Safety of anticoagulants in children with arterial ischemic stroke

Tal Schechter, MD1,2, Adam Kirton MD MSc3, Suzanne Laughlin MD4, Ann-Marie Pontigon, MSc5, Yaron Finkelstein, MD2,6,7, Daune MacGregor, MD2,5, Anthony Chan, MBBS8, Gabrielle deVeber MD*2,5, Leonardo R. Brandão MD#1,2

1Division of Hematology/Oncology, Department of Pediatrics, The Hospital for Sick Children, Toronto
2Department of Pediatrics, University of Toronto, Toronto, ON, Canada
3Stroke Program, Alberta Children’s Hospital, Pediatric and Clinical Neuroscience, University of Calgary, Alberta, Canada
4Department of Diagnostic Imaging, The Hospital for Sick Children, Department of Medical Imaging, University of Toronto, Toronto, ON, Canada
5Children’s Stroke Program, Division of Neurology, Department of Pediatrics, The Hospital for Sick Children, Toronto
6Division of Pediatric Emergency Medicine, The Hospital for Sick Children, Toronto
7Division of Clinical Pharmacology and Toxicology, The Hospital for Sick Children, Toronto
8Division of Pediatric Hematology/Oncology, McMaster University, Hamilton, ON, Canada

*Drs. Gabrielle deVeber and Leonardo Brandão contributed equally to the manuscript and are therefore co-senior authors.

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Correspondence: Tal Schechter, MD
Division of Hematology/Oncology,
Hospital for Sick Children,
University of Toronto
Tel: 1-416-813-5886 Fax:1-416-813-5327
Email: tal.schechter-finkelstein@sickkids.ca
**ABSTRACT**

Pediatric arterial ischemic stroke (AIS) is increasingly diagnosed and carries significant risks of recurrence, morbidity and mortality. Anticoagulant therapy (ACT) is commonly prescribed in childhood AIS. Hemorrhagic complication rates in pediatric stroke are unknown and adult safety data are of limited applicability. We analyzed a prospectively enrolled cohort of children (aged 1 month – 18 years) with acute AIS selected utilizing standardized criteria for protocol-based ACT over 14-year period. We assessed ACT-associated intracranial hemorrhage (ICH) including frequency, clinical and radiological characteristics, predictors and outcome. Among 215 children with AIS, 123 received ACT within seven days post-diagnosis. During anticoagulation, 14 (11%) children developed new or increased ICH, all within 26 days from diagnosis. ICH was symptomatic in five (4%), asymptomatic in nine (7%), and mild (ECASS grades HI-I or HI-2) in all but one child (ECASS PH-2). Long-term neurological outcomes following ACT-associated ICH in survivors were abnormal in 73% (8/11). Comparably, 12 of 75 (16%) children treated without anticoagulation developed new/increased ICH on follow-up imaging (p=0.3507). We conclude that ACT is relatively safe in children with AIS with a 4% risk of symptomatic ICH. Based on the safety of ACT in our study, clinical trials of ACT in childhood AIS are warranted.
INTRODUCTION

Arterial ischemic stroke (AIS) affects two to six per 100,000 children annually.\(^1\) Mortality risk due to AIS in children is 6-8%\(^2\) and approximately 75% suffer long-term neurological deficits.\(^3,4\) Recurrence rates for AIS and transient ischemic attack (TIA) in non-neonate children are 16%-50%.\(^4-6\)

Mechanisms and risk factors for AIS differ between children and adults. In children, prothrombotic disorders, cardiogenic embolism, and arteriopathy including dissection predominate. Such mechanisms may favor fibrin-based thrombosis and targeted therapy, compared to platelet-based processes common in adults, in whom aspirin is the initial mainstay of treatment. Common risk factors for hemorrhagic transformation in adults with anticoagulant therapy (ACT), including chronic hypertension and advanced atherosclerosis, are rare in childhood. Several studies have reported potentially beneficial effects of ACT at therapeutic or prophylactic doses in treating children with AIS.\(^2,7-11\)

Consensus-based pediatric treatment guidelines\(^12-14\) suggest that both anticoagulation and aspirin are reasonable initial considerations in childhood AIS. However, the evidence base for this is minimal (2C or class II),\(^12,13\) including lack of adequate safety data for ACT. This results in controversy in clinical management while impeding the development of clinical trials.

