monitoring Goal*	Frequency	Monitoring Goal*
Low-molecular-weight heparin	Once daily	0.50–1.00 U/mL anti-Xa	Twice daily	0.50–1.00 U/mL anti-Xa
Unfractionated heparin	—	—	Continuous infusion	0.30–0.70 U/mL anti-Xa
Warfarin	—	—	Once daily	INR 2.0–3.0

*For low-molecular-weight heparin, anti-Xa was measured 4 hours postdose. INR indicates international normalized ratio.

Table 3. Treatments and Outcomes

	Prophylactic Group	Treatment Group	Total
Total patient-months of anticoagulant therapy	728	601	1329
Clinically relevant bleeding episodes			
Major	0% (0/21)	0% (0/16)	0% (0/37)
Nonmajor	9% (2/21)	0% (0/16)	5% (2/37)
Cumulative probability of recurrent AIS at 1 year (95% CI)	15% (5–40%)	13% (3–41%)	14% (6–30)
Cumulative probability of recurrent AIS/transient ischemic attack at 1 year (95% CI)	25% (15–55%)	20% (7–50%)	23% (14–44%)

treatment option for secondary AIS prevention in these patients. Over a cumulative treatment duration of >1000 patient-months of anticoagulation, there were no major bleeding episodes and only 2 nonmajor clinically relevant bleeding episodes. This work substantiates prior experience that anticoagulation can be safely administered in childhood AIS⁸ and extends such experience to AIS in children with nonmoyamoya arteriopathy. Furthermore, the low risk of major bleeding observed here compares favorably with the published cumulative incidence of major bleeding of approximately 5% for children with venous thromboembolism receiving a therapeutic course of low-molecular-weight heparin.⁹

A few limitations of this study are notable. Although the cumulative probability of recurrent cerebrovascular event at 1 year, at 23%, was appreciably lower than the recently published risk of approximately 57% among arteriopathy cases in a population-based retrospective cohort of childhood AIS in which anticoagulation was used sparingly,³ this observation must be strongly qualified in that: (1) patients with moyamoya arteriopathy were included in the aforementioned analysis but not in the present one; and (2) neither investigation directly compared use versus nonuse of anticoagulation. Furthermore, because heparin was limited to the acute hospitalization period of AIS in these patients, and the minimum duration of anticoagulation was 4 weeks, the present findings are most applicable to extended anticoagulant therapy with low-molecular-weight heparin or warfarin. Lastly, this study involved a relatively small population such that bleeding and recurrence risks may be imprecise.

Notwithstanding these qualifications, this is the largest series yet reported for therapeutic and prophylactic dosing of anticoagulation in childhood AIS. The high prevalence of identified thrombophilia in these children provides further rationale for the study of anticoagulation. The present cohort-level evidence of safety and potential for efficacy of anticoagulation in childhood AIS with acute nonmoyamoya arteriopathy adds growing evidence in support of randomized, controlled trials of anticoagulation versus aspirin in this disease.

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Disclosures

None.

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