Assessment of the Outcomes Associated with Periprocedural Anticoagulation Management in Children with Acute Lymphoblastic Leukemia

Maria L. Avila, MD[1], Christine A. Macartney, MD[1], Johann K. Hitzler, MD[1], Suzan Williams, MD, MSc[1], Alex Kiss, PhD[2], and Leonardo R. Brandão, MD, MSc[1]

Objective To report the outcomes of an institutional protocol for periprocedural anticoagulant (AC) management in children with acute lymphoblastic leukemia (ALL).

Study design Children being treated for ALL who received full-dose (therapeutic) anticoagulation before undergoing at least 1 lumbar puncture (LP) were included in this retrospective cohort study. The main outcome was the risk of traumatic LP; exploratory analysis included the risks of symptomatic spinal hematoma and progression/recurrence of the thrombotic event. Analyses were conducted using logistic regression analysis with a generalized estimating equation approach.

Results Twenty-two children with ALL receiving an AC underwent a total of 396 LPs. Although traumatic LP was associated with full-dose AC therapy in univariable analysis, a multiple logistic regression model controlling for other risk factors for traumatic LP showed that AC therapy was not significantly associated with the risk of traumatic LP when the ACs were held as per the institutional protocol. No patient developed symptomatic spinal hematoma. Exploratory analysis revealed that AC dose, a likely marker of thrombus burden, was significantly associated with progression/recurrence of the thrombotic event in univariable analysis.

Conclusion In our cohort, recent AC therapy was not statistically associated with an increased risk of bleeding after LP when following a specific protocol for periprocedural AC management. The risk associated with the progression/recurrence of thromboembolic events requires further evaluation. *(J Pediatr 2014;164:1201-7)*.

Children with acute lymphoblastic leukemia (ALL) typically undergo a series of lumbar punctures (LPs) during treatment as part of central nervous system–directed therapy. However, LPs may be associated with bleeding complications, such as spinal hematoma, or traumatic LP.[1]

ALL is the cancer most commonly reported in association with thrombotic events in the pediatric population.[2] The estimated incidence of symptomatic thrombosis in patients with ALL is at least 5.2%.[3] Because approximately 50% of symptomatic thrombotic events in children with ALL occur in life-threatening sites,[2] most patients are likely to require anticoagulant (AC) therapy for a minimum of 3 months.[4]

Given that LPs are a crucial part of the treatment for ALL, this concomitant need for anticoagulation poses a dilemma. On the one hand, the goal of minimizing the risk of spinal hematomas, which could lead to spinal cord compression and potentially devastating neurologic damage, and of traumatic LP, which has been linked to an increased risk of central nervous system relapse and poor event-free survival,[5-7] suggests that anticoagulation should be temporarily interrupted at the time of LP. On the other hand, the goal of preventing thrombotic event progression or recurrence suggests that any interruption of anticoagulation be as short as possible. Despite the clinical significance of this dilemma, no validated approach to patient management in this scenario has been described to date. Therefore, we evaluated the outcomes (risk of bleeding and thrombotic event progression/recurrence) of a defined institutional protocol for the periprocedural management of anticoagulation in children with ALL undergoing LP.

AC	Anticoagulant
ALL	Acute lymphoblastic leukemia
CSF	Cerebrospinal fluid
GEE	Generalized estimating equations
LMWH	Low molecular weight heparin
LP	Lumbar puncture
RBC	Red blood cells
UFH	Unfractionated heparin

From the [1]Division of Hematology/Oncology, The Hospital for Sick Children, University of Toronto; and [2]Department of Research Design and Biostatistics, Institute for Clinical Evaluative Sciences, Sunnybrook Health Sciences Center, Toronto, Ontario, Canada

M.A. was supported by a Baxter Bioscience Fellowship in Pediatric Hemostasis and Thrombosis at The Hospital for Sick Children, Toronto. The authors declare no conflicts of interest.

 http://dx.doi.org/10.1016/j.jpeds.2014.01.031

Methods

The health records of children aged <18 years with ALL treated at The Hospital for Sick Children between June 2004 and June 2010 who developed a thrombotic event and received full-dose anticoagulation before at least 1 LP were reviewed. This retrospective longitudinal study followed the patients from their first (diagnostic) to last LP. The hospital's Institutional Ethical Review Board approved the study, and informed consent was waived.