The aim of the present study is to evaluate the safety of protocol-based ACT in a longitudinal, prospectively enrolled sample of children diagnosed with AIS.

METHODS

We analyzed a prospectively enrolled cohort of children (1 month to 18 years) diagnosed with imaging-confirmed acute AIS and treated with ACT at a tertiary care hospital (The Hospital for Sick Children, Toronto) during 14 years, from January 1\(^{st}\), 1992 to December 31\(^{st}\), 2005. We also evaluated the risk for ICH in the cohort of children who were not treated with ACT. The study was approved by the Institutional Research Ethics Board of The Hospital for Sick Children, Toronto.
Clinical data

Clinical data were collected from the databases of the Canadian Pediatric Ischemic Stroke Registry-Toronto site based initially on standardized health record review. In addition, stroke-specific history and neurological examination utilizing an expanded version of the Pediatric Stroke Outcome Measure (PSOM) were conducted at follow-up visits in the Children’s Stroke Clinic. Stroke risk factors were categorized as: vasculopathy (including dissection, moya-moya disease, transient cerebral arteriopathy, vasculitis, post-varicella arteriopathy and non-specific arteriopathy); head and neck infections; other head and neck pathologies; and cardiac disorders (congenital or acquired). Clinical presentations of AIS (e.g., hemiparesis, seizures) were documented.

Anticoagulation therapy

All children with AIS who received ACT for a minimum of 24 hours were included. Treatment regimens were based on published institutional antithrombotic (from 1992) and stroke (from 1995) regimens. ACT was individualized at the discretion of the caring team in consultation with our institutional Hematology (from 1992-1995), Thrombosis (from 1995), Neurology (1992-1998) or in-patient Stroke (from 1998) services.

ACT included monotherapy or combination therapy (either sequential or concurrent) with initial unfractionated heparin (UFH), Coumadin or low molecular weight heparin (LMWH) (Enoxaparin, Rhone Poulenc Rorer). Concomitant aspirin (ASA) or clopidogrel use was noted. ACT dose intensity, duration, side-effects and safety were recorded. ACT doses were adjusted based on published algorithms. Intravenous UFH was initiated without loading dose and titrated to activated Partial Thromboplastin Time (aPTT) of 60-85 seconds or anti-factor Xa (anti-Xa) level of 0.35-0.7 U/ml. LMWH was injected subcutaneously twice daily, 1 mg/kg/dose (1.5 mg/kg/dose for infants < 2 months age) and titrated to anti-
Xa levels of 0.5-1.0 U/ml at four hours post-injection. Coumadin initial dose was 0.2mg/kg/day titrated to INR 2.0-3.0. Patients were considered to be still receiving ACT for the following intervals after receiving the last dose: up to 24 hours for UFH; 48 hours for LMWH; five days for Coumadin; and seven days for ASA. Children who received multiple ACT medications over time were represented in multiple categories. Brain computed tomography (CT) or magnetic resonance imaging (MRI) scans were performed at three and seven to ten days post-ACT initiation and with any clinical suspicion of intracranial hemorrhage (ICH).

**ACT Safety**

The primary safety outcomes of the study were ACT-associated death, ICH or serious systemic bleeding. ICH episodes were categorized clinically as ‘asymptomatic’ or ‘symptomatic’ and by radiological severity (see below). Symptomatic ICH included new or increased neurological deficit (focal, diffuse), headache or seizures. Laboratory parameters at the time of ICH included complete blood count, coagulation tests and anticoagulant therapeutic drug monitoring.

**Radiological Data**

Radiological data included: number and location of infarcts (vascular territory, brain structures, laterality) and presence of ICH, including hemorrhagic conversion of infarcts at AIS diagnosis and during ACT. For every child with ACT-associated ICH, all brain imaging studies were re-evaluated by the study pediatric neuro-radiologist (S.L.) and a pediatric neurologist (A.K. or G.D.) blinded to patient clinical data including ACT. ICH scoring was classified according to the European Cooperative Acute Stroke Study (ECASS) definitions: H0-no hemorrhage detected; HI1-hemorrhagic infarct 1: small petechiae, <50% of infarct area (includes laminar necrosis); HI2-hemorrhagic infarct 2: confluent petechiae, >50% of infarct area; PH1-parenchymal hemorrhage 1: blood ≤30% of infarct area, no or slight space effect; PH2-
parenchymal hemorrhage 2: blood ≥30% of infarct area, substantial space effect. Changes in ECASS scores over time were documented.

**Neurological Outcome**

Children were evaluated in the Children’s Stroke clinic, The Hospital for Sick Children three and 12 months after diagnosis and annually thereafter with the PSOM. The PSOM is a standardized, validated likert-scaled neurological assessment with five spheres: sensori-motor right, sensori-motor left, language production, language comprehension and cognitive/behavioral. Summary scores for each sphere reflect no deficit (0), mild (0.5), moderate (slowed function, 1) or severe (missing function, 2). Clinical outcome was dichotomized as favorable (no or mild deficits) or unfavorable (total PSOM score ≥1 with impact on function). Outcomes were compared in children receiving ACT either with or without ICH.

**Statistical analysis**

We employed descriptive statistics and association testing for potential predictors for ICH. A-priori variables include treatment, multiple infarcts and cardiac risk factor. Group comparisons and association of ICH and neurological outcome were also conducted. Univariate analyses included fisher exact, chi square for nominal data and Wilcoxon/Mann-Whitney for non-parametric continuous data. Associations with p-values ≤0.05 (2-tailed) were considered significant and values between 0.05 to 0.10 were considered trends.

**RESULTS**

Two-hundred and fifteen children were diagnosed with AIS during the study period (Figure 1). We excluded 17 children treated with ACT because ACT was initiated more than seven days after AIS diagnosis (n=10, none had ACT-associated ICH), or because ACT was limited to prophylactic dosing provided for preventing systemic thrombosis (n=7). Table 1 presents patient characteristics of 198
children (123 treated with ACT initiated within 7 days post-AIS and 75 receiving only ASA (n=25) or no ACT/ASA (n=50)). In the 198 children, mean patient age was 6.2 yrs (range 1 month -17.7 years) and 115 (58%) were male. Common presentations included hemiparesis (77%) and seizures (29%). Risk factors for AIS frequently included cardiac disorders (34%) and vasculopathy (44%; three in ACT group had arterial dissection). Infarcts at presentation were multiple in 82 (41%) and basal ganglia structure was affected in 96 children (48%). Fourteen children (6 ACT group and 8 No ACT Group) had ICH at stroke diagnosis.

ICH post-AIS diagnosis occurred in 12/75 (16%) patients in the No ACT group and 14/123 (11%) in the ACT group. No significant predictors of ICH were found: treatment with ACT (p=0.3507), multiple infarcts (p=0.7430), and cardiac disease (p=0.7227). In addition, no difference was found in ICH rates between the first 7 years and last 7 years of enrolled patients (p=0.4837).

**Anticoagulant therapy**

ACT was initiated within 72 hours from AIS diagnosis in 102 (83%) of the 123 children treated with ACT. Among 123 children receiving initial ACT within seven days post-AIS, 51 received a single ACT medication, 64 had two sequential ACT medications, and eight had three sequential ACT medications during the treatment period. Seventy-two (58%) children switched ACT medication during treatment. ICH rates were similar for each ACT regimen/combination. Median duration of ACT was 74 days (range: 1 day-6.4 years). Six children received ACT despite evidence of ICH at diagnosis, either because the ICH was minor (ECASS grade HI-1) or the treating physician graded the risk of recurrent thromboembolism as major.
Intracranial hemorrhage

Fourteen (11%) children had ACT-associated ICH. Nine children had asymptomatic ICH, detected within 6-26 days (mean 12.4 days) from AIS diagnosis. Five children had symptomatic ICH, and symptoms began 2-15 days post-AIS diagnosis and 2-13 days post-ACT initiation. ICH symptoms included: irritability, seizures, headache, facial droop, aphasia, or decreasing LOC (Table 2). The incidence of ICH on ACT in the first 4 weeks was: 4% in the first week, 6.4% in the second week, 2.3% in the third week and 1.3% in the fourth week. Table 2 summarizes additional clinical and radiological data, respectively, on the 14 children with ACT-associated ICH (the first 9 children are the asymptomatic group and the last 5 are the symptomatic group). Non-ICH systemic bleeding did not occur in any patient. All the patients without evidence of ICH had brain imaging immediately after AIS diagnosis to rule-out ICH or AIS progression as well as additional follow-up imaging from 7 days post-diagnosis (52 patients imaged 7-30 days after diagnosis of AIS; 30 patients between day 30-90; 84 patients more than 90 days).