The institutional periprocedural protocol specifies holding low molecular weight heparin (LMWH) for 24 hours and unfractionated heparin (UFH) for 4 hours before an LP, then resuming AC therapy with UFH at 4-6 hours and LMWH at 6-9 hours after LP. Procedures are performed under sedation, in a dedicated procedure area or under imaging guidance, by a hematology-oncology fellow or staff, or neuroradiology staff. ALL treatment at our institution is based on the protocols of the Children's Oncology Group.

Outcomes

We chose traumatic LP as the main outcome because it is a meaningful, easily quantifiable, objective, and sensitive marker of bleeding events. Here, traumatic LP was defined as the presence of >10 red blood cells (RBCs)/μL cerebrospinal fluid (CSF).[5,8] We also explored the risk of symptomatic spinal hematomas (determined based on health record notes and diagnostic imaging reports) and of thrombosis progression (ie, presence of documented extension of the original thrombotic event by an objective imaging technique) or recurrence (ie, documentation of a new local or distant thrombotic event).

Predictors of Traumatic LP

AC dose, classified as full therapeutic dose, prophylaxis (in accordance with pediatric guidelines[4]) or no therapy, served as the main predictor. The type of AC was also recorded (eg, enoxaparin, tinzaparin, UFH). Other risk factors for traumatic LP include[8] age <1 year, African-American ethnicity, experience of the operator performing the procedure, platelet count at the time of LP $<100 \times 10^9$/L, time since the previous LP <16 days, previous traumatic or bloody LP (ie, >500 RBCs/μL of CSF for the latter), and platelet count at the time of previous LP $<100 \times 10^9$/L. These variables were collected and classified in a similar manner. The LP operator was categorized as "fellow" or "staff" to indicate his or her experience. In addition, owing to known coagulation derangements that occur during the early phases of treatment, the phase of chemotherapy when LP was performed was categorized as induction/consolidation phase (<6 months from diagnosis) or maintenance phase (>6 months from diagnosis).

Given that LP may be more difficult to perform in overweight or obese patients, body mass index percentiles were estimated for children aged >2 years. For younger patients, weight-for-length percentiles were calculated.

Finally, because our institution does not recommend routine coagulation testing before an LP, we anticipated a high number of missing laboratory values, and thus analyzed the association between coagulation test results (normal vs abnormal, defined as age-appropriate reference values for international normalized ratio or activated partial thromboplastin time) and traumatic LP in an exploratory manner, and only when the tests were performed within 72 hours before the LP.

Predictors of Thrombotic Event Progression/Recurrence

We sought to explore whether sex, type of thrombotic event, AC dose, number of LPs performed before documentation of thrombosis progression/recurrence, and presence of major hereditary or acquired thrombophilia were associated with thrombotic event progression/recurrence. For the variable AC dose, we compared the dose of AC that patients were receiving at the time of thrombosis progression/recurrence, or the dose administered at the time of the last LP in patients without thrombosis progression/recurrence. This comparison was considered to reflect a patient's overall thrombotic risk, in that a high-risk patient would have received a therapeutic dose for a longer time. The number of LPs performed before documentation of thrombotic event progression/recurrence was considered a surrogate for interruptions of AC therapy. Major hereditary thrombophilia was defined as the presence of low protein C, S, and/or antithrombin (values below normal age-dependent reference values measured on at least 2 occasions at least 3 months apart), and/or homozygous or double heterozygous for prothrombin gene mutation or factor V Leiden. Acquired thrombophilia was considered present if anticardiolipin and/or lupus AC antibodies were present on at least 2 occasions, at least 3 months apart, or if factor VIII was elevated (ie, levels >90th percentile for age measured on at least on 2 occasions at least 3 months apart).

Statistical Analyses

We performed univariable analysis relating each predictor to the outcome traumatic LP using logistic regression analysis with a generalized estimating equations (GEE) approach with robust SE estimates. The GEE method estimates the average population response as a function of covariates, accounting for the nonindependence of within-subject observations.[9] Statistical significance was set at $\alpha = 0.05$.

Variables associated with traumatic LP at a conservative P value of <.25 in univariable analysis were considered for a repeated-measures multivariable logistic regression model using GEE. The quasi-likelihood information criterion was used to assess model fit. The autoregressive variance-covariance structure was used in the analysis. Nonparametric statistical tests (Fisher exact, Wilcoxon rank-sum) were used to explore associations between thrombotic events progression/recurrence (yes/no) and each of the predictors. Again, statistical significance was set as $\alpha = 0.05$. Variables shown to be associated with thrombotic events progression/recurrence in the univariable analysis at a conservative P value of <.25, were considered for a multivariable logistic regression model. Analysis of data was generated using SAS version 9.2 for Windows (SAS Institute, Cary, North Carolina).