Anticoagulant therapy at time of ICH

Among 9 children with asymptomatic ICH, 7 children were receiving ACT monotherapy with LMWH (n=4), UFH (n=2) or Coumadin (n=1). Two had ICH on combination therapy with UFH and ASA (n=1) or LMWH and Coumadin (n=1) during medication transition. Two children had hematological risks for ICH. One child developed thrombocytopenia (platelets count -32,000) during catastrophic anti-phospholipid antibody (APLA) syndrome and had mildly elevated UFH level (anti-Xa=0.81; therapeutic range: 0.35-0.7). The second child had an INR of 3.0 (normal range: 0.8-1.2) while on LMWH.

Among the 5 children with symptomatic ICH, 3 children were receiving ACT monotherapy with LMWH (n=1) and UFH (n=2). Two had ICH on combination therapy with UFH and ASA (n=1) or LMWH and Coumadin (n=1) during medication transition.
For children treated with single or combination ACT medications the risk for ICH for each regimen was: 8% (4/50 children) for UFH alone; 6% (5/81 patients) for LMWH alone, 3% (1/39 patients) for Coumadin alone and 14% (2/14 children) for UFH plus ASA and 9% (2/22 children) for LMWH plus Coumadin.

**Radiological Findings of ICH following ACT**

Eleven of the 14 children with ICH had images available for re-analysis and ECASS grading of ICH severity (Table 2). The ACT-associated ICH grades in the 7 asymptomatic patients were: HI-1 (no cortical laminar necrosis) in 3, HI-2 in 3, and PH-2 in 1. All 4 symptomatic ICH patients had HI-1 (including cortical laminar necrosis) bleed severity. Among them, one had evidence of laminar necrosis only, 2 patients had evidence of both laminar necrosis and petechial hemorrhage and the fourth had petechial hemorrhage.

**Potential Risk-factors for ACT-associated ICH**

Potential risk-factors for ACT-associated bleeding were evaluated in all 123 patients. No significant predictors of ACT-associated ICH were found for multiple infarcts [4/14 (29%) vs. 46/109 (42%) p=0.3283] or cardiac disease [7/14 (50%) vs. 38/109 (42%) p=0.2683].

**Neurological outcome in the ACT group**

Three of the 14 children with ICH after ACT died due to underlying cardiac disorder (n=2) or fatal leukemia-induced catastrophic APLA-syndrome (n=1). None died from ICH. Moderate to severe neurological deficits were documented in 8/11 (73%) surviving children. Outcomes in the 7 survivors with asymptomatic ACT-related ICH were: severe deficit (n=4), moderate deficit (n=1), mild deficit (n=1), and normal (n=1). Outcomes in the 4 survivors with symptomatic ACT-related ICH were: severe
deficit (n=2), moderate deficit (n=1), and mild deficit (n=1). There is no significant difference in the neurological outcomes between patients with asymptomatic [poor outcome, 7/9 (78%)] and symptomatic [poor outcome, 4/5 (80%)] ACT-related ICH (p=0.9227).

Follow-up data was available for 95 of the 109 ACT treated children who did not develop ICH. Fifty (53%) had poor outcome including 9 patients who died. Neurological outcomes in the 86 survivors were: severe deficit (n=24), moderate (n=17), mild deficit (n=24), and normal (n=21). Children with ACT-associated ICH had a trend toward abnormal outcome compared to those who did not (P=0.068). It is possible that prior ICH affects long-term neurological outcome. The data from the 6 patients treated with ACT despite ICH at diagnosis suggests that there is also variability in the outcome: normal (n=1), mild (n=1), severe (n=2), deceased (n=1), and data unavailable for one.

DISCUSSION

We studied the risk of ICH in a prospectively enrolled cohort of 215 children with AIS over 14 years. To addressed the question of ACT safety, we focused on symptomatic and asymptomatic ACT-related ICH in a cohort of 123 children treated with protocol-based ACT for acute ischemic stroke. Symptomatic ICH developed in 4%, and overall the ICH risk was 11%. ICH was mild with ECASS grades HI-1 or HI-2 in 10 of 11 affected children, and occurred in all within the first month of ACT. The risk for new or increased ICH in children managed without ACT was similar at 16%. Although no ICH episodes were fatal, long-term follow-up demonstrated a moderate or severe neurological deficit in two-thirds of children with ACT-associated ICH.

Our relatively low rate of ACT-associated ICH is consistent with several previous studies in childhood AIS. In a recent study, 37 children with childhood AIS and non-moyamoya arteriopathy received ACT in prophylactic (57%) or therapeutic (43%) doses. None developed ICH or major bleeding over a period of 1329 patient-months.\(^{(20)}\) Dix et al. reported 29 newborns and children treated with
LMWH for ischemic stroke. None developed ICH, although extra-cranial bleeds (one major and eight minor) were observed primarily in neonates. Burak et al. (7) reported two minor bleeding episodes in eight children with AIS receiving LMWH. Strater and colleagues (10) published a non-randomized study of 135 children with AIS (idiopathic, n=79; cardiac, n=15; vascular, n=30; infectious, n=11) of whom 86 received prophylactic dose LMWH (4-hour anti-Xa activity, 0·2 to 0·4). No drug-related adverse events or major bleeding were reported. Conversely, a recent study of 63 children with AIS reported 30% of them to develop hemorrhagic transformation in the first month of therapy. However, only two (3%) of the 19 children had symptomatic ICH. Five out of the 24 children treated with ACT developed ICH (21%) and 12 out of the 34 children treated with anti-platelet therapy. The development of ICH was not significantly associated with ACT vs. anti-platelet therapy but was associated with larger infarct volume. A trend toward increased risk of ICH was found in children with cardiac conditions and meningitis (21).

In our study, ICH was mild in almost all patients: ECASS grades were HI-1 or HI-2 in all but one child who progressed to PH-2 from HI-1 at diagnosis. We included children with cortical laminar necrosis in our definition of ‘ICH’ and assigned them an ECASS grade of HI-1 (n=1). In routine CT or MRI imaging of pediatric patients it is challenging to differentiate whether cortical laminar necrosis is due to petechial cortical bleeding or cortical neuronal death with mineralization. Therefore, our conservative approach to assign an ECASS HI-1 ICH score to all cortical laminar necrosis cases implies that our estimation of risk is maximal, and overall ICH risk in children receiving ACT for AIS may be even lower. In a study performed in 15 children with cortical laminar necrosis, susceptibility-weighted MR imaging identified bleeding in only 20%. This is supported by our observation that most children with ICH were asymptomatic and were diagnosed solely by scheduled follow-up imaging. The implication is that in children with AIS treated with ACT routine imaging is necessary to detect subclinical ICH. Despite the mild severity of most ICH episodes on imaging, the neurological outcome tended to be worse in children with ACT-related ICH compared to children with no ICH.
In our study, ACT-associated ICH occurred early, within 26 days of AIS diagnosis. Although the majority of children continued therapy beyond the first month from AIS diagnosis, and up to 6.4 years after, none has experienced ICH beyond the first month. This finding may identify a short vulnerable period for development of ICH in children receiving ACT for stroke. Physiological vascular and tissue stabilization likely develops over several weeks, decreasing ICH risks. Similarly, in adults, heparin-related ICH typically occurs early after stroke onset, usually within 72 hours.\(^{(23)}\) Also as in adults, the most common type of treatment-related ICH in our study was hemorrhagic conversion of a bland infarct, which is expected to occur in the days and early weeks post-stroke onset.

The underlying risk factors for ICH differ between pediatric and adult stroke. In adults, hypertension, atherosclerosis and concomitant thrombolytic therapy\(^{(17,24)}\) are major risk factors for hemorrhagic conversion. These factors are not represented in most pediatric stroke series. Conversely, children with AIS have either normal brain arteries (most children with cardiac-related stroke) or arteriopathy limited to focal involvement of intracranial arteries.

No risk factors for ICH were identified in our study, possibly due to limited sample size. However, nearly half of children with ACT-associated ICH in our study had underlying cardiac disorders. In adults, cardio-embolic AIS is associated with an increased risk of hemorrhagic conversion\(^{(25)}\). Since many cardiac strokes are associated with cardiac surgery, additional surgical factors may further increases the risk of hemorrhagic conversion. Since multivariate analysis was not feasible, due to a relatively small cohort compared to adult series, whether presentation with seizures and pre-existing ICH are independent of cardiac disorders could not be definitively determined.

In the treatment of childhood AIS current approaches frequently include ACT. Recent observational data from the International Pediatric Stroke Study indicates that among all 640 children with AIS treated since 2003, 43% received in-hospital ACT.\(^{(26)}\) In children with AIS due to cardiac disease, arterial dissection or major prothrombotic disorders, initial treatment with ACT is now
recommended by multiple published pediatric stroke guidelines.\(^{(13,14,27)}\) In these scenarios ACT use is favored over anti-platelet agents because thrombus formation is believed to involve predominantly fibrin thrombus formation by the coagulation system, against which anti-platelet agents are ineffective. These predisposing conditions are also frequently treated with ACT in adults. In children with AIS due to other causes, the use of ACT is controversial. In our study most children were treated with initial ACT regardless of suspected etiology, and then transitioned to anti-platelet agents after the initial week(s) of therapy, if dissection, cardiac or prothrombotic disorders were excluded. The relatively low rate of serious ICH, observed with ACT in the current study supports the safety of this practice. However, efficacy data remain to be determined, since in observational studies, children selected for ACT may have higher inherent rates of recurrent stroke than those selected for anti-platelet agents (selection bias).

Adult stroke trials comparing aspirin versus ACT have yielded consistent findings that hemorrhagic risks outweigh the benefits of ACT in non-cardiac stroke. A Cochrane meta-analysis reported an absolute risk increase of 0.9% in symptomatic intracranial and 0.9% for additional extra-cranial hemorrhage risk with ACT compared to anti-platelet therapy, offsetting the benefits of ACT in preventing stroke recurrence.\(^{(28)}\) However, individual prospective studies have reported benefit of LMWH in adult AIS without increased risk of ICH.\(^{(29,30)}\) A sub-analysis of the, Warfarin Aspirin Recurrent Stroke Study, demonstrated overall improved outcomes with ACT over ASA in the sub-group of stroke patients most similar to children with stroke, namely non-hypertensive adults with cryptogenic stroke. This included a 30% risk reduction for recurrent stroke (P<0.02).\(^{(31)}\)

The main limitations of our study are the small number of safety outcome events (ICH or major extra-cranial bleeding) and relatively small number of subjects, compared to adult series. This factor may have accounted for our inability to determine statistically significant predictors of ICH. Another limitation was the shift in practice from UFH to LMWH as initial ACT when LMWH became increasingly available several years after study initiation. Also, our limited number of routine follow-up CT scans, necessitated
by concerns about radiation exposure of the pediatric brain, resulted in only one consistent early time-point for CT detection of asymptomatic ICH. Finally, clustering of ACT-associated ICH occurring early post-diagnosis may result from methodological biases, namely loss of subjects for follow-up and incomplete and non-uniform imaging frequency over time after the initial week post-diagnosis.

Importantly, in this non-randomized study, though we didn’t find ACT to increase the risk for ICH, the possibility of selection of patients with inherently lower risk of ICH for initial ACT makes this comparison inconclusive.

In summary, we found that protocol-based ACT for pediatric AIS was safe with a 4% risk of symptomatic ICH, limited to low-grade imaging score (ECASS grades HI-1 or HI-2) in all but one patient. The risk for developing ICH was low compared to the risk in adults. Importantly, this risk was limited to the first four weeks of anticoagulant therapy in children with AIS. The favorable safety profile we observed supports the inclusion of ACT in current consensus-based management guidelines and the advancement of therapeutic clinical trials in childhood AIS.
Authorship and Acknowledgments

Dr. Tal Schechter-Performed the data compilation, literature search, interpreted the data and wrote the initial manuscript

Dr. Adam Kirton-Collected additional clinical details regarding presentations of bleeds and stroke, and assisted in assembling and reviewing the neuro-radiology images with Dr. Laughlin

Dr. Suzanne Laughlin-Analyzed the neuro-radiology imagings and classified using ECASS grades

Ann-Marie Pontigon-Collected the clinical data, created database, planned and performed statistical data analysis

Dr. Yaron Finkelstein-Assisted with data analysis and interpretation and preparation of the manuscript

Dr. Daune MacGregor-participated in the database design and outcome assessments for patients

Dr. Anthony Chan-participated in the study design and development of anticoagulation protocol

Dr. Gabrielle deVeber*, Leonardo Brandao* both participated in developing the study plan, supervised the study progress and analysis and co-wrote the manuscript with Dr. Schechter

Dr. deVeber also provided neurological outcomes for some patients and final revisions of manuscript

Dr. Brandao also provided additional anticoagulation treatment details for the patients.

Conflict of Interest Disclosure

The authors have no conflicts of interest to disclose.
REFERENCES


Table 1: Patient characteristics of 198 children

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>All Patients</th>
<th>ACT (N=123)</th>
<th>No ACT (N=75)</th>
<th>P-value**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age: Mean (range)</td>
<td>6.2y (1mth-17.7yrs)</td>
<td>6.8y (1mth-17.7yrs)</td>
<td>5.2y (1mth-16.0yrs)</td>
<td>0.0272</td>
</tr>
<tr>
<td>Stroke event before 1998</td>
<td>81 (41%)</td>
<td>42 (34%)</td>
<td>39 (52%)</td>
<td>0.0132</td>
</tr>
<tr>
<td>Male</td>
<td>115 (58%)</td>
<td>79 (64%)</td>
<td>36 (48%)</td>
<td>0.0248</td>
</tr>
<tr>
<td>Clinical presentation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemiparesis</td>
<td>152 (77%)</td>
<td>101 (82%)</td>
<td>51 (68%)</td>
<td>0.0225</td>
</tr>
<tr>
<td>Seizures</td>
<td>57 (29%)</td>
<td>32 (26%)</td>
<td>25 (33%)</td>
<td>0.2700</td>
</tr>
<tr>
<td>Stroke Features</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multiple Infarcts</td>
<td>82 (41%)</td>
<td>50 (45%)</td>
<td>32 (43%)</td>
<td>0.7799</td>
</tr>
<tr>
<td>Basal Ganglia Affected</td>
<td>96 (48%)</td>
<td>67 (54%)</td>
<td>29 (39%)</td>
<td>0.0309</td>
</tr>
<tr>
<td>ICH at stroke diagnosis*</td>
<td>14 (7%)</td>
<td>6 (5%)</td>
<td>8 (11%)</td>
<td>0.1232</td>
</tr>
<tr>
<td>Risk Factors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac Disease</td>
<td>67 (34%)</td>
<td>45 (37%)</td>
<td>22 (29%)</td>
<td>0.2955</td>
</tr>
<tr>
<td>Vasculopathy</td>
<td>44 (22%)</td>
<td>31 (25%)</td>
<td>13 (17%)</td>
<td>0.1963</td>
</tr>
<tr>
<td>Head &amp; Neck Infection</td>
<td>23 (12%)</td>
<td>11 (9%)</td>
<td>12 (16%)</td>
<td>0.1328</td>
</tr>
<tr>
<td>Head &amp; Neck Pathology</td>
<td>43 (22%)</td>
<td>31 (25%)</td>
<td>12 (16%)</td>
<td>0.1276</td>
</tr>
<tr>
<td>Neurological Outcome</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PSOM ≥ 1 or death</td>
<td>94/158 (59%)</td>
<td>61/109 (56%)</td>
<td>33/49 (67%)</td>
<td>0.1776</td>
</tr>
</tbody>
</table>

*One patient had ICH at diagnosis while on LMWH (the treatment was for Femoral Vein Thrombosis; cardiac patient).

**ACT vs. No ACT group comparisons analysis conducted using chi-square and wilcoxon rank-sum test.
Table 2: Pediatric AIS patients with ICH during ACT

<table>
<thead>
<tr>
<th>Case #</th>
<th>Age</th>
<th>Gender</th>
<th>Pre-existing condition</th>
<th>Pre-existing ICH</th>
<th>Treatment at time of ICH</th>
<th>Interval Event to ICH</th>
<th>ECASS Grade</th>
<th>Change over time</th>
<th>Clinical Presentation at time of ICH</th>
<th>Risk Factor for Bleed</th>
<th>Clinical Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>15.7</td>
<td>F</td>
<td>Acute myeloid leukemia, Antiphospholipid syndrome</td>
<td>None</td>
<td>UFH</td>
<td>7</td>
<td>HI1</td>
<td>progression, remained HI1</td>
<td>Asymptomatic then coma due to recurrent AIS &amp; ICH</td>
<td>Abnormal lab: PLT-32, anti Xa-0.81, Hgb-85 APLA Syndrome</td>
<td>Died (fatal catastrophic APLA syndrome with recurrent emboli and bleeds)</td>
</tr>
<tr>
<td>2</td>
<td>10.4</td>
<td>M</td>
<td>CHD</td>
<td>None</td>
<td>Coumadin</td>
<td>10</td>
<td>HI2</td>
<td>regression, HI1</td>
<td>Asymptomatic</td>
<td></td>
<td>Died (cardiac)</td>
</tr>
<tr>
<td>3</td>
<td>11.5</td>
<td>M</td>
<td>CHD-S/P heart transplant.</td>
<td>None</td>
<td>LMWH</td>
<td>20</td>
<td></td>
<td></td>
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<td></td>
<td>Mild Neurological Deficit</td>
</tr>
<tr>
<td>4</td>
<td>11</td>
<td>M</td>
<td>CHD</td>
<td>None</td>
<td>UFH &amp; ASA</td>
<td>6</td>
<td>HI1</td>
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<td></td>
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</tr>
<tr>
<td>5</td>
<td>5.8</td>
<td>M</td>
<td>Vasculitis</td>
<td>None</td>
<td>UFH</td>
<td>9</td>
<td></td>
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<td></td>
<td></td>
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</tr>
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<td>6</td>
<td>1.5</td>
<td>F</td>
<td>CHD</td>
<td>None</td>
<td>LMWH &amp; Coumadin</td>
<td>9</td>
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<tr>
<td>7</td>
<td>14.8</td>
<td>M</td>
<td>Hyperlipidemia</td>
<td>None</td>
<td>LMWH</td>
<td>12</td>
<td>HI2</td>
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<td></td>
<td>Normal</td>
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<td>8</td>
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<td>M</td>
<td>CHD-post Fontan surgery</td>
<td>Yes ECASS HI1</td>
<td>LMWH</td>
<td>26</td>
<td>PH2</td>
<td>Asymptomatic</td>
<td>Abnormal lab: INR-3</td>
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<td>Severe Neurological Deficit</td>
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<td>9</td>
<td>2.6</td>
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<td>Post varicella vaccine</td>
<td>None</td>
<td>LMWH</td>
<td>13</td>
<td>HI1</td>
<td>Asymptomatic</td>
<td></td>
<td></td>
<td>Moderate Neurological Deficit</td>
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<td>10</td>
<td>7.9</td>
<td>F</td>
<td>Post varicella</td>
<td>None</td>
<td>UFH</td>
<td>4</td>
<td></td>
<td>Facial drop and aphasia</td>
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<td>Moya-moya disease</td>
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<td>3</td>
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<td>progression, HI1</td>
<td>Focal seizure and irritability</td>
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<td>F</td>
<td>CHD- post Catheterization</td>
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<td>LMWH &amp; Coumadin</td>
<td>15</td>
<td>HI1</td>
<td>Irritability</td>
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<td>14</td>
<td>M</td>
<td>CHD-post Catheterization</td>
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<td>UFH</td>
<td>2</td>
<td>HI1</td>
<td>Loss of consciousness/coma</td>
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<td>HI1</td>
<td>Headache and vomiting</td>
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<td>Severe Neurological Deficit</td>
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</table>

* Case 8 ACT despite initial ICH administered ACT for cardiac indication (shunt). Patient also had history of femoral vein thrombosis.
Figure 1: Study cohort of children with AIS

Out of 14 patients who bled, 1 patient had ICH at Diagnosis: Stroke Post-Cardiac Surgery, History of Femoral Vein Thrombosis.

Out of 109 patients, 5 patients had ICH at Diagnosis:
1. Anticoagulation for deep vein thrombosis.
2. Cardiac Patient. Restarted for Femoral Vein Thrombosis and continued for stroke after 2nd CT.
3. Treated for systemic clot and mechanical valve.
4. Cardiac Patient with extensive infarcts – both AIS and CSVT.
5. Comatose, fixed dilated pupil and retinal hemorrhage.
Figure 2. ICH in children with AIS

Intracranial hemorrhages are classified according to the ECASS grading system. Representative examples of the three grades encountered (HI1, HI2, and PH1) are shown for both children on ACT (top row) and those not on ACT (bottom row). No larger hematomas or ECASS PH2 were observed in the ACT treated group.

White arrows point at areas of ICH
Safety of anticoagulants in children with arterial ischemic stroke